



Neurodevelopment of Infants with a Birth Weight $\leq 1500\text{g}$ at Two and Four Years of Age

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Abstract

Background: Extremely low weight has been associated with a high risk of sequelae or Neurodevelopmental disorders, including personality disorders and emotional distress.

Objective: to learn the differences in neurodevelopment at 2 and 4 years of infants with a weight $\leq 1500\text{g}$.

Material and Methods: observational, analytical retrospective, comparative study of a cohort of children with a birth weight $\leq 1500\text{g}$ compared with children $>1500\text{g}$ who attended the Pediatric Follow-up at the National Institute of Perinatology. BSID II and the Stanford-Binet Intelligence Scale by Terman-Merrill 4th ed were used.

Results: 128 patients were included in the comparative analysis; significant differences were found in MDI and PDI of BSID II. For the group $\leq 1500\text{g}$ presented a higher incidence in behavior (Orientation, Commitment and/or Emotional Regulation).

In the Intelligence Scale, the group of children $<1500\text{g}$ at birth presented a statistically significant difference in all cognitive abilities and IQ.

Conclusions: At two and four years of age, children weighing $<1500\text{g}$ have lower scores in neurodevelopment when compared to the group $>1500\text{g}$. Behavioral problems are a factor that influences MDI and PDI at two years of age.

Keywords: Neurodevelopment; Neuropsychology; Prematurity; Extremely Low Birth Weight

Introduction

In recent years, there have been significant technological advances in perinatal and neonatal care, contributing to a reduced neonatal mortality, though this has opened the opportunity to learn about the complications to which survivors are exposed, including an increased pediatric high-risk population, increasing health and developmental concerns in this population. Hence [1,2] the technological advances have contributed to increasing survival and reducing mortality in preterm infants [1-3].

Morbidity and mortality in children can be considered an important indicator to evaluate the quality of health care provided to a population. In Mexico, it is estimated that there is a significant decrease in neonatal mortality; the National Institute of Statistics and Geography reported a considerable decrease according to weight and weeks of gestation in 2017 [4].

The 2017 Statistical Yearbook of the National Institute of Perinatology (INPer) reported a birth weight from 400 grams (0.12%) to 44,99 grams (0.15%), with the mean weight located from 2,990-2,999 grams (7.72) [5].

In 2018, the INPer reported the lowest weight and gestational ages belonged to those who died during the study; among survivors admitted to the neonatal intensive care unit in the same study, bronchopulmonary dysplasia was found in 38%, followed by intraventricular hemorrhage grade III/IV in 20% [6].

Scientific advances aimed at neonatal care have had a significant impact on mortality, allowing for the survival of high-risk newborns, a group considered vulnerable due to its high morbidity, but leading to an increase in neurodevelopmental disorders [7].

In this respect, the WHO [8] has reported that neonatal comorbidities that have a greater risk of affecting neurologic development are those derived from prematurity, quality of care and the care received during delivery and the postpartum period. Galindo [2] reported a greater risk of presenting neurodevelopmental disorders at a smaller gestational age, involving decision making ethical aspects concerning viability and resuscitation regarding outcomes in quality of life.

At the present time, speaking of preterm birth is not just speaking of the weeks of gestation, but also involves using weight as a reference parameter. The normal weight of a newborn is greater than 2500 grams and newborns are classified according to weight as follows:

- **Low birth weight:** Lower than 2500g and greater than 1500g
- **Very low birth weight:** Lower than 1500g and greater than 1000g
- **Extremely low birth weight:** Less than 1000g [9].

Establishing a relationship between weight parameters and gestational age marks the difference between low birth weight and low birth weight for gestational age, two different concepts that are not similar or equivalent, the first referring to weight at birth and the second to the relationship between the parameters of weight and gestational age [9].

In developed countries, newborns with an extremely low birth weight have a 200-fold greater risk of death, compared with newborns with an appropriate weight. Extremely low birth weight is a cause of sequelae and family disturbances in children, and combined with diverse socioeconomic and environmental factors, survivors rarely suffer from only one condition [2,10,11].

Similarly, extremely low birth weight has been related to a high risk of sequelae or neurodevelopmental disorders such as cognitive, attention, and motor function disorders, as well as blindness and deafness. Cognitive disability is not recognizable before 2 years of age, so the actual incidence of these disorders is underestimated [2,12].

Literature has reported that children with a low birth weight present more frequently with personality disorders and emotional distress such as: passive character, deficient impulse control associated to deficiency in regulating attention, slower and disharmonic adaptive responses; these children tend to be more insecure, dependent and with behavioral disorders, fears, tics, and anxiety [13-15].

On the other hand, a strong emotional impact is described in parents and families of newborns who required intensive care during the neonatal period, determined by the situation they experience; limited parent-child interaction due to prolonged separation during the time of hospitalization causing a link failure between parents and children, parental emotional distress, number of days of hospitalization and economic burdens more than just factors exclusive of the child [16].

Therefore, a high risk birth places the family in a crisis in which a series of attitudes are described that modulate parenting; a greater perception of the vulnerability of their child throughout development, greater overprotection and control than that exerted over other children, generating isolation and decreased interaction. All these attitudes generated by family trauma are defined as "vulnerable child syndrome", where infants are at greater risk of developing behavioral problems as a consequence of factors such as anxiety, frustration, fear, ambivalence and parental stress, all of these being important psychological factors for the minor's adequate development [3,16].

Considering the vulnerability of the child, subsequent problems can occur in social-emotional development including behavioral problems, emotional and learning difficulties; children have been

described as anxious, shy, passive or aggressive, reporting higher incidence of hyperactivity, attention deficit disorder, greater emotional reliance on adults or less social competence that affects their school performance, social adaptation and family life in general [13,16].

Hence the assessment of neurodevelopment and family care is of outmost importance, this group must have regular follow-up to assess anthropometric, neurological, social-emotional development among others, establishing multidisciplinary care programs, where the psychologist has an important role in performing assessments and more complex interventions considering a stress-coping process that begins with birth and the acceptance of a high risk. This influences family dynamics and the development of its members due to prenatal, perinatal and postnatal circumstances that generate stress and how parents cope with this situation can also influence their child's neurodevelopment [17].

During the child's development, as of the first year brain development and maturity undergo important changes, later at two years a crucial phase occurs in which motor, social-emotional, language and thinking skills evolve according to the environment where they take place, considering that not all evolve at the same time and in the same way [18,19].

In a study by Cano-Giménez, *et al.* [20] concerning neonatal means and development of children at 24 months, it is discussed that when better physical neonatal conditions are present, the better mental and psychological development will be. This means, those who present more difficulties at birth such as those weighing less than 1500 grams, will present more developmental problems.

Regarding motor characteristics the key biological phenomenon in psychomotor development is the strengthening of cortical circuits. Myelination of these circuits begins at 8 months of gestation and is basically complete at 2 years of age, describing an active child [18].

In a similar manner, some studies report in these children sensory-motor deficits at 2 and 4 years, and during preschool years complex motor skill difficulties including oral language; impulsivity, behavioral problems and at 8 years of age short term memory deficiencies, resulting in a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), especially in males. Symptoms prevail during school years and academic difficulties emerge, such as specific or non-specific learning difficulties [21,22].

At the same time, other studies have found that low weight has an impact on the speed at which higher psychological functions, such as cognitive development and learning are established, occurring at a slower pace during the first school years due to difficulties such as processing speed [23].

On the other hand, Erickson's theory of Psychosocial Development describes the second stage called "autonomy vs shame", which presents itself approximately at the age of two; in this stage the child leaves the mother's side looking for independence. If the parents are restrictive or overprotective they can cause shame, leading to a feeling of insecurity. Satisfactory development in this stage provides autonomy and independence for the child; they tend to be whimsical, like to attract attention and tantrums begin. The role of parents is important at this stage because it is crucial to establish limits and clear rules that allow the orientation of behavior in order to learn to interact [24].

Piaget in his cognitive development theory describes the beginning of a "preoperational" stage at two years of age: "egocentrism" is the tendency to concentrate on only one concept of an object or situation, referring to the inability to see another person's point of view, assuming other people see, hear, and feel exactly what he does, reason why tantrums and outbursts are common [25].

This is why the family and the environment in which the child unfolds are responsible for providing the necessary affection to accomplish activities in an independent manner, strengthening achievements to encourage confidence [20].

Therefore, at this age the foundations are laid for posterior development, constituting a period of crucial importance, given by neurophysiological processes that establish connections and functions of the brain within different areas and their relationship with the environment, which greatly contribute to defining the nature and the breadth of adult abilities [21,26].

Learning difficulties and emotional distress, as well as calculation, reading and writing difficulties, may be recognized as early as 5 years of age. At this age, it is possible to obtain an intellectual quotient (IQ) through assessment with Intelligence Scales. It is reported that children with extremely low birth weight have a significantly lower cognitive performance, and there is a relationship between learning difficulties and/or school behavior and very low birth weight [23].

Therefore, it is of outmost importance to view patients from an integral point of view, recognizing the importance of the environment in which they unfold and the importance of their family in order to provide the care they need to reach the maximum development of their abilities and the best quality of life possible. During follow-up we can gradually decrease uncertainty and increase family adaptability to the child's birth, as well as the environment in which development takes place, hence the importance of family care for the child with low birth weight [3,16]. The objective of this study was to learn the differences in neurodevelopment of infants with a weight $\leq 1500\text{g}$ compared to infants $>1500\text{g}$ seen at the Pediatric Follow-up of the National Institute of Perinatology at 2 and 4 years of age.

Materials and Methods

An analytical, observational, retrospective cohort study of children that were part of the program of Pediatric Follow-up of INPer was conducted, comparing those with a birth weight ≤1500g with children >1500g; complete clinical files of children between 2004 to 2014 were revised using the following criteria: Assessment by the Bayley II Scale of Infant Development at 2 years of age, assessment by the Terman-Merril Intelligence Scale at four years of age.

Instruments

Bayley II scale of infant development [27]

Assesses functional development through age maturity level, without considering chronological age. The areas assessed are 1) cognitive developmental aspects: sensory-perceptive acuity, discrimination, ability to respond to stimuli, early acquisition of object permanence, memory, learning, problem solving ability, basis of abstract thinking, early ability to generalize and classify. 2) Language: ability for receptive and expressive communication. 3) Social personal.

Psychomotor development index: Provides information about the degree of body control, coordination of large muscle groups and the ability to manipulate with hands and fingers, dexterity and psychomotor coordination. Behavioral record: the areas evaluated are Attention-Factor response, Orientation-Compromise, Emotional Regulation and Motor Quality. It analyzes the nature of social orientations and objectives towards the environment. Items include evaluation of social orientation and objective towards the environment, interests, emotions, activity, relationship to the mother or tutor and towards stimuli and the relationship established with the test materials.

It analyzes the nature of social orientations and objectives. In cognitive, language and psychomotor areas, the mental age is given in months.

The results obtained by the child in both scales are expressed in two indexes: the mental development index (MDI) and the psychomotor index (PDI). The mean score for both indexes is 100 ± 16; 116 or more implies accelerated development, 85-115 normal development, 70-84 mild developmental delay; less than 69 significant developmental delay. It provides a mental age in months for cognitive, language and psychomotor areas. Behavioral area assesses normal, questionable and not optimal [19].

Stanford-binet intelligence scale by terman-merril 4th Ed. [28]

Test assessing cognitive abilities, obtaining an intellectual quotient or mental adaptability to new problems through practical judgment, memory for different kinds of materials, visual-motor and spatial ability, reasoning and abstract concept management and verbal aptitude that prevail in higher mental functions, as well

as knowledge acquired in school including reading and arithmetic's.

It is assessed through four sub-scales in its short version: Verbal Reasoning, Visual Abstract Reasoning, Numerical Reasoning and Short Term Memory. The scores for cognitive abilities are: >132, very superior, 121 a 131: superior, 111-120 above average, 89-110 average, 79-88 below average, 76-80 slow learning and <67 mental retardation [10].

To analyze the results demographic variables, central tendency measures, student's T test and chi square test were used.

The analysis was conducted using the SPSS statistical package.

Results

128 patients were included, with 25.3 to 41.6 weeks of gestation; <1500g with M = 30.88 (SD = 2.63) and for those >1500g M = 35.05 (SD = 2.41); the group less than 1500g had a hospital stay of 48.56 (SD = 25.5) and a morbidity of M = 6.83 (SD = 4.45) diseases and the second group had a morbidity of M = 3.49 (SD = 2.19) diseases and a hospital stay M = 17.21 (SD = 12.36). Table 1 shows the neonatal variables.

Variables	≤1500 F	% N = 75	>1500 F	% N = 53
Gender				
Male	35	(46.7)	26	(49.1)
Female	40	(53.3)	27	(50.9)
Type of Pregnancy				
Single	43	(57.3)	32	(60.4)
Twin	23	(30.7)	12	(22.6)
Triplets	9	(12.0)	9	(17.0)
Weight				
>1000	17	22.7		
1001 a 1500	58	(77.3)		
1501 a 2500			45	(84.9)
≤2500			8	(15.1)
Weeks of Gestation				
≤33.6	65	(86.7)	34	(75.4)
≥34	10	(13.3)	13	(24.5)
Hospital stay				
<30 days	15	(20)	46	(86.8)
31 a 60 days	42	(56.1)	7	(13.2)
61 a 90 days	11	(14.6)	0	(0)
>90 days	7	(9.3)	0	(0)

Table 1: Neonatal Variables.

It calls our attention that respiratory problems and sepsis presented with a greater frequency in the group greater than 1500g. For the rest of pathologies no differences were found. See table 2.

Pathology	≤1500 F	% N = 75	>1500 F	% N = 53
Hyperbilirrubinemia	44	(58.7)	21	(39.6)
Pulmonary pathology	62	(82.7)	29	(54.7)
Intrauterine growth restriction	28	(21.9)	19	(25.3)
Metabolic problems	28	(21.9)	9	(17)
Sepsis	34	(45.3)	6	(11.3)
Intraventricular hemorrhage	10	(13.3)	1	(1.9)
Maternal pathology	22	(17.2)	10	(13.3)
Bronchopulmonary dysplasia	23	(18)	12	(22.6)

Note: Pulmonary problems (Respiratory distress syndrome, Hyaline membrane disease, Transient tachypnea of the newborn, Pneumoniae, Mother's Pathology, Hypothyroidism, Diabetes, Human immunodeficiency virus.

Table 2: Associated Neonatal Pathology.

As to sociodemographic variables, maternal age was observed: M = 31.20 (SD = 7.3) and 32.9 (SD = 9.7). The most frequent mother's schooling was middle school (36%) and the most frequent occupation was housewife (69.3%). 52% had previous losses (See Table 3).

In the comparative analysis, significant differences were found for MDI and PDI for the Bayley II Scale of Infant Development at two years of age. For the group ≤1500g at birth, a significant delay was found with p = 0.003 and .001, respectively and for the group >1500g a mild developmental delay was found with scores below 80. Comparing the mental age for both groups a difference of two to three mental months is observed in less than 1500g compared with group 2, although not significant with a p = 0.87. For motor and

language areas significant scores were found, favoring the group >1500g, p = 0.006 and 0.10, respectively. In the intelligence scale we can observe that for the group ≤1500g, there is a difference of 4 to 8 points compared with the group of children greater than 1500g, being statistically significant in all cognitive abilities and the intellectual quotient, p = 0.001 (See Table 4).

Variables	≤1500 F	% N = 75	>1500 F	% N = 53
Mother's schooling				
Elementary	8	(10.7)	3	(5.7)
Middle school	27	(36.0)	12	(22.6)
High school	25	(33.3)	29	(54.7)
Bachelor	15	(20)	9	(17)
Occupation				
Housewife	52	(69.3)	31	(58.5)
Professional	6	(8.0)	6	(11.3)
Other	33	(25.8)	16	(30.2)
Type of familia				
Nuclear	27	(36.0)	22	(41.5)
Trigenerational Nuclear	31	(41.3)	20	(37.8)
Recreated	6	(8.0)	3	(5.6)
Only parent	11	(14.6)	8	(15.1)
Planned pregnancy	38	(50.7)	32	(60.4)
Previous losses	58	(44)	66	(35.8)

Note: Trigenerational Nuclear Family: Three or more generations live together. Recreated family: Mom or dad have another partner, and the child lives with one parent. Only parent: the child lives with only one parent.

Table 3: Sociodemographic Variables.

Valoración	≤ 1500g μ	DE	>1501g μ	DE	Prueba t (g126)	p	d de cohen
MDI	65.05	(23.75)	77.72	(22.81)	-3.02	.003	0.54
PDI	58.04	(29.30)	75.06	(26.29)	-3.30	.001	0.61
CMAM	20.99	(5.47)	22.83	(6.56)	-1.72	.087	0.30
LMAM	20.04	(5.31)	23.32	(7.25)	-2.80	.006	0.51
PMAM	19.52	(6.32)	22.64	(7.02)	-3.55	.010	0.46
IQ	89.32	(12.67)	97.17	(11.75)	-3.55	.001	0.64
VR	91.83	(13.25)	97.28	(15.72)	-2.12	.036	0.37
VAR	88.53	(12.80)	92.26	(14.25)	-2.79	.006	0.27
NR	93.05	(13.79)	99.0	(13.22)	-2.44	.016	0.44
STM	90.09	(13.97)	96.91	(11.06)	-2.95	.004	0.54

Note. MDI: Mental Development Index, PDI: Psychomotor Development Index, CMAM: Cognitive Maternal Age in Months LMAM Language Mental Age PMAM Psychomotor Mental Age in Months IQ: Intellectual Quotient VR: Verbal Reasoning VAR: Visual Abstract Reasoning NR: Numerical Reasoning STM: Short Term Memory

Table 4: Comparative analysis of neurodevelopment at two and four years of age.

For the behavioral scale it is observed that the group ≤1500g presented a lower incidence of Orientation compromise and/or Emotional Regulation (See Table 5).

Bayley N = 128	≤1500	N = 75	>1500	N = 53	P
	Orientation/ Compromise n (%)	Emotional Regulation n (%)	Orientation compromise n (%)	Emotional regulation	
MDI ≤P	0	1(1.3)	3(5.6)	4(7.54)	.056
MDI ≥P	22(29.33)	21(28)	16 (30.18)	17(32.07)	
PDI ≤P	3(4%)	4(5.3)	3(5.6)	3(5.66)	.188
PDI ≥P	19(25.3)	18(24)	16(30.18)	18(33.96)	

Pearson's Chi squared test, Fisher's exact test.
 Note: Mental Developmental Index (MDI); Psychomotor Developmental Index (PDI); Average or greater ≤ 85 (≤P); Below average ≥84 (≥P).

Table 5: Behavioral problems in: Orientation Compromise or Emotional Regulation.

Discussion

The objective of this study was to know the differences in neurodevelopment at 2 and 4 years of infants with a birth weight ≤1500g compared to infants >1500g. In this study it is observed that infants with a weight of ≤1500g present lower scores in neurodevelopment as compared to infants with a weight >1500g. As mentioned in literature, low and extremely low birth weight infants present difficulties in neurodevelopment [10,12,15,20].

Studies of factors associated to low weight [11] concluded that psychomotor developmental delay is one of the most important complications presented by newborns with extremely low and very low birth weight. As shown by the present study comparing ≤1500g with greater than 1500g, a significant developmental delay is found for PDI. Diaz [2] mentions that in managing children with a birth risk, there is greater probability of presenting neurodevelopmental disorders at a lesser gestational age, the majority being transient tone alterations, as shown in this sample according to the child's progression at 4 years of age.

On the other hand, it is mentioned in literature that children with a low birth weight show alterations in cognitive abilities and intellectual quotient [11]. Studies of children with very low birth weight have shown an incidence of subnormal (70-84) and deficient IQ (<70) [29]; nevertheless, in this sample it can be observed that children at 4 years of age have normal intellectual quotient scores (≥89), as well as cognitive abilities: Verbal Reasoning, Numerical Reasoning and Short Term Memory, contrary to what is referred to in literature [2,11,12,29]. When compared to the group greater than 1500g there is a statistically significant difference of up to 8 points with a p 0.001.

In Mexico [30] a study relating socioeconomic factors found a low socioeconomic level to be an important risk factor for low birth weight, independent from other factors. Other studies show protective factors for low birth weight are female gender and middle or high parent schooling [2,10]; in this sample with a higher percentage of females (53.3%), we observe that in the group less than 1500g there is little difference related to gender. In relation to mother's schooling: 53.3% have middle or high schooling, as referred in literature; however, these variables together with occupation, type of family, planned pregnancy, type of pregnancy and previous losses, did not show a statistical difference for neurodevelopment in this sample.

Neonatal complications of newborns with low and extremely low birth weight include hyponatremia, hypoglycemia, asphyxia, respiratory distress, hyperbilirubinemia, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia [10,29]. In this sample it is observed that these morbidities occur as referred to in literature, the highest frequency being pulmonary pathology and multifactorial hyperbilirubinemia in both groups, showing the highest frequency in the group ≤1500g.

Emotions generated during hospitalization and the perinatal period cause parents to perceive their child as vulnerable seeing him so small. Premature neonates rarely present with only one morbidity, as shown in this investigation; factors that contribute to alterations are respiratory complications, bronchodysplasia, maternal infections and neonatal sepsis¹⁴, also confirmed in this sample, thus generating emotional sequelae by the impact experienced and provoking altered parenting [14], presenting socioemotional developmental in minors, as mentioned by Belaustegui., *et al.*

On the other hand, emotional development at two years of age is a stage where the child shows a tendency to be capricious, likes to attract attention, is egocentric and where tantrums begin. Therefore, the role of parents is important, being crucial to establish limits and clear rules that allow the guidance of behavior and the interaction according to what is expected by age [24]. In this way, emotional sequelae presented by parents hampers the establishment of clear and consistent limits by the perception of a vulnerable child [16], as can be observed in this study, given that 69.5% of the total sample showed behavioral problems in one of the areas assessed at two years of age.

In literature it is reported that children with a low birth weight frequently have more alterations and emotional difficulties [13-15], among which stand out behavioral problems, passive character, deficient impulse control associated to deficit in regulation, disharmonic and slower adaptive responses in attention, tendency to be insecure children, shy, passive, dependent, fearful, with anxiety disorders, excessive adult reliance or less social competence, which influences family life in general [13,16]. This sample shows

that children ≤ 1500 g have less problems in behavior, emotional regulation and compromise-orientation than >1500 g, contrary to what is reported in literature.

This can be explained because children in this sample belong to a program of pediatric follow-up, where there is attention for the family during the process of facing stress and accepting high risk, involving continuous neurodevelopmental assessments, generating a protective factor, as mentioned by Belaustegui, *et al.* [16] Helping parents in the identification and management of behavioral problems in preterm children improves the interaction with their child, protects the child from overprotection and facilitates development. Due to the vulnerability perceived in their children, parents of children with low and extremely low birth weight may generate a greater compromise and adherence to guidelines given by the multidisciplinary treatment.

Maturity, family context, quality and security of care during hospitalization are key for survival and preventing sequelae. Scientific evidence shows that if a very low birth weight child is born in a safe place the probability of sequelae decreases and if involved in a follow-up program, these sequelae may be mitigated or anticipated and treated [3,16,17,20], as shown in this study through the results obtained when comparing neurodevelopment at 2 and 4 years of age. Both groups show a similar course independent from weight, recognizing the importance of pediatric follow-up and the attention to the family to provide care in the most adequate form in order to develop maximum capacities and have an adequate socioemotional development. As mentioned by Cano-Giménez, *et al.* [20] no risk variable is predictive on its own; the probability of predicting an effect is more evident if accumulated, reason why treating these children and their families since early stages and facing risk factors may reduce these and avoid negative consequences. Early treatment programs may be developed by knowing most neonatal measures, not just in a hospital setting, but also in the family generating strategies that avoid the appearance of problems and favor the child's welfare and cohabitation.

The usefulness of a pediatric follow-up in children with low and extremely low birth weight is to make an early detection in the different areas of development with an interdisciplinary management, with participants from different health areas; it is transcendental for early detection of sequelae, in such a way that every unit that handles newborns with a weight less than 1500g should have these follow-up programs in order to make detections [9,16].

In order to delve into the subject, it is suggested to broaden the age ranges and assess children in schooling age, as well as investigate with their parents in relation to facing and parenting.

Conclusion

At two and four years children with a birth weight ≤ 1500 g have lower neurodevelopmental scores when compared to the group

>1500 g.

Behavioral problems are a factor that influences MDI and PDI at two years of age, nevertheless, care and attention through pediatric follow-up may work as a protective factor by promoting the child to have a better utilization of his/her abilities and obtain scores within the expected range for his age in cognitive abilities and IQ, in spite of low birth weight.

Conflict of Interest

The authors declare no conflict of interest.

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