

## Impact of Cesarean Delivery on Childhood Neurocognitive Development

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**Abstract:** *Starting from the words of Victor Marin - "the end is a bad beginning", this narrative review aims to draw attention to the impact played by the perinatal period on the balance and subsequent evolution of the child at the beginning of the journey. The medical literature of the last decade is strongly developed regarding the homeostatic imbalances induced by the type of delivery of the fetus on it. Among these we briefly state intestinal or pulmonary dysbiosis, entities frequently incriminated in escalating the predisposition towards the development of atopy, autoimmune, cardio-vascular, gastrointestinal, metabolic, renal or neurological diseases. Neurocognitive integrity is defined by its importance both in terms of the child's optimal transition to adolescence and later to adult life, as well as in its psycho-social integration. We will therefore develop in the following current considerations regarding the development of the neurological system, emphasizing its variability depending on the type of birth. The desired practical purpose is to raise awareness of the unwanted effects of cesarean section, to discourage its choice when medical considerations are not in question and thus to reduce the burden induced by neurological disorders both on the patient and the family, as well as on the global medical system.*

**Keywords:** *pregnancy; caesarean section; neurodevelopment; child.*

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## **Introduction**

Birth is a physiological process, being the characteristic of the final stage of pregnancy. It consists of the sequence of clinical and mechanical events that result in the removal of the fetus and fetal appendages from the internal environment (maternal body) in which they were formed. Depending on its characteristics, childbirth can be briefly divided into two types: naturally or by caesarean section. In the first situation, this occurs after the initiation of labor, the fetal mobile undergoing various rotational processes designed to optimally position and direct it for expulsion. In contrast to natural birth, cesarean section - the most common operation globally, is performed through a low transverse (preferable) or vertical incision at the level of the anterior uterine wall. It must be used in certain situations (maternal/fetal) when the natural birth presents risks. The most common of these are eclampsia, previous cesarean/uterine operations, acute fetal distress, macrosomic fetus, dystocia of presentation (e.g., transverse, twin pregnancy) or cephalo-pelvic disproportion, obstruction of the birth canal, failure in labor progression, prolapse of the umbilical cord, placenta previa or separation from the normally inserted placenta. Regardless of these, we also find in medical practice the preference of pregnant women for cesarean section (caesarean section at the request of the mother) (Lupu et al, 2023; Nilsson et al, 2018; Smith et al., 2008; Oliveira & Penna, 2018).

Certainly, similar to the period of intrauterine development, the method of delivery of the product of conception brings with it effects felt both at the level of the maternal and the fetal body. As far as this is concerned, the current medical literature abounds in data related to the hemodynamic consequences and developmental disorders of the newborn, dependent on the perinatal period. Of these, we particularly note the neurodevelopmental vices, partly due to the burden felt in the medium and long term (Sharma & Dhakal, 2018; Usui & Shimada, 2022). Consequently, the promotion of information regarding the imbalances that can be induced by birth on demand by surgical means is essential in discouraging this unjustified medical practice.

## **Epidemiology**

The world statistics are worrying both regarding the incidence of caesarean section, as well as its effects on the mother and the child. Medical data certify the growing frequency of its practice, which exceeds 31%. Of these, it is estimated that in only 10% of cases the option is doubled by a

medical indication. The leading countries in terms of preference for it are the Caribbean, Latin America and North Africa (58.1%), in contrast to Sub-Saharan Africa (3.5%). The main factors that tip the decision-making balance towards cesarean surgery seem to be scientific progress, social and cultural changes and medico-legal considerations. The risks of the procedure are minimized, therefore we reiterate the need to discourage its practice when its benefits are not certain (Mylonas & Friese, 2015; Belizán et al., 2018).

### **Disorders of neurocognitive development**

Neurodevelopmental disorders represent a group of conditions that begin during childhood and often persist into adulthood. The etiological study is currently a challenge due to the multitude of objectified interrelations. Both the involvement of a hereditary component and environmental factors (antenatal, prenatal and postnatal) are suggested. The strong impact of the prenatal period on the child's neurodevelopment is already known. The pathologies whose incidence frequently increases, being correlated with endogenous and exogenous maternal imbalances, are autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) (Usui & Shimada, 2022). More recently, in the pathogenesis of neurological deficits, theories that aim to involve the methods of assisted human reproduction (intracytoplasmic sperm injection, in vitro fertilization) in the imprinting of the risk of behavioral disorders, intellectual disability, cerebral palsy or ASD (Djuwantono et al., 2020).

The birth itself, carried out by caesarean section, is a medical act with various consequences. Depending on their type, they can be classified as intra-operative/post-operative and maternal/fetal/subsequent pregnancies. At the level of the child's internal microenvironment, post-operative complications are frequently identified with dysbiosis. This is due in part to the different variability of the bacteria with which the fetus comes into contact at the time of delivery. Microorganisms that colonize the skin -  $\beta$  diversity and opportunistic pathogens (*Enterococcus*, *Klebsiella*, *Enterobacter* and *Staphylococcus*) are predominant, with a decrease in the abundance of bacteria beneficial to the body such as those of the genus *Bifidobacterium*, *Lactobacillus* and *Bacteroides*. At the same time, the consequences of the caesarean section are reduced in the case of children for whom it is performed "warm" - once labor has started. The imbalances seem to fade after 6 months of life, while at 5 years the studies do not identify significant differences depending on the type of birth. However, the medical literature attests through numerous meta-analyses the link between caesarean section and neurocognitive

deficiencies, the increase of infectious, atopic, autoimmune and pediatric oncological risk (Lupu et al., 2023; Ríos-Covian et al., 2021; Pantazi et al., 2023). In conclusion, it is estimated that the prenatal period and the first three years of the newborn's life represent the pillar of harmonious development and the most opportune moment for microbial modulation interventions aimed at preventing/reducing damage and long-term consequences (Rutayisire et al., 2016).

### **Interference between cesarean section and child's neurodevelopment**

In light of the above, knowing and counteracting the negative effects of cesarean section on neurocognitive integrity is a hot topic of current research. Various theories have been proposed, among which we bring into discussion the alteration of the microbiota-intestine-brain axis, hormonal dysregulation (oxytocin) and neurotoxicity following general anesthesia. At the same time, the mode of delivery seems to transiently influence brain volume, integrity and myelination of the white matter (Deoni et al., 2019; Deoni et al., 2018).

The current hypotheses regarding how intestinal dysbiosis can influence the occurrence and potentiation of multiple diseases are centered around the intestines-vital organs axis. Thus, in previous works we detailed the connection between the intestine and kidneys, heart, lungs and even the immune system (Pantazi et al., 2023; Mocanu et al., 2023; Lupu et al., 2023a; Lupu et al., 2023b; Lupu et al., 2023c; Lupu et al., 2023d). In addition, the gut-brain axis involves a bidirectional communication between the two entities, based on endocrine, humoral and metabolic components. The translocation of toxic microbial metabolites beyond the blood-brain barrier, occurring predominantly during the critical window, is responsible for long-term structural and functional neuroalteration (Checa-Ros et al., 2021; Holzer & Farzi, 2014). Numerous studies have highlighted the involvement of the intestinal microbiome in modulating the body's emotional and behavioral responses through vagal afferents. Pathogenic agents are involved in inducing fears, anxious, depressive, schizophreniform or bipolar behaviors. Also, the intestinal microbiome influences either the de novo generation of neurotransmitters (dopamine, serotonin, acetylcholine, glutamate,  $\gamma$ -aminobutyric acid), or the metabolic pathways related to them. The gut microbiome also regulates apoptosis and neurodegeneration, in part by modulating brain-derived neurotrophic factor (BDNF) expression or microglial maturation and function. Beneficial effects were obtained in the case of therapeutic intervention by supplementing with probiotic strains of *Lactobacillus* and *Bifidobacterium* or transplantation of fecal matter (Góralczyk-

Bińkowska, Szmaida-Krygier & Kozłowska, 2022; Socala et al, 2021; Liang et al, 2018; Abdel-Haq et al, 2019).

Oxytocin is a peptide hormone produced in the paraventricular and supraoptic hypothalamic nuclei and stored in the neurohypophysis, from where it is released into the bloodstream. It modulates anti-inflammatory and anti-stress reactions (blood pressure, heart rate, cortisol level), enhances the activity of the parasympathetic system, initiates labor, expulsion of the fetus and placenta, breastfeeding and influences social behavior. During natural birth, oxytocin has a double implication, maternal and fetal. In children, it relieves pain and the consequences of hypoxia. In the mother it peaks in the first hour after birth to reduce pain, stress levels and promote mother-child interaction. Cesarean birth disrupts the release of oxytocin. Dysregulation of oxytocin release may affect infant brain development, although its therapeutic effects remain open to study (Moberg et al., 2020; Rajamani et al., 2018; Chirita et al., 2012; Leithead et al., 2021).

Regarding the impact of in utero exposure to general anesthesia on long-term neurodevelopment, there is little data in the literature. Exposure of the developing fetal/neonatal brain to inhalational and intravenous anesthetics during periods of most rapid synaptogenesis can lead to significant neurodegeneration by apoptosis with subsequent neurological impairment. Human studies on the influence of postnatal anesthesia exposure report conflicting results. Regarding the immediate results, the evidence from the specialized literature does not indicate significant fetal differences between neuraxial and general anesthesia. Some studies suggest an association between early exposure to anesthesia and long-term learning ability or behavioral abnormalities, while others show no association between single exposure and adverse neurodevelopmental prognosis. In the long term, the rate of learning disabilities is not higher among those born by caesarean section under general anesthesia compared with neuraxial anesthesia (Burlea, Burlea & Milici, 2010). Newborns by caesarean section exposed to general anesthesia are not associated with neurodevelopmental delays at the age of two years, but have an increased risk of severe motor delays and a prolonged length of hospital stay in the Neonatal Therapy ward (Sprung et al., 2008; Flick et al., 2011; Yang et al., 2021; Robbins et al., 2021).

## **Conclusions**

The rate of cesarean births, particularly those performed without medical indication, is increasing worldwide. In this context, increasing information about its long-term risks and benefits for expectant mothers,

their offspring and future pregnancies is important. Although a causal relationship is difficult to establish due to multiple confounding factors, cesarean delivery has the potential to cause structural and functional changes in the newborn brain. Children born this way have an increased risk of developing ASD and ADHD. There is no clear evidence to support its association with other neurodevelopmental or psychiatric disorders. Among the mechanisms that interfere with optimal development, we note the alteration of the microbiota-intestine-brain axis, the hormonal changes occurring during cesarean delivery as well as the neurotoxicity due to general anesthesia. In conclusion, the risk of neurobehavioral disorders associated with cesarean birth in children should discourage its performance for non-medical reasons.

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