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BRIEF REPORT

New challenges beyond nutrition: c-section, air pollution and domestic violence

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The DOHaD research field has successfully associated adult non-communicable diseases with inadequate nutrition in early periods of life. More recently, different types of exposure have been linked with impaired developmental outcomes and later health consequences, such as cesarean section at delivery, air pollution and domestic violence during pregnancy. The aim of this work is to bring up this issue looking at the published evidence on these three highly prevalent hazards in Latin American countries.

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Introduction

Many observational epidemiological studies in different settings and times, as well as many intervention studies in animals and some in humans provided us enough evidence of the association between nutritional exposures during developmental periods and later health outcomes, such as adult non-communicable diseases (NCD).

However, less focus has been given to exposures different from nutrition during these developmental periods, even if some of them are highly prevalent, mainly in developing countries. Exposures linked to health practices, such as type of delivery, to environmental conditions, such as air pollution, and to social–cultural aspects, such as domestic violence are examples of that. We intend to bring up this issue and its possible consequences on the development of later health outcomes, as there seems to be a good amount of evidence that these exposures are linked to impaired fetus growth or/and adult NCD.

C-section

C-section is frequent in developing countries. The highest rates are concentrated in Latin America (LA) and Asia. WHO estimated a median frequency of 33% of c-section deliveries in 2005 in LA.[1] A similar study in Asia in 2007–2008 estimated 27.3%.[2] In both places, this type of delivery was more associated with maternal and neonatal mortality and morbidity. In Brazil, nearly 50% of babies are delivered by c-section.[3]

Late health outcomes linked to c-section have only recently been appointed. Even if this is still a controversial topic there is a good amount of evidence that links it to obesity, and immunological system disorders (asthma, allergy, inflammatory bowel disease and type I diabetes).

Obesity is the most studied outcome. A recent meta-analysis studied 24 publications of 28 studies found out that children born from c-section had a 34% greater risk [RR = 1.34 (95% CI: 1.18–1.51)] during childhood and adolescence of being obese.[4] Maternal pre-gestational weight is normally considered an important confounder. After adjustments for it the size effect was [RR = 1.29 (95% CI: 1.16–1.44)]. A study in Brazil in two highly different socio-economic parts of the country was able to adjust for several possible confounders [maternal schooling, maternal smoking during pregnancy, duration of breastfeeding, gender, birth weight (BW) and gestational age, type of school] and found a positive association between c-section and obesity in school age children [OR = 1.74 (95% CI: 1.04–2.92)].[5]

Another meta-analysis, covering a broader age-range, also found a higher risk for overweight/obesity. In the 3–8-year age sub-group, there was a OR = 1.32 (95% CI: 1.15–1.51), in the 9–18-year sub-group an OR = 1.24 (95% CI: 1.00–1.54) and in the older sub-group (⩾19 years) an OR = 1.50 (95% CI: 1.02–2.20).[6] Other studies, however, did not find any association.[7,8]

The immunological system seems to suffer some influence as well. A meta-analysis with 23 studies found an increased odds of asthma among c-section born individuals [OR = 1.20 (95% CI: 1.14–12.6)].[9] The population attributable risk fraction was estimated in a study from Danmark, which included a huge population, adjusted for age, calendar year, gender, parity, BW and maternal heredity. There was an elevated risk for asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel diseases, immune deficiencies and leucemia.[10]

Finally the association with type I diabetes mellitus (DM) has also been investigated. A meta-analysis with 20 studies showed a 23% increase in the risk for DM.[11]

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These results must be seen cautiously because of the heterogeneity of the studies and because of confounders, such as use of anesthetic agents and antibiotics during cesarean section, diet, hospital environment, as well as genetic diversity of study populations.[12]

The biological pathways that have been hypothesized to explain these findings are the gut colonization (c-section born children have a microbiota similar to obese individuals); different levels of adaptive stress at birth (stress in vaginal delivery would facilitate the maturation of the immune system) and long-lasting epigenetics modifications.[12]

Air pollution

Follow-up studies have been conducted in recent years to evaluate the impact of prenatal exposure to pollutants on fetal growth and development.[13] The primary effects of prenatal pollutants exposure seem to affect particularly BW and other parameters of fetal biometry. The most frequently studied pollutants are particulate matter (PM) and nitrogen dioxide (NO_2).

Pendersen *et al.* compiled data from 14 prospective birth cohorts involving 12 European countries. Increase of 5 $\mu g/m^3$ in prenatal exposure to PM2.5 and PM10 were associated with an increased risk of low birth weight [LBW; OR = 1.18 (95% CI: 1.06–1.33) and OR = 1.16 (95% CI: 1.00–1.35), respectively]. Even exposures to PM2.5 concentrations below the minimum recommended by the European Union were also associated with an increased risk of LBW.[14]

A recent meta-analysis has examined the results of the effects of prenatal exposure to PM on the BW of infants born at term. An increase of 10 $\mu g/m^3$ throughout pregnancy, in PM10 exposure [OR = 1.03 (95% CI: 1.01–1.05)] and in PM2.5 exposure [OR = 1.10 (95% CI: 1.03–1.18)] have been associated with decreased BW. This increase in exposure to PM10 contributed to a reduction in BW of 8.9 g.[15]

The effects on the fetus were also observed in the meta-analysis undertaken by Zhu *et al.*, which included 25 observational studies. Increased exposure to PM2.5 was directly associated with LBW [OR = 5.1 (95% CI: 1.02–1.07)], prematurity [OR = 1.10 (95% CI: 1.03–1.18)], and small infants for gestational age [OR = 1.15 (95% CI: 1.10–1.20)]. A 10 $\mu g/m^3$ increase in PM10 exposure was associated to a 14.8 g (95% CI: 9.86–19.31) decrease in BW.[16]

The impacts on BW noted in several studies may seem small individually because they represent only a few grams of reduction; however, the great worldwide exposure and population impact make the effects an important public health problem. Pedersen *et al.*[14] estimated that a reduction in the number of cases of LBW of 22% could be achieved by reducing exposure to PM2.5–10 $\mu g/m^3$ during pregnancy.

Concerning NO_2, a meta-analysis that included 14 European cohorts (ESCAPE) demonstrated that increased exposure to NO_2 was associated with decreased BW [OR = 9.1; (95% CI: 1.00–1.19)] and a greater risk of low BW among individuals living near high-density vehicular traffic routes, with an OR of 1.0 (95% CI: 1.01–1.11).[14]

However, some studies have noted positive correlations between exposures to pollutants and perinatal parameters. In the Netherlands, the birth cohort DUTCH PIAMA evaluated 3853 pregnant women exposed to NO_2, PM2.5 and soot during the entire pregnancy, during each trimester and during the final month. Exposure levels were not associated with outcomes at term.[17]

A historical cohort study (PAMPER study) analyzed data from pregnancies between 1962 and 1992, including 90,537 births and 812 abortions, in northern England. The black smoke emission data were collected from 20 monitoring stations during the study period. The authors noted no relationships between exposure to PM during pregnancy and the risk of miscarriage and preterm birth; however, there was a significant negative correlation between greater levels of exposure and BW.[18]

Some studies have sought to understand the mechanisms by which fetal development may be impaired following exposure to air pollutants. Higher levels of NO_2 and PM10 seem to be associated with lower levels of maternal blood markers of placental growth during both the 2nd and the 3rd trimesters. Throughout pregnancy, the highest levels of exposure to PM10 and NO_2 were associated with an anti-angiogenic state in cord blood.[19]

Domestic violence

Violence is a major public health issue in developing countries, where 90% of the events occur. In LA, it is characteristically an urban phenomenon. This trend has been linked to the pattern of urbanization, such as rapidly created metropolises with deprived peripheries, areas that lack services, leisure, quality of life and opportunities. The distribution of violent events is highly concentrated in these peripheries.[20]

Violence towards women during pregnancy is prevalent and of particular concern, with an estimated 2–23% of pregnancies in developed countries involving physical violence against the female partner.[21] This is higher than other common pregnancy problems like gestational diabetes, placenta previa and preeclampsia. Studies in India[22] and China[23] reported rates of violence in pregnant women of 25 and 18%, respectively. In LA, a Brazilian study reported rates of 33.8%.[24]

A meta-analysis of 14 published studies from developed countries found a small but significant effect of violence during pregnancy on LBW [OR = 1.4 (95% CI: 1.1–1.8)].[25] Fewer studies were produced in developing countries, but in China[23] and India[22] negative outcomes were also reported. A more recent meta-analysis with 30 studies found an association between violence and birth outcomes, with an adjusted OR = 1.53 (95% CI: 1.28–1.82) for LBW and an adjusted OR = 1.46 (95% CI: 1.27–1.67) for preterm birth.[21]

Later outcomes have been linked to maternal psychosocial stress and not specifically to domestic violence. Li *et al.*[26] have reported an increased risk for obesity in later at school age

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among children of mothers who suffered prenatal stress. Entriger *et al.*[27] reported higher insulin, c-peptide and leptin levels as well as BMI among young adults whose mothers had had a healthy pregnancy but during which they had gone through a major life stress.

The mechanisms through which violence affect birth outcomes are not clear. Violence might have a direct impact on fetal growth through trauma, or may indirectly cause low weight gain and/or increase smoking and drinking during pregnancy. Female victims of sexual violence have more sexually transmitted diseases and urinary tract infections, and both are causes of impaired fetal growth. An associated poor mental health could affect the infant outcome by poor maternal self-care, such as poor appetite or lesser access to antenatal services.

Some of the biological mechanisms underlying this type of exposure and physiological alterations have been defined. Extensive animal literature has demonstrated that the association between maternal psychosocial stress and LBW is mediated by changes in the hypothalamic–pituitary–adrenal (HPA) axis. There is increasing evidence in humans that the HPA axis is in overdrive in pregnant women subjected to psychosocial stress.[28] Cortisol crosses the placenta, which has been demonstrated to inhibit intrauterine growth when present in high levels.[29,30] In addition to this, despite the large pregnancy-associated changes in maternal endocrine physiology, the neuroendocrine system is responsive to maternal psychosocial states.[31]

Conclusion

There is a good amount of evidence linking c-section, air pollution and violence with health consequences in the early period of life. Less frequent or more controversial are evidence associating them with adult NCD. These non-nutritional exposures are of key public health concern. Impaired fetal growth induced by inadequate health practices, environmental conditions and social–cultural aspects is something preventable. While NCD are often fought by modifying risk factors mostly at the individual level, these exposures need a more comprehensive approach to be dealt with. More evidence confirming their effect on human development will facilitate influencing political agenda.

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