Developmental Origin of Non-Communicable Diseases in children in the Western Cape

Hein Odendaal, Naomi Levitt, Krisela Steyn

Department of Obstetrics and Gynaecology, Stellenbosch University, Stellenbosch, South Africa
Head Division of Diabetes and Endocrinology Department of Medicine, University of Cape Town, Director, Chronic Disease Initiative for Africa, Cape Town, South Africa
Associate Director, Chronic Disease Initiative for Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa

There is convincing evidence that many of common chronic diseases such as ischaemic heart disease (IHD), hypertension and diabetes mellitus have their origin, or at least part of it, during fetal development. The idea of the fetal origin of diseases, or the developmental origin of health and disease (DOHaD) as it is called today, originated in 1986 when Barker and Osmond, on division of the United Kingdom into different regions, observed a strong geographical relation between IHD mortality rates in 1968-78 and infant mortality in 1921-25. They further found that IHD strongly correlated with both neonatal and post-neonatal mortality. As these neonatal conditions were associated with poor living circumstances, poor nutrition in early life was identified as a possible causing factor. In the follow-up of 5664 men, born during 1911-1930, Barker et al. found that men with the lowest weights at birth and at one year had the highest death rates from IHD in later life, leading them to suggest that measures that promote healthy prenatal and postnatal growth may reduce deaths from IHD. In the follow up of 1084 men, Law et al. found that the mean waist to hip ratio at 51 to 64 years was inversely related to birth weight. The same group studied 702 people born in Amsterdam during the famine of 1944-45 and found that prenatal exposure to poor nutrition, especially during late gestation, was linked to decreased glucose tolerance in adults.

These findings highlight the major influence of conditions during fetal development on human health where adverse circumstances in early development may lead to a small size or modified metabolism to ensure later survival. Adaptation to their mothers' condition before birth generally prepares individuals such that they are best suited to the environment forecast by cues available in early life. However, rapid improvements in nutrition and other environmental conditions may bring stresses not prepared for. The crucial fact is that the embryo and fetus are very sensitive to toxic and stressful environments or poor nutrition. The underlying mechanisms are most likely epigenetic based changes.

A most recent study by Jaddoe et al. demonstrated that impaired first trimester fetal growth is associated with an adverse cardiovascular risk profile in school age children, leading the authors to conclude that early fetal life might be a critical period for cardiovascular health in later life.

As the understanding of the early determinants of adult chronic diseases has emerged, the call for a life-course approach to chronic disease prevention has become widely accepted. In fact, an extensive body of knowledge has emerged in the last 20 years suggesting that a range of antenatal and early life experiences predispose these children to develop chronic disease risk factors early in life that will, in due course, emerge as premature chronic diseases in adult life. This phenomenon is particularly important where the pregnant mother is exposed to stressful life events such as poor nutrition, smoking tobacco, drinking alcohol and using recreational drugs (Figure 1).

Alcohol

The fetal alcohol spectrum disorders (FASD), apparent in early childhood, are a well-documented outcome of exposure to a toxic environment during pregnancy, i.e. alcohol, during a period when rapid developing cells and organs are extremely sensitive. There is also a dose-response relationship, as low birth weight and small for gestational age (SGA) are associated with the consumption of more than 10 g of pure alcohol per day in contrast to reduced risks of SGA, low birth weight and preterm birth in moderate drinkers.

Alcohol misuse is a major social and health problem in South Africa. It is reported that about one in four adult men and one in 10 adult women experience symptoms of alcohol related problems. In addition the mortality attributable to alcohol misuse, an estimated 7.1% (95% uncertainty interval
The period most sensitive to alcohol’s adverse effects appears to be gastrulation, which corresponds to prenatal weeks 3-8 in the human. It is important to note that these epigenetic changes can persist long after the transient environmental signal has disappeared.

There are sparse published data on the long term follow up of children diagnosed to have FASD. However, the limited information demonstrates that the devastating effects of intrauterine exposure to alcohol persisted into early adulthood, severely limiting careers paths and independent living. To date little or no attention was given to the early indicators of cardiovascular or renal disease.

**Smoking**

Smoking during pregnancy is strongly associated with poor pregnancy outcome such as fetal growth restriction, preterm delivery and placental abruption. The impact of smoking is dose-dependent and carries the highest risk in the second and third trimester. Nicotine causes vasoconstriction of uteroplacental blood vessels, which reduces blood flow to the placenta, thereby reducing the delivery of oxygen and nutrients to the fetus. The fetal circulation is also compromised as the nicotine concentration increases to higher levels in the fetal circulation than in the mother’s circulation. In addition, carbon monoxide influences the development of the placenta and leads to an increase in fetal carboxyhaemoglobinemia with a subsequent decrease in oxygenation of developing organs and tissues.

In a study conducted in the Netherlands young adults exposed to tobacco in utero had increased carotid intima media thickness, compared to those who were not exposed in utero, suggesting permanent damage in the vasculature of off spring of mothers who smoke, thereby increasing their children’s risk to develop strokes and heart attacks in adulthood.

Smoking in the of the Tygerberg area of the Western Cape, where the coloured population is in the majority, is very high, ranging between 39% and 57%. It is therefore not surprising that the highest smoking attributable mortality rates in South Africa are seen in the coloured population. Smokers have about 50% higher overall mortality than otherwise similar non-smokers or ex-smokers. Smoking-attributed proportions for overall death rates at ages 35-74 years are 27% for men and 17% for women. However, these deaths do not include the effects of prenatal exposure to cigarette smoke which is still unknown.

**Alcohol and Smoking**

Very little is known about the combined effects of alcohol and tobacco smoke on the outcome of pregnancy, as only crude outcomes such as birth weight and gestational age have been assessed.

In a meta-analysis Odendaal et al. showed that the risks of preterm labour, term low birth weight and low birth weight as such are increased by the concomitant use of alcohol and tobacco when compared to the effects of alcohol or tobacco on their own. In addition, Aliyu et al. found that the risk of fetal growth restriction increases almost five fold when the mother smoked during pregnancy and had five or more drinks per week.

A good way to study these effects of alcohol is by looking
at the placenta- associated syndromes which include IUGR and preterm delivery. Positive associations were found with both alcohol consumption and tobacco smoke and placenta associated syndromes, but this again is only on crude outcomes such as IUGR and preterm delivery.

There seems to be a paucity of published literature on the follow up of children and adults, exposed to both alcohol use and cigarette smoking during pregnancy.

Cardiovascular disease

Although early precursors of atherosclerosis have been found during childhood and adolescence, it develops silently for decades before clinical events such as myocardial infarction or stroke occur, usually in middle aged people. Consequently the identification of indicators of risk factors and measurements that can foresee early changes in vascular function and reactivity, and that are able to characterize childhood cardiovascular risks are needed. Endothelial dysfunction is recognized as the first step in the development of atherosclerosis. Its crucial role in both cardiovascular morbidity and mortality has been confirmed. In the past, research was hampered by the invasive character of endothelial function assessment.

Pulse wave velocity (PWV), is now widely used as a non-invasive method for studying vascular distensibility as it is generally accepted as the most simple, non-invasive, robust, and reproducible method with which to determine arterial stiffness. Carotid-femoral PWV is a direct measurement, and it corresponds well to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, the carotid–femoral PWV is the most clinically relevant indicator of arterial stiffness, since the aorta and its first branches are what the left ventricle “sees” and therefore are responsible for most of the pathophysiological effects of arterial stiffness. The PWV is calculated as the ratio between the distance covered by the wave and the transit time.

In adults, PWV has been shown to be an independent predictor of cardiovascular events and all-cause mortality. This technique has been successfully used in children of 10 years and has demonstrated that boys are likely to have adverse changes in vascular health earlier than the age-matched girls.

Increased arterial stiffness is an emerging problem associated with maternal alcohol exposure. Morley et al. assessed reported alcohol intake during pregnancy on postnatal day 4 in mothers of 147 twin pairs born in Tasmania from 1991 to 1993. When the children were aged 9 years, their carotid-femoral PWV was 0.2 m/s higher (indicating stiffer vessels) in those whose mothers drank alcohol in the 2nd trimester compared to those whose mothers abstained, after adjusting for potential confounding factors. They concluded that as they found an association between prenatal alcohol exposure and carotid-femoral PWV at 9 years, a permanent change in vessel wall structure or function is possible.

Comparing the effects of maternal smoking during pregnancy on their children with the children of non-smokers, Taal et al. found that smoking of more than 10 cigarettes per day resulted in a significant increase in diastolic blood pressure when the children were 6 years old.

Regarding South African follow up studies, Levitt et al. examined the relation between birth weight and blood pressure in a cohort of 849 black children in Soweto. Systolic blood pressure at 5 years was inversely related to birth weight, independent of current weight, height, gestational age, maternal age or socioeconomic status.

In rat models, consumption of significant amounts of alcohol by the mother during pregnancy may markedly increase serum triglycerides in adult male offspring.

Metabolic syndrome

Childhood obesity is increasing worldwide and is associated with an increase in cardiovascular risk factors in childhood. Obesity tracks from childhood to adult life and predicts adverse levels of risk and an increase in cardiovascular endpoints.

Both extremes of birth weight have been identified as risk factors for childhood obesity, but it is still uncertain how much specific causes of low birth weight such as cigarette smoking and alcohol use during pregnancy contribute to the eventual childhood obesity.

There is also an association between rapid weight gain after birth and their glucose tolerance when children are 7 years old. The long term maintenance of these early childhood determinants of adult cardiovascular disease have been illustrated in many studies, one being that of Levitt et al. who showed that low birth weight babies compared to normal birth weight babies, at the age of 20 years, had higher baseline cortisol levels and a greater cortisol response to low dose ACTH stimulation than the latter group. In addition, the adult low birth weight babies had higher blood pressure and glucose levels, and more frequent glucose intolerance than the adult normal birth weight babies making the first group more at risk to develop adult premature cardiovascular disease. This relationship between low birth weight and later glucose metabolism has been reported in a meta-analysis of studies assessing this association.

The impact of antenatal smoking in this study was examined in this study which illustrated that mothers who smoked had significantly lower birth weight babies compared to that of babies whose mothers did not smoke.

In a prospective study of Australian children followed from the 16th week of gestation to 8 years, weight and height, blood pressure measured by automated oscillometry, and fasting blood lipids and glucose were analysed. At the age of 1, 3, 6 and 8 years, children with overweight including obesity showed significantly more adverse cardiovascular risk factors. Blood pressure was significantly higher, HDL was significantly lower by 8% and triglycerides were significantly higher by 27%.

Data from the 1958 British birth cohort indicated that although infants from mothers who smoked during pregnancy were lighter at birth than infants of non-smokers, from adolescent age they had an increased risk of being in the highest decile of BMI.

Renal disease

The concept of DOHaD has stimulated great interest in the effect of various complications of pregnancy on early indications in childhood, of adult diseases and triggered the
publication of several review articles of the effects of preterm delivery, intrauterine growth restriction, birth weight and low birth weight on renal disease. Other reviews looked more at cardiovascular disease as an outcome of these just mentioned obstetric complications or both hypertension and kidney disease. Some reviews were more specific, addressing for example elevated blood pressure in the offspring born prematurely to hypertensive pregnancies. All the identified renal conditions were associated with a reduction in the number of nephrons at birth.

Laycock and Brenner examined the association between low birth weight and hypertension. They found that the nephron numbers in the kidney were lower in adults with essential hypertension and that glomeruli tended to be larger in humans with low birth weight. An increase in glomerular size is consistent with hyperfiltration necessitated by a reduction in total filtration surface area, which suggests a congenital nephron deficit. The perinatal programming of abnormal glucose metabolism and hypertension, as well as of lower nephron number, may have a synergistic impact on the development of hypertension and kidney disease in later life.

Low birth weight infants have smaller kidneys because of decreased nephron numbers which may be as much as 30–35%. The reduction in nephron numbers leads to a reduction in renal sodium handling, increased filtration pressure and increased glomerular filtration rate per glomerulus. The sustained exposure of nephrons to higher glomerular perfusion pressure gradually results in the development of focal and segmental glomerular sclerosis which subsequently results in further glomerular loss, further reduced ability to excrete sodium, and a self-perpetuating cycle of increasing blood pressure and progressive kidney disease.

Rodriguez-Soriano followed 40 children, who weighed less than 1000 g at birth, until they were 6 to 12 years old and compared them with 43 healthy children of similar age and gender. Study children were significantly smaller and thinner than controls and their glomerular filtration rates were significantly lower. This finding was confirmed by a recent meta-analysis which demonstrated that the risk for developing proteinuria and decreased kidney function is increased by 81% and 79% respectively in low birth weight neonates.

The link between adult hypertension and low birth weight in animal models appears to be in part mediated by an associated congenital deficit in nephron numbers. In the rat model it has been established that maternal under nutrition could cause differential apoptosis in the interstitial mesenchyme, a possible mechanism for the reduction in the number of nephrons in the kidney. This reduced number of nephrons leads to increased arterial pressure in adulthood. Vehaskas demonstrated an almost 30% reduction in glomerular number in low birth weight rats compared with those of normal weight, and systolic blood pressures 20 to 25 mmHg higher by 8 weeks of age and their 18 month survival was decreased significantly.

As far as we could ascertain, there are no reported human studies that directly relate a reduction in nephron numbers to the use of alcohol during pregnancy although Hoy et al. indicated that alcohol may play a role in the high prevalence of renal disease in Australian aboriginals.

Common non-communicable diseases in the local community

Erasmus et al. recently determined the prevalence of diabetes mellitus and the metabolic syndrome in an urban coloured community in Bellville South, Cape Town. In a cross-sectional survey, 643 participants of 31 years or more were drawn from the community. The crude prevalence of type 2 diabetes was high, 28.2%, so too was the crude prevalence of the metabolic syndrome, with the prevalence ranging from 55.4% to 62.0%, depending on which criteria were used.

The cardiovascular risk factor pattern in the coloured community of the Western Cape is concerning as it indicates a population group at high risk for the development of cardiovascular disease. This unfavourable risk profile has been known for the past 2 decades and is accompanied by the highest prevalence of smoking in South Africa, high rates of uncontrolled blood pressure and abnormal lipid profiles.

The associations between IUGR and preterm delivery and later complications in later life such as renal and cardiovascular disease are well accepted, as are their associations with alcohol consumption and tobacco smoking during pregnancy; but it is still uncertain whether these exposures contribute directly to adult disease in later life and how soon early markers disease can be observed in children.

The enormity of the economic, social and health costs related to the misuse of alcohol have recently been reviewed by Matzopoulos et al. The combined total costs of alcohol harm to the economy were estimated at 10% to 12% of the gross domestic product of 2009. Alcohol is the third largest contributor to death and disability, after sexually transmitted infections and interpersonal violence. Yet the authors did not consider the role of alcohol in the developmental origins of non-communicable diseases, as this is still unknown.

Prospective studies are being designed to fill this knowledge gap, i.e. to determine the role of perinatal alcohol exposure, and that of smoking during pregnancy, in the development of cardiovascular and metabolic diseases in later life.

References
