

Editorial

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Pakistan Developmental Origins of Health and Disease (DOHaD) Society: addressing the 'DO' component of DOHaD

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Abstract

Adverse intrauterine environment could serve as an important stimulus for postnatal altered health status and for increased susceptibility to long-term non-communicable diseases (NCDs). The notion is now recognized as the Developmental Origins of Health and Disease (DOHaD), which was first proposed by Sir David Barker. Since then, several scientific disciplines have strived to measure the magnitude of the early fetal programming and later risk of diseases. Pakistan, with striking figures of morbidity and mortality from NCDs, is currently tackling with double burden of diseases and requires planned efforts to counteract the threat of NCDs. Considering the growing needs and available evidences, Pakistan DOHaD Society was officially instigated in September 2016. The Society aims to explicitly address the association of life *in utero* with future health and disease and to endorse early screening and interventions to reduce the burden of NCDs, mental health issues and learning disorders along the life course. It has shown significant progress toward investigating the influence of adverse *in utero* environment such as diabetes, maternal under-nutrition and pre-eclampsia on fetal programming under two major research lines, that is, cardiovascular and cerebrovascular programming. The Society has been successful in disseminating its research findings through several esteemed international scientific conferences. Pakistan DOHaD Society encourages scientific community for collaborative research aimed at improving the quality of life during early childhood, adolescence and adulthood through provision of appropriate pre-pregnancy and antenatal interventions targeted to address at-risk *in utero* conditions.

Exposure to adverse *in utero* conditions of varied magnitude could change the normal biological programming of the fetus and can have a detrimental influence on the fragile beginning to life. Through adaptive response and programming, such fetuses are likely to be at risk for altered cognitive functions during early childhood and for non-communicable diseases (NCDs) later in life during adulthood. The former Barker hypothesis that conceived the idea of fetal origin of adult diseases is now popularly known as 'Developmental Origins of Health and Disease (DOHaD)'.^{1–3}

Substantial basic science, clinical and epidemiologic evidence now suggest that antenatal factors such as placental insufficiency, maternal stress, smoking, exposure to toxins, infections and obesity are the major contributors to the adverse health in the offspring.^{4–8} Likewise, several animal models with low protein diet during periconceptional period were linked with later risk of hypertension.^{9,10} Hypoxia during pregnancy has been associated with transformations at cellular level leading to increased risk of stroke in late adulthood.^{2,11} Similarly, hyperglycemia in pregnancy has shown association with impaired cognitive function in terms of behavior, attention span, social relations, learning ability and motor functioning.^{12,13}

Although cardio-metabolic disorders have become *sine qua* non-phenomenon of developed nations, these disorders are at parallel rise in low- and middle-income countries. As per World Health Organization estimates, NCDs from developing nations contribute to >80% of mortality globally.¹⁴ To make the matters worse, susceptibility to NCDs is greater among younger population who often present with acute forms of NCDs than their counterparts in industrialized countries. Pakistan too, does not stand any different. Adaptation of industrialized lifestyle along with improved economic growth and development has led to changes in the disease pattern. Simultaneous struggle with infectious disease encounters has put Pakistan now at the verge of dealing with the so-called double burden of diseases. Although it has the highest new born mortality rate with 1 in 22 annual deaths per 1000 live births according to the recently released UNICEF report,¹⁵ a shocking report published in 2013 revealed that an estimated 32 million individuals suffer from heart ailments; 24 million from obesity, ranking

Pakistan at number 9 globally; 40 million from high blood pressure; 8 million from diabetes; 18 million from high cholesterol and approximately 50 million from different forms of mental health disorders.¹⁶ Alarming, the mortality figures show that every day 2000 Pakistanis lose their lives due to NCDs.¹⁷ Unprecedented challenges of NCDs in Pakistan along with the growing awareness toward the crucial phenomenon of early fetal programming and its effect on the metabolic profile in adulthood led to the official instigation of Pakistan DOHaD Society in September 2016.¹⁸ The Society asserts:

1. To address the complex interaction between the maternal intrauterine environment and the growing fetus and its implication on the subsequent life course, health and wellbeing through research, education, policy and advocacy.
2. To promote interventions, before and following conception, for advancement of healthy early development so as to reduce the burden of NCDs, mental ill-health and learning disorders across the life course.

In the light of its objectives, the Pakistan DOHaD Society held its first conference in January 2017 at The Aga Khan University, Karachi, Pakistan, on the theme, 'Stress Response and Conditioning: Impact on Maternal and Generation Health.' The meeting brought together scientists, health-educationists, clinicians, clinician-researchers, policymakers, fellows, trainees and nurses for the first time on one platform for discussion on this vital issue.

The proceedings highlighted that:

1. Innovations in cardiac and neurosonographic imaging through advanced ultrasound of a fetus's heart and brain can provide early detection of delays in heart and brain development.
2. First 2000 days of a child's life are extremely important. Investing in healthcare during this period could result in the greatest returns for society in terms of health and wellbeing.
3. The link between fetal nourishment and lifelong health is well established. Interventions aimed at *in utero* and childhood periods have significant and sustainable effect compared with those aimed at adulthood.
4. Interventions aimed earlier in life will help meet targets of sustainable development goal (SDG) 3.
5. Unhealthy lifestyle before and during the pregnancy, marginalization of adolescence health care and growing prevalence of chronic diseases among adults are making Pakistan's newborns more vulnerable for NCDs and mental health disorders. Further, due to the trans-generational effect, susceptibility to NCDs is likely to pass to the next set of generation.
6. High levels of stress hormones during pregnancy due to economic or social pressure can trigger epigenetic changes in the brain of a developing fetus that can influence adversely its future learning capabilities and social interactions.

Pakistan DOHaD Society, emanating from the platform of The Aga Khan University, Karachi campus comprises researchers from diverse disciplines, including fetal medicine specialists, obstetricians, neonatologists, pediatric cardiologists, epidemiologist, biostatisticians, nurses, biological scientist, pathologist and early childhood development assessors. The Society is currently examining the influence of *in utero* environment during adverse

maternal conditions, such as diabetes, maternal under-nutrition and pre-eclampsia on cardiovascular and brain programming.

Perinatal/childhood cardiovascular programming research line

Cardiovascular research line aims to detect the structural and functional changes in the fetal and pediatric cardiovascular systems through various parameters using functional echocardiography on two-dimensional ultrasound. Our preliminary results in fetuses born as growth restricted demonstrated altered vascular programming in the form of increased aortic intima media thickness as compared to those born with birth weight of appropriate for gestational age (AGA). This vascular remodeling in the form of arterial thickening and stiffening in response to compromised growth *in utero* may be a potential marker for the long-term pathological structural changes in the vascular systems in the adulthood.¹⁹ These research findings were presented at the 10th World Congress of DOHaD held in Rotterdam, The Netherlands (2017). Another cohort of AGA fetuses exposed to maternal hyperglycemia showed globular hearts with reduced global sphericity index as compared to those born to non-diabetic mothers, an indicator for cardiac remodeling and potential susceptibility for cardiovascular disease later in life.²⁰ This work has been accepted for presentation at the DOHaD Australia New Zealand conference to be held in July 2018.

Human development and perinatal/childhood brain programming research line

Using two-dimensional imaging and vascular perfusion assessment, we aim to identify neurocognitive parameters and its relation with neurodevelopment during early childhood. Our study detected smaller corpus callosum length among fetuses exposed to under-nourished *intrauterine* environment secondary to placental insufficiency and those exposed to maternal hyperglycemia compared with their respective reference groups.^{21,22} This could signify adaptive fetal brain programming under such conditions and enhance the risk of fetuses to altered neurobehavioral outcome during early childhood. On the contrary, resistance in middle cerebral artery blood flow was higher among the near-term AGA fetuses born to diabetic mothers than those born to non-diabetic mothers. This could be an indicative of an adaptive cerebrovascular response to maternal hyperglycemia-driven insulin resistance in the fetal brain.²³ The findings were shared at the 10th World Congress of DOHaD. Another study carried out on children 4–36 months old showed significantly lower neurodevelopment scores for those born to diabetic mothers as compared to the offspring of non-diabetic group.²⁴ The work was presented at the 2nd International Conference on Early Childhood Development in Dar-es-Salaam, Tanzania (2017).

Conclusion

Maternal and fetal medicine no longer favors the traditional cliché of live births with normal Apgar scores, but broadens our outlook to comprehend the lifelong influences of our antenatal interventions. The overwhelming epidemiological evidences attesting the significance of DOHaD is no less than a bitcoin to the scientific community linking maternal and child health to

NCDs. Healthcare system in Pakistan is currently geared more toward treating those suffering from NCDs. Ironically, clinical and public health practices in Pakistan lack integration of the concept of DOHaD into services.

By focusing on the notion of DOHaD, we can bring significant reduction in lifelong risk of NCDs which would promote achievement of maximum health potential for each individual. Developing countries carry the major burden of NCDs and related mortality and thus, should embrace DOHaD as a part of their public health agenda. Many of the SDGs, such as elimination of poverty and hunger, provision of quality education, clean water and sanitation and reduced inequalities are closely linked to DOHaD.²⁵ Mutual collaboration of diverse scientific discipline in DOHaD endeavors could bring a remarkable breakthrough in overcoming growing health challenges.

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