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Fetal Origin of Cardiovascular Disease: A review of mechanisms

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Abstract: *Non-communicable diseases are the major cause of morbidity and mortality globally. Studies have shown that cardiovascular diseases are the main cause of lost hours from work globally and that the prevalence of cardiovascular disease is rising in populations without the traditional risk factors for developing cardiovascular disease. This rise in prevalence has been shown to have a close association with the intrauterine milieu of the affected persons which back then turned out to be appropriate adaptive responses. From the epidemiological studies and hypothesis formulated by Dr. Barker 2 decades ago about Developmental Origin of Health and Disease (Fetal programming), these adaptive responses may help explain the increasing prevalence of cardiovascular morbidity and mortality in such populations. Experimental studies in animals have tried to elucidate the mechanisms involved in fetal programming of cardiovascular disease. This article seeks to review the mechanisms implicated in fetal programming of cardiovascular disease.*

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I. Introduction

Cardiovascular disease has been a major burden of the human kind because of its contribution to morbidity and mortality(1–3). Global estimates in the year 2015 showed that 422.7 million cases of cardiovascular diseases were reported and 17.2 million deaths in 2015 were cardiovascular related(2). Lifestyle factors that promote artherosclerosis(cigarette smoking, physical inactivity, low fiber diet, high fat diet) as well as familial predisposition have been traditionally known to be the risk factors for cardiovascular diseases(4) but recently, long term observational and cohort studies are showing an inverse and graded correlation between maternal nutrition, fetal growth retardation and adulthood non-communicable cardiovascular diseases(4-8). Cardiovascular disease has been shown to be existent in sub-clinical forms quite early in life in growth retarded fetuses regardless of the aetiology(9) and the clinical manifestations in adulthood are just a reflection of longstanding subclinical cardiovascular disease(4,6-8) whose pathogenesis can be traced back to intrauterine life(6,10,11). This article seeks to review literature on mechanisms behind the fetal origin of non-communicable cardiovascular diseases with an emphasis on metabolic programming.

II. Embryohistogenesis of the cardiovascular system

Embryohistogenesis of the cardiovascular system in vertebrates, including humans, has been inferred greatly from studies done on chick embryos(12). The cells that end up forming the heart are usually the 1st mesodermal cells to be sourced from the primitive streak during formation of the trilaminar germ disc(12,13). The cardiac precursors are located in the rostral half of the primitive streak posterior to the primitive node. At this point, the newly formed mesoderm translocates anterolaterally towards the anterior lateral plate mesoderm(primary heart field)(13) then condenses into cardiogenic cresents on both sides(12,14). The cardiogenic cresents later merge to form the cardiac tube composed of one/two cell layer of cardiomyocytes, endocardium and a cardiac jelly that lacks cells(acellular)(13,15). By definition, cardiac jelly is acelluar and occupies the myoendocardial space between the basement membrane of the primary myocardium and endocardium. The cardiac jelly functions as a hydraulic skeleton by offering structural support to the primitive heart tube and has distinct histomorphological organization and properties in the different primitive heart chambers (15). After the first heart beat, the heart undergoes looping and later five cardiac compartments are formed which have distinct structural and molecular properties(14). The first chamber is the sinus venosus which acts as a blood reservoir and pacemaker. It is made up of small size cardiomyocytes, thin walls and little intracellular myofibrils. The unpartitioned atria lack cardiac jelly(15) and trabeculae whereas the atrioventricular channel myocardium has strong circular myocyte fiber organization and a lining cardiac jelly(12,14). The cardiac jelly gets organized into the atrioventricular cushions that will later participate in chamber partitioning and formation of tricuspid as well as the bicuspid valve(15). The ventricles are characterized by extensive trabeculation on the inner aspect and accelerated differentiation of cardiomyocytes which reflects their contractility potential and energy consumption. The outflow tract/conotruncus is the last primitive heart chamber and is characterized by circular cardiomyocyte organization. It is sourced from the secondary heart field as a transitory structure that gets re-organized to different structures of the heart(divides the heart outlet into an aortic and pulmonary part as well as the two major outflow valves)(14). Its muscle component normally undergoes programmed cell death type I i.e. apoptosis(12,16) apart from the part that yields the pulmonary infundibulum(12,13).

The molecular regulation of cardiac development is quite complex making the heart quite sensitive to pertubations(13). Congenital cardiac anomalies are the commonest birth defects with a prevalence of almost 1% globally. 1%-2% of the population is born with subtle anomalies that manifest with advancing age(17). Other than signaling molecules, epigenetic factors play a key role in differentiation of cardiac myocytes and chamber histomorphogenesis thus epigenetic factors contribute to cardiac malformations(13).

III. Fetal programming

Cardiovascular disease is one of the leading causes of morbidity and mortality globally and several factors have been associated with the risk of developing cardiovascular disease i.e. cigarette smoking, physical inactivity, obesity and high fat diet(1–3). Currently, there is a paradigm shift from these traditional risk factors with epidemiological evidence showing that low birth weight babies, high birth weight babies(7,18) and babies that had fetal growth retardation have an increased death rate that is related to high blood pressure, stroke, type II diabetes mellitus, ischaemic heart disease and impaired glucose tolerance(19–21). The risk of developing cardiovascular disease following fetal growth retardation and maternal malnutrition has been termed fetal programming and two mechanisms have been hypothesized i.e. metabolic programming and cardiovascular system remodeling(5).

IV. Oxidative stress in metabolic programming

Oxidative stress, which is a disparity between the manufacture and removal of reactive species/free radicals (Reactive Oxygen Species-ROS and Reactive Nitrogen Species-RNS) (22)with a favor for manufacture, has been majorly implicated in fetal programming(23,24). Intra-uterine growth restriction, regardless of the cause, is linked with reduced oxygen concentration in the placenta with consequent placental oxidative stress and anomalous placental function(25). The over accumulation of reactive species results in oxidative destruction of macromolecules(23). Manufacture of reactive species follows aerobic metabolism and the body has defined mechanisms for striking a balance between manufacture and removal(24,26). An offset of this established equilibrium either in form of over-manufacture or a reduction in antioxidant molecules results in accumulation of destructive ROS and RNS(25). Reactive Oxygen Species found in human beings comprise superoxide($O_2^{\cdot-}$), hydrogen peroxide(H_2O_2), hydroxyl radical(.OH) and peroxynitrite($ONOO^-$) their main source being uncoupled mitochondrial electron transport chain following normal metabolism(18,22). Cardiomyocytes consume lots of energy thus have high numbers of mitochondria and high O_2 demand which in-turn contributes to the high production of ROS making them very vulnerable to oxidative stress injury(22). ROS have been shown to act as signaling molecules, inducers of gene transcription and participate in placenta formation thus they play a key role in embryo-fetal maturation(23,27). Despite their influential role in embryo-fetal maturation,

an excess of ROS destroys macromolecules(proteins, nucleic acids-DNA, lipids in cell membranes) which leads to fatigue or dysfunction of striated muscles including the cardiac muscle(22). The antioxidant levels in embryos and fetuses are usually low, making them very vulnerable to oxidative stress following an increase in the levels of reactive species(23).

Despite the injurious nature of reactive oxygen species, studies have shown that they are required for optimum embryo development(18). Embryos and fetuses develop in environments of low oxygen and have low antioxidant capacity which makes them to be more susceptible to oxidative stress(18). With further placenta formation and maturation, oxygen transfer to the embryo and fetus increases, which in-turn increases the intracellular formation of reactive oxygen species. The reactive oxygen species participate in cellular signaling pathways that result in induction of transcriptional genes like HIF1A, NFKB1 and CREB1 which participate in cell differentiation, multiplication and oxygen sensing(17,18,28). An imbalance between production and removal of reactive oxygen species will result in oxidative stress injury with the plasma membrane and other membrane bound intracellular structures being the most severely affected because of their high concentration of phospholipids that are easily oxidized by the superoxide anion(O_2^-)(18). Other than phospholipids, nucleic acids and proteins are also a major target for oxidative stress injury and reactive oxygen species may interact with proteins and Deoxyribonucleic Acid(DNA) resulting in aminoacid oxidation that alters normal structure and function(29). The mitochondria in particular is very susceptible to oxidative stress injury because its DNA is not wound on histone proteins and furthermore it lacks tight DNA repair mechanisms(18,23,29). Reactive oxygen species may as well interact with DNA base pairs resulting in epigenetic and genetic alterations, the former through interference with DNA methylation and histone modification(24,26,30) in tissues within the heart and pulmonary arteries(18). The epigenetic alteration of genes involved in cardiovascular embryohistogenesis and physiological control mechanisms result in impaired renal development thus reduced nepphron mass which manifests as poor renal handling of sodium, remodeling of blood vessels(stiffening and endothelial dysfunction) and reduced numbers of cardiomyocytes with resultant fibrosis, hypertrophy and later cardiac dysfunction(23).

V. Maternal nutrition and fetal programming

The prenatal period is a very critical period in future cardiovascular morbidity(31) for it presents the most vital phase of developmental plasticity with subsequent fetal programming(32). Studies have shown a connection between intrauterine hormonal and nutritional environment as a major influence for full expression of the fetal genome(19,31,33). Both nutrient excess and deficiency has been associated with fetal programming with nutrient deficiency leading to an excess of glucocorticoid exposure whereas nutrient excess leads to oxidative stress(32). Fetal programming as a manifestation of developmental plasticity becomes apparent later in life as an adaptation mismatch(32,33). Human and animal studies have shown low a nephron mass and cardiac muscle cells in offspring's of undernourished mothers during pregnancy which has a direct correlation with the risk of developing renal failure and hypertension(32). Malnutrition and low birth weight are a major contributor to reactive oxygen species in-utero which creates an imbalance between production and removal thus oxidative stress in a fetus whose mechanisms to eliminate reactive oxygen species is limited(18,34). The excess reative oxygen species may result in modulation of gene expression as well as damage to the plasma membrane(24,30). The oxidative stress damage has been shown to have a direct causal link to metabolic syndrome, ischaemic heart disease, diabetes mellitus and hypertension. Studies on human cord blood have demonstrated low levels of non-enzymatic antioxidants(vitamin A, C and E) in preterm infants as compared to term infants with a positive correlation between maternal vitamin A and E with that of the preterm infant, implying that fetal vitamin A and E levels are dependent on maternal levels(34,35). Gestational diabetes is a source of oxidative stress as these mothers have been shown to have high levels of malondialdehyde, an indicator of oxidative stress and low levels of non-enzymatic antioxidants vitamin A and E as well as low levels of enzymatic anti-oxidants, glutathione peroxidase and superoxide dismutase(32,34).

Pregnancy presents a high metabolic state and a high macro- and micronutrient demand state with the former playing a major role as antioxidants and in antioxidant enzymatic pathways(7,23,24). Iron is one of the micronutrients in high demand in pregnancy and maternal anaemia is one of the major causes of maternal morbidity with a causal link to low birth weight infants and preterm delivery which in-turn is associated with fetal metabolic programming through dysregulation of corticotropin releasing hormone and insulin like growth factor 1(7). Under nutrition in pregnancy has been shown to influence the passage of cortisol through the placental barrier through a mechanism that reduces the enzymatic barrier 11 Beta Hydroxysteroid Dehydrogenase(11βHSD) leading to high levels of cortisol in the fetus which establishes a high catabolic state that is associated with an increase in production of reactive oxygen species thus off-setting the delicate balance between the levels of antioxidants and reactive oxygen species in the developing human(7).

VI. Conclusion

Intrauterine growth retardation is a major cause of fetal and neonatal illness and it has been shown to be one of the contributors to cardiovascular morbidity later in life regardless of the cause as it presents a general state of low oxygen levels with subsequent generation of reactive species, both ROS and RNS that alter the epigenome with resultant cardiovascular remodeling early in life which presents as subclinical cardiovascular disease that progresses throughout one's life.

References

[1]. Carter HE, Schofield D, Shrestha R. Productivity costs of cardiovascular disease mortality across disease types and socioeconomic groups. 2019;1–8.
[2]. Roth GA, Johnson C, Abajobir A, Abd-allah F, Abera SF, Ms C, et al. Global , Regional , and National Burden of Cardiovascular Diseases for 10 Causes , 1990 to 2015. 2017;70(1):1–25.
[3]. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global Burden of Cardiovascular Disease Global and Regional Patterns in Cardiovascular Mortality From 1990 to 2013 Measuring the Global Cardiovascular. 2015;1667–78.
[4]. Faculty N, Canada M. Programming of chronic disease by impaired fetal nutrition Evidence and implications for policy and intervention strategies.
[5]. Reviews E. Long-term cardiovascular consequences of fetal growth restriction : biology , clinical implications , and opportunities for prevention of adult disease. 2018;(February):869–79.
[6]. Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS. reviews epigenetic mechanisms that underpin metabolic and cardiovascular diseases. Nat Publ Gr [Internet]. 2009;5(7):401–8. Available from: http://dx.doi.org/10.1038/nrendo.2009.102
[7]. Fernandez-twinn DS, Ozanne SE. Early life nutrition and metabolic programming. 2010;1212:78–96.
[8]. Drake AJ, Walker BR. The intergenerational effects of fetal programming : non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. 2004;1–16.
[9]. Jonker SS, Kamna D, LoTurco D, Kailey J, Brown LD. IUGR impairs cardiomyocyte growth and maturation in fetal sheep. J Endocrinol [Internet]. 2018;239(2):253–65. Available from: https://joe.bioscientifica.com/view/journals/joe/239/2/JOE-18-0382.xml
[10]. Nilsson P. Early vascular aging syndrome : background and proposed definitions. 2011;1:1523–31.
[11]. Friedman JE. Developmental Programming of Obesity and Diabetes in Mouse , Monkey , and Man in 2018 : Where Are We Headed ? 2018;67(November):2137–51.
[12]. E. YK, David B. Diversification of Cardiomyogenic Cell Lineages During Early Heart Development. Circ Res [Internet]. 1995 Aug 1;77(2):216–9. Available from: https://doi.org/10.1161/01.RES.77.2.216
[13]. Srivastava D. Review Making or Breaking the Heart : From Lineage Determination to Morphogenesis. 2006;1(Figure 1):1037–48.
[14]. Manuscript A. NIH Public Access. 2009;4(3):235–45.
[15]. Yelbuz TM. Functional Morphology of the Cardiac Jelly in the Tubular Heart of Vertebrate Embryos. 2019;(January):1–32.
[16]. Malik A, K Kweri J, Kanyoni J, Ngugi V, Wairimu A. Apoptosis: It's Role in Colorectal Cancer. Vol. 8. 2019. 1-4 p.
[17]. Maele K Van De, Devlieger R, Gies I. In utero programming and early detection of cardiovascular disease in the offspring of mothers with obesity. Atherosclerosis [Internet]. 2018;275:182–95. Available from: https://doi.org/10.1016/j.atherosclerosis.2018.06.016
[18]. Thompson LP, Al-hasan Y. Impact of Oxidative Stress in Fetal Programming. 2012;2012.
[19]. Langley-Evans SC. Fetal programming of cardiovascular function through exposure to maternal undernutrition. Proc Nutr Soc [Internet]. 2007/02/28. 2001;60(4):505–13. Available from: https://www.cambridge.org/core/article/fetal-programming-of-cardiovascular-function-through-exposure-to-maternal-undernutrition/D988B087C84E1B4BE797980B886E4390
[20]. Iruretagoyena JI, Gonzalez-tendero A, Garcia-canadilla P, Amat-roldan I, Torre I, Nadal A, et al. Cardiac dysfunction is associated with altered sarcomere ultrastructure in intrauterine growth restriction. Am J Obstet Gynecol [Internet]. 2014;210(6):550.e1-550.e7. Available from: http://dx.doi.org/10.1016/j.ajog.2014.01.023
[21]. Lule SA, Elliott AM, Smeeth L, Webb EL. Is birth weight associated with blood pressure among African children and adolescents ? A systematic review. 2019;9(2018):270–80.
[22]. He F, Zuo L. Redox Roles of Reactive Oxygen Species in Cardiovascular Diseases. 2015;(September):27770–80.
[23]. Rodríguez-rodríguez P, Ramiro-cortijo D, Reyes-hernández CG, Pablo ALL De, González MC, Arribas SM. Implication of Oxidative Stress in Fetal Programming of Cardiovascular Disease. 2018;9(May):1–13.
[24]. Rao GHR. Cellular Signaling Pathways and Vascular Dysfunctions. 2018;12(4).
[25]. Giussani DA, Camm EJ, Niu Y, Richter HG, Blanco CE, Gottschalk R, et al. Developmental Programming of Cardiovascular Dysfunction by Prenatal Hypoxia and Oxidative Stress. 2012;7(2).
[26]. Govindsamy A, Naidoo S, Cerf ME. Cardiac Development and Transcription Factors : Insulin Signalling , Insulin Resistance , and Intrauterine Nutritional Programming of Cardiovascular Disease. 2018;2018.
[27]. Hittmann WM. Fetal Programming and Risk of Cardiovascular Diseases. 2018;(November).
[28]. Dearden L, Bouret SG, Ozanne SE. Sex and gender differences in developmental programming of metabolism. Mol Metab [Internet]. 2018;15(April):8–19. Available from: https://doi.org/10.1016/j.molmet.2018.04.007
[29]. Manuscript A. NIH Public Access. 2013;116(8):659–68.
[30]. Gicquel C, Bouc Y Le. Epigenetic regulation and fetal programming. 2008;22(1):1–16.
[31]. Pitale S, Sahasrabuddhe A. Review Article Fetal origin of vascular aging. 2011;15:289–97.
[32]. Brenseke B, Prater MR, Bahamonde J, Gutierrez JC. Current Thoughts on Maternal Nutrition and Fetal Programming of the Metabolic Syndrome. 2013;2013.
[33]. Fall CHD. Europe PMC Funders Group Fetal malnutrition and long-term outcomes. 2016;
[34]. Arribas L, Almansa I, Miranda M, Muriach M. Serum Malondialdehyde Concentration and Glutathione Peroxidase Activity in a Longitudinal Study of Gestational Diabetes. 2016;1–13.
[35]. Statusgestational A, Patients D. Journal of clinical and diagnostic research. 2007;(4):235–8.

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