Fetal origin of vascular aging

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ABSTRACT
Aging is increasingly regarded as an independent risk factor for development of cardiovascular diseases such as atherosclerosis and hypertension and their complications (e.g., MI and Stroke). It is well known that vascular disease evolve over decades with progressive accumulation of cellular and extracellular materials and many inflammatory processes. Metabolic syndrome, obesity and diabetes are conventionally recognized as risk factors for development of coronary vascular disease (CVD). These conditions are known to accelerate ageing process in general and vascular ageing in particular. Adverse events during intrauterine life may programme organ growth and favour disease later in life, popularly known as, ‘Barker’s Hypothesis’. The notion of fetal programming implies that during critical periods of prenatal growth, changes in the hormonal and nutritional milieu of the conceptus may alter the full expression of the fetal genome, leading to permanent effects on a range of physiological functions and structures. Increasing evidence suggests that conditions like CVD, metabolic syndrome, and Type 2 Diabetes Mellitus (type 2 DM) are programmed during the early stages of fetal development and are manifested at a far later stage, when there is an added impact of lifestyle and other conventional acquired environmental risk factors that interact with the genetic factors. Thus fetal programming or fetal imprinting is a crucial period that may modulate adult disease. Programmed changes in the structure and functions may include reduction in the number of cells, or changes in the distribution of cell types and in the organ structure or else resetting hormonal feedback. Barker published a study in 1989, which suggested that intrauterine environment influences blood pressure in adult life. In addition, he concluded that the geographical differences in average blood pressure and mortality from cardiovascular disease in Britain, partly reflect past differences in the intrauterine environment. Human data from industrialized nations show that systolic blood pressure in individuals over the age of 50 continuously rises throughout life,
whereas, diastolic blood pressure remains stable.\textsuperscript{[7-9]} Pulse pressure may be regarded as an index of vascular aging.\textsuperscript{[10]} There is evidence from several studies that intrauterine fetal programming, as a consequence of an altered intrauterine environment (whether by diet alteration or hormonal changes) can be passed transgenerationally,\textsuperscript{[11-15]} through either the maternal or paternal cell line. This transgenerational inheritance of programming may be due to changes in the primordial germ cells from which the next generation develops or due to recapitulation of metabolic or endocrine conditions that the mother experiences with a fetus \textit{in utero}, due to programmed adaptations in her Physiology [Figure 1]. Alternatively it may reflect meiotic inheritance of epigenetic marks. Incomplete erasure of these marks may lead to an inheritable memory of the epigenetic state at specific alleles.\textsuperscript{[16]} Studies have confirmed this transgenerational altered vascular programming both \textit{in vivo} and \textit{in vitro} in an animal model of fetal programming induced by genetic predisposition.\textsuperscript{[10]}

**Pathogenesis of Vascular Aging**

Vascular aging is characterized by transition of the endothelium from an anti-atherosclerotic state to a pro-atherosclerotic state.\textsuperscript{[17]} In a normal aging-related arterial stiffening process, arteriosclerosis results not only due to quantitatively less elastin and more collagen, but also due to qualitative changes in the content of the arterial vessel wall, in association with impaired endothelial-mediated vasodilation.\textsuperscript{[18]} In patients with hyperglycemia, and overt type 2 diabetes, an additional component of glycemic changes in vessel wall proteins (glycosylation) will add to the process of arterial stiffening, a process that is reflected not only by HbA1c, but also by the advanced glycation end products.\textsuperscript{[19]} In the presence of arterial hypertension and other cardiovascular risk factors the process of vascular aging occurs earlier than normal.\textsuperscript{[20]} The prodromal stages are already formed during fetal development. Fatty streaks containing characteristic accumulations of lipids, lipid peroxidation products, and monocytes / macrophages occur in the aorta of premature fetuses. Intimal thickening is also observed in fetal coronary arteries. Although the fetal lesions occur at the same predilection sites as the more advanced lesions in adults and adolescents, the size is minute and there may be partial regression of them during the final stages of gestation or early infancy, when the cholesterol levels are low. In children and young adults, fatty streaks become increasingly prevalent and some of them progress to more advanced stages of atherosclerosis. Once initiated, the progression of atherosclerotic disease is influenced by classical risk factors that promote vascular inflammation and plaque rupture.\textsuperscript{[21]}

**Molecular Changes of Vascular Aging**

Considerable evidence has been accumulating showing that aging in several tissues, including the endothelium, is associated with an increased production of reactive oxygen species (ROS).\textsuperscript{[22,23]}

Aging-induced vascular oxidative stress is associated with a globally increased pro-oxidant milieu, characterized by increased expression of inducible nitric oxide synthase,\textsuperscript{[24]} mitochondrial enzymes such as NAD(P)H oxidases,\textsuperscript{[25]} and a downregulation of antioxidant systems such as the superoxide dismutases.\textsuperscript{[23]} The increased production of ROS observed with aging mediates a multitude of detrimental effects. One of the critical consequences of the increased production of ROS is the scavenging of nitric oxide by a superoxide (O2) to produce peroxynitrite (ONOO-).\textsuperscript{[26,27]} ONOO- easily penetrates the phospholipid membrane and produces substrate nitration, thereby inactivating important regulatory receptors and enzymes, such as, free radical scavengers [Figure 2].\textsuperscript{[23,27]} The drastic decrease of nitric oxide bioavailability observed in aging is exacerbated by a concomitant age-related decline in the expression of the endothelial isoform of NOS (eNOS) and decreased intracellular L-arginine availability.\textsuperscript{[24]} In recent times, it has been suggested that decreased nitric oxide production in aging also enhances apoptosis of endothelial cells.\textsuperscript{[28]} The same mechanism has been shown to hasten the process of aging in the altered metabolism seen in the metabolic syndrome and type 2 DM.

**Role of mitochondria**

Lines of evidence indicate that mitochondrial damage is central to this process and that the reactive oxygen species (ROS) may act as a double-edged sword. On the one hand, it is well-accepted that the mitochondria are a major source of chronic ROS production under physiological conditions. On the other hand, it is known that ROS generation damages lipids, proteins, and mitochondrial DNA, leading to dysregulated mitochondrial function. Elevated mitochondrial ROS production is associated with endothelial cell dysfunction as well as vascular smooth muscle cell proliferation and apoptosis. Smoking, obesity, insulin-resistant type 2 DM, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia, the major traditional precursors of atherosclerosis, are all linked to mitochondrial dysfunction.

The reactive oxygen species are also thought to be directly implicated in proinflammatory processes by acting as second messengers. For instance, nuclear factor κ, light
Figure 1: Highlighting the combined and individual role of genetic composition, intrauterine conditions, and epigenetic transmission in fetal programming (ROS: reactive oxygen species; IUGR: intrauterine growth retardation; PIH: pregnancy-induced hypertension; NO: nitric oxide; HPA: hypothalamus pituitary adrenal axis).

Figure 2: Endothelial mechanisms responsible for vascular aging (ROS: Reactive oxygen species, NO: Nitric oxide, eNOS, gene coding for nitric oxide synthase, NF-κB: Nuclear factor kappa B, ET-1: Endothelin-1; ONOO−: Peroxynitrite; TNF-α: tumor necrosis factor α).
chain enhancer of activated B cells (NF-κB), is a redox-sensitive transcription factor, expressed by both endothelial and smooth muscle cells, which can be activated by ROS. Activation of NF-κB by increased ROS levels promotes the transcription of several genes implicated in the inflammation that are thus critical for atherogenesis, including cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), and chemokines and adhesion molecules. In line with this, it is generally believed that chronic activation of NF-κB predisposes arteries to atherosclerosis.[28]

Animal models have shown that the cyclooxygenase pathway may be responsible for endothelium-dependent contractions to acetylcholine, which could be blocked by indomethacin.[29]

**Maternal-fetal Factors Affecting Vascular Aging**

**Fetal programming**

Fetal programming involves a complex interplay of genetic composition, intrauterine conditions, and epigenetic transmission; all of which contribute to the phenotypic development of the fetus [Figure 1]. Multiple genetic and environmental factors contribute to fetal programming. Although fetal genome plays an important role in the growth potential in utero, increasing evidence suggests the role of intrauterine environment as a major determinant of fetal growth. Embryo transfer studies have shown that it is the recipient mother rather than the donor mother who more strongly influences fetal growth.[30] Cellular processes that may be programmed by intrauterine manipulation of the nutritional or hormonal environment are as follows: (1) Hormone receptors, (2) Intracellular signaling pathways, (3) Ion channels, (4) Transporters for nutrients (e.g., glucose or amino acids) or minerals, (5) Protein synthesis, (6) Enzyme activities by de novo synthesis or phosphorylation through intracellular signaling pathways and/or ion channels, and (7) Mitochondrial oxidative phosphorylation and thermogenic activity.[10]

**Genetic basis of aging**

Growing evidence shows that, within individuals telomere length tracks with cardiovascular health and aging and is also affected by growth variation, both prenatally and postnatally. Kirkwood (1977) and Kirkwood and Holliday (1975) suggested that the degenerative changes that are seen during senescence — including the two primary causes of death, vascular degeneration through atherosclerosis and decline in insulin sensitivity — are the outward manifestations of cell deaths caused by failure to maintain integrity of DNA, RNA, and proteins, and by the inability to replace defective cells with normal cells. Kirkwood and colleagues have shown that there is selective advantage in reducing the accuracy of proof reading after some period of life. As somatic mutations accumulate in the aged, increasing numbers of cells function abnormally or die because of the accumulation of random genetic inaccuracies and somatic damage, which contribute to disease (Kirkwood 1998; Kirkwood and Holliday 1986). Telomere shortening itself can signal cells to enter senescence and telomerase is critical to cellular immortality. Once telomere length is critically shortened, DNA strand breaks occur, which can signal cell death by activating a number of different genes, including the tumor-suppressor gene p53 (Di Leonardo et al. 1994). The vascular wall becomes injured over time by mechanical, hemodynamic, and immunological factors, stemming from hypertension, smoking, and hyperlipidemia, among other common stressors. In response, the vascular endothelium initiates an immunological cascade, characterized by the adhesion of platelets and macrophages at the sites of damage (Ross 1993). What begins as a protective mechanism eventually becomes a pathological condition, in that, excess lipid becomes sequestered within the adhered monocytes, infiltrating the vascular wall, and forming atherosclerotic plaques. As would be expected, given this model, telomere attrition is accelerated in arterial tissue exposed to high levels of shear and oxidative stress, as cellular replication increases, to repair the damaged tissues (Chang and Harley 1995; Okuda et al. 2000). Strong correlations between telomere length and the severity of atherosclerosis and coronary heart disease than in controls has been reported, with age being strong predictor of severity of atherosclerosis (Okunda, Samani). Telomere length is also shown to be a biomarker for earlier stages of endothelial cell senescence, initiation of the atherosclerotic process, elevated homocysteine concentration, increased expression of endothelial cell inflammatory markers like ICAM-1 and PAI-1 (Xu), and may provide a possible link to glucose tolerance, (Jeanclos). From this it can be hypothesized that during fetal development when cellular proliferation occurs at a very fast rate, exposure to oxidative stress or any other stress induced by intrauterine conditions can modulate the fetal telomere length. One such condition leading to oxidative stress is maternal hyperlipidemia.[31]

Gene mutations of p66shc (p66shc-/−) mice have an increased life span and reduced early atherogenesis after high-fat diet consumption,[32] and are resistant to oxidative stress-induced apoptosis.[33]

Nitric oxide synthase knockout has a transgenic effect on fetal vascular programming due to uteroplacental insufficiency induced by lack of nitric oxide synthase. Nitric oxide plays an important role in the development of the placenta. Inhibition of nitric oxide synthesis by NOS
Inhibitors or eNOS knockout results in intratherine growth retardation (IUGR).\textsuperscript{[34]} It is hypothesized that first seven weeks of the postnatal period could pose an appropriate therapeutic window to prevent cardiovascular disease later in life.\textsuperscript{[35]}

**Ontogeny of atheromas**

Prodromal stages of atherosclerotic lesions are now well-recognized to arise early in human life. Compelling data on early lesions come from autopsy studies: The fate of early lesions in children (FELIC) showed unequivocally that minute fatty streaks are common in fetal aortas and have the characteristic repertoire of macrophages, monocytes, and oxidized LDL found in adult plaques.\textsuperscript{[3,21,32]} After birth the plaque size increased linearly with age in the aortic arch and the abdominal aorta from 1-14 years. Moreover, and of great importance, the plaque size was much greater in children born of mothers who were hypercholesteremic during pregnancy, although none of these children had hypercholesterolemia. The variability of the lesion size increased during later childhood in the FELIC study, which suggested an input from traditional cardiovascular risk factors such as diet, exercise, and socioeconomic status.\textsuperscript{[32]}

**Epigenetic alterations and vascular aging**

The effects of programming may pass across generations by mechanisms that do not necessarily involve changes in the gene. Attempts made after birth to reverse the consequences of programming may have their own unwanted consequences.\textsuperscript{[36]}

**Maternal factors**

Exposure to maternal obesity or high birth weight also represents an increased risk for childhood and adult obesity. In addition, fetal exposure to select chemicals (e.g., phytosterogens) or environmental pollutants (e.g., tobacco smoke) may affect the predisposition to adult disease. Animal models have confirmed human epidemiological findings and provided an insight into putative programming mechanisms, including altered organ development, cellular signaling responses, and epigenetic modifications (i.e., control of gene expression without modification of the DNA sequence). Prenatal care is transitioning, to incorporate goals of optimizing maternal, fetal, and neonatal health, to prevent or reduce adult-onset diseases.\textsuperscript{[37]}

Not only does the gestational period affect fetal development, but if the growth of a female fetus is constrained by lack of nutrients, there are persisting changes in her physiology and metabolism, which lead to reduced fetal growth and raised blood pressure in the next generation.\textsuperscript{[38]}

Another maternal factor that plays a key role in fetal programming and future vascular aging is placental development. Conditions like pre-eclampsia, gestational diabetes mellitus (GDM), and type 1 DM adversely affect placental development.\textsuperscript{[39]}

**Role of oxidative stress and epigenetic alterations induced by pregnancy induced hypertension**

The very preliminary data of Stefano F. Rimoldi\textsuperscript{[40]} suggested that offspring of restrictive diet pregnancy in pregnancy induced hypertension (PIH) may display pulmonary endothelial dysfunction in vitro. These epigenetic changes could be reversed by histone deacetylase inhibitors (i.e., butyrate).

Studies have demonstrated that in humans, pathological events during the perinatal and fetal period cause pulmonary and systemic vascular dysfunction in the offspring. The pulmonary vascular dysfunction predisposes to exaggerated hypoxic pulmonary hypertension and the defect in the systemic circulation may contribute to premature cardiovascular disease later in life. Consistent with this hypothesis, the offspring of mothers with pre-eclampsia are predisposed to systemic arterial hypertension and are at an increased risk for stroke. More studies are required to know whether pharmacological interventions during pre-eclampsia may allow preventing vascular dysfunction and premature cardiovascular morbidity in the offspring.\textsuperscript{[40]}

**Role of maternal nutrition**

Administration of a low protein diet (8% instead of 18% in normal rats) to pregnant rats, either until term or weaning, has been seen to produce offspring of reduced birth weight with elevated systolic and diastolic blood pressures, as early as four weeks of age.\textsuperscript{[41]} Hypertension was prevented in this model by the administration of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, but not by nifedipine.\textsuperscript{[42,43]} This largely suggests a role of renin-angiotensin (RAS) in disease pathogenesis. The process of differentiation and development is accompanied by the selective methylation of genes that are not needed for the function of differentiated cell. As this process of methylation takes place in utero and in early postnatal development, it is a good candidate for disturbance by environmental interference, and thus, provides a potential mechanism for fetal programming. There is evidence that methylation patterns can change with aging.\textsuperscript{[44]} It has been seen that a maternal low-protein diet is associated with reduced global methylation, and it may be that the deficiency of amino acids, like the glycine required to generate methyl donors, underlies such changes.\textsuperscript{[45]} Supplementation with glycine or folate reverses these programming effects.\textsuperscript{[46,47]} A study by Bogdarina et al. on offsprings of rats fed on a low-protein diet, showed that there was an increased expression...
of the AT1β receptor. Changes were apparent very early in the life of the programmed offspring and persisted till at least 12 weeks of age. It was possible that undernutrition led to the deficiency of methyl donors and conceivably certain genes might have been more susceptible to this influence than others. Substantial evidence suggests that programmed phenomena can result from excessive glucocorticoid action as a result of maternal stress. In humans mutation in the 11βHSD2 (11 beta hydroxy steroid dehydrogenase 2) gene has been reported, in association with low birth weight and reduced 11βHSD2 activity; and increased fetal cortisol levels have been reported in IUGR. Glucocorticoids are produced by the fetus, the levels of which are regulated by 11βHSD2. These impair the expression and function of the GLUT Transporters. Exposure of the rat fetus to excess maternal or exogenous glucocorticoids causes growth restriction, hypertension, hyperglycemia, increased activity of the hypothalamic pituitary adrenal axis (HPAA), and anxiety-like behavior in aversive situations. The placenta plays an important role in the expression of 11βHSD2 activity. Thus, the placenta plays an instrumental role in fetal programming not only through the above-mentioned mechanism, but also by altering oxidative and nitrate stress to which the fetus is exposed.

Maternal undernutrition and intrauterine growth retardation
In both animals and humans, maternal undernutrition during gestation reduces placental and fetal growth. Fetal growth is most vulnerable to maternal dietary deficiencies of nutrients, both proteins and micronutrients, during the peri-implantation period and the period of rapid placental development. The most common causes of this undernutrition are: Hyperemesis gravidarum, nausea, limited supply of food or closely spaced pregnancies.

Offsprings of undernourished mothers in experimental models exhibit later development of hypertension, insulin resistance, glucose intolerance, and frank diabetes across various species, the extent of each depends on the species and experimental model.

Dietary restriction during the periconceptional period has also been shown to shorten gestation and cause hypertension and abnormal hypothalamic-pituitary-adrenal axis (HPA) function in adult sheep.

Maternal overnutrition and fetal growth
Extensive studies have shown that maternal overnutrition retards placental and fetal growth. Overweight and obese women unknowingly enter pregnancy and continue overeating during pregnancy. They gain more weight during the first pregnancy and accumulate more fat during subsequent pregnancies. Both result in fetal growth restriction and development of the thrifty phenotype.

Role of other nutritional factors
The role of various nutritional factors on the vascular programming of the fetus has been reported by different studies. These include isoflavones-enriched soy proteins, the arginine family of amino acids, calcium, iron, cofactors (folic acid, taurine), and vitamins (A and D). Arginine is a common substrate for nitric oxide (NO) and polyamine syntheses via NO synthase (NOS) and ornithine decarboxylase (ODC). NO is a major endothelium-derived relaxing factor, and plays an important role in regulating placental-fetal blood flows, and thus, the transfer of nutrients and O2 from mother to fetus. Likewise, polyamines regulate DNA and protein synthesis, and therefore, cell proliferation and differentiation. Thus, NO and polyamines are key regulators of angiogenesis (the formation of new blood vessels from the pre-existing vessels) and embryogenesis, as well as placental and fetal growth. Maternal arginine deficiency causes IUGR and dietary arginine supplementation reverses fetal growth restriction in the rat models of IUGR.

Exposure of the fetus to prenatal hypoxia and cocaine has also been shown to have deleterious effects on the fetal cardiovascular system, which manifests itself later in adult life.

Nutritional insult during a critical period of gestation may leave a permanent ‘memory’ throughout life, and some of the effects (e.g., insulin secretion and action) may be gender-specific. There is growing evidence that maternal nutritional status can alter the epigenetic state of the fetal genome and imprint gene expression. Animal studies have also demonstrated that the timing, duration, and exact nature of the insult during pregnancy are important determinants of the pattern of intrauterine growth and the specific physiological outcomes.

Role of maternal hypercholesterolemia
Maternal hypercholesterolemia is associated with greatly increased fatty streak formation in human fetal arteries and accelerated progression of atherosclerosis during childhood. Experiments on rabbits have shown that temporary diet-induced hypercholesterolemia is sufficient to enhance fetal lesion formation. The ensuing pathogenic process in the fetus leads to increased postnatal atherogenesis in response to hypercholesterolemia.

Role of the placenta
In utero programming, resulting from chronic exposure
to oxidative stress and inflammation is a cause of atherosclerosis in the fetus. Endothelial cell dysfunction may be the initial injury arising from adverse antenatal conditions, and may be responsible for the early changes in the vascular function seen in children. After considering the critical role of the mitochondria in atherogenesis through endothelial function abnormalities it is proposed that placental mitochondrial dysfunction is present in cases of placental insufficiency and may be critical in the fetal programming of atherosclerosis.[62]

Developmental changes arising before implantation are likely to affect many cell lineages, although adaptations later in gestation, such as upregulation of placental nutrient and O2 transport, may compensate for the early defects and normalize birth weight. Once placenta has begun, the programming effects of the environmental signals may be mediated via changes in placental development.[62] However, the extent to which early insults program the placenta per se remains unknown.

**Scope for Intervention**

Studies have shown the beneficial effects of antilipid agents like cholestryramine and antioxidants like vitamin E which are used for treating maternal hypercholesterolemia, on fetal atherosclerosis. However, if proven safe during pregnancy in humans they may help in retarding atherosclerosis in the human fetus. The role of angiotensin blockers needs to be further studied. Animal models for the study of fetal programming of vascular aging have demonstrated that the elevation of adult blood pressure, associated with fetal exposure to a maternal low-protein diet, is prevented by early administration of an angiotensin-converting enzyme inhibitor. The actions of angiotensin II in the late suckling period may be a critical determinant of long-term cardiovascular functions in these animals.[42,43] Whether there is scope for intervention in humans and under which conditions, is not yet known.

Most of the chronic illnesses like the metabolic syndrome, obesity, cardiovascular diseases, and hypertension are well-recognized, as they have an inflammatory origin. The role of antioxidants in reducing the maternal oxidative stress can be established with well-designed placebo-controlled trials.[31,40]

Proper monitoring of maternal nutrition and health, not only during the antenatal period, but also the prenatal and postnatal period is of utmost importance. This should involve preparing a female for motherhood before she gets pregnant. Thus, pregnancy should be well planned and not an accident. Over nutrition should be strictly avoided.[34]

Although the selection of genes during the phenotypic development of the fetus is not under control, what can be modified is the desirable BMI before gestation, proper nutrition, and early detection and treatment of maternal complications (should also include maternal dyslipidemia and pregnancy induced hypertension (PIH)). Importance of the normal intake of micronutrients along with macronutrients should be emphasized.[21,34,57,61]

Practicing regular yoga, deep breathing exercises, and meditation has shown to have a beneficial effect on pregnancy outcomes and can be of help in the reduction of maternal oxidative stress.[33]

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Cite this article as: Pitale S, Sahasrabuddhe A. Fetal origin of vascular aging. Indian J Endocr Metab 2011;15:289-97.

Source of Support: Nil, Conflict of Interest: None declared.