Chapter

Maternal and Fetal Complications Due to Decreased Nitric Oxide Synthesis during Gestation

Sonia Jurado, Kaelly Saraiva, Cauane Marceliano, Vanessa Souza and Izabela Vieira

Abstract

Nitric oxide (NO) is synthesized from L-arginine by the constitutive NO synthase in vascular endothelial cells and plays an important role in the regulation of blood pressure and coronary vasomotion. Normal pregnancy is associated with major adaptations in maternal cardiovascular function, which help the woman to accommodate the growing fetus. The vascular endothelium is stimulated during pregnancy to release increased amounts of NO, and the abnormality in the L-arginine NO pathway may play a role in the etiology of preeclampsia. The objective of this study is to discuss the importance of nitric oxide during gestation and the maternal and fetal complications associated with decreased NO synthesis during this period. Maternal arterial hypertension due to inhibition of nitric oxide synthesis during pregnancy impairs fetal development, mainly the reduction of the wall/lumen ratio of the cardiac and renal microvasculature as well as the reduction in the number of nephrons. These changes may contribute to the development of hypertension. Despite these findings, more studies are needed to understand the programming of fetal development, and the intrauterine environmental factors. influence this process.

Keywords: nitric oxide, pregnancy, preeclampsia, growth fetal, intrauterine environment

1. Introduction

Normal pregnancy is associated with intensive changes in the maternal cardiovascular system that enables adequate oxygen delivery and nutritive ingredients to the fetus. Physiological vascular adaptation (increased blood volume, increased cardiac minute volume, and reduced vascular resistance) is followed by increased endogenous production of nitric oxide (NO) and improved response of smooth muscles on the reaction of NO [1].

Nitric oxide is synthesized from L-arginine by the constitutive NO synthase in vascular endothelial cells and plays an important role in the regulation of blood pressure and coronary vasomotion. Abnormalities in its production and/or bioavailability are related to diseases such as hypertension, atherosclerosis, and disorders associated with angiogenesis [2].

In normal pregnancy, there is an increase in blood volume and maternal cardiac output, although a decrease in systemic blood pressure occurs. In addition, the responsiveness to various vasoconstrictors is attenuated. This is due to the contribution of nitric oxide (NO) to the vasodilatory phenomena of pregnancy [3].

Nitric oxide is a potent vasodilator and plays an important role in mild relaxation muscles and helps in the vasodilation of maternal blood flow. NO is derived from the amino acid L-arginine, which is in the proteins of all life forms. It is classified as a semi-essential or conditionally essential amino acid [4]. In addition to nitric oxide, other chemical mediators have been implicated in this phenomenon, including estradiol and prostacyclin [5].

Serum NO concentration of the healthy pregnant women was significantly higher during the second and the third trimester of pregnancy in relation to control nonpregnant subjects [1]. Thus, increased production of nitric oxide by the endothelium contributes to the hemodynamic changes associated with normal pregnancy; conversely, a reduction in NO signaling has been observed in preeclampsia and in several forms of chronic hypertension [6, 7].

Preeclampsia is considered to be one of the most significant health problems in pregnancy, complicating 6–10% of all gestation over 20 weeks, 14–20% of multiple gestations, and 25% of patients with chronic hypertension and/or chronic renal disease [8, 9]. It is characterized of the symptomatic triad: hypertension (systolic pressure $\geq$ 140 mmHg and/or diastolic pressure $\geq$ 90 mmHg), proteinuria, and edema [10, 11]. This disease is one of the leading causes of fetal growth disorders, fetal morbidity and mortality, premature labor, and mother's death [4, 10].

Preeclampsia is a specific condition of gestation that involves the failure of several organs. The increase in blood pressure causes deleterious effects on several systems, especially the vascular, hepatic, renal, and cerebral. The complications observed in these systems may explain the high incidence of fetal and maternal mortality and morbidity, which makes preeclampsia one of the leading causes of maternal death in the world [1, 12].

It is interesting to note that there are some risk factors that increase the probability of a pregnant woman presenting with preeclampsia, such as hypertension and preexisting diabetes mellitus, obesity, and ethnicity [12].

Endothelial cell dysfunction can cause hypertension with its increased production of vasoconstrictor agents such as plasma endothelin or reduced release of vasodilator agents such as prostacyclin and NO [13].

Nitric oxide has been proposed as the physiological agent involved in this mechanism as it regulates feto-placental vascular permeability and resistance and platelet aggregation in the placenta. Maturation and development of the placenta is affected significantly by an epigenetic molecule such as nitric oxide which has been postulated to affect fetal programming and survival [14, 15].

The specific cause of NO increase during normal pregnancy is unknown, but it is suggested that increased shear stress during pregnancy stimulates the activity of the endothelial nitric oxide synthase (eNOS). Specifically in the placenta, the activity of this enzyme is important in the sense that NO synthesized locally maintains low vascular resistance, in addition to attenuating the action of vasoconstrictors [16].

The role of nitric oxide in the pathogenesis of preeclampsia was studied by Rachel et al. [4] who concluded that the circulating levels of nitrite are decreased in women with preeclampsia. One study showed that supplementation with L-arginine in women with preeclampsia lowered blood pressure through increased synthesis or bioavailability of nitric oxide [17].

Some studies point to the importance of nitric oxide to the outcome of pregnancy. Nitric oxide levels are altered in the blood serum of women who have had an abortion or ectopic pregnancy. The levels in recurrent abortions are decreased,

leading to an increase in myometrial contraction, whereas in ectopic pregnancy levels are higher, leading to decreased uterine tube motility and ectopic implantation [18, 19].

2. Nitric oxide and uteroplacental circulation

The endothelial cells in the uteroplacental circulation play an important physiological role in the maintenance of vasodilation of placental vessels, since these are not innervated. These endothelial cells produce prostacyclin and nitric oxide, causing vasodilation and also preventing platelet aggregation and platelet adhesion to endothelial cells [19].

Nitric oxide (NO) regulates implantation and trophoblastic invasion as well as embryonic development [20]. In addition, vascular tone in the placenta is controlled by several vasoactive mediators, with NO being the most important [21].

Nitric oxide participates at the onset of placental vasculogenesis. The onset of vasculogenesis requires the expression of vascular endothelial growth factor (VEGF), the mitogenic effects of which are mediated by nitric oxide. There is no well-established level of NO required for adequate placental angiogenesis. Elevated levels of NO may prevent angiogenesis, and its effect on cell survival and proliferation depends on its concentration [22].

NO has an important role in facilitating pregnancy-induced expansive remodeling in the uterine circulation, especially in the larger arteries [7].

The NO signaling has an important role in the expansive circumferential gestational remodeling of the uterine circulation. It provides an interesting link to the theory that preeclampsia results from elevated levels of sFlt-1, a soluble receptor for vascular endothelial growth factor and placenta growth factor, in preeclamptic women [23].

An excess of soluble receptor would reduce the availability of these ligands to the maternal vascular wall and fetal growth retardation. The sFlt-1, when infused in pregnant rats, promotes glomerular proteinuria and endotheliosis, characteristics of the preeclampsia picture [24].

Since both placenta growth factor and vascular endothelial growth factor stimulate endothelial NO release, a reduction in their signaling would create a vasoconstrictor imbalance and increase peripheral resistance and blood pressure. Thus, a reduction in NO signaling also impacts vessel remodeling in a way that would further increase uterine vascular resistance. This effect on structure, combined with loss of function (vasodilation), would further mitigate the increases in uterine [7].

In addition to the decrease in the synthesis of nitric oxide in the uteroplacental circulation in preeclampsia, the endothelium-dependent relaxation in response to acetylcholine is impaired in preeclamptic arteries. Additionally, the increased plasma fibronectin levels in preeclampsia may reflect fibronectin which has been shed by injured endothelial cells. Furthermore, soluble circulating endothelial cell adhesion molecules such as soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), and sE-selectin are significantly increased in preeclampsia compared to normal pregnancies. This suggests that there is an altered and pathological endothelial phenotype in preeclampsia [25].

3. Animal models for the study of nitric oxide during pregnancy

Animal models using rats or mice are very useful for the study of the pathogenesis, diagnosis, and treatment of preeclampsia. N-Nitro-L-arginine methyl

ester (L-NAME) is an inhibitor of NO synthase, and it has been shown to promote arterial hypertension in pregnant rats [26, 27].

The administration of L-NAME in adult rats, in addition to causing hypertension [28], promotes cardiac and aortic tissue damage [29], proteinuria, and glomerular endotheliosis [30].

Several animals have already been used as models of experimental hypertension, such as rhesus monkeys, dogs, and sheep. Most of the experimental studies use rats and mice. In these animals, four categories of preeclampsia are produced: (i) animals with surgically induced reduced uteroplacental blood flow, (ii) animals with preclinical symptoms induced by drugs, (iii) genetic animal models, and (iv) animals with preexisting hypertension developing preeclampsia [31].

Few studies address the effects of inhibition of nitric oxide on fetal development. Most of the work on this subject is from the 1990s. In pregnant rats, this nitric oxide synthesis inhibitor causes fetal growth restriction by a reduction in cellular proliferation due to induction of apoptosis [32], reducing the body weight and causing hemorrhagic necrosis of neonate's hind limbs [33, 34].

This suggests that L-NAME crosses the placental barrier and affects the fetal NO synthesis, leading to cell death in the limbs because the NO has a role in limb and digit developments [35]. Reactive oxygen species (ROS) formation by L-NAME induces hemorrhages, oxidative stress, and limb reduction defects [30].

The administration of L-arginine, the precursor of nitric oxide, in mice during gestation promoted an increase in fetal weight presumably due to the contribution of NO in improving fetal-maternal circulation by vasodilation and subsequently increased blood volume and viscosity in the fetal-maternal circulation [36].

4. Effects of inhibition of nitric oxide on fetal heart development in animal models

The first studies on the importance of nitric oxide in cardiac development go back to the beginning of the year 2000. The role of nitric oxide on fetal cardiovascular development is only partially known. In addition, in women who had preeclampsia, their children are at greater risk of developing cardiovascular disease later in life [37].

The nitric oxide probably contributes to the transformation of the epithelium-mesenchyme in the areas of the endocardial cushion, myocardial survival and angiogenesis, and myocardial remodeling. Impaired production of NO in the heart leads to structural congenital abnormalities, resulting in heart failure and increased mortality [38].

Inhibition of nitric oxide during cardiac development is known to promote bicuspid aortic valve defects [39], congenital septal defects, and increase in cardiomyocyte apoptosis [40].

Apoptosis occurs in situations of cardiac remodeling during or after pathological processes and was observed in the myocardium of newborns from rats with hypertension induced by L-NAME. Thus, apoptosis can also occur in postnatal maturation of the heart and other tissues of the cardiovascular system, which need to adapt to the new hemodynamic role [41].

In newborns from L-NAME mothers, the most significant change in the myocardium involved the microvasculature. The wall/lumen ratio of arterioles was significantly higher in neonates of L-NAME and spontaneously hypertensive rats (SHR) than of normotensive mothers at 2 and 15 days postnatal [42].

It is possible that the myocardial vascular changes induced by the blockade of nitric oxide synthesis in rats are due to the activation of the local angiotensin

I-converting enzyme (ACE). Takemoto et al. [43] found an increase in ACE in the coronary arteries and increase of the wall/lumen ratio in the myocardial vasculature of adult rats treated with L-NAME.

A decreased NO generation induces the synthesis of growth-promoting factors from the endothelium. The ACE activation would increase the formation of angiotensin II, which in turn directly induces vascular smooth muscle proliferation [44].

Possibly, the factors involved in hyperplasia/hypertrophy of the smooth muscle cells of the microvasculature of newborns born to hypertensive mothers who received L-NAME during pregnancy are activation of the renin-angiotensin system and activation of the sympathetic nervous system that contributes to the remodeling of intramyocardial vessels [42].

In rats treated with L-NAME, the blood pressure increases via the renin-angiotensin system, and, therefore, angiotensin II can promote the narrowing of the lumen of the microvasculature [45].

In neonates of hypertensive rats induced by L-NAME, in addition to cardiac microvasculature being affected, the pyloric musculature is also compromised, observing hypertrophy and hyperplasia of smooth muscle cells [46].

The rat offspring from L-NAME parents, with sustained NO-induced hypertension, had a remarkably higher blood pressure [47]. In addition to impairment in cardiovascular development, there are other damages in the offspring of rats treated with L-NAME as in the hippocampus, affecting cognitive and learning abilities [48].

5. Effects of inhibition of nitric oxide on fetal renal developmental in animal models

The fetal kidney appears to be extremely vulnerable to the effects of growth retardation. Studies on human infants with growth retardation indicate that the kidneys are disproportionately affected relative to other organs [49].

One study noted that maternal hypertension during pregnancy results in reduced birth weight and a decreased area and number of glomeruli [50]. Certainly, there is a link between maternal environmental factors, particularly nitric oxide inhibition, and the development of hypertension in adulthood.

Some models of arterial hypertension have been studied in animals in order to detect imbalances in fetal development, including protein restriction, excessive sodium intake, impaired uterine or placental circulation, blockade of the renin-angiotensin system (RAS), and increased exposure to maternal glucocorticoids, all of them leading to hypertension in offspring [51–54].

Experimental studies indicate that fetal exposure to an adverse maternal environment may reduce glomerular filtration rate by decreasing the surface area of the glomerular capillaries. In addition, fetal responses to environmental insults, such as maternal hypertension, may contribute to the development of hypertension early in life, including increased expression of apical or basolateral tubular Na^+ carriers and increased production of renal superoxide leading to reabsorption which increased Na^+ [55].

Reductions in NO synthesis decrease renal sodium excretory function, not only through direct action on the renal vasculature but also through modulation of other vasoconstrictor processes and through direct and indirect alterations in tubular sodium transport [56].

Moreover, environmental factors of intrauterine life may worsen the prognosis of offspring hypertension, at least in part, by determining the number of nephrons. The reduced number and size of nephrons may also predispose the individual to the development of progressive renal disease [54, 57].

Kidneys with lower numbers of nephrons maintain their hemodynamic and excretory functions by increasing local vascular resistance and glomerular pressure. The increase in glomerular pressure within the nephrons can trigger a cascade leading to progressive deterioration and loss of nephrons [56].

Nitric oxide is produced within the kidney and plays an important role in the control of many intrarenal processes. NO contributes to the regulation of sodium excretion and thus maintenance of vascular volume and arterial pressure in the adult [50]. Studies have shown that certain animal models of genetic hypertension and forms of human hypertension are associated with a decrease in NO synthesis [58].

The deficient production of NO in the intrauterine period is associated with a reduction in the mass and number of nephrons in the initial period of life. NO is involved in maturation and renal function in the postnatal period [50].

Inhibition of NO synthesis during gestation in rats treated with L-NAME promoted structural changes of the renal microvessels (thickening of the media) in newborns. The remodeling of the microvasculature of the kidneys of the newborns can be involved with adaptive responses to maternal arterial hypertension, activation of local/systemic of RAS in newborns, and enhanced synthesis of peptide growth factors, such as platelet-derived growth factor, which promote smooth muscle cell hyperplasia of the microvasculature [59–61].

Spontaneously hypertensive rats (SHR) at 2 days of age also showed an increase in the area and in the media/lumen ratio of the renal microvasculature due to hypertrophy or hyperplasia of the media layer. Hypertrophy and polyploidy are preferentially found in conduit arterioles, whereas hyperplasia and remodeling are found mainly in small arteries and arterioles [62].

Pups of spontaneously hypertensive rats (SHR) had significantly higher concentrations of renin than Wistar-Kyoto pups from birth until the beginning of the third postnatal week [63] as well as increased expression of angiotensinogen mRNA [64].

The elevated renin concentration of the SHR is linked to increased renal vascular resistance and thus to a reduced renal blood flow and glomerular filtration rate [65]. Also, it appears that sustained activity of the renin-angiotensin system may be required for exaggerated vascular growth responses in SHR [66].

Intrauterine growth restriction by nitric oxide inhibition during pregnancy is associated with a decrease in the number and size glomeruli and microvascular remodeling. Therefore, the nitric oxide inhibition during pregnancy may be linked to structural changes in the kidney which potentially lead to hypertension in later life [54].

Therefore, individuals born after intrauterine growth restriction, such as the L-NAME-induced hypertension model in rats, are at increased risk for kidney and heart morbidities. Endothelial dysfunction, with inhibition of NO synthesis, increases oxidative stress, dysfunction of endothelial progenitor cells, and accelerated vascular aging. L-arginine supplementation and treatment with NO modulators represent promising strategies to improve endothelial function and mitigate long-term outcomes and possibly vascular problems in newborns that have undergone growth restriction during maternal hypertension [67].

6. Conclusions

The inhibition of nitric oxide synthesis during pregnancy promotes changes in the renal and cardiac microvasculature and, in addition, reduction in the number of fetal nephrons, leading to hypertension in the adult life of rat pups and, potentially, in humans. In this sense, the effects of preeclampsia for the mother and the fetus should be considered.

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Conflict of interest

The authors declare no conflict of interest.

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