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Impacts of Exogenously Derived Nitrogen Oxide and Sulfur Compounds on the Structure and Function of the Vascular Endothelium Link Pregnancy Hypertension with Later Life Hypertension

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Abstract

The relationship between pregnancy hypertension and later life hypertension is explained by long-term impacts of environmental oxidants on the vascular endothelium. These impacts may precede the onset of the disease as a primary defect and may participate in the pathogenesis of hypertension itself. Continuous exposure to strong exogenous oxidants such as NO_x (NO and NO₂) reversibly oxidizes oxyhemoglobin (Fe²⁺) to methemoglobin (Fe³⁺), and irreversible methemoglobinemia can arise because of disruption of the oxidant/antioxidant balance supported by SO₂ metabolites, as inhibitors of antioxidants, and by synergistic degradation of antioxidant thiols. Methemoglobin by itself and from heme, redox-active ferric iron as product of methemoglobin catabolism, have prooxidant properties and cause important structural and functional changes in the vascular endothelium such as growth arrest, senescence, morphological alterations and cell apoptosis. In 1975, an epidemiological study among 204 pregnant women in Labin (Croatia) identified 30 (14.7%) cases of preeclampsia and 25 (12.3%) cases of hypertension in pregnancy. Ten years later, we found a significant number of hypertension cases (N=5; P=0.0027), and among them, we found a significant number of pregnancy-induced hypertension cases (N=3; P=0.0003) and a significant number of psychoneurotic disturbances (P=0.0190), but these conditions were not found in the normotensive women ten years after giving birth (P = 0.1161). Our original findings confirm that hypertension in pregnancy is not a transient impairment but instead is an extension of the effects of exogenously induced oxidative stress on the structure and function of the vascular endothelial, and indicate delayed effects plausibly manifesting as hypertension in later life.

Keywords: Pregnancy Hypertension; Later Life Hypertension; Endothelial Dysfunction; Nitrogen-Sulfur Compound Synergism; Methemoglobin and Heme Prooxidant Property; Redox-Active Ferric Iron

Introduction

The pathogenesis of pregnancy-induced hypertension and its association with hypertension in later life is unclear and not well understood. In our opinion, the relationship between hypertension during pregnancy and hypertension in later life is explicable by the long-term impacts of environmental oxidants on the vascular endothelium. As a further main aim we want to make a contribution to the establishment of sources of oxidants as key factors in understanding the role oxidants play in the pathogenesis of cardiovascular endothelial dysfunction. Strong exogenous oxidants such as NO_x (NO and NO₂) reversibly oxidize oxyhemoglobin (Fe²⁺) to methemoglobin (Fe³⁺), and irreversible methemoglobinemia can arise because of the disruption of the oxidant/antioxidant balance, supported by the synergic SO₂ metabolites degradation of antioxidant thiols. This correct view is based on original observations and on confirmation in scientific literature. The formation of methemoglobin-ferric iron (Fe³⁺) from hemoglobin-ferrous iron (Fe²⁺) leads to the destruction of erythrocytes, so that free hemoglobin from hemolysis can be directly cytotoxic and can alter the state of endothelial cells, promoting hemolysis-associated smooth muscle dystonia, vasculopathy and endothelial dysfunction [1]. From the methemoglobin and heme catabolism there is released into the blood-stream cytotoxic redox-active ferric iron, which contributes to endothelial injury and the development of vascular diseases.

The role of methemoglobin (MetHb) on the structural and functional changes in the vascular endothelium

Methemoglobin by itself, and heme have prooxidant properties and induce structural and functional changes in the vascular endothelium. These changes include growth arrest, senescence, morphological alterations and cell apoptosis, and they lead to both vessel thrombosis and endothelium denudation under the influence of redox-active ferric iron, a toxic ROS (Reactive Oxygen Species) with paramagnetic quality as a product of heme oxygenase, responsible for methemoglobin-heme degradation (Figure 1). The endogenous production of nitric oxide (NO) by nitric oxide synthase (NOS) plays an important role in vascular homeostasis, neurotransmission and immunological host defense mechanisms [2]. The major pathway for NO metabolism is stepwise oxidation to nitrite (NO₂⁻) and nitrate (NO₃⁻) as RNS (Reactive Nitrogen

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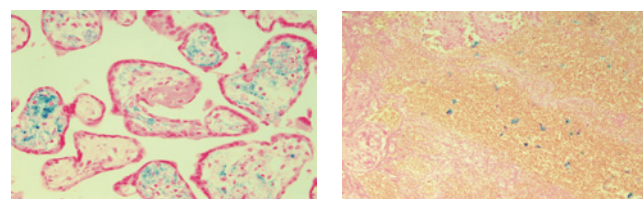
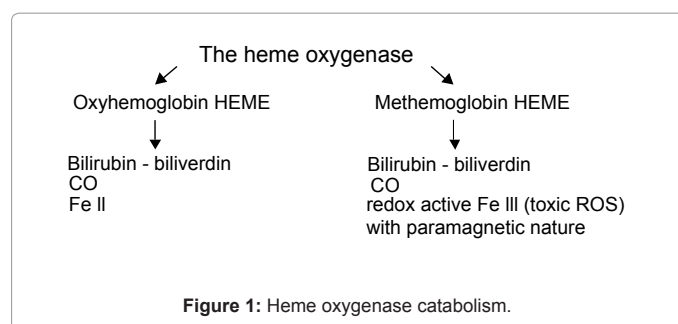
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Species), possessing by itself oxidant property [3]. It is known that superoxide (O_2^-) reacts with NO to produce peroxynitrite (ONOO), a strong oxidant that readily catalyzes membrane lipid peroxidation [4]. The effects of peroxynitrite on erythrocyte membranes have been studied [5], and it was found to transiently decrease intracellular glutathione, oxidize membrane protein-SH groups, and initiate membrane lipid peroxidation. Moreover, peroxynitrite interacts with lipids, DNA and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms, and this triggers cellular responses to overwhelming oxidative injury, committing cells to necrosis or apoptosis [6]. A study evidently reviewed that implicates hypertension in pregnancy as a risk factor for CVD later in life. The putative mechanisms underlying this association, including the possibility that hypertensive disorders of pregnancy increase the risk of future CVD by causing long-term metabolic, inflammatory and vascular changes [7].

Utero-placental changes in complicated pregnancy are not the cause but rather consequence of increased systemic oxidative stress

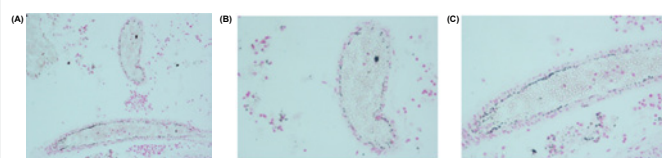
Investigators are attempting to elucidate the placental factors that are responsible for mediating the activation/dysfunction of the maternal vascular endothelium [8]. Recent intensive studies have indicated that oxidative stress is the source of endothelial dysfunction in atherosclerosis, and they propose that oxidative stress can lead to endothelial dysfunction in pregnancy [9]. This proposal links two stages, failed vascular remodeling of the vessels that supply the placental bed (**Stage 1**) and the multisystemic maternal syndrome of preeclampsia (**Stage 2**). According to our hypothesis, a pregnant woman continuously inhaling nitrogen oxides and sulfur dioxide as fuel burning products, will traverse three, not two from current thought, distinct stages: **First** blood circulation stage, **Second** decido-placentation stage and **Third** systemic disease stage. The main difference between **Two** and the proper **Three Stage** hypothesis is the assertion that, in the pathogenesis of early and late pregnancy complications, methemoglobin plays an important role by subjecting vital organs to systemic oxidative stress [10]. Moreover, we was also observed that utero-placental changes in complicated pregnancies such as “locus minoris resistentiae” are not the cause but rather a consequence of increased systemic oxidative stress. This assertion is based on very important environmental factors such as from preconception **Continuous** inhalation of oxidants, the **Intensity** of exposure, the **Accumulation** of oxidants and the **Synergism** of nitrogen oxide-sulfur dioxide metabolites.

When the high level of methemoglobin ($> 1\%$) becomes irreversible, the deficiency of antioxidants persists, and oxidative stress continues, attacking the vascular endothelium of the kidneys, brain and other vital organs and tissues of the mother. This can result in eclampsia and/or death as the final form of “maternal preeclampsia”. Symptoms of increased levels of methemoglobin in the mother include headache, dyspnea, pallor, cyanosis, palpitations, chest pain, confusion, delirium potentially leading to tonic-clonic convulsions, coma and death. The corresponding author has personally observed that these symptoms are also common in patients with severe anemia, preeclampsia and eclampsia, suggesting that methemoglobinemia may also be a precursor to these conditions. As oxidants possess the capacity to cross the damaged fetomaternal placental barrier, for instance from the methemoglobin catabolism ferric iron placental chorionic deposition appearance (Figure 2), “fetal preeclampsia” is an expected manifestation. Under these adverse conditions, ferric iron positivity in capillary endothelial cells of the blood-brain barrier in the fetus rise, also resulting in preterm birth, stillbirth or early neonatal death (Figure



Positive ferric iron deposits A) in an intervillous hemorrhage (x4), B) placental chorionic villi stroma (x20) in a placenta from stillbirth after 38 weeks of gestation. Mother Methb $>1\%$. Source: Stifter Sanja, Department of Pathology, University of Rijeka School of Medicine, 2011.

Figure 2: Prussian blue staining of a histological placental tissue section.



Source: Lavezzi AM, Mohorovic L, Alfonsi G, Corna MF, Maturri L. Brain iron accumulation in unexplained fetal and infant death victims with smoker mothers - The possible involvement of maternal methemoglobinemia. BMC Pediatrics 2011, 11:62.

Figure 3: Iron positivity in capillary endothelial cells of the blood-brain barrier in a victim of SIUD aged 36 gestational weeks. Staining: Perl's Prussian Blue reaction for ferric iron. Magnification: A) 10x; B) and C) 20x.

3). Continuous exposure to inhaled toxic substances in addition to oxidants (from food, water, drugs) and their associated cumulative effects cause increased oxidative stress. Maternal and fetal serum concentrations of total nitrites and nitrates (indices of nitric oxide production) were found to be significantly increased in preeclampsia and eclampsia [11,12], and the increase in nitric oxide production is directly related to the severity of eclampsia. When the continuous action of oxidants has exhausted the mother's self-defences (enzymatic and non-enzymatic), increased production of ROS, super oxide anion and hydrogen peroxide, reduced nitric oxide synthesis, and decreased bioavailability of antioxidants play pivotal roles in both experimental and human hypertension [13].

Methods and Results

To illustrate our hypothesis about the relationship between hypertension in pregnancy and hypertension in later life, we draw on the results of a retrospective study, which spanned the period from 1975 to 1985 in the same area surrounding the coal-only thermoelectric power plant Plomin 1 located in the community of Labin (Croatia). To give an appropriate and competent comment about the research

findings, we used the results of a proper prospective and retrospective study. The link between, the continuous exposure to exogenously induced oxidative stress on the structure and function of the vascular endothelial, and the blood methemoglobin and sulfhemoglobin raised concentrations, has been considered. Since the plant was periodically closed it was possible to evaluate the effects in two periods: the 'control' period from April to July 1989, and the 'exposure' period from December 1989 to March 1990. A proper prospective laboratory study about the blood level of methemoglobin (MetHb) and sulfhemoglobin (SulfHb) in pregnancy revealed a significant increase in MetHb and SulfHb levels during the air pollution exposure period (Figure 4). The MetHb and SulfHb levels (Ref. values MetHb < 1%, SulfHb 0.0-0.4%) in the bloodstream of the pregnant women were determined in blood samples taken three times with a 1-month period between each test in the course of regular monthly obstetric check-ups and analyzed in the laboratory by spectrophotometer based on the difference in absorbance between MetHb and cyanmethemoglobin, during the exposure ('dirty') period when the power plant was in operation (N = 122), and during the control ('clean') period when the power plant was closed (N = 138). Using linear correlation statistical tests, methemoglobinemia and stillbirths, recorded over the 'exposure' period, were significantly higher than in the 'control' period ($p = 0.0205$) and the frequencies of miscarriages and stillbirths were significantly lower in the 'control' period than in the 'exposure' period ($p < 0.05$) [14]. In 1987 the coal power plant operated for 4772 hours. In 1988 and 1989, it worked at the lower capacity of 2754 and 579 work hours respectively. In 1987 we found an increased and statistically (Chi-square test) significant number of premature births ($p=0.026$) and a relative risk of 1.76 in comparison to 1988 and 1989 (normalized to coal power plant working hours).

A computer program was specially designed for the purpose of defining the most critical gestation period for adverse effects of environmental toxics in terms of preterm delivery (<37 weeks) and low birthweight (<2500 g) in humans. Therefore 704 pregnant women were

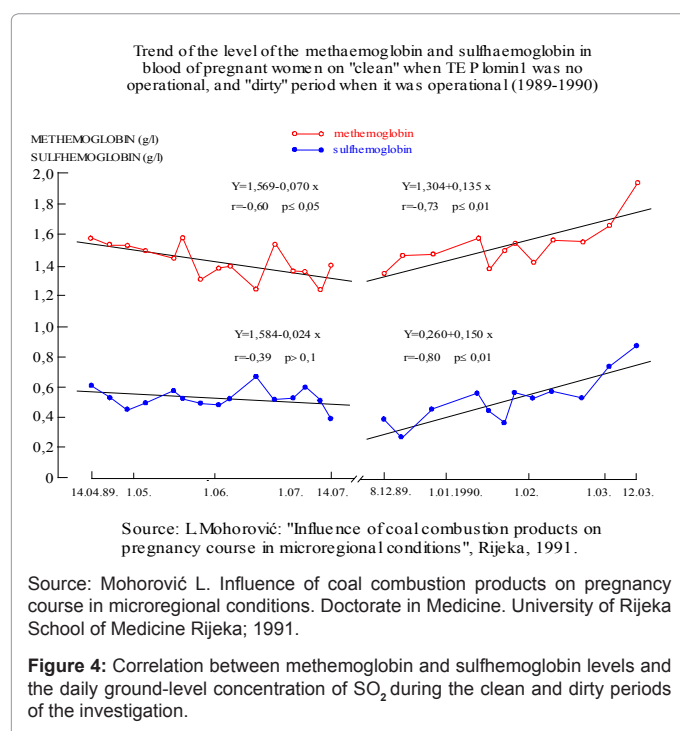
covered from 1 January 1987 to 31 December 1989. Coal consumption and SO_2 discharges were calculated for each individual pregnant woman daily, weekly, monthly, and an average for the 9 months of gestation, as were also biological variables which point to the condition of the mother during pregnancy. The mean age of the pregnant women included in the study was 25.8 years (range 15–41 years, S.D.=4.79); 48.9% were primiparae, 40.8% had one previous childbirth, and 8.2% had two previous child births. The mean value of birthweight was 3377 g, (S.D.=610 g, range 550–5150 g). The mean preterm birth was 34.4 weeks (S.D.=4.2, range 22–43 weeks), and the mean birthweight of preterm newborns was 2076.8 g (S.D.=537.6 g, range 550–3650 g). The results of our epidemiological retrospective study show that there is a statistically significant association (Coefficient of intercorrelation-Pearson) between exposure to sulfur dioxide at the end of the first and second month of pregnancy and a negative correlation between the length of gestation (end of the first month: -0.0914 , $p=0.008$; end of the second month: -0.0806 , $p=0.016$) and lower birthweight of newborns (end of the first month: -0.0807 , $p=0.016$; end of the second month: -0.0733 , $p=0.026$). The exposure to SO_2 during the whole pregnancy negatively correlates with gestation length, -0.0932 $p=0.007$, but not with the birthweight of the newborn. In 704 deliveries between 1987 and 1989, there were 0.7% preterm births to 28 weeks, 2% to weeks 29–32, and 7.2% to weeks 32–37. Altogether, 9.9% of all births were preterm. There were 0.9% newborns with a birthweight of below 999 g, 0.1% between 1000 and 1499 g, 6.1% between 1500 and 2499 g, and 92.9% above 2500 g [15].

In 1975, an epidemiological study included a population of pregnant women living in similar conditions of harmful environmental air pollution based on clinical observations. We used urine, body weight and RR (Riva Rocci) upper arm blood pressure data recorded from pregnant women during regular monthly obstetric and laboratory check-ups and post-partum data from the family doctors of the Labin Primary Health Care Center. The study was conducted on 204 pregnant women or 75.6% of total births registered from January 1 1975 to December 31 1975. The community of Labin (Croatia) had 30 (14.7%) cases of preeclampsia and 25 (12.3%) cases of hypertension in the terminal phase of pregnancy, defined as elevated blood pressure over 140 mmHg systolic and 90 mmHg diastolic, which is higher than the 7-10% estimated for all pregnancies.

Ten years later (1985), we found a significantly persistent incidence of hypertension (N=5; $p=0.0027$) among the same women, and among some of them we found a statistically significant number of pregnancy-induced hypertension cases (N=3; $p=0.0003$). There were no cases of hypertension in the control sample of normotensive women ten years after giving birth. The incidence of urinary tract infections in women with hypertension was not significantly different from that in the control sample of healthy women ten years later ($p=0.5184$). The group of women with hypertension demonstrated a significantly higher incidence of psychoneurotic disturbances ($p = 0.0190$) ten years after giving birth. The control group of healthy pregnant women presented 4 patients with psychoneurotic disease ten years after the birth, a level not statistically significant ($p = 0.1161$). The incidence of pyelonephritis-cystitis was not statistically different ($p = 0.5184$) in the sample of pregnant women (1975) in comparison with the same women ten years later (1985) (Table 1).

Discussion

Not until after 1986, just at the time of our epidemiologic study, did a great deal of basic and clinical research appear on the physiological



and pathophysiological role of NO in cardiovascular function [16-18]. Less attention was paid to gaseous pollutants such as carbon monoxide (CO), nitrogen oxides (NO and NO₂) and sulfur dioxide (SO₂) despite the fact that gaseous pollutants are also involved in cardiovascular toxicity [19]. Briet M. et al. demonstrated that exposure to gaseous pollutants (SO₂ and NO₂) leads to a significant alteration in endothelial function in both large and small arteries [20]. There is mounting evidence that second-generation “reactive sulfur species” (RSS) with stressor properties rapidly oxidize and subsequently inhibit the functions of thiol-dependent proteins and enzymes [21-25]. The formation of methemoglobin-ferric iron from hemoglobin-ferrous iron leads to the destruction of erythrocytes, and free hemoglobin from hemolysis can be directly cytotoxic and alter the state of endothelial cells, promoting endothelial dysfunction [26] and disrupts the normal vascular control of coagulation, vessel tone, vessel tension and vessel permeability [27,28]. Methemoglobin is a source of heme and iron, and it has been shown that elevated iron storage is associated with increased cardiovascular events [29-32]. Redox-active iron may contribute to lipid peroxidation and endothelial cell activation via Fenton chemistry to produce an increase in both reactive oxygen species (ROS) and hydroxyl radicals (OH[•]) [33]. The role of heme oxygenase-1 in methemoglobin catabolism, thereby confirming our hypothesis about the specific role of methemoglobin and its catabolic product ferric iron, with a deleterious effect causing endothelial dysfunction [34,35], loss of endothelial cells, and leads to plaque denudation, the main cause of plaque complications [36].

When oxidized, Hb in plasma transfers heme to the endothelium and lipoproteins, endothelial cells upregulate heme oxygenase-1 and ferritin, which are effective at protecting the endothelium against the damaging effects of heme and oxidants, but lack of adaptation to an iron-rich environment leads to extensive endothelial damage in humans [37]. Zhu MT et al. indicated that both ferric oxide and ferrihydrous oxide nanoparticles generate oxidative stress for endothelial cells [38]. The investigation of Gobe G. et al. demonstrated a role for endothelial cell apoptosis, but not necrosis, in the development of micro vascular rarefaction in hypertension [39]. In vivo examination of the potential role of endothelial apoptosis in endothelial erosion and vessel thrombosis has confirmed that the induction of endothelial apoptosis leads to both vessel thrombosis and endothelial denudation [40]. Under normal conditions, mature endothelial cells remain quiescent for many years because they are mutual physical contact (contact inhibition). Eventually, these cells undergo apoptosis, are removed by circulating blood and are replaced rapidly by regenerated endothelial cells and contribute to this regeneration process [41,42]. Gaseous pollutants affect large artery endothelial function, whereas particulate matter exaggerates the dilatory response of small arteries to ischemia. Whatever their origin, regenerated endothelial cells appear to be dysfunctional and the first step in the atherosclerotic process [43,44].

| Year Total | Hypertension | Pyelonephritis-Cystitis | Psychoneurotic disturbances |
|------------|--------------|-------------------------|-----------------------------|
| 1975* | 25 | 7 | 0 |
| 1985** | 5 | 4 | 6 |
| 1985*** | 0 | 1 | 4 |

*Data from the general practitioner's office and the Center for Women's Health Care

**Testing the same women at a 10-year interval

***Testing a random sample of healthy women at a 10-year interval

Table 1: Incidence of hypertension, pyelonephritis, cystitis and psychoneurotic disturbances during pregnancy (1975) - (n=32)* and ten years after giving birth (1985).

In pathological situations (hypertension, hyperlipidemia), endothelial cells can proliferate rapidly with a turnover time of less than 5 days, but the capacity of an endothelial to divide is limited and enter a state of growth arrest (i.e., senescence), increase their generation of reactive oxygen species, decrease their production of NO and increase their release of endothelin-1 [45,46]. Endothelial cells also become more sensitive to apoptotic stimuli, and the reduced regenerative capacity of the endothelium and endothelium senescence increase the rate of endothelial cell apoptosis [47-49].

We point out that elevated exogenously derived nitrogen oxides (NO and NO₂) also cause structural and functional changes of the vascular endothelium such as growth arrest, senescence, morphological alterations and increased reactive oxygen species generation.

Moreover, recent studies have suggested that endothelial dysfunction occurs long before a preeclamptic pregnancy [50,51]. Agatisa et al. demonstrated that women with a history of preeclampsia exhibit impaired endothelial function up to one year postpartum, which may explain their increased risk of hypertension and cardiovascular disease [52].

Preeclampsia is characterized by vasospasms, multiple organ hypoperfusion, endothelial cell damage associated with hypertension, proteinuria and endothelial dysfunction, and there is a significant correlation between nitrite/nitrate and endothelin-1 [53]. As endothelial damage is a known stimulus for endothelin synthesis, increases in the production of endothelin and the activation of endothelin receptors may participate in the pathophysiology of preeclampsia. Most investigators have found two- to three-fold higher plasma endothelin concentrations in women with preeclampsia [54]. Small arteries (prearteriolar vessels with lumen diameter less than approximately 500 microns) contribute importantly to and participate actively in the regulation of peripheral resistance [55,56]. Huang A. et al. hypothesized that high intravascular pressure itself elicits the production of superoxide, which then interferes with the nitric oxide-mediated responses of arterioles [57]. These findings lead us to highlight the enhanced oxidative stress in microvessels contribute to the elevated wall shear stress and peripheral resistance in both post-partum and later life hypertension. Balla J. et al. demonstrated that hemoglobin in cultured endothelial cells when oxidized to methemoglobin greatly enhances oxidative hydrogen peroxide-mediated endothelial cell injury. They also posited that ferrimethemoglobin (Fe³⁺), but not ferroheme (Fe²⁺), releases its hemes, which incorporate rapidly into endothelial cells, thereby increasing their heme oxygenase, and ferritin production is also markedly increased [58]. Recently, researchers have found that methemoglobin is a potent activator of endothelial cells and the production of chemokines and cytokines [59,60]. Vascular endothelial cells are direct targets of free hemoglobin and of its oxidative derivative methemoglobin which readily release heme, an abundant source of redox-active iron, and act out with sulfur compounds synergy during pregnancy, causing early and late vascular endothelial dysfunction in vital organs and the CNS [61-63].

Comment and Conclusion

Our results make an original contribution to a better understanding of the potential mechanism underlying the pathogenesis of pregnancy-induced hypertension, which has not yet been fully elucidated.

The research results cited in the discussion paper lead us to suppose that methemoglobin formation and catabolism, based on exogenously derived nitrogen oxides NOx (NO, NO₂) supported by the synergic

SO₂ metabolites degradation of antioxidant thiols, is not only a useful biomarker but also has a degree of predictive validity. From the methemoglobin and heme catabolism there is released into the blood-stream cytotoxic redox-active ferric iron, contributing to endothelial injury and the development of vascular diseases, confirming our hypothesis about the deleterious effects of ferric iron from exogenously induced oxidative stress on the structure and function of the vascular endothelial, and which indicate delayed effects plausibly manifesting as hypertension in later life.

Conflict of Interest

The authors declare no conflict of interest.

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