Reactive Oxygen Species and the Uterine Circulation

122

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Contents

Introduction 2774
ROS and Pregnancy 2774
Sources of ROS in the Uterine Circulation 2776
ROS and the Placenta 2776
ROS-Mediated Uterine Artery Dysfunction 2779
ROS, Circulating Factors and Uterine Artery Dysfunction 2780
ROS and the Inflammatory Response 2781
Endogenous Antioxidants and Antioxidant Therapy 2782
Conclusions 2783
References 2783

Abstract

Arteries of the uterine circulation undergo a number of key changes during pregnancy to accommodate the large increases in blood flow necessary to ensure a successful pregnancy. These include an increase in endothelium-dependent vasodilation and a blunted response to vasoconstrictors. Endothelial dysfunction of these arteries is associated with complications of pregnancy, and there is an increasing body of evidence that suggests this dysfunction is mediated in part by reactive oxygen species (ROS).

Pregnancy itself is a condition of mild oxidative stress, with an increase in various biomarkers of oxidative stress and a decrease in total antioxidant capacity. Such markers are further increased in pregnancies complicated by preeclampsia, fetal growth restriction, and gestational diabetes.

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A feature that is unique to pregnancy is that circulating factors, produced by the placenta, may result in increased uterine artery ROS. These include oxidized lipids, autoantibodies, inflammatory cytokines, and antiangiogenic factors. A further source of ROS in the uterine circulation is activated leukocytes, which are a significant source of superoxide.

Studies have begun to link an increase in oxidative stress with abnormal uterine artery function and poor pregnancy outcomes. A key player in mediating the altered uterine artery response in healthy pregnancies is nitric oxide (NO). Given the ability of superoxide to scavenge NO, it is clear that increased production of superoxide in the uterine artery may significantly impact pregnancy-related adaptations in this circulation.

Keywords

Endothelial dysfunction • Fetal growth restriction • Gestational diabetes • Preeclampsia • Pregnancy • Uterine artery

Introduction

During pregnancy, a number of important cardiovascular adaptations occur, including an expansion of blood volume and an increase in cardiac output. These changes ensure there is sufficient transfer of oxygen and nutrients to the fetus and hence facilitate a successful pregnancy. The arteries of the uterine circulation also undergo a number of key changes including remodeling of the spiral arteries to allow for the development of a high-flow, low-resistance state. This change partly accommodates the tenfold increase in blood flow to the uterus that occurs during gestation. Additionally, there is an increase in endothelium-dependent vasodilation, increased flow-mediated dilation, and a blunted response to vasoconstrictors in the uterine circulation. These changes, while allowing for an increase in blood flow, also play a role in the utero- and non-uteroplacental circulation in mediating the decrease in total peripheral vascular resistance that is observed during pregnancy. It is unsurprising, therefore, to note that endothelial dysfunction of arteries of the uterine circulation is associated with complications of pregnancy, in particular preeclampsia. There is a large body of evidence which supports the hypothesis that this endothelial dysfunction is mediated, in part, by reactive oxygen species (ROS), indicating a key pathological role of ROS in complications of pregnancy.

ROS and Pregnancy

Pregnancy itself is known to be a condition of mild oxidative stress. An increase in markers of oxidative stress and a reduction in antioxidant capacity have been noted in samples from women with a healthy pregnancy compared with nonpregnant controls (Morris et al. 1998; Palm et al. 2009; Toescu et al. 2002).

A study of healthy pregnant women throughout gestation determined that pregnancy was associated with a decreased serum total antioxidant capacity compared with nonpregnant controls, which then gradually increased towards term (Toescu et al. 2002). Additionally, studies have noted an increase in lipid hydroperoxides and malondialdehyde (MDA, a product of lipid peroxidation) in both erythrocytes and plasma samples obtained from healthy pregnant women compared with nonpregnant controls (Kaur et al. 2008; Morris et al. 1998).

It has been observed, however, that such markers of oxidative stress are further increased in complicated pregnancies, suggesting a pathophysiological role of ROS. A study by Kaur et al. (2008) observed that the increase in MDA observed in erythrocytes taken from healthy pregnant women was increased further in women with preeclampsia (Kaur et al. 2008). This was also accompanied by a reduction in the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Kaur et al. 2008). A further study observed that other markers of oxidative stress, namely, the concentration of hydrogen peroxide and peroxynitrite, were significantly increased in erythrocytes of women with preeclampsia compared with a normal pregnancy (Dordevic et al. 2008). Additionally, the activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione reductase, was again significantly reduced in women with preeclampsia (Dordevic et al. 2008). A prospective study by Peter Stein et al. (2008) determined urinary excretion of two biomarkers of oxidative stress, namely, 8–oxo–7,8 dihydro–2–deoxyguanosine and 8–iso–PGF2α, markers of DNA and lipid oxidation, respectively (Peter Stein et al. 2008). This study observed that increased excretion of these biomarkers in early gestation (12 weeks of gestation) was associated with a number of complications including preeclampsia, shorter duration of gestation, and a lower birth weight. A study of women immediately following delivery determined that, compared with healthy pregnant women, increased oxidative stress (increased plasma hydroperoxide and carbonyl protein concentrations) and reduced plasma total antioxidant status were associated with women who gave birth to babies born small for gestational age (Saker et al. 2008). It has also been observed that pregnant women with the complication of intrauterine growth restriction demonstrate increased serum markers of oxidative stress (malondialdehyde) and decreased total antioxidant capacity of serum (Karowicz-Bilinska et al. 2007). Finally, a study of women throughout gestation observed that women with pregnancies complicated by diabetes (both preexisting and gestational diabetes) presented with an increased concentration of serum lipid hydroperoxides along with decreased total antioxidant capacity compared with women with a healthy pregnancy (Toescu et al. 2004). These studies together provide evidence that, despite the wide-ranging and multifactorial etiologies of the various complications of pregnancy, an increased production of ROS and/or decreased antioxidant capacity may provide a common pathophysiological mechanism by which increased morbidity/mortality is mediated.

Sources of ROS in the Uterine Circulation

There are a number of sources of ROS in the uterine circulation during either a healthy or a complicated pregnancy (detailed in Fig. 122.1). It has been observed that a healthy pregnancy is associated with a mild systemic inflammatory response, including the activation of leukocytes such as granulocytes and monocytes. When compared with samples from nonpregnant women, it was determined that these cells produced significantly more intracellular ROS (Sacks et al. 1998) and thus may be an important source of ROS in the maternal circulation during pregnancy. This is of importance as pregnancy complications such as preeclampsia are associated with an increased inflammatory response when compared with a healthy pregnancy (Szarka et al. 2010). It was further noted that the ROS-generating capacity of granulocytes and monocytes was significantly increased in samples from women with preeclampsia (Sacks et al. 1998). The increased production of ROS by granulocytes and monocytes obtained from women with preeclampsia has since been noted by other investigators (Gervasi et al. 2001; Lee et al. 2003).

There are also a number of circulating factors which may increase the production of ROS in the uterine vasculature via the activation of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase. These include TNF-α, angiotensin II, and oxidized lipoproteins; their role in mediating uterine artery vascular dysfunction has been previously reviewed (Sankaralingam et al. 2006).

ROS and the Placenta

When investigating the possible pathophysiological roles of ROS during pregnancy, it is important to consider the placenta, an organ, which is subjected to increased oxidative stress during complicated pregnancies. As a result of this insult, circulating factors are produced which are able to not only increase production of ROS in the uterine vasculature but also directly mediate vascular dysfunction (detailed in Fig. 122.1).

It has been demonstrated that NAD(P)H oxidase, which produces superoxide, is present in placental trophoblasts (Matsubara and Sato 2001). A study of placental tissue both early in gestation (11 $\pm$ 1 week), as well as at term, determined significant NAD(P)H oxidase activity at both time points, although activity was significantly higher during the first trimester (Raijmakers et al. 2006). The placenta also contains a high proportion of mitochondria, another important source of superoxide (Jones and Fox 1991; Lenaz 2001). A further source of superoxide is xanthine oxidase; expression of this enzyme in placental tissue was described by Many et al. (1996), and it has been determined that expression levels increase throughout gestation (Many et al. 2000, 1996).

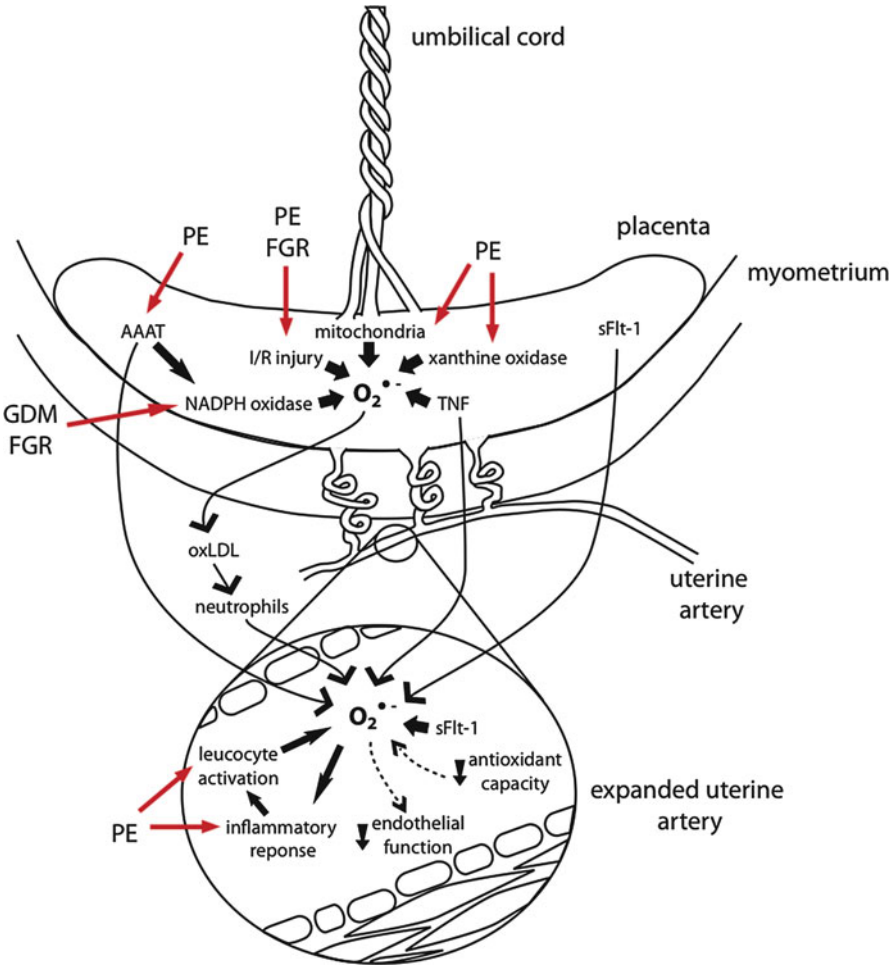

Fig. 122.1 Mechanisms of uterine artery ROS production in healthy and complicated pregnancies. There are numerous sources of ROS in the uterine artery. These include the increased inflammatory response seen during a healthy pregnancy, which results in increased superoxide ($O_2^{\bullet-}$) production. This inflammatory response is further increased in pregnancies complicated by preeclampsia (PE), resulting in a greater production of superoxide. There are also a number of circulating factors, produced by the placenta, which increase production of ROS. These factors include autoantibodies (AAAT), cytokines (TNF), anti-angiogenic factors (sFlt-1) and oxidized lipids (oxLDL). Again, production of these circulating factors may be increased in complicated pregnancies, including PE, gestational diabetes (GDM) and fetal growth restriction (FGR), further exascerbating the production of superoxide. Increased superoxide production may mediate uterine artery dysfunction via the scavenging of nitric oxide and an impairment of EDHF-mediated vasodilation. AAAT = autoantibodies against angiotensin AT (1) receptors, TNF = tumor necrosis factor, sFlt-1 = soluble fms-like tyrosine kinase-1, NAD(P)H oxidase = nicotinamide adenine dinucleotide phosphate oxidase, oxLDL = oxidized low density lipoprotein

There is substantial evidence that placentas associated with complicated pregnancies demonstrate increased oxidative stress. Placentas obtained from women with preeclampsia show increased lipid peroxidation and xanthine oxidase activity (Khong et al. 1986; Walsh et al. 2000). Increased nitrotyrosine residues, an indication of increased production of peroxynitrite, have also been observed in placentas taken from women with preeclampsia (Myatt et al. 1996) and pregestational diabetes (Lyall et al. 1998), suggesting increased superoxide production. Further, a significant increase in a biomarker of cellular oxidative stress, 8–hydroxydeoxyguanosine (8–OHdg; an oxidized nucleoside of DNA), was observed in placentas taken from women following a pregnancy complicated by intrauterine growth restriction, with or without concomitant preeclampsia (Takagi et al. 2004).

It is believed that in complicated pregnancies, such as preeclampsia, abnormal placentation may be the cause of increased ROS production. An important process, which occurs early in pregnancy, is the invasion of the uterine wall and associated arterioles (spiral arteries) by trophoblasts, namely, extravillous cytotrophoblasts. Much of the endothelium and muscular tissue of these arteries are replaced by the invading trophoblasts, generating low-resistance vessels that allow for adequate perfusion of the fetoplacental unit. Many complications of pregnancy, including preeclampsia and fetal growth restriction, are associated with defective trophoblast invasion of the spiral arteries (Khong et al. 1986), leading to a degree of hypoxia- or ischemia/reperfusion-type injury to the placenta (Burton and Caniggia 2001; Hung et al. 2001). This may be one mechanism which leads to an increased production of ROS (Wang and Walsh 2001). There are, however, other possible mechanisms by which increased ROS are produced. It has been noted that an autoimmune antibody to the angiotensin II type 1 receptor develops in women with preeclampsia and is able to mediate NAD(P)H oxidase activation in the placenta (Dechend et al. 2003). The mitochondria are another possible source of superoxide; a detailed study of placentas from women with preeclampsia noted that there was an increased number of mitochondria, which were abnormal in appearance (Jones and Fox 1980). Wang and Walsh (1998) observed a significant increase in mitochondrial protein and the activity of the mitochondrial enzyme, citrate synthase, in placentas of women with preeclampsia (Wang and Walsh 1998). An increase in expression of xanthine oxidase has also been observed in the placentas of women with preeclampsia (Many et al. 2000). Interestingly, the primary activator of this enzyme is ischemia/reperfusion (Hung et al. 2002), a hypothesized event in placentas of pregnancies complicated by preeclampsia; thus, it may be an additional source of superoxide. Regardless of the source, there is evidence of increased production of superoxide in placentas from women with preeclampsia (Sikkema et al. 2001).

One further marker of increased oxidative stress is the formation of lipid peroxides; increased concentrations of both lipid peroxides and their breakdown product, MDA, have been observed in the circulation of women with complicated pregnancies (Karowicz-Bilinska et al. 2007; Kaur et al. 2008; Morris et al. 1998). Lipid metabolism is altered during normal pregnancy, with increases in plasma triglyceride concentrations being observed (Sattar et al. 1997b).

Further, low-density lipoproteins (LDL) are smaller, denser, and more susceptible to oxidation during pregnancy (Winkler et al. 2000), leading to an increased production of oxidized LDL (oxLDL) even during normal pregnancy (Morris et al. 1998). A major site of production of these oxidized lipids is the placenta, from where they may be released into the maternal circulation (Walsh and Wang 1993, 1995). Placental production of oxidized lipids is significantly increased in women with preeclampsia (Walsh et al. 2000; Walsh and Wang 1995), suggesting they may play a role in mediating the pathophysiology of this disorder. Oxidized lipids are potent activators of neutrophils (Gorog 1991; Vaughan et al. 2006), which may then be a further source of ROS in the maternal circulation.

ROS-Mediated Uterine Artery Dysfunction

Given the observations that complicated pregnancies are associated with increased oxidative stress and the ability of ROS to mediate impaired vascular function, either directly or via activation of secondary pathways and the production of circulating factors, the hypothesis that increased production of ROS in complicated pregnancies mediates impaired uterine artery function is an attractive one, and much effort has been expended in investigating this potential mechanism.

Despite their varying etiologies, one common phenotypic feature of complicated pregnancies is abnormal uterine artery function. This may be manifested as abnormal Doppler waveforms (Ozkaya et al. 2007; Papageorghiou et al. 2001), as an increased vasoconstrictor response to pressors (Anderson et al. 2005; Shah 2005; Verlohren et al. 2008), or as impaired endothelium-dependent vasodilation (Anderson et al. 2005; Kublickiene et al. 2000; Verlohren et al. 2008). Many studies of complicated pregnancies have further demonstrated the link between abnormal uterine artery Doppler waveforms and poor obstetrical/fetal outcomes. There are numerous studies that demonstrate a link between reduced uterine artery diameter, reduced uterine artery blood flow, and an increased incidence of preeclampsia and fetal growth restriction (Browne et al. 2011; Julian et al. 2008).

One of the key changes which occurs in the uterine artery during gestation is a reduced pressor response and an increased vasodilator response which have been observed to be endothelium dependent (Nelson et al. 1995, 1998; Weiner et al. 1989b, 1992a; Weiner et al. 1992b). There is considerable evidence that this is mediated, in part, by an increase in nitric oxide (NO) production and/or release in the uterine artery (Magness et al. 1997; Nelson et al. 2000; Weiner et al. 1989a; Xiao et al. 1999). The importance of NO in mediating uterine artery remodeling and maintaining sufficient uteroplacental blood flow has been demonstrated in both women and experimental animal models (Beinder et al. 1999; Di Iorio et al. 1997; Miller et al. 1999; van der Heijden et al. 2005). Given the ability of ROS to scavenge NO, any increase in ROS in the uterine artery would therefore likely significantly impact the pregnancy-related adaptations observed in this circulation in a healthy pregnancy. An association between increased ROS production, impaired uterine artery function and alterations in NO-mediated vasodilation has

been observed in an animal model of complicated pregnancies (Stanley et al. 2011). Similar changes have been observed in women with complicated pregnancies. A study of women at both low and high altitude determined that reduced uterine artery diameter and blood flow, with an associated increase in the endothelin-1 (ET-1)/NO metabolite ratio, occurred before subsequent reductions in fetal growth at high altitude and were likely causative (Julian et al. 2008). The increased ET-1/NO metabolite ratio may be due, at least in part, to both scavenging of NO by ROS and increased ROS-mediated ET-1 production by the placenta (Fiore et al. 2005). This would result in a change in the balance of vasoconstrictors/vasodilators, tipping towards increased vasoconstriction. This is further supported by the smaller uterine artery diameter and lower blood flow seen in the high- vs. low-altitude women (Julian et al. 2008). However, the relationship between NO and ET-1 is more complex than just that of opposing vasodilator/vasoconstrictor actions. Studies have demonstrated that NO is able to significantly modulate the ET-1 pathway in a number of ways, which have been recently reviewed (Bourque et al. 2011). Scavenging of NO by ROS, therefore, may not only reduce NO-mediated vasodilation but may also reduce its inhibitory effects on the ET-1 pathway, leading to further vasoconstriction.

Although studies of uterine artery function have largely concentrated on alterations in NO-mediated vasodilation, there are other mediators of endothelium-dependent relaxation, including endothelium-dependent hyperpolarizing factor (EDHF). Studies of myometrial arteries from nonpregnant women indicate that endothelium-dependent relaxation is mediated largely by NO; in comparison, those from healthy pregnant women demonstrate a significant contribution of EDHF (Kenny et al. 2002). This increased contribution of EDHF, however, was not observed in arteries from women with preeclampsia (Kenny et al. 2002). A more recent study observed that EDHF responses in myometrial arteries from healthy pregnant women were mediated primarily through myoendothelial gap junctions; this pathway was negligible in arteries from women with preeclampsia (Luksha et al. 2010). Given that animal studies have demonstrated the ability of superoxide to impair EDHF-mediated relaxation (Leo et al. 2011; Ma et al. 2008), this may be one further mechanism by which increased ROS directly impairs uterine artery function in complicated pregnancies. Interestingly, Luksha et al. (2010) did note an increased contribution of hydrogen peroxide to the remaining reduced EDHF-type response observed in arteries from women with preeclampsia (Luksha et al. 2010). This partly compensated for the loss of relaxation mediated by myoendothelial gap junctions, highlighting that, on occasion, ROS are able to perform beneficial roles in the vasculature.

ROS, Circulating Factors and Uterine Artery Dysfunction

As stated previously, increased production of ROS in the placenta may indirectly mediate uterine artery dysfunction via the production of circulating factors. An increased production of placental ROS results in an increased production of factors,

including oxLDL in placentas of women with complicated pregnancies; these are then secreted into the maternal circulation. It has been observed that complications of pregnancy are associated with a significant increase in circulating levels of oxLDL (Hubel et al. 1998; Sattar et al. 1997a). oxLDL may bind to the lectin-like oxidized LDL receptor-1 (LOX-1), a type II membrane protein cell surface receptor which is expressed on endothelial cells (Sawamura et al. 1997). The binding of oxLDL to LOX-1 is associated with an excess production of superoxide via activation of NAD(P)H oxidase (Cominacini et al. 2001) and may be a further mechanism by which uterine artery dysfunction is mediated. This hypothesis is supported by recent evidence which demonstrated increased LOX-1 expression in the maternal vasculature of women with preeclampsia (Sankaralingam et al. 2009) and in an experimental model of preeclampsia of reduced placental perfusion (Morton et al. 2012).

While increased uterine artery vasodilation plays a crucial role in ensuring adequate placental perfusion, remodeling of the uterine circulation should not be ignored. This remodeling involves a number of cellular processes and mechanisms, which include trophoblast invasion, changes in extracellular matrix composition, hyperplasia, and hypertrophy; impaired uterine artery remodeling is observed in a number of complications of pregnancy (Brosens et al. 2002; Ong et al. 2005). Studies in rodent models, such as the endothelial nitric oxide synthase knockout ($eNOS^{-/-}$) mouse and rats treated with an NOS inhibitor, suggest that NO plays an important role in mediating uterine artery remodeling (Osol et al. 2009; van der Heijden et al. 2005). Given the ability of ROS to scavenge NO, it is likely that the increased oxidative stress observed in complicated pregnancies may adversely affect the normal remodeling response observed in a healthy pregnancy.

Studies have also begun to link changes in the production of placental angiogenic factors to maternal vascular dysfunction in complicated pregnancies. Noori et al. (2010) observed that increased serum levels of the antiangiogenic factors soluble endoglin and soluble fms-like tyrosine kinase-1 (sFlt-1) correlated with an increased uterine artery pulsatility index and reduced flow-mediated dilation of the brachial artery in women who subsequently developed preeclampsia (Noori et al. 2010). Increases in sFlt-1 concentration have been associated with increased production of superoxide by NAD(P)H oxidase (Tam Tam et al. 2011) and may, therefore, be a further stimulant of ROS-mediated uterine artery dysfunction.

ROS and the Inflammatory Response

Uterine artery dysfunction may also be partly mediated by ROS as a consequence of an increased inflammatory response. As previously discussed, the increased inflammatory response observed in complicated pregnancies may be one source of ROS. In turn, ROS may play a role in mediating the inflammatory process. Vascular inflammation has been observed in women with preeclampsia; infiltration of neutrophils has been observed in the maternal systemic vasculature of women with preeclampsia and was accompanied by a significant increase in markers of

inflammation such as nuclear factor-kappa B, COX-2, and IL-8 (Leik and Walsh 2004; Shah and Walsh 2007). A study by Walsh et al. (2009) observed that plasma from women with preeclampsia was able to significantly increase IL-8 production and induce transendothelial neutrophil migration in an endothelial cell-line in vitro. Both of these effects were inhibited following pretreatment with an antioxidant (vitamins C and E) (Walsh 2009), suggesting a role for ROS in mediating, at least in part, the endothelial dysfunction resulting from an inflammatory response. These data further support the feed-forward progression of ROS-mediated vascular dysfunction.

Endogenous Antioxidants and Antioxidant Therapy

The production of ROS is a normal, physiological cellular process which often occurs as a by-product of cellular energy production; oxidative stress, however, results from an imbalance between increased ROS formation and defects in antioxidant defense mechanisms. As discussed above, normal pregnancy is a state of mild oxidative stress, which is associated with a decrease in serum total antioxidant capacity (Toescu et al. 2002). There is conflicting evidence, however, to support the hypothesis that decreased antioxidant capacity contributes to the increase in oxidative stress observed in complicated pregnancies. One study, which examined blood samples from women with either a healthy pregnancy or with PE, observed increased antioxidant enzyme activity in erythrocytes from women with PE (Llurba et al. 2004). Other studies, however, have observed a decrease in circulating levels of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, in women with PE compared with healthy pregnant controls (Madazli et al. 2002; Sharma et al. 2006). Additionally, it has been observed that a decrease in plasma total antioxidant status may persist in women with a history of preeclampsia compared with nonpregnant women (Ozan et al. 2002). Conversely, endogenous antioxidants may play a protective role in other complicated pregnancies. It has been observed that increased maternal antioxidant enzyme activity may confer protection against altitude-associated decreases in birth weight in the Andean population (Julian et al. 2012).

Given the possible role increased oxidative stress may play in mediating the pathology of complicated pregnancies, it is perhaps unsurprising that antioxidants have been considered as a possible therapeutic option. There is evidence from animal studies that antioxidants may have a therapeutic benefit. Hoffmann et al. (2008) demonstrated that treatment with Tempol, a superoxide dismutase mimetic, was able to normalize placental ROS levels, ameliorate increased maternal blood pressure and proteinuria, and improve fetal growth and survival in a mouse model of preeclampsia, the BPH5 mouse (Hoffmann et al. 2008). The ability of Tempol to improve fetal growth has also been observed in a different mouse model of FGR, the eNOS$^{-/-}$ mouse (Stanley et al. 2012); there were, however, also signs that Tempol treatment may adversely affect placental vascular development. Other antioxidants have been also proven to be beneficial in animal models of complicated pregnancy. For instance, Richter et al. (2012) observed that vitamin C prevents placental

oxidative stress and increases birth weight following a hypoxic pregnancy in rats (Richter et al. 2012). Melatonin, which is able to scavenge free radicals and upregulate antioxidant pathways, has also been observed to improve placental efficiency and improve fetal growth in a rat model of undernourished pregnancy (Richter et al. 2009). It was also able to increase umbilical artery blood flow and improve fetal growth in an ovine model of FGR (Lemley et al. 2012).

One of the difficulties in developing new therapeutic treatments for complications of pregnancy is the potential risk unknown pharmacological entities may pose to both mother and child. Supplementation with dietary factors that have antioxidant capacity, such as vitamins C and E, is therefore an attractive option. One of the largest studies of antioxidants in pregnancy is the Vitamins in Pre-eclampsia (VIP) Trial, which aimed to determine the effects of the antioxidant vitamins C and E on women at risk for PE. This study found that supplementation with vitamins C and E did not prevent the development of PE but did increase the rate of babies born with a low birth weight (Poston et al. 2006). Combined vitamin C and E therapy has been the most trialed antioxidant therapy in a bid to prevent the development of PE. However, a systematic review of the use of antioxidants in preventing the development of PE concluded that there was no evidence to support routine antioxidant supplementation to reduce the risk of PE or other serious complications of pregnancy (Rumbold et al. 2008).

Although data from animal models suggest antioxidant treatment may be a possible therapeutic option for complicated pregnancies, evidence from both animal and clinical trials demonstrate that antioxidant supplementation may also have detrimental effects on both placental and fetal development; as such further studies should proceed with caution.

Conclusions

The uterine artery, and its subsequent remodeling and altered response to vasoactive mediators during pregnancy, plays a crucial role in facilitating a successful pregnancy. There is considerable evidence that ROS play a crucial role in mediating uterine artery dysfunction in complicated pregnancies, either directly or via activation of secondary pathways. Moreover, feed-forward mechanisms may ensue whereby ROS-mediated vascular dysfunction is further exacerbated until delivery of the placenta (which at this time is the only definitive treatment for preeclampsia). Thus, ROS remain an attractive, if challenging, therapeutic target by which to reduce maternal and fetal morbidity and mortality.

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