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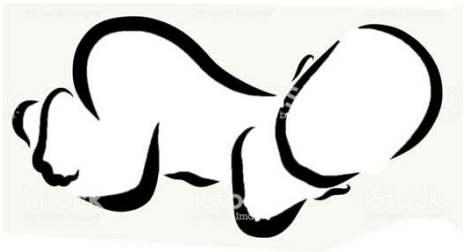
DIABETIC PREGNANCY
MICROVASCULAR COMPLICATIONS (HYPERTENSION, NEPHROPATHY, RETINOPATHY, PERIPHERAL NEUROPATHY)

MATERNAL COMPLICATIONS
Preeclampsia, gestational hypertension, preterm birth

METABOLIC ALTERATIONS
Oxidative & Nitrosative stress
Hyper/Hypoglycemia
Chronic hypoxia



FETAL AND NEONATAL COMPLICATIONS
Congenital malformations, intrauterine hypoxia, stillbirth, abnormal growth, impaired cognitive function

Free Radical Biology & Medicine

Fetal chronic hypoxia and oxidative stress in diabetic pregnancy

Could fetal erythropoietin improve offspring outcomes?

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Conflicts of interest

The authors of this manuscript declare not having anything to disclose.

Key words

Fetus, chronic hypoxia, oxidative stress, diabetes mellitus, pregnancy, erythropoietin

Abstract

Oxidative stress is responsible for microvascular complications (hypertension, nephropathy, retinopathy, peripheral neuropathy) of diabetes, which during pregnancy increase both maternal and fetal complications. Chronic hypoxia and hyperglycemia result in increased oxidative stress and decreased antioxidant enzyme activity. However, oxidative stress induces also anti-oxidative reactions both in pregnant diabetes patients and in their fetuses. Not all type 1 diabetes patients with long-lasting disease develop microvascular complications, which suggests that some of these patients have protective mechanisms against these complications. Fetal erythropoietin (EPO) is the main regulator of red cell production in the mother and in the fetus, but it has also protective effects in various maternal and fetal tissues. This dual effect of EPO is based on EPO receptor (EPO-R) isoforms, which differ structurally and functionally from the hematopoietic EPO-R isoform. The tissue protective effects of EPO are based on its anti-apoptotic, anti-oxidative, anti-inflammatory, cell proliferative and angiogenic properties. Recent experimental and clinical studies have shown that EPO has also positive metabolic effects on hyperglycemia and diabetes, although these have not yet been fully delineated. Whether the tissue protective and metabolic effects of EPO could have clinical benefits, are important topics for future research in diabetic pregnancies.

Introduction

Diabetes during pregnancy increases complications in the mother, the fetus and the newborn infant. Pregnancies in women with type 1 or type 2 diabetes have the most frequent and serious complications, but similar complications, although less frequent and less serious, occur also in women with gestational diabetes. Typical maternal complications in diabetic pregnancies are preeclampsia, gestational hypertension and preterm birth while congenital malformations (MF), intrauterine hypoxia, stillbirth and abnormal growth are common fetal complications. It is not quite clear whether these complications have a common background in diabetic pregnancies. In this review we discuss the possible roles of chronic hypoxia and oxidative stress in the pathogenesis of maternal and fetal complications in diabetic pregnancies.

Oxidative stress in diabetic pregnancy

Perinatal morbidities and mortality in type 1 diabetic pregnancies have remained relatively unchanged over the past 20 years. This bears out the fact that the precise mechanisms that cause the

type 1 diabetes related conditions have not yet been clearly established nor taken into account in the clinical practice [1]. Nevertheless, the influence of the oxidative stress, understood as an imbalance in the redox steady states, have proved to be a determining factor in type 1 diabetes related metabolic pathways. Hyperglycemia results in increased production of reactive oxygen species (ROS) through different abnormal metabolic pathways [2]. The most common ROS in human biology consist of superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide and proxy nitrite. While on the one hand both chronic hypoxia and high glucose levels result in increased oxidative stress, on the other hand it decreases antioxidant enzyme activity and impairs the endogenous antioxidant defense system [3]. This triggers a range of reactive molecules that can produce cellular damage by free radicals and includes lipid peroxidation and nitration, protein-thiol depletion, nucleic acid hydroxylation and nitration, DNA strand breakage and DNA adduct formation [4] and formation of ROS [5,6]. Furthermore, hyperglycemia causes an overproduction of advanced glycation end-products (AGE) and activates hexosamine biosynthesis [7]. Oxidant overproduction can ensue from either enhanced engagement of Nicotinamide adenine dinucleotide phosphate (NAPH) oxidase through an Angiotensin II type 1 receptor (AT1R)-mediated event or excessive mitochondrial oxidant production due to an energy surplus [8]. Consequently, both NAD synthesis and rebuilding of glutathione (GSH) by GSH reductase are reduced. The oxidants can be activated, at least in part, through various metabolic pathways such as polyol pathway, protein kinase C pathway and p38-MAPK pathway and other stress-activate kinases dependent mechanism (including JUNK, GSK-3β and potentially IKK-β) [9–11]. Finally under a pro-oxidant status, a series of redox-sensitive transcription factors such as fetal NFκB, activator protein-1 (AP-1), HIF-1α and insulin signaling factors that regulate GLUT-4 translocation become activated ultimately reducing the capacity for insulin-dependent glucose transport activity [12].

Erythropoietin (EPO), in addition to its regulation of erythropoiesis, has also anti-oxidative properties by acting anti-apoptotic and by being a potent scavenger of the hydroxyl, 2,2-diphenyl-1-picrylhydrazyl and peroxyl radicals [13]. EPO also stimulates vasculogenesis by increasing the number of endothelial cells [13]. Angiogenesis is stimulated by low oxygen tissue content and regulates expression of EPO, vascular endothelial growth factor (VEGF), placental growth factor (PGF), and angiopoietins 1 and 2 [14]. Prolonged hypoxia is known to be the major stimulus of EPO production in the fetus [15]. In a study by Escobar et al, biomarkers of oxidative and nitrosative stress in amniotic fluid (AF) clearly correlated with AF concentration of EPO in type 1 diabetic or insulin-treated gestational diabetes pregnant women [16]. Since EPO is not stored and does not cross the placenta, elevated concentration of EPO in fetal plasma and AF reflect EPO

synthesis and elimination, and significantly correlate with the intensity and duration of hypoxia [15,17]. Hence, under maternal metabolic stress fetuses experience prolonged hypoxia with the subsequent inherent risks [18].

Metabolic roles of erythropoietin

In addition to the regulation of erythropoiesis and its tissue protective properties [19], EPO effects also glucose metabolism. EPO decreases blood glucose levels both in non-diabetic human subjects and in rodents with diabetes [20,21]. Recombinant human EPO (rHuEPO) prevents diabetes in mice by promoting anti-apoptosis, anti-inflammation, cell proliferation and angiogenesis in pancreatic β-cells [22,23]. EPO-receptors (EPO-R) are present both in human and rat pancreatic islets [24], which suggests that EPO can protect β-cells from apoptosis and possibly even prevent diabetes [25]. Experimental studies in rodents have shown that EPO reduces insulin resistance via regulation of EPO-R-mediated signaling pathways [20,26]. EPO-R in proopiomelanocortin (POMC) neurons in the hypothalamus regulate food intake and energy expenditure both in rodents and in humans [22,27]. During hypoxia glucose metabolism is regulated via POMC neurons [28]. EPO-Rs are highly expressed in these neurons, which suggests that EPO has several favorable effects on hyperglycemia [22,27]. EPO also decreases inflammation in white adipose tissue in animal models and normalizes insulin sensitivity in humans [22].

Maternal complications

The pathogenesis of diabetic microvascular complications is extremely complicated involving several different pathways resulting in oxidative stress and ROS formation [2]. Hypertension, diabetic nephropathy and/or retinopathy are especially important complications in pregnant diabetic women, because of potential serious complications to the fetus and the newborn infant.

Diabetic hypertension

Maternal and fetal endothelial dysfunction have been evidenced in type 1 and in type 2 diabetes, and also in gestational diabetes [29,30]. One of the most common disorders associated with hypertensive state during pregnancy is preeclampsia responsible for severe perinatal morbidity. The production of various mediators implying the cardiovascular and renal systems such as

inflammatory factors (e.g. TNF-α, IL-6), AT1R and ROS perturb the vascular homeostasis and mediate endothelial dysfunction in pregnant women [31]. Furthermore, nitrosative stress increase nitration of proteins in pregnant women with gestational diabetes, leading to endothelial and vascular dysfunction both in placental vessels and in the umbilical vasculature [32]. These changes together with maternal metabolic alterations in glucose, fatty acid, amino acid and placental ion transport mechanisms contribute to enhancing fetal hypoxia and acidosis and may lead the fetus into a catabolic state with deleterious postnatal consequences.

Diabetic nephropathy

Hyperglycemia, duration of diabetes and hypertension are risk factors for diabetic nephropathy. Several studies have shown that improvement of glucose control will decrease the development of diabetic nephropathy [33,34] but presently there are no known methods that could cure or prevent diabetic nephropathy. Both experimental and human studies suggest that hyperglycemia and renal hypoxia are the leading causes of diabetic nephropathy [35]. Mechanisms by which hyperglycemia can cause renal damage have recently been described [36]. Briefly, hyperglycemia can cause activation of vasoactive, inflammatory and fibrotic cytokines, increase formation of ROS and AGE, which all can decrease renal function, cause renal structural damage and finally lead to end-stage renal disease.

Antioxidants prevent or ameliorate hyperglycemic unfavorable effects in the kidneys and vascular endothelium in experimental diabetes [37,38]. Interestingly, not all diabetics with a long-lasting duration of the disease develop microvascular complications [39]. The Joslin Medalist Study has revealed that occurrence of diabetic nephropathy or retinopathy did not correlate with glycemic control in some diabetic patients over a long period of time in contrast to the majority of diabetics with a much shorter duration of the disease [40]. This suggests that some of the type 1 diabetics have protective mechanisms against development of diabetic nephropathy [36]. Both *in vitro* and *in vivo* experimental studies have shown that high glucose results in ROS generation in renal tubular cells and that EPO can prevent this ROS generation [41]. A more recent study has shown that exogenous EPO has protective renal effects in type 2 diabetes mellitus patients with diabetic nephropathy [42]. However, the authors of a recent meta-analysis concluded that exogenous EPO or other erythropoiesis stimulating agents did not delay the progression of nephropathy [43].

Diabetic retinopathy

Hypoxia induces EPO expression in the retina [44] and exogenous EPO administration protects retinal neurons from acute ischemia-reperfusion injury [45]. High concentration of EPO has been observed in the vitreous fluid of patients with diabetic retinopathy [46]. This has led to controversy whether high levels of EPO in the eye of diabetes patients with proliferative retinopathy is a pathogenic cause of diabetic retinopathy [47] or whether these high levels of EPO is a compensatory neuroprotective mechanism of the retina [48]. Importantly, both preclinical and clinical studies suggest that EPO may actually have beneficial effects on diabetic proliferative retinopathy [49].

The placenta in diabetic pregnancies

Previous studies have suggested that fetal complications in type 1 diabetic pregnancies are mainly a result of placental structural abnormalities and function [50,51]. However, a recent study using more sophisticated methods, found only minimal structural differences between placentas of type 1 diabetic and healthy non-diabetic pregnancies [52]. Importantly, villous surface area, placental capillary surface area and villous membrane thickness were not altered in type 1 diabetic pregnancies. It is very unlikely that the increased frequency of fetal chronic hypoxia in diabetic pregnancies is caused by placental structural changes with the exception of fetal intrauterine growth restriction caused by diabetic nephropathy and/or hypertension.

Fetal and neonatal complications

Congenital malformations

Congenital malformations are 3-4 times more frequent in type 1 diabetic pregnancies than in normal pregnancies [53,54]. Although poor glycemic control (high HbA_{1c} levels) during the first trimester of pregnancy is associated with an increased risk of fetal MF [54], the exact pathogenetic mechanism of fetal MF is not well understood. Most likely the pathogenesis of fetal MF is multifactorial, including hyperglycemia, hypoxic and endoplasmic stress, which induce oxidative stress and increased production of ROS (for review see Eriksson and Wentzel 2015) [55].

Abnormal fetal growth

Fetal overgrowth is the most common fetal complication in type 1 diabetic pregnancies with high frequencies of birth weights over 2 SD-units above the mean of the background population [1,56]. Chronic fetal hyperinsulinemia in euglycemic Rhesus monkeys results in fetal overgrowth and organomegaly [57]. Fetal birth weight z-scores correlate directly with fetal insulin levels [58] and with fetal EPO levels [59], which indicates that fetal overgrowth is often associated with chronic fetal hypoxia. Small-for-gestational age fetuses occur less frequently in pregestational diabetic pregnancies compared with the general population, because relative birth weights are shifted to the right also among growth restricted fetuses [60]. However, amniotic fluid EPO levels correlate with birth weight z-score in a U-shaped fashion in type 1 diabetic pregnancies [59]. Amniotic fluid EPO correlates negatively with birth weight z-score below -0.6 SD-units, which implies that these newborn infants are actually growth restricted and at risk of chronic hypoxia.

Perinatal mortality

Perinatal mortality is presently 4-5 times higher in both type 1 and type 2 diabetic pregnancies than in the general populations [61,62]. Pregestational diabetes is an independent risk factor for late stillbirths [63]. Before fetal electronic surveillance methods were available, stillbirths increased linearly during the last weeks of type 1 diabetic pregnancies reaching 20% at 40 weeks of gestation [64]. It can be assumed that the basic factors for the tendency of increasing stillbirths towards the end of type 1 diabetic pregnancies, although poorly understood, have not disappeared. Approximately half of the stillbirths in these pregnancies occur before 30 weeks of pregnancy [18]. These stillbirth fetuses are in most cases growth restricted due to maternal hypertension and/or diabetic nephropathy, which suggests placental insufficiency (decreased nutrients and oxygen to the fetus) as the etiologic factor. In contrast, after 35 weeks of gestation stillbirth fetuses are usually overgrowth, but unexpected stillbirths occur also among normal weight fetuses [18]. The etiology of late stillbirths in diabetic pregnancies is most likely chronic intrauterine hypoxia caused by fetal hyperglycemia and hyperinsulinemia as indicated by high amniotic fluid and fetal plasma EPO levels [59,65].

Chronic fetal hypoxia

Chronic hypoxia is associated with oxidative and nitrosative stress. The fetus can adapt to reductions in oxygen delivery without life-threatening damage but with reduced somatic growth [66]. Interestingly enough, fetal oxygen delivery is the same but the glucose transfer to the fetus is

decreased resulting in fetal hypoinsulinemia and increased fetal lactate levels [67]. Nonetheless, under these circumstances the fetus becomes increasingly hypoxic and acidotic due to the increased anaerobic metabolism of glucose, and the fetus can enter into a catabolic state with long-term postnatal consequences [68].

Hyperinsulinemia during constant glucose concentration increases glucose oxidation and a fall in the arterial oxygen content both in adult human and experimental fetal sheep studies [69,70]. Moreover, hyperinsulinemia in the fetal sheep increases blood flow to the carcass but decreases blood flow to the placenta, which further enhances fetal hypoxia [71]. Hyperglycemia in fetal sheep results also in increased oxygen consumption, in a decrease in arterial oxygen content and in an exponential increase in fetal EPO concentration [72]. A similar exponential increase in fetal EPO concentration at birth was observed in type 1 diabetes pregnancies when umbilical artery pO_2 fell below 2.0 kPa [59].

Increased fetal plasma and amniotic fluid levels of EPO are observed in approximately 14% of type 1 diabetic pregnancies [59], which gives further evidence that fetal chronic hypoxia often complicates these pregnancies. There are multiple maternal and fetal factors that can cause alone or in combination fetal hypoxia, and ultimately fetal demise in diabetic pregnancies. High HbA_{1c} concentration shifts the maternal oxyhemoglobin dissociation curve to the left, which hampers oxygen delivery to the fetus. During maternal ketoacidosis the oxygen delivery to the fetus is even further reduced, especially during the recovery period, explaining the high stillbirth rate during maternal ketoacidosis [73]. Ante- and intrapartum fetal heart rate changes, cord blood acidosis at birth and low Apgar scores, all associated with fetal hypoxia, occur more frequently in type 1 diabetic pregnancies, especially in women with poor glycemic control, than in non-diabetic pregnancies [56,74–76]. It is possible that placental abruption is more common among diabetic pregnancies, at least in pregnancies with large-for-gestational fetuses [77].

The fetus adapts to chronic hypoxia by redistributing its cardiac output in order to maintain adequate blood flow to the brain and heart and by increasing its EPO synthesis in order to increase its red cell production and oxygen-carrying capacity of blood.

Prolonged hypoxia triggers the activation of transcription factor HIFs in several fetal tissues. This master regulator of hypoxia response is a heterodimeric transcription factor comprising of HIF1α and HIF-1β subunits. In the presence of oxygen, the enzyme prolyl hydroxylase modifies HIF1α in proline sites within two oxygen-dependent degradation domains. This modification in HIF1α facilitates the ubiquitination for its degradation by the proteasome [78]. Under conditions of

hypoxia, the enzyme proline hydroxylase is unable to modify HIF1α, which is translocated to the nucleus where it binds to the hypoxia response elements (HREs) in the regulatory region of a number of genes, and stimulates the transcription of the *Vefg* gene and *Epo* genes and other hypoxia response genes [79].

In addition to regulating erythropoiesis, EPO has tissue-protective properties and repairing effects [19,80]. The tissue-protective effect of EPO is a result of EPO-R isoforms, which differ structurally and functionally from the erythropoietic EPO-R isoform. EPO levels needed for tissue-protection are 100-1000 times greater than EPO levels needed for erythropoiesis [19]. Local EPO synthesis has also been shown to take place in the fetal brain [81], which is another adaptive fetal response against hypoxia. Exogenous rHuEPO crosses the blood-brain barrier in concentrations known to cause tissue protection in the fetal sheep [82]. In asphyxiated newborn infants high EPO levels in the cerebrospinal fluid correlate with simultaneously obtained neonatal plasma EPO levels [83]. Exponential increases in amniotic fluid EPO concentrations have been shown in pregnancies complicated by hypertension or type 1 diabetes [59,84]. Over 10,000 mU/ml EPO plasma concentrations have been measured in the cord blood at birth of asphyxiated newborn infants [84]. Although the exact reason for these high fetal EPO concentrations are unknown, we have hypothesized that the fetus increases its EPO synthesis during chronic hypoxia in order to protect its brain and other vital organs against deleterious effects of hypoxia [85].

Fetal iron deficiency

Iron is mandatory to fetal metabolism, energy production, and brain function. Newborn infants of diabetic mothers have often low ferritin levels and abnormal iron distribution at birth as a result of chronic intrauterine hypoxia [86,87]. Iron stores in the liver, heart and brain are almost totally depleted in fetuses who die *in utero* after 35 weeks in diabetic pregnancies [88]. This indicates that fetal death has been preceded by a prolonged period of fetal hypoxia, which results in increased production of red cells, for which iron stores are preferentially used for hemoglobin synthesis. Fetal and neonatal iron deficiency has long-term negative effects on cognitive and behavioral scores later in life [86,89].

Necrotizing enterocolitis of the newborn infant

Fetal hypoxia and birth asphyxia are associated with gut injury, impaired intestinal motility and necrotizing enterocolitis (NEC), especially in the preterm newborn infant [90,91]. In neonatal rat models, exogeneous EPO stimulates vasculogenesis of microvascular endothelial intestine cells and protects intestinal cells from NEC [92,93]. The fetus swallows up to 700 ml of amniotic fluid each day towards the end of pregnancy [94], although the reason for this is not well understood. One possibility could be that EPO and other cytokines in the amniotic fluid could exert protective effects locally in the fetal and neonatal intestine and hence improve neonatal feeding tolerance and prevent NEC [85,95].

Adolescent cognitive function after intrauterine exposure to diabetes

Maternal pre-conceptional and gestational control of hyperglycemia have relevant implications on short- and long-term offspring neurodevelopment [96]. Brain maturation is characterized by a pre-established sequence of complex biological processes that encompass from the early embryonic period to late adolescent and young adulthood [97]. However, there is a large number of potential adverse factors during pregnancy that may inevitably alter brain maturation pattern. Among others, maternal obesity [98], prenatal famine [99], maternal infections [100], or insulin dependent diabetes [89] have been associated in epidemiological studies with neurocognitive impairment. Moreover, hyperglycemic intrauterine environment, hypoglycemia or ketoacidosis may directly exert a harmful effect upon the fetal brain. Finally, negative conditions associated with diabetic pregnancy such as prematurity or preeclampsia, also put the fetus at high risk of severe complications [101]. Recent studies have shown that infants born to diabetic mothers exhibited significantly higher mortality, hospital admissions and use of medications to the age of 15 [102]. In addition, intellectual assessment scales for the outcomes such as composite intelligence, verbal and nonverbal intelligence, composite memory, reading and writing difficulties, and attendance to classes showed a significant lower scoring for normalized and standardized intelligence indices among offspring of diabetic mothers as compared with controls [97,103,104]. However, no correlation with mothers' glycated hemoglobin was found suggesting that maternal diabetes despite being adequately controlled has a negative impact on the neurodevelopment of the offspring [96]. But it can also be argued that "adequately controlled" was not adequate enough to prevent intrauterine negative effects.

The pathophysiological explanation of impaired cognitive functions has not been fully clarified. During fetal life, the predominant source of brain energy is glucose, which crosses the placenta by

facilitated diffusion [105]. Maternal diabetes is associated with continuous fluctuations of *in utero* blood glucose levels but also with disturbances in fatty acid metabolism with a decreased transfer of docosahexaenoic acid to the fetus [106]. Docosahexaenoic acid accumulates in the brain especially in the third trimester and is essential for neurogenesis, neurotransmission, and protection from oxidative stress. Reduced bioavailability of this key metabolite has been suggested as a putative mechanism for programming altered neurodevelopment [106,107]. In addition, induced oxidative stress by hyperglycemic environment causes damage to the blood-brain barrier contributing to the infiltration of macrophages and pro-inflammatory cytokines. Altogether, these processes cause neuroinflammation, brain damage and contribute to neuronal cell death and long-term brain dysfunction [108].

Conclusions

Oxidative stress is the likely common etiologic factor of microvascular complications of diabetes. Both pregestational and gestational diabetes increase complications in the mother, the fetus and the newborn infant, which can have long-lasting negative effects in the offspring later in life. Maternal hyperglycemia results in fetal hyperglycemia, which leads together with fetal hypoxia to increased oxidative stress and decreased antioxidant activity. Oxidative stress induces also anti-oxidative reactions both in pregnant diabetes patients and their fetuses. In this review we discuss the possible roles of chronic hypoxia and oxidative stress in the pathogenesis of maternal and fetal complications in diabetic pregnancies. Fetal EPO, besides regulating hematopoiesis, has also fetal tissue protective effects, which are based on EPO's anti-apoptotic, anti-oxidative, anti-inflammatory, cell proliferative and angiogenic properties. More recent studies have shown that EPO has also positive metabolic effects in diabetic patients and in non-diabetic individuals. Whether the tissue protective and metabolic effects of EPO could be used clinically to prevent or delay the occurrence of diabetic complications both in the mother and her offspring, are important topics for future research on diabetic pregnancies.

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Legend to Figure:

Microvascular complications of diabetes during pregnancy (hypertension, nephropathy, retinopathy, peripheral neuropathy) are associated with maternal complications (preeclampsia, gestational hypertension, preterm birth) as well as with fetal and neonatal complications (congenital malformations, intrauterine hypoxia, stillbirth, abnormal growth, impaired cognitive function later

in life). Oxidative and nitrosative stress, hyperglycemia, hypoglycemia and chronic hypoxia can further modulate maternal and fetal complications during diabetic pregnancy.

Highligths

- Maternal hyperglycemia and fetal hypoxia result in increased oxidative stress
- Increased oxidative stress triggers cellular damage by free radicals in the fetus
- Erythropoietin has both hematopoietic and tissue protective properties in the fetus
- Studies have shown that erythropoietin has positive metabolic effects on diabetes
- Weather erythropoietin has clinical benefits for the offspring needs more studies