Placenta 52 (2017) 41–48

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Effect of glucocorticoids on mechanisms of placental angiogenesis

Aslı Ozmen, Gozde Unek, Emin Turkay Korgun*

Department of Histology and Embryology, Medical Faculty, Akdeniz University, 07070 Antalya, Turkey

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
8 February 2017
Accepted 13 February 2017

Keywords:
Glucocorticoids
Placenta
Angiogenesis
Human
Rat

ABSTRACT

The benefits of antenatal glucocorticoid (GC) treatment to promote human fetal lung maturation are well established. However, reports have emerged indicating that maternal exposure to high concentrations of circulating GCs alters placental and fetal development. Because many adult-onset metabolic and cardiovascular disorders have their origins in utero, the importance of prenatal conditions should be considered in detail. Therefore, this review aims to present an overview of the GC effect on placental and fetal development, specifically with regard to mechanisms of placental angiogenesis.

We assumed that GC overexposure affects fetal development by altering placental angiogenesis. Disturbances in the development of the villous tree and pathological changes in the villous vascular system with insufficient uteroplacental blood flow have been linked to the pathogenesis of intrauterine growth retardation. Moreover, low birth weight is a serious risk factor known to correlate with an increased risk of adult-onset diseases. Although there have been many circumstances in which maternal GCs are elevated, we focused on exogenous synthetic GCs that are applied for therapeutic reasons. However, some questions about the use of steroids remain unanswered, which will require further studies that lead us to review alterations in placental angiogenesis under the perspective of GC overexposure.

1. Introduction

There is a growing body of evidence suggesting that prenatal life can have long-lasting effects on the developing fetus and adult health [1]. Changes in placental growth represent an important link between disorganizations in the maternal compartment, such as reduced placental blood flow and alterations in fetal growth. Indeed, placental growth appears to provide information about the long-term outcome of the baby [2].

During pregnancy, the fetus may be exposed to exogenous glucocorticoids (GCs) resulting from maternal conditions such as allergy, asthma [3], or autoimmune disease such as systemic lupus erythematosus [4] or under the risk of preterm delivery caused by several underlying reasons such as preterm premature rupture of membranes [3], intraventricular hemorrhage, and periventricular leukomalacia [5]. Preterm infants, especially those born before 32 weeks' gestation, are at high risk of respiratory distress syndrome (RDS), a serious complication that remains the primary cause of early neonatal death and disability [6]. The Cochrane review "*Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth*" showed that a single course of antenatal corticosteroids significantly reduced the incidence of RDS [7]. In the fetal lung, the action of corticosteroids leads to an increase in the protein production, biosynthesis of phospholipids, and appearance of surfactant [8]. Corticosteroids have become the standard of care for women at risk of preterm birth before 32–34 weeks' gestation in many countries [9,10]. Despite their widespread use, there is currently variation in clinical practice regarding the type of corticosteroid used, the dose and frequency given, and the route of administration of corticosteroid doses.

Clinical trials have demonstrated that increasing the number of GC courses leads to adverse outcomes in fetal development, which includes the programming of postnatal hypertension and of increased postnatal activity in the HPA axis, effects on fetal brain development, which is associated with alterations in pre- and postnatal behavior [11],and reductions in birthweight with no additional benefit to the fetus [12,13]. This implies that low birth weight is a serious risk factor known to correlate with an increased risk of adult-onset diseases, such as hypertension, ischemic heart disease, and insulin resistance [14].

To explain the association between prenatal environments, altered fetal growth, and lifespan effects, the "programming" phenomenon is proposed [15–17]. "Programming" or "imprinting" reflects the action of a factor during a sensitive period that affects

* Corresponding author.
E-mail address: korgun@akdeniz.edu.tr (E.T. Korgun).

http://dx.doi.org/10.1016/j.placenta.2017.02.015
0143-4004/

the development or organization of tissues such that a permanent physiological response is established [18]. Thus, in the conditions in which GCs are used, some tissue-specific pathophysiologies may be "programmed" by GCs. GCs suppress uterine natural killer cells, stimulate the secretion of human chorionic gonadotropin, and promote trophoblast proliferation and invasion. However, chronic administration of GCs may result in the induction of apoptosis and inhibition of embryonic and placental growth [3]. Although GCs may have direct effects on fetal and/or maternal metabolism, there is evidence suggesting that the GC-induced reduction in birthweight is (also) mediated by the placenta [19].

Adequate nutrient and substrate supply is essential for normal intrauterine development of the fetus. Disturbances in uterine blood supply are associated with higher perinatal morbidity and mortality caused by preterm delivery, pre-eclampsia, or intrauterine growth restriction (IUGR). Adaptation of the uterine vasculature to the rising needs of the fetus occurs through both vasodilation and development of new vessels [20]. Regular placental angiogenic development reflects the accompanying villous morphology. In other words, fetoplacental angiogenesis shapes villous development [21–23]. Therefore, it is essential to understand the importance of proper vascular development for normal placental development, which affects both fetal and maternal health.

Disturbances in the development of the villous tree and pathological changes in the villous vascular system with insufficient uteroplacental blood flow have been linked to the pathogenesis of IUGR [24,25]. Spectral Doppler imaging studies have determined abnormal placental blood flow associated with vascular abnormalities in most cases indicating a relationship between placental vascular pathology and IUGR [20,26,27].

In brief, interrupted placental angiogenesis is one of the major causes of IUGR. Therefore, it is critical to review the adverse effects of GC overexposure on placental angiogenesis. In this study, we review how the placenta responds to changes in maternal GC environment and discuss the possible ways in which placental angiogenesis mechanisms would be affected. Literature (PubMed) was searched using the keywords "antenatal glucocorticoids, placenta, angiogenesis, pregnancy.". In addition, animal and human literature was included, and search was extended using the keywords "steroid, stress, mineralocorticoid, trophoblast, placental development" when necessary.

1.1. Glucocorticoids and glucocorticoid receptors in placenta

GCs are steroid hormones predominantly secreted by the adrenal glands [28]. GCs can program tissues in utero and may also mediate the nutritional and environmental challenges that affect pregnancy [29]. For instance, third-trimester GC exposure is sufficient to induce adult hypertension in rats and also programs permanent hyperglycemia and particularly hyperinsulinemia in the adult offspring, modeling the insulin resistance "metabolic syndrome" phenotype, which is a key feature of human "fetal origins" observations [17]. Moreover, corticosteroid delivery directly to the fetus did not result in IUGR in sheep [19]. This supports the possibility that the placenta mediates the effects of corticosteroids on fetal growth.

Cortisol can activate both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The affinity of the MR for cortisol and corticosterone is similar to that for aldosterone. GR and MR have been demonstrated to be functionally expressed in human trophoblast [3]. Although physiological GCs can also activate MR, synthetic GCs can only activate GRs [11].

GCs mediate their effects on target tissues by binding to GRs. GC receptors are ligand-activated nuclear transcription factors, which regulate the expression of numerous genes [30]. Saif, Z. et al. reported that the human placenta expresses multiple cell-specific GR isoforms: 12 isoforms in the trophoblast, 5 isoforms in the endothelium, and 4 isoforms in the cord blood immune cells [31]. In pregnancies complicated by maternal asthma, GR gene activity and cord blood cortisol levels were positively correlated when compared to those in healthy pregnancies [31,32].

In another paper, Bivol, S. et al. proposed that GC-induced changes in the placental GR mRNA and protein levels (accompanying GC-induced changes in the placental structure and function) is a contributing factor for fetal abnormalities associated with high fetal exposure to GCs during gestation [33]. This particular interest in GR mRNA and protein level is important in the context of pregnancy because GC responses are mediated through intracellular GRs. GC excess affects the relative abundance and subcellular localization of the GRs, the intracellular transcription factors controlling the expression of 10%–20% of genes in the human genome [34].

It is suggested that because GRs are essential for sustaining life and the development of the human embryo, any changes in the GR levels in the placental tissues during critical periods in fetal development may modify fetal organ structure and function, considerably affecting both in utero growth of the fetus and its lifelong health [33].

1.2. Cause of increased concentrations of glucocorticoids

During pregnancy, circulating levels of maternal GCs are elevated under many circumstances. Three mechanisms are proposed for the increased GC concentrations in utero; (I) impaired cortisol metabolism within the decidua, placenta, or fetus; (II) elevation of maternal cortisol concentrations (as occurring during maternal stress); and (III) administration of synthetic GCs as a drug or treatment [11]. This review focuses on the exogenous GCs that are generally synthetic, such as betamethasone, dexamethasone, and prednisone.

Periods of stress, both physical (illness, excess exercise, and famine/undernutrition) or psychological (anxiety) in origin, result in the elevation of endogenous GCs [35]. Stress during pregnancy in association with increased maternal cortisol levels has been shown to impair mental and motor development in the young infant [36] and lead to low birth weight and reduced birth length, whereas miscarriages in early pregnancy are associated with increased cortisol levels in the first 3 weeks after conception [37].

An epidemiological study that examined women who were pregnant at the time of the 2001 terrorist attacks on the World Trade Center found that there was a higher incidence of low-birthweight babies among women who were residing in New York at the time. The greatest proportion of these low-birth-weight babies were born from women who were in their first or second trimester at the time of the attacks [38]. These studies also revealed an increased incidence of male fetal death in New York after September 2001 [39,40]. High maternal stress and thus fetal exposure of cortisol are believed to be the cause of these poor fetal outcomes.

1.3. Placental glucocorticoid barrier

GCs are lipophilic and readily cross the placenta. During human pregnancy, endogenous maternal cortisol concentrations are 5–10 times higher than the fetal cortisol concentrations [41]. This transplacental gradient is maintained by the presence of 11β-hydroxysteroid dehydrogenase (11β-HSD).

Two isoforms of 11β-HSD have been cloned and characterized in humans. The type 1 enzyme (11β-HSD1) primarily acts as an oxoreductase, converting cortisone to cortisol. The type 2 enzyme