Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age

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A diagnosis of fetal growth restriction and subsequent preterm birth is associated with increased risks of adverse perinatal and neurodevelopmental outcomes and potentially long-lasting effects to adulthood. Most such cases are associated with placental insufficiency and the fetal response to chronic intrauterine hypoxemia and nutrient deprivation leads to substantial physiological and metabolic adaptations. The management of such pregnancies, especially with respect to perinatal interventions and birth mode, remains an unresolved dilemma. The benefits from standard interventions for threatened preterm birth may not be necessarily translated to pregnancies with small-for-gestational-age fetuses. Clinical trials or retrospective studies on outcomes following administration of antenatal glucocorticoids and magnesium sulfate for neuroprotection when preterm birth is imminent either have yielded conflicting results for small-for-gestational-age fetuses, or did not include this subgroup of patients. Experimental models highlight potential harmful effects of administration of antenatal glucocorticoids and magnesium sulfate in the pregnancies with fetal small for gestational age although clinical data do not substantiate these concerns. In addition, heterogeneity in definitions of fetal small for gestational age, variations in the inclusion criteria, and the glucocorticoid regime contribute to inconsistent results. In this review, we discuss the physiologic adaptions of the small-for-gestational-age fetus to its abnormal in utero environment in relation to antenatal glucocorticoids; the impact of antenatal glucocorticoids and intrapartum magnesium sulfate in pregnancies with fetal small for gestational age; the current literature on birth mode for pregnancies with fetal small for gestational age; and the knowledge gaps in the existing literature.

Key words: birth route, corticosteroid, fetal growth restriction, neonate, neuroprotection, preterm

Introduction

Fetal growth restriction (FGR) refers to fetuses not attaining biologically determined growth potential.[1] To date, the most widely used correlate of FGR has been an estimated fetal weight <10th percentile for gestational age (GA), otherwise known as small for GA (SGA).[2-4] Strictly speaking, FGR requires serial studies to document a change in growth trajectory while SGA is diagnosed largely based on birthweight or estimated fetal weight for GA. In the majority of cases, fetal SGA is due to a spectrum of chronic placental disease, commonly described by clinicians as "placental insufficiency."[5] Other causes of fetal SGA include genetic disorders, congenital anomalies, or infections.[5] Fetal SGA is associated with stillbirth, adverse neonatal outcomes, altered neurological and cognitive development, and potentially cardiovascular and endocrine diseases in adulthood, with significant social and economic implications.[6-10] Fetal SGA fetuses undergo substantial physiologic adaptation in response to fetal hypoxemia and nutrient deprivation[11-13] and thus may render standard perinatal and intrapartum interventions such as antenatal glucocorticoids or intrapartum magnesium sulfate less effective or ineffective and at times harmful.[14-16] Not surprisingly, management of pregnancies with FGR likely to deliver at preterm gestation remains an unresolved dilemma and there is subsequent wide variation in clinical practice. These variations include array of surveillance methods and very different parameters considered in contemplating management decisions such as timing of birth.[3,17-19]

In this article, we review: (1) the physiologic adaptions of SGA fetuses in relation to antenatal glucocorticoids; (2)

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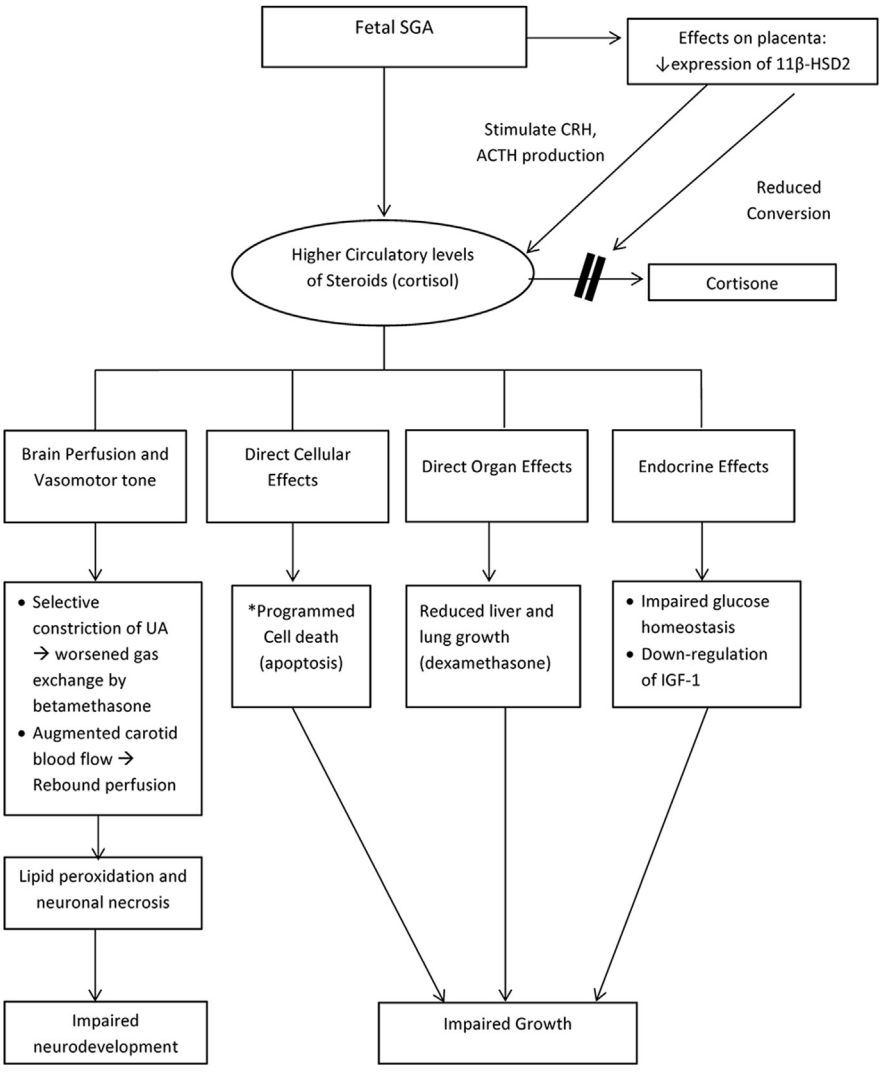
the impact of antenatal glucocorticoids and intrapartum magnesium sulfate for pregnancies with fetal SGA likely to deliver at preterm gestation; and (3) the mode of birth after suspected fetal SGA.

Fetal SGA and antenatal glucocorticoids

Overview of benefits and concerns of antenatal glucocorticoid use in preterm births

Antenatal glucocorticoids administration to improve newborn outcomes has become the mainstay of prophylactic treatment before anticipated preterm birth.[20,21] In otherwise healthy fetuses, antenatal glucocorticoids promote pulmonary surfactant synthesis and secretion, enhance structural maturation of the alveoli to support postnatal lung function, increase lung compliance, and generate an enhanced response to postnatal surfactant treatment.[22] Glucocorticoids also have similar maturational effects on other fetal organs including the brain, kidneys, and intestine.[22] A Cochrane review of 30 studies concluded that a single course of antenatal glucocorticoids prior to preterm birth was associated with a reduction in neonatal mortality (risk ratio [RR], 0.69; 95% confidence interval [CI], 0.59–0.81), respiratory distress syndrome (RR, 0.66; 95% CI, 0.56–0.77), intraventricular hemorrhage (RR, 0.55; 95% CI, 0.40–0.76), necrotizing enterocolitis (RR, 0.50; 95% CI, 0.32–0.78), need for mechanical ventilation (RR, 0.68; 95% CI, 0.56–0.84), and systemic infections in the first 48 hours after birth (RR, 0.60; 95% CI, 0.41–0.88).[20] Currently a single course of glucocorticoids is recommended for pregnant women between 24^0 weeks (or 23^0 weeks, based on a family's decision regarding resuscitation) and 33^6 weeks of GA who are at risk of preterm birth within 7 days, including for those with ruptured membranes and multiple gestations.[23] For decades, it has been assumed that chronic intrauterine stress that occurs in tandem with fetal SGA may cause prolonged stimulation of adrenal gland, accelerate pulmonary maturation, and thus result in a lower risk for respiratory distress syndrome than appropriate-for-GA neonates.[24] This rationale implies that growth-restricted fetuses may not benefit from antenatal corticosteroids in contrast with appropriately grown fetuses.

FIGURE
Pathophysiological changes associated with fetal SGA in relation to antenatal glucocorticoids



ACTH, adrenocorticotrophic hormone; *CRH*, corticotropin-releasing hormone; *HSD2*, hydroxysteroid dehydrogenase type 2; *IGF*, insulin-like growth factor; *UA*, umbilical artery.

Ting. Interventions for SGA fetus. Am J Obstet Gynecol 2018.

Pathophysiological changes associated with fetal SGA in relation to antenatal glucocorticoids

The effects of glucocorticoids are complex in the setting of fetal SGA, and both basic and translational science studies have raised specific concerns in this regard (Figure).

First, chronic fetal stress associated with fetal SGA stimulate placental corticotropin-releasing hormone release.[25] Corticotropin-releasing hormone,[26] adrenocorticotrophic hormone,[26] and cortisol levels[27] are all significantly elevated in fetal SGA in a graded manner as shown in studies where the degree of hypoglycemia in fetuses correlated with the extent of placental vascular compromise.[28] Circulating levels of glucocorticoids can