

Maternal cardiac function in fetal growth restriction

Thesis

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LIST OF ABBREVIATIONS

AC : abdominal circumference

ADH : anti diuretic hormone

ANP : Atrial natriuretic peptide

BMI : body mass index

CMV : cytomegalovirus

BPD : biparietal diameter

CO : cardiac output

CSA : cross sectional area

DHEAS : dihydro-epiandrosteredione

FGR : fetal growth restriction

GH : growth hormone

HR : heart rate

IGF : insulin growth factor

IGFBP : insulin growth factor binding protein

IUGR : intrauterine growth restriction

LV : left ventricle

MCA : middle cerebral artery

MTHFR : methylenetetrahydrofolate reductase

NOS : nitric oxide synthase

PE : **Pre-eclampsia**

PG : prostaglandin

PI : pulsatility index

PSV : peak systolic velocity

RI : resistance index

LIST OF ABBREVIATIONS (Cont...)

S/D : the systolic/ diastolic

SGA : small for gestational age

TA : thoracic aorta

UPD : Uniparental disomy

VEGF : vascular endothelial growth factor

Introduction

Intrauterine growth restriction (IUGR) complicates up to 10% of all pregnancies. It is associated with a perinatal mortality rate that is 6 to 10 times higher than that for normally grown fetuses and is the second most important cause of perinatal death after preterm delivery (**Silver et al., 2003**).

The cause of IUGR is multifactorial. Worldwide, maternal nutritional deficiencies and inadequate uteroplacental perfusion are among the most common causes of IUGR (**Silver et al., 2003**).

In addition to long-term morbidity where, provocative epidemiologic studies have suggested that IUGR is a risk factor for the development of essential hypertension and hyperlipidemia in later life and insulin resistance and death from cardiovascular disease and stroke (Creasy, 1999, and Godfrey et al., 2000).

Fetal growth restriction (FGR) is a common cause of neonatal morbidity and mortality and is now increasingly recognized as a risk factor for cardiovascular and metabolic disease in later life (**Bilardo et al., 2004**).

Although multiple etiologies exist, defective trophoblastic invasion of the maternal spiral arteries is a universally accepted pathophysiological finding (**Khong et al., 1986, and, Bamfo et al., 2006**).

Normal placentation is thought to trigger a fall in systemic vascular tone and to create a state of intravascular volume depletion. This provokes an increase in plasma volume, heart rate (HR) and hence cardiac output (CO). To cope with this physiological stress, the maternal heart increases its compliance, its contractility and its size, thus modifying the

function of the left ventricle. This reorganization results in 50% increase in CO and uteroplacental perfusion (**Mesa et al., 1999**).

There is some evidence that impaired placentation is associated with altered maternal cardiovascular function. **Bosio et al.** demonstrated that pregnancies complicated by preeclampsia are characterized by a hyperdynamic circulation, which crosses over a low CO high peripheral resistant state at the onset of preeclampsia (**Bosio et al., 1999**).

In normotensive pregnancies with FGR, there is contradictory evidence about maternal hemodynamics, with some studies reporting reduced CO and left ventricular (LV) diastolic function in the first and third trimesters (**Duvekot et al., 1995, and Vasapollo et al., 2002**), and others reporting no difference in LV function between normal pregnancies and those affected by FGR (**Veille et al., 1991**).

Doppler velocimetry of the fetal circulation is a useful tool in the assessment of fetal compromise and prediction of hypoxemia and acidemia. Classification based on the temporal changes in fetal circulation will select truly compromised fetuses (**Harrington et al., 1995, and Hecher et al., 1995**).

Assessment of the maternal hemodynamics in such a clearly defined homogenous group will provide useful information, which may correlate with fetal outcome (**Bamfo et al., 2006**).

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Arabic Summary

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Intrauterine growth restriction (IUGR)

Introduction:

Normal fetal growth follows the critical regulation of cell proliferation, organization, and differentiation of the embryo and encompasses maturational growth of the different organ systems. This process depends on the genetic profile of the embryo, the maternal–placental–fetal unit, adequate nutrient and oxygen supply to the developing fetus, and the hormonal fetal and maternal milieu.

Lowbirth weight (less than 2500 g) and birth weight that is small for gestational age (SGA) are associated with increased perinatal mortality, short- and long-term childhood morbidity and mortality and a range of cardiovascular and metabolic diseases later in life. Prevention of fetal growth restriction (FGR) and lowbirth weight, if possible, is therefore of immense clinical and economic importance.

In spite of many studies dealing with different aspects of IUGR in human pregnancies the pathophysiological processes underlying this disorder are complex and incompletely understood. Fetal growth retardation (FGR) etiology has been differentiated according to maternal, placental and fetal factors (*Schlembach et al., 2007*).

Classification:

The terms intrauterine growth retardation (restriction) or fetal growth restriction (IUGR, FGR) and small for gestational age (SGA) are related but not synonymous.

IUGR/FGR is a pathological reduction in an expected pattern of fetal growth that leads to attenuation of fetal growth potential due to an insult that has occurred in utero. This diminution in intrauterine growth may result in SGA, which is an infant with a birth weight lower than a predetermined cutoff value according to standard curves, referring to the weight of the infant at birth and not to the growth pattern (*Schlembach et al., 2007*).

Thus, SGA may reflect a normal pattern in a given population. *Lubchenco* created birth weight curves comparing birth weight to gestational age. This information allowed a clearer size description of live-born infants ranging from 24 to 42 weeks' of gestation (*Lubchenco et al., 1963*).

Based on these growth curves, SGA infants were classified as those with birth weights two standard deviations (<3%) below the mean for gestational age (*Usher & McLean, 1969*).

IUGR is further differentiated as “symmetric” or “asymmetric”. Symmetric IUGR is a proportionate decrease in length, weight, and head size for gestational age that generally occurs early in gestation. In asymmetric IUGR, the length and weight are decreased for gestational age but there is head

sparing such that fetal head circumference is appropriate for gestational age (*Dashe et al., 2000*).

The pattern of intrauterine growth is based upon the following ultrasound determinations: biparietal diameter (BPD), abdominal circumference, femur length and crown rump length (*Resnik, 2002*).

Prevalence:

Low birth weight continued to rise in the United States despite improved prenatal care, from 7.8% in 2002 to 7.9% in 2003 (*Hamilton et al., 2004*).

In approximately 250,000 yearly births in the United States, about 40,000 term infants weigh less than 2500 g (*McIntire et al., 1999*).

The definition of IUGR depends upon maternal and environmental factors that are not always measurable. Since birth-weight data are precisely recorded they are used in most studies to define the characteristics of a given population. Hence, the prevalence of low birth weight rather than IUGR is usually given.

A significant increase in the percentage of macrosomic infants (greater than 4000 g), from 3 to 14% in the last 15 years was found. White infants weighed on average 179 g more than black infants.