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Maternal body mass index impacts fetal-placental size at birth and umbilical cord oxygen values with implications for regulatory mechanisms

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ABSTRACT

Background: Maternal under- and over-nutrition are known to effect fetal growth with altered placental development and nutrient transport, but whether fetal oxygenation is also altered remains unknown.
Aims: To examine linkages between maternal BMI and birth weights, placental weights, and umbilical vein and artery PO_2, with implications for signaling mechanisms.
Study design: Population-based cohort study.
Subjects: Analysis of hospital database information on all patients with pre-pregnant BMI values delivering viable, singleton infants between Jan 1, 1999 and Dec 31, 2010 (N = 29,212). BMI was categorized into underweight, normal weight, overweight, and obese, with birth weights categorized into small (SGA), appropriate (AGA), and large for gestational age (LGA).
Outcome measures: Maternal BMI, birth and placental weights, umbilical vein and artery PO_2.
Results: Underweight mothers with smaller infants and overweight/obese mothers with larger infants had disproportionately large placentas, suggesting compensatory and/or enhanced placental growth in these pregnancies. All SGA infants had lower umbilical vein and artery PO_2, consistent with aberrant placental development leading to diffusional impairment of oxygen. Both maternal overweight/obese BMI and LGA resulted in lower artery PO_2, likely due to increased growth rates with the larger size in these infants.
Conclusions: These findings support fetal hypoxemia as a common determinant of growth restriction, whether in underweight mothers and due to under-nutrition or in overweight/obese mothers and due to placental insufficiency. However, oxygen is unlikely to be the primary promotor for fetal growth in overweight/obese mothers and LGA infants, with other substrates of more importance as nutritional cues in these pregnancies.

1. Introduction

Clinical studies in underweight mothers with low body mass index (BMI) support the notion that maternal under-nutrition is causative for fetal growth restriction (FGR) dependent upon severity [1–6]. This has led to animal models of maternal under-nutrition that show placental weights to be decreased less than fetal weights, but with structural alterations and reduced glucose, amino acid and lipid transport, and evidence of chronic hypoxia as nutritional cues for related FGR [7–12]. However, whether fetal oxygenation is also decreased in human pregnancy with under-nutrition-related FGR as seen with placental insufficiency-related FGR [13–16], remains unknown.

Clinical studies in overweight mothers with increased BMI show maternal over-nutrition causative for fetal macrosomia with an increased incidence of large for gestational age (LGA) infants [3–6,17,18]. This has led to human and animal studies of maternal obesity that show up-regulation of placental transporters for glucose, amino acids and fatty acids as nutritional cues for related macrosomia [11,19–22]. However, whether fetal oxygenation is also increased through enhanced placental development, or is instead decreased with

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excessive fetal growth, remains unknown.

We have shown that umbilical vein oxygen values are decreased in FGR and increased in LGA compared to appropriate for gestational aged (AGA) infants, supporting oxygenation as a primary determinant of fetal growth across the entire range of birth weights in humans [16]. Umbilical artery oxygen values were also decreased in FGR but unchanged in LGA infants indicating that FGR infants have lower systemic oxygen levels despite their reduction in growth, while LGA infants normalize their systemic oxygen levels with their increased growth. We now report the impact of maternal BMI on birth weights, birth weight categories, and umbilical vein and artery PO_2 as measures of placental oxygen transport and fetal systemic oxygen levels, respectively. We hypothesize that smaller infants, whether from underweight mothers and more likely to be under-nutrition related, or from overweight/obese mothers and more likely to be placental-insufficiency related, will have similarly lower umbilical vein and artery PO_2 implicating fetal hypoxia as a causal factor in their reduced size at birth. However, while larger infants from normal weight mothers are likely to have higher umbilical vein PO_2 as previously reported [16], this may not be seen in larger infants from overweight/obese mothers if other nutritional cues are leading to their macrosomia. Placental weights and birth to placental weight ratios have additionally been studied as measures of placental development in relation to size at birth and the impact of maternal nutrition.

2. Materials and methods

The computerized Perinatal database of St Joseph's Health Care London, London, Ontario, provides targeted information on all births occurring at the hospital, with data prospectively entered by dedicated database personnel. During the period of this study, the hospital was the tertiary care facility for southwestern Ontario serving a population of approximately 1.5 million. The study population was formed based on the following inclusion criteria: all patients delivering between January 1, 1999, and December 31, 2010; singleton; live-born; gestational age > 25 completed weeks; no major anomalies; and availability of maternal pre-pregnant weight and height and thereby BMI. The database was used to obtain the following information for this study population: maternal pre-pregnant BMI as the primary independent variable; birth weight, placental weight, and umbilical cord gases/pH, as primary outcome variables; and maternal age, parity, smoking/alcohol/illicit drug usage, pregnancy complications, gestational age at birth, labor/mode of delivery, non-reassuring fetal heart rate (FHR) pattern as indication for cesarean delivery, and fetal sex as secondary outcome and potentially confounding variables. The study design was approved by the University of Western Ontario Research Ethics Board for Human Subjects (no. 103311, January 18, 2013).

According to clinical practice, gestational age was derived from the last menstrual period or corrected based on ultrasonographic measurements as previously reported [16]. An electronic weight scale was used by nursing personnel to weigh infants immediately after delivery. Placentas were weighed by nursing assistants with membranes and umbilical cord, again using an electronic weight scale. Umbilical cord blood was routinely sampled by nursing personnel immediately after delivery for all infants deemed to be viable as previously reported [16].

Maternal pre-pregnant weight and height values were those reported by patients at their first prenatal visit and recorded in the patient's antenatal record. These values were entered in the database by the database personnel if consistent with the weight and height values recorded at the patient's first prenatal visit. Pre-pregnant BMI values were divided into the following 4 BMI categories: (1) underweight < 18.5, (2) normal weight 18.5–24.9, (3) overweight 25–29.9, and (4) obese > 30. Fetal size at birth was divided into the following 3 birth weight categories based on birth weight percentile in relation to weeks of pregnancy attained at the time of delivery and using the fetal growth nomograms of Hadlock et al. [23] as previously reported [24]: (1) small for gestational age (SGA), birth weight < 10th percentile, (2) AGA, birth weight ≥ 10th percentile and ≤ 90th percentile, and (3) LGA, birth weight > 90th percentile.

Maternal smoking, alcohol and illicit drug use were scored as being present with any sustained use after pregnancy was diagnosed. Maternal pregnancy complications included chronic hypertension, gestational hypertension, pre-eclampsia/eclampsia, gestational diabetes, overt diabetes, preterm premature rupture of membranes (PPROM), and preterm delivery < 37 completed weeks using standard clinical criteria for these.

2.1. Data analysis

The effect of maternal pre-pregnant BMI category on fetal birth weight, placental weight, birth/placental weight ratio, birth weight category and umbilical cord PO_2 was examined, along with the relationship to maternal age, parity, smoking/alcohol/illicit drug usage, incidence of given pregnancy complications, gestational age at birth, labor/mode of delivery (spontaneous/induced labor, elective cesarean, laboring cesarean), non-reassuring FHR pattern for cesarean delivery, and fetal sex. Data are presented as grouped mean ± SD. Statistical significance between BMI groups, birth weight groups, and birth weight sub-groups within each BMI group as the sub-analysis of interest, were determined using analysis of variance with post hoc Dunnett's test for continuous variables, Chi squared analysis with a Bonferroni adjustment for dichotomous variables, and ordinal logistic regression for the birth weight category incidences. A statistical interaction test was used to determine if differences in the primary outcomes across the BMI categories were dependent on the birth weight categories. Adjustments to the statistical significance between groups for potentially confounding variables were made by means of analysis of covariance. The maternal normal weight BMI group was used as the reference against the other three BMI groups, while the respective fetal AGA group was used as the reference against the other two birth weight groups.

3. Results

3.1. Characteristics of the study population

There were 35,320 patients meeting the study delivery criteria of whom 29,212 had pre-pregnancy weight and height available from the database. Most missing data were due to failure to record this information in the patient's antenatal record rather than discrepancies from weight and height recorded at the first prenatal visit. The distribution of the underweight, normal weight, overweight, and obese BMI categories was ~5%, 55%, 23%, and 16%, respectively, with the study population characteristics shown in Table 1 which are similar to that reported in other large population studies over the past two decades in developed countries [1,2,17,18,25,26].

3.2. Birth weight, placental weight, and birth weight categories

Although birth weights were available for all 29,212 infants, placental weights were missing for 173 patients. Additionally, to avoid including data from incomplete placental material (e.g. piecemeal manual extraction of placenta) or pathologically enlarged placentas (e.g. hydropic placentas), those placental weights < 0.5% and > 99.5% for each of the birth weight categories were excluded. Accordingly, there were 28,749 placental weights for analysis. The birth weight, placental weight, and birth weight category incidences are shown in Table 2, while the birth/placental weight ratios are shown in Tables 3, and 4. The significant effects shown have been adjusted for the confounding effects of the pregnancy related variables noted. Whereas underweight mothers had infants with lower birth weights and placental weights, overweight and obese mothers had infants with higher birth weights and placental weights when compared to that of