Abstract—In healthy pregnancy, glucose and oxygen availability are essential for fetal growth and well being. However, how substrate delivery and fetal uptake are affected in human pregnancy complicated by fetal growth restriction (FGR) is still unknown. Here, we show that the human FGR fetus has a strikingly reduced umbilical uptake of both oxygen and glucose. In 30 healthy term and 32 FGR human pregnancies, umbilical volume flow (Qumb) and parallel umbilical vein (uv) and artery (ua) blood samples were obtained at elective Cesarean section to calculate fetal glucose and oxygen uptake as Qumb \( \Delta (uv - ua) \) differences. Umbilical blood flow was significantly lower in FGR pregnancy \((-63\%; P<0.001)\) but not when normalized for fetal body weight. FGR pregnancy had significantly lower umbilical oxygen delivery and uptake, both as absolute values (delivery: \(-78\%\); uptake: \(-78\%\)) and normalized (delivery: \(-50\%\); uptake: \(-48\%\)) for fetal body weight \((all P<0.001)\). Umbilical glucose absolute delivery and uptake were significantly reduced (delivery: \(-68\%\); uptake: \(-72\%\)) but only glucose uptake was decreased when normalized for fetal body weight \((-30\%; P<0.05)\). The glucose/oxygen quotient was significantly increased \((+100\%; P<0.05)\) while glucose clearance was significantly decreased \((71\%; P<0.001)\) in FGR pregnancy \((both P<0.05)\). The human fetus in FGR pregnancy triggers compensatory mechanisms to reduce its metabolic rate, matching the proportion of substrate consumption relative to oxygen delivery as a survival strategy during complicated pregnancy. (Hypertension. 2020;75:748-754. DOI: 10.1161/HYPERTENSIONAHA.119.13727.)

Key Words: fetus ■ glucose ■ oxygen consumption ■ pregnancy ■ umbilical vein

Fetal growth restriction (FGR) is associated with poor placentation and incomplete remodeling of the uteroplacental spiral arteries.\(^1\) This implies reduction of uteroplacental blood flow, thereby impairing oxygen and substrate delivery to the fetus and slowing its growth trajectory.\(^2\) Progressive severity of FGR based on increased uteroplacental vascular resistance and fetal heart rate trace abnormalities is associated with increasing fetal hypoxia and potential fetal brain damage.\(^3,4\) Individuals who are born following FGR are known to be at increased risk for cardiovascular diseases.\(^5\) This is likely due to fetal metabolic adaptations essential to allow fetal survival within the adverse intrauterine environment but also increases the risk of pathology in the offspring in later life. However, the nature of these fetal compensatory metabolic adaptations in FGR pregnancy remains very unclear, particularly for the human fetus.

Fetal conversion of energy into mass can most easily be determined by measurement of the rate of fetal oxygen uptake.\(^6\) As there is no long-term storage of oxygen, its uptake and utilization are almost identical over short periods of time. Over the years, the chronically catheterized pregnant sheep model has permitted the estimation of fetal oxygen consumption by measuring the rate of umbilical blood flow together with the umbilical venous-arterial difference in oxygen content.\(^7\) Similarly, glucose uptakes have been measured in the pregnant sheep model\(^7\) and recently in human pregnancy.\(^3\) Glucose represents the most important fetal nutrient and in human pregnancies the glucose/oxygen quotient has revealed that the utilization of glucose accounts for \(\approx 80\%\) of oxygen uptake.\(^8\)

More recently, the technical improvement in the accuracy of measurement of umbilical venous blood flow in the human fetus from the second half of gestation\(^10,11\) has made it possible to estimate the fetal uptake of oxygen in human pregnancy.\(^12\) However, for human pregnancy, any information on fetal oxygen consumption in complicated pregnancy is still limited compared with measurements in normal pregnancies at term. Further, no information exists for the consumption of glucose in the human fetus.

Therefore, the objective of this study was to determine changes in the umbilical uptake of both oxygen and glucose in human fetuses of FGR compared with healthy term pregnancy. The study tested the hypothesis that the human fetus in
FGR pregnancy reduces its metabolic rate, changing the proportion of substrate consumption relative to oxygen.

Methods

The study was performed at the Department of Mother and Child of the Luigi Sacco Hospital and at the Department of Mother, Child and Neonate “L. Mangiagalli”. The protocol of the study was approved by the Institutional Review Board of the University of Milan. Informed consent was obtained from all pregnant women before inclusion in the study.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Thirty healthy control pregnancies (Controls) and 32 pregnancies complicated by fetal FGR were studied at the time of elective Cesarean section. Gestational age was calculated from the last menstrual period and confirmed by routine ultrasonography performed between 11 and 13 weeks. Exclusion criteria were maternal chronic diseases, gestational diabetes mellitus, alcohol abuse, drug addiction, any maternal therapy interfering with fetal growth, labour, abnormal fetal karyotype, and fetal malformations or infections. All pregnancies were singleton and none of the women smoked during pregnancy.

Controls

Normal healthy pregnancies were studied at term (37–41 weeks of gestation). All patients had a normal pre-gravid body mass index (Table 1), and none had medical or obstetric pathologies. Indications for cesarean section were singleton and none of the women smoked during pregnancy.

FGR

 Fetuses with FGR were identified by ultrasound through repeated longitudinal measurements that demonstrated a reduction in fetal growth velocity, FGR was defined by measurements of abdominal circumferences below the 10th percentile of reference values for fetuses of similar ages, together with a shift in the growth curve by greater than 40 centiles. This definition is now also included in a recent consensus document. None of the fetuses were affected with abnormal karyotype, genetic syndromes, viral infection, or major malformations. FGR was confirmed at birth by neonatal weight below the 10th percentile according to Italian standards for birth weight and gestational age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=30)</th>
<th>FGR (n=32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>35.3±0.7</td>
<td>35.3±1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.1±0.4</td>
<td>22.3±0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gestational age at birth, wks</td>
<td>38.8±0.1</td>
<td>32.7±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal weight, g</td>
<td>3340.8±52.9</td>
<td>1313.3±90.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal weight centile (%)</td>
<td>50.6±3.0</td>
<td>7.3±0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placental weight, g</td>
<td>520.0±23.7</td>
<td>252.1±20.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Feto/placental ratio</td>
<td>6.6±0.2</td>
<td>5.6±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fetal sex (female/male)</td>
<td>17/13</td>
<td>17/15</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are presented as mean±SE. Independent-samples t-test: FGR vs controls. n.s. indicates not significant.

Oxygenation and Metabolic Data

Both umbilical venous (uv) and arterial (ua) blood were immediately sampled from a doubly clamped segment of the cord. Samples were collected in heparinized syringes that were sealed and stored on ice. Blood gases (pO₂ and pCO₂), pH, hemoglobin concentration and O₂ saturation, lactate and glucose concentrations were measured using a GEM Premier 3000 portable system (Instrumentation Laboratory). Oxygen (O₂) content was calculated as: Oxygen (O₂) Content (mmol/L)=Hemoglobin (g/L)·O₂ saturation (%) · 0.05982.

Calculations

Umbilical O₂ uptake was calculated according to the Fick principle:

\[
\text{Umbilical O}_2 \text{ Uptake (µmol/min) } = \frac{Q_{\text{umb}} (\text{mL/min})}{V_{\text{ua}} O_2 \text{ Content (mmol/L)}} - D \text{ (uv-ua)}
\]

O₂ delivery and the coefficient of fetal O₂ extraction were respectively calculated as:

\[
\text{Fetal O}_2 \text{ delivery (µmol/min)=Q}_{\text{umb}} (\text{mL/min}) \cdot \text{ uv O}_2 \text{ Content (mmol/L)}}/1000\]

\[
\text{Fetal O}_2 \text{ extraction } \% = \frac{[D \text{ (uv-ua)}]/[D \text{ (uv-ua)}] + \text{ uv O}_2 \text{ Content (mmol/L)}]}\]

\[
\text{Umbilical O}_2 \text{ delivery and Uptake were calculated as for oxygen.}
\]

Fetal glucose clearance (mL/min)=Umbilical Glucose Uptake (µmol/min)/umbilical arterial glucose concentration (mmol/L).

Statistical Analysis

Data are presented as mean±SE. The coefficient of variation for mean umbilical venous volume flow was 8.1%, as previously reported. Differences between groups were assessed using the Student t test for independent samples, with applied correction when equality of variances assumption was violated (Levene test). Differences among variables, according to severity of FGR, were compared by 1-way ANOVA, with an appropriate post hoc test. Correlations describing the strength and direction of the relationships between 2 variables were assessed using the Pearson Product-Moment correlation. Linear regression analyses were performed by the least squares method.
Umbilical blood flow, O₂, and glucose utilization were also compared statistically using a General Linear Model test with repeated measures when appropriate. For all comparisons, a P value < 0.05 was considered significant. All tests were performed using the statistical package SPSS (IBM SPSS Statistics, v. 21.00, Armonk, NY).

Results
Maternal and fetal characteristics for control and FGR are presented in Table 1. Maternal age, BMI, and the fetal sex ratio were not significantly different between groups. Gestational age, neonatal and placental weight, and the fetal/placental weight ratio were significantly lower in the FGR group. When the weight of fetuses of control pregnancy was estimated at the corresponding mean gestational age at delivery for FGR fetuses (32.7 weeks; Est FW 32.7wks), fetuses of FGR pregnancy remained significantly lighter (Est FW 32.7wks, Control: 2083.2±69.8 g versus FGR: 1313.3±90.2 g; P<0.001). When considering the severity of FGR, no significant differences were found for maternal characteristics between FGR 1, FGR 2, and FGR 3 (data not shown).

Gestational age and fetal and placental weight were significantly lower in FGR 2 and 3 compared with FGR 1 (Table S1 in the online-only Data Supplement). However, no significant differences in fetal characteristics were found between FGR 2 and FGR 3 (data not shown). Therefore, for further analysis, severity groups for FGR 2 and 3 were combined.

Umbilical oxygenation and blood lactate levels. Umbilical venous and arterial values for pH, pO₂, pCO₂, SatO₂, Hb, O₂ content, glucose, and lactate concentrations are presented in Table S2. Compared with controls, fetuses of human FGR pregnancy showed lower values for umbilical vein and artery pH, pO₂, SatO₂, O₂ Content, and uv glucose concentration, as well as higher values for umbilical vein and artery pCO₂, lactate, and ua Hb. Significant differences were observed between FGR 1 and FGR 2+3 for umbilical artery pH and lactate and umbilical vein lactate concentration (Table S3).

Umbilical Blood Flow Measurements
Both mean umbilical venous cross-sectional area and mean umbilical blood flow velocity were significantly lower in fetuses of FGR compared with control pregnancy. Therefore, calculated mean umbilical blood flow was also significantly lower for fetuses of FGR relative to control pregnancy (Table 2) and with increasing FGR severity (Table S4). However, when umbilical blood flow was normalized for fetal weight, there were no differences between control and FGR and no differences were found according to the severity of FGR (Table 2; Table S4). Umbilical blood flow was positively related to gestational age, placental weight, and fetal weight in all groups, showing FGR 2+3 fetuses to the left of the relationship, FGR 1 in the middle, and control fetuses to the right of the relationship (Figure 1A through 1C).

Umbilical O₂ Delivery, Uptake, and Extraction
Fetal O₂ delivery resulted significantly lower in FGR compared with control pregnancy also when normalized for fetal body weight (Table 2).

As the mean values of umbilical venoarterial O₂ content decreased in FGR, umbilical O₂ uptake was significantly lower in FGR compared with control, either when expressed as absolute values or when normalized for fetal body weight.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=30)</th>
<th>FGR (n=32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>uv flow, mL/min</td>
<td>263.3±15.8</td>
<td>98.2±10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>uv flow/kg, mL/min per kg</td>
<td>78.4±4.3</td>
<td>74.8±5.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>O₂ delivery, µmol/min</td>
<td>1182.5±117.8</td>
<td>254.8±45.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O₂ delivery/kg, µmol/min per kg</td>
<td>354.9±35.1</td>
<td>179.7±26.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O₂ cont D (uv−ua), mmol/L</td>
<td>3.1±0.2</td>
<td>1.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>umb O₂ uptake, µmol/min</td>
<td>808.5±70.6</td>
<td>181.9±35.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>umb O₂ uptake/kg, µmol/min per kg</td>
<td>243.1±21.7</td>
<td>126.5±18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fetal O₂ extraction, %</td>
<td>71.0±2.8</td>
<td>70.7±4.2</td>
<td>ns</td>
</tr>
<tr>
<td>Glucose delivery, µmol/min</td>
<td>942.1±70.6</td>
<td>305.8±35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose delivery/kg, µmol/min per kg</td>
<td>281.6±18.5</td>
<td>237.4±20.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Glucose D (uv−ua), mmol/L</td>
<td>0.79±0.06</td>
<td>0.61±0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>umb glucose uptake, µmol/min</td>
<td>210.9±23.4</td>
<td>58.6±9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>umb glucose uptake/kg, µmol/ min per kg</td>
<td>63.2±6.7</td>
<td>44.1±4.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glucose clearance, mL/min</td>
<td>81.84±11.13</td>
<td>24.12±3.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>glucose D (uv−ua)/O₂ cont D (uv−ua)</td>
<td>0.27±0.03</td>
<td>0.57±0.11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glucose/O₂ metabolic quotient</td>
<td>1.65±0.18</td>
<td>3.45±0.70</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are presented as mean±SE. Unpaired t-test and GLM FGR vs controls. n.s. indicates not significant.

Assuming constant umbilical oxygen consumption/kilogram, the calculated umbilical O₂ uptake/kg at 32.7 weeks (FW 32.7wks) for fetuses of Control pregnancy was 398.8±38.4 compared with 126.5±18.3 µmol/minute per kg in the FGR group, reflecting a reduction of ca. 68% in FGR pregnancy.

Values for oxygen delivery and uptake per kilogram body weight were also significantly lower when FGR 1 and FGR 2+3 fetuses were separately compared with Controls, with no significant difference between the 2 FGR groups (Figure 2A and 2B).

The average coefficient of fetal O₂ extraction was similar in fetuses of Control and FGR pregnancy (Table 2), and there was no significant relationship between fetal O₂ extraction and delivery in fetuses of Control or FGR pregnancy (Figure 3A).

However, for both control and FGR pregnancies, a significant negative correlation between fetal O₂ extraction and umbilical artery pO₂ was found, meaning fetuses with lower pO₂ values in the umbilical artery extracted more O₂ (Figure 3B).

No significant difference was observed for any of the above parameters in relation to fetal sex.

Umbilical Glucose Delivery, Uptake, Clearance, and Metabolic Quotient
Glucose concentration in the umbilical vein, fetal glucose delivery, and mean umbilical venoarterial glucose concentration difference were significantly lower in fetuses of FGR compared with Control pregnancy (Table 2; Table S2). When FGR fetuses were evaluated according to severity, significant differences persisted for glucose concentration in the umbilical vein.
and for fetal glucose delivery (Tables S3 and S4). Fetal glucose delivery per kilogram body weight was not significantly different in FGR compared to controls (Table 2) nor when different severity groups of FGR were considered (Table S4). Umbilical glucose uptake was significantly lower in fetuses of FGR compared with control pregnancy, either when expressed as absolute values or when normalized for fetal body weight (Table 2). When evaluated according to FGR severity, umbilical glucose uptake was significantly different among the 3 groups but this difference was not significant when normalized for fetal weight (Table S4). Fetal glucose clearance was also significantly decreased in fetuses of FGR pregnancy compared with controls (Table 2). When evaluated according to severity, FGR 1 and FGR 2+3 had significantly lower fetal glucose clearance compared with controls but the difference was not significant between the 2 groups of FGR (Table S4). The glucose/O2 metabolic quotient was significantly increased in fetuses of FGR compared with controls (Table 2). When analyzed according to FGR severity, 1-way ANOVA comparisons revealed no significant difference between FGR groups (Table S4). Significant positive relationships occurred between umbilical glucose uptake and umbilical oxygen uptake normalized for fetal body weight (Figure 4A) and between umbilical glucose uptake and umbilical oxygen delivery (Figure 4B) in all fetuses, independent of control or FGR pregnancy, with no significant differences between the 2 groups.

Discussion
In the present study, we found significantly lower umbilical venous and umbilical venoarterial pO2 differences, with O2 delivery and utilization decreased by 50% in growth-restricted human fetuses. We also report significantly lower umbilical
venous and umbilical venaarterial glucose differences, together with a significant reduction of ≈1/3 in umbilical glucose uptake in FGR compared with healthy term pregnancy. These novel data support the hypothesis tested in this study that the human fetus in FGR pregnancy triggers compensatory mechanisms to reduce its metabolic rate, decreasing the proportion of substrate consumption relative to oxygen delivery as a survival strategy.

Oxygen Delivery and Consumption

Since fetal growth is accompanied by a progressive increase in both the fetal demand and the placental supply of nutrients with advancing gestation, it is striking that fetal oxygen consumption is significantly reduced on a per kilogram body weight basis in human FGR compared with fetuses of control pregnancy, in spite of low oxygen delivery rates, and increased levels of mitochondrial content in placenta and cord blood.18,19 These data are novel for human pregnancy and are in good agreement with data obtained from experimental animal models of FGR. In an ovine hyperthermic pregnancy model of FGR, Regnault et al20 reported a 25% reduction in fetal oxygen uptake and also suggested that placental oxygen utilization may represent a limiting step in fetal growth restriction, restricting oxygen delivery to the fetus.20 Similarly, we have previously reported an increase in the uterine-umbilical oxygen gradient in human FGR pregnancy,21 together with increased placental mitochondrial DNA content and changes in the mitochondrial function of cytotrophoblast and mesenchymal stromal cells in FGR pregnancy,18,22 confirming that placental oxygen consumption may have a limiting role in the delivery of oxygen to the fetus.

Although growth restriction will likely limit long-term survival, it seems to provide opportunities for metabolic compensations, which increase hypoxia tolerance.23 This is similar to what happens in small immature neonates that are able to reduce their oxygen demand in response to impaired supply, a condition known as hypoxic hypometabolism.24

The present data and results reported by Regnault et al20 are different from data reported by Zamudio et al25 in a comprehensive study of human pregnancy at high altitude. They reported that human fetuses during high-altitude pregnancy were able to extract sufficient oxygen to result in similar fetal oxygen delivery and consumption rates. In an experimental study,26 growth-restricted ovine fetuses obtained by reduction in uterine blood flow were normoxic and normoglycemic, that is, showing an adaptive response to the reduced uterine blood flow. These data illustrate differential fetal strategies to withstand reductions in oxygenation of varying magnitude. The chronic fetal hypoxia at high altitude is likely much milder compared with the significant chronic fetal hypoxia associated with severe FGR. Therefore, the capacity of the human fetus to extract oxygen to maintain oxygen delivery as an adequate compensatory response may have a threshold set by the severity of impaired
oxygenation, beyond which it must also recruit reduced oxygen consumption as a survival strategy to maintain viability.

**Glucose Consumption and Metabolic Quotient**

Additional data in the present study show reduced glucose consumption in the FGR human fetus, even when correcting for fetal body weight. These data are also consistent with results from an ovine model of hyperthermic fetal growth restriction, which reported a reduced substrate uptake as a consequence of decreased fetal oxidative metabolism, and thereby lower fetal substrate demand. In human high altitude pregnancy, Zamudio et al also reported that the preferential anaerobic placental consumption of glucose spares oxygen but limits glucose availability for fetal growth. In a recent paper, Michelsen et al employed a 4-vessel sampling technique in term human pregnancies and showed that uteroplacental glucose uptake correlates with placental glucose consumption, which modulates maternal to fetal glucose transfer and fetal glucose consumption such that high placental use of glucose limits fetal glucose delivery and consumption.

Interestingly, in the present study, while umbilical glucose uptake corrected for fetal body weight was significantly lower in FGR fetuses, the glucose/oxygen metabolic quotient was increased in FGR pregnancy. This is consistent with human and experimental animal data in FGR pregnancy that show a reduced glucose transport capacity proportionally lower than the rates of placental and fetal glucose utilization. These findings combined suggest that the utilization of glucose also depends on the availability of oxygen, which is reduced in the FGR fetus. This is confirmed in the present study by the significant positive relationship between fetal glucose consumption and oxygen uptake per kilogram body weight, irrespective of healthy or complicated pregnancy. In addition, in the present study, values for fetal glucose clearance, the rate at which fetal metabolism clears glucose from the fetal circulation, was significantly reduced in fetuses from FGR compared with those of control pregnancy. This would tend to increase the fetal maternal ratio for glucose, possibly further contributing to impaired glucose placental transfer in human FGR pregnancy.

**Impact of Decreased Oxygen and Glucose Metabolism in the Human FGR Fetus**

The human FGR fetus is likely to be delivered much earlier than at term, when higher fetal metabolic rates are expected due to the higher rates of protein synthesis when fetal growth demands are maximal. In addition, the FGR fetus is likely to trigger a circulatory brain sparing effect, in relation to chronic fetal hypoxia, preferentially redistributing oxygen and glucose delivery to the central nervous system. However, considering that glucose is the main substrate utilized by the fetal brain, and that the fetus is not able to increase its own blood glucose concentration by gluconeogenesis, the fetal brain, with proportionally higher nutritional demands, may be particularly affected by these reductions in oxygen and glucose availability.

Placental transfer of other relevant energy sources, such as amino acids and lipids, has also been shown to be altered in FGR, further reducing fetal nutrient availability.

**Study Limitations**

Limitations are mostly inherent to the impossibility of complete standardization of the experimental conditions in the human clinical situation. The first is related to the estimation of umbilical blood flow by Doppler velocimetry. A second limitation is the potential confounding effects of anesthesia on the maternal cardiovascular physiology. Finally, differences in gestational age between Control and FGR human pregnancies could also limit the interpretation of results. This potential bias is difficult to overcome in human pregnancy, as preterm delivery of babies from compromised FGR pregnancy is needed to prevent potential severe morbidity and intrauterine demise. Potential control subjects delivered prematurely are not likely to be electively delivered by cesarean section (in the absence of labor) and their clinical condition would also introduce other confounding factors.

Experimental animal models suggest that fetal metabolism is higher in the preterm compared with the term fetus, likely associated with accelerated rates of protein synthesis. In the present study, although we did not find significant differences in umbilical oxygen or glucose consumption in human FGR fetuses of different severity, we cannot exclude that differences may have been masked by the differences in gestational age between FGR groups. However, if we were able to correct for gestational age by using the mean flow value reported for 31 weeks in healthy pregnancy, multiplied by the mean umbilical venoarterial O₂ or glucose difference measured in our term fetuses from Control pregnancy, the hypothetical, corrected for gestational-age values would make the difference between fetuses of Control and FGR human pregnancy even more striking. Therefore, the potential error in this study is likely in the underestimation of differences between human infants of control and FGR pregnancy related to oxygen and glucose umbilical uptake.

**Perspectives**

We provide novel insight into the nature of fetal metabolic compensations in human pregnancy complicated by FGR. The human FGR fetus shows a strikingly reduced umbilical uptake of both oxygen and of glucose independent of fetal body weight. Therefore, the human fetus in FGR pregnancy triggers compensatory mechanisms to reduce its metabolic rate, matching glucose consumption to glucose delivery in relation to oxygen availability.

**Acknowledgments**

This study is dedicated to the memory of Giorgio Pardi and his continuous interest in fetal growth restriction. We thank the pregnant women who took part in the study and our colleagues and midwives in the Luigi Sacco and Mangiagalli Hospitals.

**Sources of Funding**

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**Disclosures**

None.

**References**

Novelty and Significance

What Is New?

- The human fetal growth restriction fetus has a strikingly reduced umbilical delivery of both oxygen and glucose.
- Umbilical oxygen and glucose delivery and uptake are reduced both as absolute values and normalized for fetal body weight.
- The glucose/oxygen quotient is significantly increased while glucose clearance is significantly decreased in fetal growth restriction pregnancies.

What Is Relevant?

- This study highlights potential compensatory intrauterine mechanisms predisposing to metabolic syndrome and hypertension in later life.

Summary

The human fetal growth restriction fetus triggers compensatory mechanisms to reduce its metabolic rate, matching the proportion of substrate consumption relative to oxygen delivery as a survival strategy.