Changes in placental morphology of small for gestational age newborns

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Abstract

Objective: to verify changes in placental morphology of small for gestational age newborns, considering that the occurrence of placental alterations is more frequent in small for gestational age (SGA) infants than in appropriate for gestational age (AGA) infants.

Methods: fifty SGA newborns were included in a cross-sectional study, which involved gross anatomy and light microscopy of placenta, membranes and umbilical cord. An equal size sample of randomized AGA newborns was used. All children were born at Maternidade Terezinha de Jesus, Juiz de Fora - MG, between February and November, 1996. After an informed consent was given by the mothers, the newborns were weighted at birth with assessment of length and head circumference. Every child’s placenta, membranes and umbilical cord were sent to the laboratory of histology and embryology of the Department of Morphology of Universidade Federal de Juiz de Fora and Department of Pathology and Forensic Medicine of Universidade Federal de Minas Gerais.

Results: placentas of SGA newborns differed significantly with greater incidence of chorioamniotitis, placental infarction, extensive perivillous fibrin deposition and multiple foci of parabasal chronic villitis. They were also lighter and had smaller diameters. Placentary index (placental weight/newborn’s weight ratio) was also significantly greater, indicating that although both placenta and small for gestational age newborn presented low weight, placentas impairment was smaller.

Conclusions: placentas of small for gestational age newborns differed significantly if compared to those of adequate gestational age.


Introduction

The relationship between obstetrics and pediatrics is progressively expanding; particularly, pediatrics has been demonstrating great interest for intrauterine life, a vital stage for a healthy postnatal life.

The human placenta is the functional center of the maternal-fetal system, and is responsible for respiratory, nutritional, excretory, endocrine, and immunological functions. Aggressions that affect the uterine-placental interaction may deviate the fetus from its genetic growth potential, determining intrauterine growth retardation (IUGR).

For a long time, researchers have been emphasizing the benefits associated with the pathoanatomical examination of the placenta. The literature presents several studies on small for gestational age (SGA) newborns and placental pathologies. An association between SGA infants and low placental weight has been described in the literature.1-3
Other studies have emphasized the higher incidence of chorioamnionitis in the placentas of SGA newborns, associating it with socioeconomic factors, prolonged amniorrhexis (rupture of fetal membranes) and ascending infections. The association between placental infarction and IUGR is fully described in the literature, as well as its association with perivillous fibrin deposition. A pathoanatomical finding frequently discussed in the literature is the association between chronic villitis and IUGR, which indicates that inflammatory processes on the villous surface that reduce maternal-fetal exchanges may lead to intrauterine malnutrition. The presence of ischemic lesions corresponding to placental circulatory disorders has been observed in 43% of the cases of villitis.

The present article aims at evaluating the placental morphology of full-term infants, small and appropriate for gestational age, through macroscopic examination and optical microscopy of the placenta, membranes and umbilical cord.

Material and methods

We performed a cross-sectional study with data collected from full-term infants who were considered small for gestational age according to the parameters established by Lubchenco et al. We consecutively studied the placentas of all SGA infants born at Maternidade Terezinha de Jesus (Juiz de Fora, MG, Brazil) between February and November 1996 who did not match any of the exclusion criteria. For the control group, we randomly included, according to birth order, appropriate-for-gestational age full-term infants, in the proportion of one control to each case. The sample size was subject to the time interval established for data collection, as well as to the limitations imposed by the paucity of lab material needed for processing the placentas.

We considered as exclusion criteria the presence of one or more of the following conditions:
- neonatal neurological disorders that hindered the assessment of gestational age by way of Capurro’s method (somatoneurological);
- immediate clinical evolution preventing or interfering in the performance of the proposed measurements;
- multiple congenital malformations;
- multiple gestation;
- placenta accreta or other placental condition modifying the integrity of the placenta or other membranes;
- congenital infection diagnosed during the prenatal period.

Altogether, we collected data from 50 SGA and 50 appropriate for gestational age (AGA) newborns. We obtained the placenta, umbilical cord and membranes from these 100 subjects; based on the technique described by Fox, all material was processed and examined in the

Histology and Embryology Lab, Department of Morphology, Universidade Federal de Juiz de Fora (UFJJ), and in the Department of Pathological Anatomy and Legal Medicine, Universidade Federal de Minas Gerais (UFMG).

The collected placentas were examined macroscopically, after removal of excess blood, removal of the membrane and cutting of the umbilical cord at 1cm from the placental disc. Afterwards, placentas were fixed in 10% formalin during an average period of eight days, when parallel sections of the placental disc were performed. Routinely, samples of the placenta, umbilical cord and membranes were collected in order to prepare the histological sections: umbilical cord - two cross-sections in opposite extremities; membranes - cross-section of the membrane roll; placenta - one sample from each quadrant, in addition to samples from other suspicious areas. Selected fragments were submitted to routine histological analysis, and were stained with hematoxylin-eosin. The sections were histologically analyzed by means of optical microscopy, by the research coordinator, who was not aware of the established classification of the newborns. The observed histopathological findings were photographed for documentation.

Mothers were interviewed, and the newborns were evaluated according to gestational age, weight, length and head circumference. The placental ratio was also calculated by dividing placental weight by birthweight, both expressed in grams. To estimate gestational age, we used the information provided by the mother in regard to the date of her last menstruation, whenever they could inform it with certainty; this information was confirmed, if possible, with ultrasonography before the twentieth gestational week, or through the clinical and neurological exam proposed by Capurro et al., considering a difference of up to two weeks.

Once the forms were completed, they were reviewed, codified, typed and analyzed using Epi-Info 6.0.

This study was submitted to previous evaluation, and it was approved and authorized by the Board of Directors of Maternidade Terezinha de Jesus, by the Department of Morphology and the Department of Mother-Child Health, both at UFJJ, and by the Department of Pathological Anatomy and Legal Medicine, at UFMG, as well as to the committees of technical standards and ethics, or equivalent. The study was also approved by the Ethics Research Committee of UFMG.

Results

The age of the mothers varied from 13 to 44 years; in regard to education, 72% had not finished elementary school; and only 2% had finished high school. Most mothers belonged to low-income families; 61% lived on a monthly income of less than one minimum wage per capita. In regard to marital status, 27% of the mothers were living apart from the child’s father at the time of birth.
We observed that 69% of the mothers did not smoke cigarettes throughout pregnancy; 91% reported that they did not consume alcoholic beverages during this period. In one case, a mother reported the use of cocaine and marijuana.

Among the most significant diagnoses or clinical conditions found, we observed 7% of hypertensive disorders of pregnancy (HDP), 5% of chronic arterial hypertension, and 3% of severe anemia.

We verified that nine mothers had not received prenatal care. Among the women who had received prenatal care, the average number of appointments was 5.9 (± 2.1). In regard to the number of pregnancies, 33% of the mothers were primiparous, and 5% had had more than four pregnancies. Considering only the multiparous women (n=67), we observed that 19 mothers showed previous history of low birthweight. We verified a slight predominance of c-sections, with a 52% incidence. Among the newborns, there was a predominance of females, with an incidence of 58%.

Table 1 presents some data that revealed a positive tendency of association with the birth of SGA infants. Such data include maternal age - mothers younger than 16 or older than 35 years (p<0.05); prenatal - absence of prenatal care or only one appointment (p<0.01); parity - primiparous and multiparous >4 (p<0.05); and history of low birthweight in previous gestation (p<0.05).

The average weight of the newborns, considering the entire sample, was 2,783 ± 436g; the median was 2,670g; the minimum weight was 1,920g and the maximum, 3,640g. We observed low birthweight (<2,500) in 27% of the newborns. The average length was 46.5 ± 2.2 cm; the median was 46.5; the minimum length was 41.2 cm and maximum, 50.5 cm. The average head circumference was 34± 1.5 cm; the minimum was 30.5 cm and maximum, 37 cm (Table 2). The distribution of newborns according to birthweight in the SGA and AGA groups is shown in Table 3. The distribution of newborns according to birthweight in relation to sex and gestational age can be better analyzed in Figures 1 and 2.

Data concerning placental examination are described below and summarized in Table 4. In 86% of the cases, we did not find any umbilical cord disorders. When present, these disorders included hemorrhage, single umbilical artery, umbilical artery thrombosis and funiculitis. None of these findings were statistically associated with SGA newborns.

The examination of the membranes revealed a large number of cases with normal results (78%). Chorioamnionitis was the most frequent disorder (17%) observed in the membranes, and was statistically associated with the birth of SGA infants (p<0.05).

The average placental weight was 402 ± 67.2 g, and the median was 392.5g. Low placental weight was positively associated with SGA newborns (p=0.00001). Placental weight was also evaluated in relation to fetal weight through the placental ratio. The average ratio was 0.15 ± 0.02, and the median was 0.14. When the average placental ratio was used, we observed that higher ratios were statistically associated with the birth of SGA infants (p<0.05).

When the average diameter was used as cutoff point, we noted a statistically significant association between placental diameters and the weight/gestational age ratio. Smaller placentas were favorably associated with the birth of SGA infants (p<0.01).

On placental examination, the presence of at least one histopathological alteration was verified in 95% of the cases. Only 5% of the examined placentas were exempt from any abnormalities. The specific findings often included, placental infarction, perivillous fibrin deposition, chronic villitis, abnormal calcifications, intervillous thrombosis, signs of villous immaturity, maternal sickle cells in the intervillous space, vascular disorders, in addition to other sporadic findings.

![Figure 1](image-url)
The presence of multiple areas of villitis, in the parabasal layer, was found in 15% of the placentas. A statistically significant association between chronic villitis and the birth of SGA infants was observed when villitis in multiple areas in the parabasal layer was specifically considered (p<0.05). The presence of abnormal calcifications was observed in 29% of the examined placentas; intervillous thrombosis in 17%; signs of relative or mild villous immaturity in 22%; chorioangiosis in 10%; and maternal sickle cells in the intervillous space in 8%. Nevertheless, these findings were not statistically associated with the birth of SGA infants (p>0.05).

Vascular disorders were observed in 16% of the placentas, represented by avascular villi, sclerosis of villous vessels, hemorrhagic endovasculitis, thrombosis of villous vessels and basal plate. Other observed disorders include chronic deciduitis, retroplacental hematoma, recent hemorrhage of the villous stroma, extrachorial placenta, and the presence of a fourth vessel in the umbilical cord. These findings did not show statistical significance.

Despite the growing scientific interest of neonatology for the placenta, we observed that there are still few works in the literature approaching this subject in a multidisciplinary way. Although intrauterine growth is determined by several factors,22-25 there are relatively few multidisciplinary studies relating placental disorders to specific groups of SGA children. To study the role of the placenta in the birth of SGA infants is to look for disorders that may be directly or indirectly associated with the etiopathogeny of intrauterine growth retardation (IUGR).

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SGA newborn) presented weight reduction, fetal weight was relatively more affected than placental weight.

Chorioamnionitis, which prevailed among SGA newborns, may occur as a consequence of the penetration of microorganisms from the vaginal canal (ascending infection); this is the most common cause of chorioamnionitis in human beings.26 The association between chorioamnionitis and fetal growth restraint is well established.5

The co-occurrence of placental infarction and IUGR points out to intrauterine hypoxia as a common denominator. Intrauterine hypoxia is a coagulation necrosis of the villous tissue, secondary to the occlusion of placental vessels in cases of improper vascular adaptation during placentation.17 Studies performed with a Doppler flow meter, in cases of IUGR, have shown a decrease in uterine-placental blood flow, associated with an increase of vascular resistance, as a cause of chronic hypoxia and IUGR.10,27-29 This increase in the resistance of uterine-placental vessels has been attributed to the absence of physiological changes in the myometrial spiral arteries, due to the failure in the second wave of trophoblastic invasion over these vessels. Although this increase in the resistance of uterine-placental vessels can occur in other disorders, it is frequently associated with hypertensive disorder of pregnancy. The presence of infarction, even though it is not the main cause of IUGR, contributes to its aggravation by restraining the villous surface area of exchange.

Extensive pervillous fibrous deposition has been associated with the decrease of blood flow in the intervillous space and has been frequently associated with the presence of placental infarction.12 Both placental infarction and pervillous fibrous deposition have uterine-placental blood flow reduction and hypoxia as their most common causes. Just like placental infarction, pervillous fibrous deposition causes a restraint on the villous surface of maternal-fetal exchanges and, although it can not be accounted for as a primary cause of IUGR, it can secondarily aggravate it.

Chronic villitis is an important pathological finding in the placenta; it usually presents an unknown etiology, and its incidence, according to literature data, varies from 6% to 26%.15 Since chronic villitis is an inflammatory process of the villous surface, it leads to a process of intrauterine malnutrition through the reduction of maternal-fetal exchanges. Villitis can be found in cases of specific infections, such as cytomegalovirus, toxoplasmosis and rubella; these cases with specific infectious etiology present an incidence between 3% and 8.7%.13,16,20 Villitis can be considered a morphological expression of fetal response to an external antigenic stimulus, resulting from maternal infection or from an immune maternal response to placental tissues.30 According to these authors, when transplacental infections are not identified, the etiology of villitis must be regarded as unknown, which is reported in the literature as the most common form of chronic villitis, being strongly associated with IUGR. Several authors, while studying idiopathic chronic villitis, did not find any specific variation in regard to maternal age, socioeconomic level, nutrition, marital status, smoking, use of illegal drugs, or episodes of acute infection during pregnancy.15,18 There are indications of a strong association between idiopathic chronic villitis and IUGR in cases of recurrent IUGR - diagnosed in two consecutive full-term gestations - without any evidence of infection in mothers or newborns.17 An association between villitis and IUGR was established, indicating that IUGR is more closely associated with a clinical status of severe chronic villitis.15 In our study, this association was significant when cases of chronic villitis in multiple areas and parabasal layers were considered.

Our findings are in agreement with those presented in the literature, showing an association between IUGR and SGA newborns. We believe that the study of placental pathology can greatly contribute to a better understanding of a complex subject such as IUGR. We believe it would be interesting to develop longitudinal interdisciplinary studies involving the fields of obstetrics, pediatrics, and pathological anatomy, so that the mother and the fetus could be followed up from the prenatal period to delivery, with a subsequent pediatric follow-up of the clinical evolution, growth and development of the newborn up to the first months of life. The placental pathoanatomical evaluation could be more comprehensive, using other techniques in addition to routine procedures, such as immunohistochemistry, more detailed morphometric methods, as well as microbiological and parasitological analysis. A greater number of cases could be studied, with a representative sample of a determined

### Table 4 - Significant disorders observed on placental examination, MTJ - FM/UFJF, 1996

<table>
<thead>
<tr>
<th>Placental disorders</th>
<th>SGA</th>
<th>AGA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chorioamnionitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>13</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>37</td>
<td>45</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Placental weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 402 g</td>
<td>41</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>≥ 402 g</td>
<td>9</td>
<td>13</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td><strong>Placental ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.15</td>
<td>24</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>≥ 0.15</td>
<td>26</td>
<td>14</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Placental diameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.2</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>≥ 18.2</td>
<td>16</td>
<td>31</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Perivillous fibrin deposition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>28</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>22</td>
<td>46</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td><strong>Chronic parabasal villitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>39</td>
<td>46</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Placental infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>35</td>
<td>48</td>
<td>&lt; 0.01</td>
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</tbody>
</table>
population, analyzing all variables that are known to be involved in IUGR, which ideally would allow the research to be evaluated in epidemiological terms.

Acknowledgments

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References