Stereological and histopathological assessment of intrauterine growth restriction placenta from Saudi women

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Abstract

Background: Placental insufficiency causes fetal adaptation, leading to fetal programming of chronic diseases. Placentas with intrauterine growth restriction (IUGR) are smaller than average and may contribute to low birth weight of the newborn. The number of patients with IUGR in the Saudi population is increasing; however, little is known about their placentas. The aim of this study was to assess morphometric and histopathological placental changes in Saudi patients with IUGR.

Methods: Overall, 20 healthy pregnant Saudi women (control group) and 20 pregnant Saudi women with IUGR were enrolled. Maternal and fetal morphometric measurements were recorded. The placentas from both groups were processed for histopathological examination using stereological techniques.

Results: The IUGR group had lower placental weight, volume, length, breadth, and surface area than the control group. The total volume of villi and surface area of the terminal villi were significantly reduced in the IUGR placentas. IUGR group had a reduction in birth weight; length; and circumference of the head, chest, abdomen, and thigh compared to control group.

Conclusion: The reduction in placental mass, specifically the reduction in the volume and surface area of villi, the functional units, may have reduced the capacity for nutrient transport. This led to a significant reduction in neonatal measurements. The fetus rearranged nutrient distribution in favor of the brain and other essential organs; however, at the expense of thigh development and growth. This fetal trade-off strategy increases the risk of developing chronic diseases in adulthood. Therefore, IUGR infants may require more clinical attention.

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Intrauterine growth restriction (IUGR) is a medical term, with no total international consensus, defined as the rate of fetal growth below average in light of the growth potential of a specific infant according to the race and sex of the fetus (Majewska et al. 2019) (Sharma et al. 2016). As a general practice in Saudi Arabian hospitals, babies with birth weights < 2500 g are classified as being affected by IUGR (Al-Shammari et al. 2017). Genetic contributes to fetal weight variation; however, maternal health status and placental functional capacity play major roles in fetal development, growth, and weight (Alwasel et al. 2010, Barker et al. 2010).

IUGR affects 30 million neonates yearly worldwide (Sharma, Shastri and Sharma 2016, Abdurabo and Alfrasheid 2017). Studies have revealed that IUGR can lead to various diseases in the future, including diabetes, cardiovascular disorders, hypertension, and emotional/behavioral disorders (Cosmi et al. 2011, Saleem et al. 2011). In many IUGR cases, the fetus suffers from nutrition and oxygen deprivation, leading to the failure of the fetus to reach its growth potential (Rom et al. 2009, Cosmi, Fanelli, Visentin, Trevisanuto and Zanardo 2011, Chapple and Mann 2018). Moreover, IUGR increases mortality by and morbidity by 10–25 % and 50–75 %, respectively (Jako et al. 2019). The risk factors for IUGR differ among populations. Al-Elissa et al., (al-Elissa et al. 1995) identified first-degree consanguinity, prim parity, and poor housing as important factors causing IUGR in the Saudi Arabian population.

IUGR may be affected by maternal, fetal, or placental factors (Sharma, Shastri and Sharma 2016); however, placental factors are considered essential causes in many IUGR cases (Visan et al. 2020). Studies have revealed the association of IUGR with placental changes, such as placental weight, fetal/placental weight ratio, type of umbilical cord insertion in the placenta, and its diameter (Visan, Balan, Costea, Caraulene, Haba, Haba, Socolov, Mogos, Bogdanici, Nemescu, Tanase, Turluc, Cucu, Scripcariu, Toma, Popovici, Ciocoiu and Petriariu 2020). A small placenta is associated with an increased risk of IUGR (Ducray et al. 2011). More specifically, IUGR has been linked to reduced volume and surface area of placental villi (Teasdale 1984). Placentas in IUGR pregnancies are characterized by several histopathological phenotypes such as chronic villitis, avascular villi, villous infarction, distal villous hydropsia, perivillous fibrinoid deposition, cytotrophoblast hyperplasia, syncytiotrophic, chorangiitis, and basement membrane thickening (Almasry et al. 2012, Veerbeek et al. 2014, Visan, Balan, Costea, Caraulene, Haba, Haba, Socolov, Mogos, Bogdanici, Nemescu, Tanase, Turluc, Cucu, Scripcariu, Toma, Popovici, Ciocoiu and Petriariu 2020). A small placenta is associated with an increased risk of IUGR (Ducray et al. 2011). More specifically, IUGR has been linked to reduced volume and surface area of placental villi (Teasdale 1984). Placentas in IUGR pregnancies are characterized by several histopathological phenotypes such as chronic villitis, avascular villi, villous infarction, distal villous hydropsia, perivillous fibrinoid deposition, cytotrophoblast hyperplasia, syncytiotrophic, chorangiitis, and basement membrane thickening (Almasry et al. 2012, Veerbeek et al. 2014, Visan, Balan, Costea, Caraulene, Haba, Haba, Socolov, Mogos, Bogdanici, Nemescu, Tanase, Turluc, Cucu, Scripcariu, Toma, Popovici, Ciocoiu and Petriariu 2020).

IUGR is relatively common in Saudi Arabia; however, few studies have investigated the role of the placenta in IUGR. A study performed in Arar City, northern Saudi Arabia, revealed a significant increase in syncytiotrophoblasts and capillaries of terminal villi of IUGR placentas compared to the control group (Abdrabo and Alfrasheid 2017). In another study performed in Al-Madinah Almonawarah City, western Saudi Arabia, investigators observed a significant correlation between IUGR and placental arterial narrowing, degeneration, decreased number of arteries in stem villi, decreased number of terminal villous capillaries, and villitis (Almasry, Eldomiaty, Elhayomy, Habib and Safwat 2012). The two latter studies in the Saudi population have provided significant IUGR placental histopathological findings; however, confirming these findings using stereological techniques is essential. Stereology converts a two-dimensional image into three-dimensional data based on mathematics and statistics in stereology (Heidari et al. 2015), providing a quantitative estimation of some important structural features, such as surface area, volume, length, and object number (West 2012).

This study aimed to determine morphometric and histopathological changes in the placentas of Saudi patients with IUGR using stereological techniques.

2. Material and methods

2.1. Ethics statement

The Committee of Human Research Ethics at King Saud University, Riyadh, Saudi Arabia approved this study (IRB 19/01104, December 10, 2019). All the women in this study signed an informed consent form for data and sample collection.

2.2. Subject details

Fresh placentas from full-term pregnancies (≥37 weeks) were collected from 40 women who attended the Department of Obstetrics and Gynecology at King Khalid Medical City, Riyadh, Saudi Arabia. Twenty placentas were collected from healthy women with no pregnancy complications (control group), and twenty placentas were collected from patients with IUGR. The exclusion criteria were twin pregnancy, preterm or post-term delivery, maternal smoking during pregnancy, and maternal chronic diseases such as diabetes or hypertension. Women from both groups did not fast or deliver during Ramadan. Maternal data, including age, height, weight, and parity, were collected from the medical records.

Gestational age was determined based on the date of the last menstrual cycle. Women in Saudi Arabia pay attention to their menstrual cycles, as it affects religious practices.

2.3. Placental morphometrics

The placenta was collected and put in a pre-labeled bag in ice box. The placenta was immediately transferred from the labor ward to the workspace within the same building. The umbilical cord and membranes were terminated, and the placental disc was submerged in saline to remove any blood clots. Photographs of maternal and fetal sides were taken using the same camera lens at the same distance in order to determine the number of cotyledons and/or the presence of gross anatomical changes. The placental weight was recorded to the nearest gram using a digital scale (3800 N, TYLOR, China). Placenta length and width were measured to the nearest 0.5 cm. The length of the surface was defined as the longest diameter on the maternal side, and the breadth as the longest diameter on the placental disc. The length of the placental surface area and thickness were calculated in a previous study (Alwasel et al. 2010).

2.4. Histopathological examination

Ten full-depth placental tissue blocks were collected from each placenta (20 control vs 20 IUGR) using systematic uniform random sampling to ensure an equal probability of sampling the entire placenta (Mayhew 2006). Each placenta was cut into strips (2 cm thickness) and rearranged in a long-continuous line. The length of the line was divided by 11 in order to determine the interval distance between blocks. The start point was determined using a random number table. The 10 blocks were collected using the same interval distance. Each block was placed on a fractionator and a random number was used to ensure the random 3D orientation of the sections (Mattfeldt et al. 1990). Each placental block was subsequently sampled using isotropic uniform random sampling to guarantee an unbiased collection of slides for paraffin embedding. On the systematic uniform random samples, an orientator was used to generate isotropic uniform random samples. The placental tissue was sampled on the first orientator with equal spacing between the numbers. The cutting angle was determined using a random number table. The largest specimen was

2
placed on the second orientator circle with its cut facing upside down. The second cut angle was determined using a random number table. During paraffin embedding, the tissue samples were oriented to maintain the right face during sectioning. Paraffin sections (5 μm) were cut and stained with hematoxylin and eosin.

Three hematoxylin and eosin-stained sections were obtained from each block. Super images were taken with a 4 × dry lens (NA 0.2) using an Olympus BX50 light microscope controlled by newCAST version 7.2.0.3197 software (Visiopharm, Hoersholm, Denmark). Fields of view were systematically sampled and photographed using a 20 × dry lens (NA 0.70). Twenty fields of view per section were counted using a point grid with six test points per field of view.

The diagnosis of histopathological phenotypes in this study was based on the Amsterdam Placental Workshop group (Redline 2015a, Redline 2015b, Khong et al. 2016). The following categories of histopathological changes in the placentas were assessed: 1) placental inflammatory-immune processes such as infectious inflammatory lesions and immune/idiopathic inflammatory lesions, 2) placental vascular forms in maternal and fetal stromal-vascular lesions 3) villous and intervillous fibrinoid, 4) and other pathological aspects such as abnormal shape, cotyledon number and umbilical insertion site.

2.5. Stereological examination

Volumes of the intervillous space and total volume of all types of villi, the functional unite, were estimated using a point grid with 24 test points per field of view. The surface area of the terminal villi, as an important measure of placental capacity of transport, was estimated using a line grid with 24 points per field of view with a length per point of 46.0 μm.

The placental volume, V(PL), was calculated using the same volume-to-weight density for each placenta: \( V(PL) = \frac{V(PL)}{P} \frac{g}{1.05} \) where \( V(PL) \) is the placental volume and \( P \) is the placental weight (g) / 1.05.

The volume density of the intervillous space (*) or all types of villi (*, where points hit either stem, intermediate or terminal villi) were estimated by point counting:

\[
V_v(*/PL)(m^3#/m^3) = \frac{\sum P(*) \cdot p(PL)}{\sum P}, \sum PL
\]

\[
I(terminal vili*) = \frac{1}{P} \sum P(PL), \sum PL
\]

where \( \sum P(PL) \) is the sum of points hitting either the intervillous space or all types of villi, \( \sum P(PL) \): the total number of points hitting the placenta, \( P(PL) \): the number of test points used to assess the placenta, \( P(\#) \): the number of test points used to assess the intervillous space, or all types of villi.

The total volume of the intervillous space and the volume of villi were estimated by multiplying by the corresponding placental volume:

\[
V_v(*, PL) (cm^3) = V_v(*/PL) \cdot V(PL)
\]

Intercepts of terminal villi were counted to estimate the surface area using the following formula:

\[
S_v(terminal vili*/PL)(\mu m - 1) = \frac{\sum I(terminal vili*)}{P} \cdot \sum P(PL), \sum PL, \sum P(PL)
\]

where \( \sum I(terminal vili*) \) is the sum of the terminal villi intercepts, \( \frac{1}{P} \) is the length per test point, and \( \sum P(PL) \) is the sum of the points hitting the placenta.

The total terminal villus surface area, \( S_v(terminal vili*/PL) (m^2) \) was then calculated as:

\[
S_v(terminal vili*/PL) (m^2) = \frac{V_v(terminal vili*/PL)}{V(PL)} \cdot V_v(terminal vili*/PL) - V(PL).
\]

2.6. Statistical analysis

Data are presented as percentages or means ± standard deviation. All statistical analyses were performed using SPSS version 25 (IBM Inc., Armonk, NY, USA). Differences between groups were analyzed using independent sample t-tests. Categorical pathological phenotype data were compared using Pearson’s chi-squared test. Differences with a \( p \)-value of < 0.05 were considered statistically significant.

3. Results

3.1. Maternal, neonatal, and placental characteristics

Table 1 shows maternal, neonatal and placental morphometrics. The maternal height, weight, BMI, and parity of the IUGR group were comparable to those of the control group. The gestational age of the IUGR group was significantly shorter by nearly 1 week than the control group. All IUGR neonatal measurements were significantly lower than those in the control group. IUGR neonates exhibited reductions in gestational age by –2.3 %; birth weight by –24 %; length by –5.9 %; and the circumference of the head by –5.3 %, chest by –8.7 %, abdomen by –7.8 %, and thigh by –17.4 %. For the placenta, weight was significantly reduced by –21.7 %, length by –11.2 %, and breadth by –10.3 % in the IUGR group than the control group. The placental/neonatal weight ratio was significantly increased in IUGR reflecting a significant reduction in IUGR placental efficiency. The number of cotyledons and length of the umbilical cord remained unchanged.

3.2. Histopathological and vasculopathies phenotypes

Fig. 1 presents the normal placental histology and various histopathological phenotypes. Most of these histopathological phenotypes were detected in the IUGR and control groups; however, the percentages differed. Fig. 1-A presents normal placental histology with a normal villus structure. Fig. 1-B presents an abnormal histological appearance in a sample from an IUGR placenta. The villous structure is abnormal, with villous lesions covering the entire villous surface. The intervillous space is reduced, and there is a decrease in the number of villi and the size of the intervillous space.

Table 1: Maternal, neonatal, and placental characteristics.

| Characteristic                      | Control mean ± SD | IUGR mean ± SD | p-value |
|------------------------------------|-------------------|----------------|---------|
| Mothers                            |                   |                |         |
| Height (cm)                        | 158 ± 5.8         | 157 ± 4.3      | 0.424   |
| Weight (kg)                        | 74.3 ± 11.1       | 71.4 ± 11.6    | 0.436   |
| BMI (kg/m²)                        | 29.8 ± 4.7        | 29.0 ± 4.2     | 0.572   |
| Parity                             | 1.42 ± 1.2        | 1.0 ± 1.3      | 0.286   |
| Neonates                           |                   |                |         |
| Gestational age (week)             | 38.7 ± 0.9        | 37.8 ± 1.2     | 0.008   |
| Birth weight (g)                   | 3235 ± 338        | 2453 ± 196     | 0.001   |
| Length (cm)                        | 50.8 ± 1.8        | 47.8 ± 3.5     | 0.002   |
| Head circumference (cm)            | 34.2 ± 0.9        | 32.4 ± 1.7     | 0.001   |
| Chest circumference (cm)           | 33.5 ± 1.3        | 30.6 ± 1.1     | 0.001   |
| Abdominal circumference (cm)       | 32.1 ± 1.8        | 29.6 ± 1.9     | 0.001   |
| Thigh circumference (cm)           | 16.1 ± 1.6        | 13.3 ± 1.0     | 0.001   |
| Placenta                           |                   |                |         |
| Weight (g)                         | 455 ± 81.7        | 356 ± 45.6     | 0.001   |
| Placenta/birthweight (%)           | 13.3 ± 1.07       | 14.5 ± 1.32    | 0.006   |
| Length (cm)                        | 20.6 ± 1.6        | 18.3 ± 1.8     | 0.001   |
| Breadth (cm)                       | 18.5 ± 1.1        | 16.6 ± 1.3     | 0.001   |
| Surface area (cm²)                 | 289.21 ± 34.1     | 248.88 ± 40.1  | 0.019   |
| Thickness (cm)                     | 1.46 ± 0.20       | 1.54 ± 0.21    | 0.134   |
| Cotyledons                         | 12.4 ± 1.8        | 12.7 ± 2.5     | 0.667   |
| Umbilical cord length (cm)         | 56.8 ± 15.8       | 47.1 ± 16.7    | 0.005   |

IUGR, intrauterine growth restriction; BMI, body mass index; SD, standard deviation.
Fig. 1. Micrographs from control (A) or IUGR placentas (B to J). (A) Normal placental structure (CV = chorionic villi), (IS = intervillous space), (FC = fetal capillary) (MB = maternal blood). (B) Syncytial knots (arrows). (C) Intervillous fibrin (arrows). (D) Fibrinoid necrosis (arrows). (E) Delayed villous maturation (arrows). (F) Villous oedema (arrows). (G) Chorangiosis (arrows). (H) Villous agglutination (arrows). (I) Calcification (arrows). (J) Avascular villi (arrows) and calcification (star). magnification 200 ×. (Hematoxylin and Eosin).
Placental histopathological percentages. (Fig. 1-D) appeared as clusters of villi agglutinated by fibrin. Delayed villous maturation (Fig. 1-E) was recognized by a reduction in vasculosyncytial membranes, a continuous cytotrophoblast layer, and centrally placed capillaries. Villous edema (Fig. 1-F) was detected by the enlarged and pale-shaped villi due to fluid accumulation between the remaining villi in the pale-pink fibrin material. Fibrinoid necrosis was recognized by increased capillaries within the villus (Fig. 1-G). Villous agglutination appeared as clusters of villi agglutinated by fibrin (Fig. 1-H). Calcification appeared under a microscope as fine deposits of calcium salts in fetal tissues, which appeared darker than those in the surrounding normal tissues. Table 2 presents the statistical analysis of the histopathological phenotypes of placentas from both groups. Table 2 presents the statistical analysis of the histopathological phenotypes of placentas from both groups.

### Table 2

| Histopathological phenotypes | Control N (%) | IUGR N (%) | p-value |
|-----------------------------|--------------|------------|---------|
| Syncytial knots             | 6 (30)       | 15 (75)    | 0.004   |
| Intervillos fibrin          | 1 (5)        | 8 (40)     | 0.008   |
| Fibrinoid necrosis          | 3 (15)       | 9 (45)     | 0.038   |
| Delayed villous maturation  | 1 (5)        | 8 (40)     | 0.008   |
| Villous edema               | 7 (35)       | 14 (70)    | 0.027   |
| Chorangiosis                | 2 (10)       | 6 (30)     | 0.114   |
| Villous agglutination       | 6 (30)       | 13 (65)    | 0.027   |
| Calcification               | 9 (45)       | 8 (40)     | 0.749   |
| Avascular villi             | 6 (0)        | 2 (10)     | 0.147   |

IUGR, intrauterine growth restriction; BMI, body mass index; SD, standard deviation.

### 3.3. Stereological outcomes

The findings of the stereological study are summarized in Figs. 2–5. Patients with IUGR had a significantly smaller placental volume than control patients by –22% (C, 432.7 ± 82.8 vs IUGR, 37.7 ± 38.6 cm³; p < 0.001), Fig. 2. The intervillous volume of the IUGR group was also significantly smaller by –22% (C, 114.2 ± 34.2 vs IUGR, 88.9 ± 16.5 cm³; p = 0.012) than the control group, as presented in Fig. 3. The results of measuring the volume of all types of villi revealed that IUGR placentas had –24% less volume than control placentas (252.3 ± 51.3 vs IUGR, 191.4 ± 29.7 cm³; p < 0.001). Fig. 4. Focusing on the surface area of the terminal villi, the IUGR group had a significant reduction (–41%) than the control group (C, 7.14 ± 3.82 vs IUGR, 4.21 ± 0.94 m²; p = 0.008), Fig. 5.

### 4. Discussion

During pregnancy, the placenta undergoes several critical developmental changes to correspond with the increasing nutritional demands of the fetus (Voicu, Bohiltea, Berceanu, Busuioc, Rosu, Paitici, Istrate-Ofiteru, Berceanu and Ditescu 2020). Placental development is affected by both maternal and fetal factors. Fetal growth depends on the placental capacity to transport nutrients from maternal blood; therefore, the placenta is an organ suspected to cause fetal programming of chronic diseases (Thornburg and Marshall 2015). This study investigated the morphometric and histopathological phenotypes of placentas from Saudi women with IUGR using histological and stereological methods.

Consistent with previous studies (Novac et al. 2018, Jako, Suranyi, Kaizer, Nemeth and Bartfai 2019), maternal measurements were unaffected by IUGR. Despite the minimal reduction in gestational age (–2.3%) in the IUGR group compared to that in the control group, the reduction in IUGR birth weight was remarkable (–24%). This reveals that maternal factors and gestational age may have limited effects on neonatal birth weight, indicating that placentals factors may play a key role in neonatal measurements. The gross placental weight, volume, and surface area of patients with IUGR were significantly reduced by –22, –22 and –14%, respectively. In contrast, placental efficiency was significantly reduced in IUGR group. The placental thickness of the IUGR group increased by 5%, although the difference was not significant. Small placentas have been extensively reported as the major cause of small size at birth and increased risk of developing chronic diseases in adulthood (Burton et al. 2011). The Decrease of placental efficiency indicates that IUGR is linked to a reduction of placental function per g of tissue (Marconi et al. 2006). This is because smaller placentas have lower nutrient and oxygen transportation capacity. Our results revealed that the total volume of placental villi in the IUGR group was significantly reduced than the control group to support this. Moreover, the surface area of the terminal villi was remarkably decreased (–41%) in the IUGR group placentas. Nutrient transports in IUGR placentas may have been altered, however, further study is necessary to link the abnormal structure to altered function.
In addition to anatomical and histological morphometrics, our study examined various histopathological changes in the placenta. Notably, the current study focused on the placental examination of IUGR pregnancies with no other maternal complications such as hypertension, diabetes, or other metabolic disorders. We speculate that, in this specific population, abnormal development of fetal-stromal vascularization, including villous capillary lesions, chorangiosis, or delayed villous maturation, occurred first, followed by complications in global/partial malperfusion with avascular villi. Other studies have focused on pregnancies with maternal complications and, therefore, mainly observed maternal stromal-vascular lesions.

Some previous studies revealed inconsistencies in placental histopathology of IUGR pregnancies (Fox 1997); however, many other studies have provided substantial evidence for distinctive structural and histological abnormality occurrences in placentas complicated by IUGR (Redline and Patterson 1994). In the present study, intervillous fibrin was significantly increased in the IUGR group than in the control group. This is consistent with the results of other studies (Nigam et al. 2014, Visan, Balan, Costea, Caraulieanu, Haba, Haba, Socolov, Mogos, Bogdanici, Nemescu, Tanase, Turluc, Cucu, Scripcuru, Toma, Popovici, Ciocoiu and Petriu 2020). The presence and expansion of intervillous fibrin are strongly correlated with a reduction in placental and fetal weight (Redline 2008). In line with other studies, we observed a remarkable increase in syncytiot knots of IUGR placentas. The increase in syncytial knots is related to an imbalance between the proliferation and apoptosis of syncytiotrophoblasts. It has been reported that increased syncytial knots are correlated with oxidative stress, such as hypoxia and high reactive oxygen species production (Heazell et al. 2007). Villous agglutination observed in IUGR placentas may represent areas of reduced intervillous perfusion and incipient infarction (Ernst 2018). Calcification was observed in the control and IUGR groups, with almost the same pattern. Calcification often occurs in mature placentas and reflects its senescence (Iskender-Mazman et al. 2014). For this reason, we could not find any relationship between IUGR and calcification. Chorangiosis levels in the IUGR placentas in this study were similar to those in the control group. This result corresponds with the findings of other research (Iskender-Mazman et al. 2014).

These alterations at the anatomical and histopathological levels in the IUGR placentas may have reduced their ability to fulfill fetal needs and resulted in fetal growth restriction. However, the fetus compensates for placental malfunction by trading off nutrients to protect vital organs such as the brain. With the head circumference being less affected, the placenta and fetus may have trade-off nutrients towards the head to ensure proper brain development. This occurred at the expense of thigh development. At this stage, it is unclear whether the reduction in thigh circumference was due to reduced fat tissue only or it was accompanied by some reduction in muscle mass.

In conclusion, the placenta in IUGR pregnancies underwent profound anatomical and histopathological changes. They had smaller sizes and surface areas; however, they were thicker than the control placentas. The stereological assessment revealed that the volume and surface area of the villi were severely reduced. This

![Fig. 3. The intervillous volume (cm³) of IUGR placentas was significantly smaller than those in the control group. * indicates that the p-value < 0.05.](image)

![Fig. 4. The volume of all types of villi (cm³) was reduced in the IUGR group compared to the control group. ** Indicates the p-value < 0.001.](image)
was accompanied by an abnormal increase in syncytiotrophoblast, intervillous fibrin, fibrinoid necrosis, delayed villous maturation, villous edema, chorangioma, and villous agglutination. These abnormal placental structures are associated with fetal growth restriction, small birth weight with a remarkable reduction in thigh circumference and a small reduction in head circumference. This disproportion supports the trade-off theory proposed by previous research. IUGR babies have survived suboptimal uterine environments at some expense; thus, they are at greater risk of chronic disease development in the future. Therefore, more clinical attention should be directed to IUGR babies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Alwasel S and Harrath H. designed the study and wrote the manuscript. Mojammamy N. and Alayed N. processed samples and performed the stereological study. Histopathology was performed by Aljerian K. and Aldahmash W.

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