REVIEW

Intrauterine growth restriction - monitoring and pregnancy outcomes: A narrative review

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Intrauterine growth restriction is described as a fetus not reaching its growth potential during pregnancy. Placental malperfusion is the main cause of Intrauterine growth restriction . Management of Intrauterine Gowth Restriction includes monitoring and determining the time of birth in order to reduce the risks of complications. Our review explore the current knowledge with regard to the monitoring of pregnancies with Intrauterine Growth Restriction and the role of biomarkers in this process. The importance of this issue is based on the poor outcomes of the pregnacies with severe intrauterine growth restriction. Our results show that different organizations make different recommendations for diagnosis and management in case of intrauterine growth restriction, somehow contradictory. Which means that in addition to ultrasound measurements, Doppler velocimetry, cardiotocography, biomarkers for prediction and diagnosis should be identified. Different biomarkers such as angiogenic factors, proteomics, genomics etc have been explored, poor pregnancy outcomes being associated with severe intrauterine growth restriction. Finding specific biomarkers is of crucial importance, in the context of multidisciplinary management.

Keywords: intrauterine growth restriction, biomarkers, placenta, umbilical arteries, Doppler evaluation

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Introduction

Intrauterine growth restriction (IUGR) is a pathology described by ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) and ACOG (The American College of Obstetricians and Gynecologists) as a fetus not reaching its growth potential during pregnancy. This definition is based on ultrasound measurement and clinical assessment. Doppler velocimetry is also included. Various maternal pathologies can lead to this disorder, along with fetal genetic or chromosomal abnormalities. However, placental malperfusion is the main cause of IUGR [1-4]. If fetal weight is less than the 10th percentile of the weight corresponding to gestational age infants are considered "small for gestational age" (SGA). IUGR is associated with increased risks of complications such as stillbirth, neonatal death, and long-term health problems. Maternal age over 40 years, different habits such as smoking, alcohol consumption, diabetes, chronic hypertension, auto-immune diseases can cause preeclampsia and IUGR [3,4].

Management of IUGR includes monitoring and determining the time of birth in order to reduce the risks of complications. A multidisciplinary follow-up is more appropriate [5,6]. It is demonstrated that baby with IUGR is more susceptible to asphyxia during labor [3].

The aim of our review is to explore the current knowledge with regard to the monitoring of pregnancies with IUGR and the role of biomarkers in this process. The importance of this issue is based on the poor outcomes of the pregnacies with severe IUGR.

Materials and Methods

An extensive literature search based on specific key words, "intrauterine growth restriction", "biomarkers", "placenta", "umbilical arteries", "Doppler evaluation" was conducted, from electronic databases such as Google Scholar, PubMed, Cochrane. Initially a number of 2860 articles was generated. The abstracts were meticulously selected by two authors, including only full text articles written in English , with appropriate study design, compatible with our study. Exclusion criteria were: duplicates, other language than English, books, editorials, short reports, manuscripts with unclear information or not aligned with the aim with our review. A number of 35 full-text articles were obtained. In cases of disagreement, resolution was achieved through consultation with a third author A narrative approach was adopted given the heterogenity of the studied populations, or variations in study design. A qualitative assessment was obtained through a descriptive analysis of the studies. The article selection process is present in the following flow diagram [7].

Intrauterine Growth Restriction Monitoring

The guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and those of the Society for Maternal–Fetal Medicine (SMFM) on intrauterine growth restriction (IUGR) make different recommendations for diagnosis, monitoring and delivery timing of IUGR pregnancies, somehow contradictory. This is why an international consensus still remains elusive [8]. For example, in the SMFM definition of IUGR, the fetal growth trajectory or Doppler assessment is not taken into accont, only the fetal size considered below the 10th per-

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centile [9] The ISUOG guideline include both fetal growth trajectory and Doppler findings [10].

When IUGR is suspected a close survailance is recommended with detailed ultrasound examination. Serial umbilical artery Doppler, middle cerebral artery assessment should be performed [4]. Also, uterine artery and fetal ductus venosus Doppler could be used as indications for delivery [11]. Screening for infections, chromosomal abnormalities or fetal malformations is also useful in unexplained IUGR [4].

Simonazzi et al on his study of 16 fetuses with IUGR developed at 20-23 weeks observed that absent end-diastolic velocities in the umbilical arteries severely affected the neonates, only 12 survived and one of them developed cerebral palsy. Placental insufficiency with this Doppler modification in the umbilical arteries is associated with a high probability of perinatal death and neonatal complications [12]. Which is why non-invasive method of Doppler velocimetry technique has become a regular component of fetal surveillance in cases of complicated pregnancies, along with cardiotocography [3]. Oligohydramnios, characterized by amniotic fluid index ≤5cm by ultrasound, is another ultrasound parameter evaluated in IUGR which has significant impact on perinatal outcome [13]. Non-invasive prenatal screening (NIPS) based on cell-free fetal DNA has been used in clinical practice, but with poor prognostic value in IUGR [14].

Biomarkers based on placental pathogenesis

Malperfusion associated with placental senescence has a key role in IUGR. Various damaging processes can activate senescence programs [15]. The mechanisms underlying placental insufficiency in case of IUGR include malperfusion. Abnormal placental development and maternal conditions could lead to placental malperfusion and dysfunction [16].

Defective maternal spiral artery remodeling with superficial endovascular invasion of cytotrophoblast have been demonstrated in PE associted with IUGR. Abnormal placentation and ischemia is followed by release of anti-angiogenic factors release, including fms-like tyrosine kinase-1(sFlt-1) and soluble endoglin (sEng). As result endothelial dysfunction occur with a negative impact on maternal and fetal organs [17].

The incomplete invasion contributes to diminished blood flow into the intervillous spaces. This process is followed by vasoconstriction and platelet aggregation, with increased systemic vascular resistance. Therefore, initiating multidisciplinary approach as soon as possible is advisable and improve maternal and fetal outcome [17].

Because screening does not predict most cases of preeclampsia, other biomarkers for placental insufficiency have been sought, of these calprotectin, anti-HIF-1 alpha and cytokeratin 7, presented interest [18]. Doppler ultrasound measurements combined with arterial blood pressure, and levels of circulating Placental Growth Factor (PlGF) have been proposed as first trimester screen alghoritm. The focus moved to placental and cardiovascular biomarkers: epigenetics, proteomics metabolomics and genetics [19]. Exosomes and miRNA have also been investigated in order to detect their relevance in PE and IUGR early prediction [20,21]. Other studies have been focused on different algorithms using Doppler measurements of uterine artery pulsatility index, combined with PlGF, PAPP-A, alpha-fetoprotein and placental volume in the first trimester of pregnancy [22].

Researchers also linked the calprotectin to abruption placentae in case of PE [23]. Calprotectin alone or associated with other proteins such as high mobility group protein B1 have been investigated as predictor for PE and IUGR but more research are needed to validate their involvement [24-26].

Neonatal outcomes in severe Intrauterine Growth Restriction

IUGR is an important risk factor for impaired fetal viability and poor obstetric outcome. After prematurity, IUGR is the second leading cause of stillbirth and perinatal mortality [27].

In Lee's et al study in the IUGR group, a birth weight less than 550 grams was significantly associated with neonatal death ($p < 0.001$). Patent ductus arteriosus was associated with poor outcome, low survival (73%), with neurodevelopmental delay [28].

Intrauterine malnutrition rather than hypoxemia was the leading cause to IUGR, and active management may not be the best option before 26 weeks of gestation [29].

Also several complications have been reported. In a study conducted by Hasmasanu et al. on 142 patients with IUGR compared to 142 normal infants, intraventricular hemorrhage, neurodevelopment impairement and hypoglycemia characterized the IUGR newborns [30].

Besides low birth weight, such as intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, other morbidities have been reported according to Baschat study (2009). He also evaluated the neurodevelopmental delay at 2 years of those infants with IUGR. Cerebral palsy, neurodevelopmental delay, hearing loss and/or blindness have been observed. But most importantly, there were 10 stillbirths, and 22 neonatal deaths [31].

Cardiometabolic syndrome developed later in life is another outcome of IUGR confirmed by several researchers. While during intrauterine life the fetus with IUGR makes a different adjustments involving several organs to compensate the adverse uterine environment, these processes may lead to permanent and irreversible changes [32].

Neonatal mortality was 13.1% among the IUGR fetuses characterized by birth weight <10th %tile associated with elevated umbilical artery index in Baschat study on 175 pregnancies with fetal growth restriction. Again abnormal ductus venosus Doppler combined with birth weight were more important than birth age [33].

In a study conducted by Brun IUGR fetuses, 245 cases included, between 22 and 25 weeks' gestation, 201 (82%) were categorized as uteroplacental cause, 13 (5%) as suspected placental cause, one (0.4%) as suspected viral cause. 30 (12%) could not be assigned to any of these categories. Overall, 101 (41%) cases survived, while 89 (36%) underwent in-utero fetal demise, and 22 (9%) neonatal death have been reported. 90% are associated with uteroplacental insufficiency [34].

The etiology of intra-uterine growth restriction should also include low maternal dietary protein intake [35].

Conclusions

Based on our findings, there is need to establish appropriate management for fetal growth restriction. Identification of the etiologies of fetal growth restriction, followed by multidisciplinary management, proper monitoring is necessary. Finding specific biomarkers is of crucial importance, based on the poor outcomes of early onset preeclampsia and severe fetal growth restriction. Further research is required.

Authors Contribution

LM (Conceptualization, Methodology, Writing – original draft), MIM (Data Curation, Investigation, Writing – review and editing), RM (Project administration, Supervision, Validation)

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Conflict of interest

None to declare.

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