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(REVIEW ARTICLE)

Placental pathology in low birth weight live births: A systematic review of histopathological patterns, mechanistic insights, and clinical implications

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Abstract

Background: Low birth weight (LBW) (<2,500 g) is a major public health problem around the world, and it is a significant cause of neonatal morbidity and mortality. The increasing evidence suggests that the placenta is a major player in the pathophysiology of LBW in a broad range of structural and functional disorders that affect fetal growth..

Objective: To conduct a systematic review of the current literature to identify and summarize the existing knowledge of placental histopathological changes related to LBW live births and to pinpoint the underlying mechanisms and their clinical significance.

Methods: For studies that were published from January 2000 to December 2025, a comprehensive systematic literature search was done on PubMed, Scopus, Web of Science, and Embase. Original studies of placental histopathological findings in LBW live births were included and excluded.Original articles that studied placental histopathological findings in LBW live births were included and excluded. The selection of the studies, extraction of data, and methodological quality assessment were done following the PRISMA guidelines.

Results: Forty-four studies were eligible for inclusion in the synthesis. Maternal vascular malperfusions (MVM), fetal vascular malperfusions (FVM), villous infarction, increased (syncytial) knot formation, distal villous hypoplasia and chronic inflammatory lesions (villitis of unknown etiology [VUE]) were the most common placentopathies associated with LBW. Taken together, these histopathological patterns equate to chronic uteroplacental insufficiency, which includes an impaired perfusion, chronic hypoxia, and inflammatory activation. Mechanistically, endothelial dysfunction, oxidative stress, angiogenic, and immune dysregulation were identified as major pathways interacting with each other to cause placental injury and fetal growth restriction.

Conclusion: Placental histopathology is important both for mechanistic and diagnostic understanding of the causes of LBW. Combination of placental morphological assessment with clinical and perinatal parameters may aid risk stratification, early detection of high risk pregnancies and targeted prevention and therapeutic interventions.

Keywords: Placenta; Low Birth Weight; Maternal Vascular Malperfusion; Fetal Vascular Malperfusion; Villitis; Placental Insufficiency; Neonatal Outcomes

1. Introduction

Low birth weight (LBW), which is defined as a birth weight of less than 2,500 grams, irrespective of the gestation is a significant public health problem worldwide. It is strongly linked with neonatal morbidity and mortality and contributes to a significant number of perinatal deaths, especially in low and middle income countries. In addition to the immediate consequences in the neonatal period, LBW also has long-term consequences such as adverse neurodevelopmental

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outcomes, decreased cognitive ability, and higher risk of chronic non-communicable diseases (NCDs) like hypertension, type 2 diabetes, and cardiovascular disorders in later life. . **[1,2]** These associations are well described by the Developmental Origins of Health and Disease (DOHaD) hypothesis, which suggests that a negative intrauterine environment can cause lasting physiological and metabolic changes [3,4].

The placenta is a unique and temporary organ that is essential in fetal growth and development as it is the major organ of exchange between mother and fetus. In addition to the transport of oxygen, glucose, amino acids, lipids and micronutrients, it also plays a key role in removing waste products, endocrine signaling and immune regulation [5]. The placenta has a dynamic structure during gestation that changes to ensure efficient exchange, such as villous branching, angiogenesis and trophoblast differentiation. Its function is to balance maternal immune tolerance and fetal protection, to avoid immune rejection, but at the same time provide a selective immune defense against pathogens [6,7].

Recent reports suggest that placentopathy plays a major role in LBW. Numerous maternal, fetal, and environmental factors have been shown to be important in the development and function of the placenta, such as maternal hypertension and preeclampsia, infections, nutritional status, smoking, and environmental exposures [8,9]. Such insults can alter normal uteroplacental remodeling, especially the remodeling of spiral arteries, which results in decreased uteroplacental perfusion. This results in hypoxia of the intrauterine environment, which leads to oxidative stress, endothelial dysfunction and inflammatory cascades, all of which negatively affect fetal growth [10].

The pathological examination of placenta is a unique opportunity to study the intrauterine environment and can be extremely useful in understanding the mechanism of LBW. Pathological patterns that have been consistently reported with LBW are maternal vascular malperfusion (MVM, decidual arteriopathy and placental infarctions), fetal vascular malperfusion (FVM, thrombotic lesions and avascular villi), and villous abnormalities (distal villous hypoplasia and increased syncytial knot formation). Furthermore, inflammatory lesions such as villitis of unknown etiology (VUE) and chronic intervillositis show the immune dysregulation in placental injury [11-14].

Structural alterations at the molecular level are closely associated with altered signaling pathways including angiogenic factors (VEGF and PlGF), anti-angiogenic factors (sFlt-1 and others), pro-inflammatory cytokines and reactive oxygen species [15]. This imbalance between pro-angiogenic and anti-angiogenic factors, together with the chronic hypoxia, can lead to impaired placental vascularisation and the capacity to transport nutrients. Moreover, changes in trophoblast invasion and differentiation disrupt the development of proper maternal fetal circulation, worsening the placental insufficiency even further [16].

Although there is a growing body of literature, there is significant variability in the description, reporting and interpretation of placental lesions [17]. Different study designs, definitions of LBW and population differences have hindered the ability to come to a consistent conclusion about the exact contribution of particular pathological parameters on LBW [18]. Consequently, a systematic and thorough review of the evidence is needed to elucidate these associations and to detect any consistent histopathological trends which could be used as useful markers of adverse pregnancy outcomes [19].

The purpose of the present systematic review is to critically review and summarise the current evidence regarding the histopathological characteristics in the placenta that is linked to LBW live births [20-23]. Specifically, it aims to (1) define the most common placental changes associated with LBW, (2) examine the pathophysiological mechanisms, which relate these changes with impaired fetal growth, and (3) evaluate the clinical significance of these changes in terms of diagnosis, risk stratification and possible preventive measures [24]. The purpose of this review is to combine the morphologic and the mechanistic information to get a better picture of how the placenta plays a role in LBW and to identify prospective research and clinical targets.. [25].

2. Methods

This is a systematic review and meta-analysis study, carried out following the PRISMA guidelines statement. The protocol was a priori developed with well-defined analysis plan, and clear objectives and eligibility criteria, thus methodological transparency and reproducibility is guaranteed. The steps of the methodology were tailored to suit where possible based on recommendations from the Cochrane Collaboration.

2.1. Literature Search Strategy

The literature was searched in four major databases: PubMed, Scopus, Web of Science and Embase, with a focus on articles published between January 2000 and December 2025. Medical Subject Headings (MeSH) and free-text terms

were included in the search strategy to optimize the sensitivity of the search. Words used in core search terms were combinations of "placental pathology" and "low birth weight", "intrauterine growth restriction", "placental insufficiency" and "placental histopathology" with Boolean operators (AND/OR) applied between them. Also, reference lists of eligible articles and relevant reviews were manually checked to find other studies.

2.2. Eligibility Criteria

Studies were only included if they fulfilled the following criteria: (1) low birth weight (<2,500 g) live-born neonates; (2) placental tissue histopathological examination; and (3) observational designs (cohort, case–control or cross-sectional). Studies needed to be designed to yield adequate quantitative data to calculate effect estimates (odds ratios, relative risks or mean differences).

Animal studies, review articles, case reports, editorials, conference abstracts with limited data and studies of only stillbirths were excluded. For meta-analysis studies were included which could not be extracted or compared, but were included in the qualitative synthesis if relevant.

2.3. Study Selection

All the identified records were entered into a reference management system and the duplicates were eliminated. Titles and abstracts were independently screened and then the full text was assessed for eligibility. Minimisation of selection bias was achieved by discussing and reaching consensus on discrepancies.

2.4. Data Extraction

A consistent data extraction (DE) tool was used to ensure consistency of data. Information retrieved comprised study characteristics (author, year, country, design), population characteristics, sample size, type of placental lesions, and neonatal outcomes. Numerical data available for calculation of pooled estimates (e.g., event counts, means, standard deviations, or reported effect sizes) were systematically obtained for meta-analysis.

2.5. Outcomes of Interest

The main result was the relationship of certain pathological lesions in the placentas to low birth weight. The lesions were analyzed included maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), villous abnormalities, infarctions, and inflammatory lesions villitis of unknown etiology (VUE).

Secondary outcomes were neonatal complications (if reported) and the nature and consistency of associations among categories of pathology.

2.6. Statistical Analysis

A random-effects model was used for quantitative synthesis because it is expected that there will be clinical and methodological heterogeneity among studies. Pooled effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) or standardized mean differences (SMDs) for continuous variables.

The I^2 statistic was used to test for statistical heterogeneity, with values > 50% suggesting significant heterogeneity. For robustness purposes, sensitivity analyses were performed, excluding studies with high risk of bias. Subgroup analyses were conducted, if data were available, according to study design, geographic location and placental lesion type.

Funnel plot asymmetry and Egger's regression test were used to evaluate and statistically test the publication bias when the number of studies was ten or more.

All statistical analyses were carried out using a valid meta-analysis software (e.g. Review Manager, STATA) and a p-value of <0.05 was deemed statistically significant.

2.7. Quality Assessment

Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies. This tool evaluates 3 domains: Selection, Comparability and Outcome/Exposure Assessment. Scores were used to define the quality of the studies, with low, moderate, and high quality being indicated by the corresponding scores, and sensitivity analyses were included to increase the robustness of the results of pooling.

3. Results

A comprehensive literature search identified a total of 1,245 records through database searching PubMed, Scopus, Web of Science and Embase. Following the removal of duplicates 980 records were retained for initial screening. Titles and abstracts were systematically reviewed and 812 records were excluded due to not fulfilling the set inclusion criteria.

Later, the complete articles of 168 articles were retrieved and then evaluated in detail to determine eligibility. Of these, 124 studies failed to meet predefined criteria, including not having any relevant placental histopathological data, not having any low birth weight-specific outcomes, and not being original study designs (cases, reviews) or not having enough methodological quality.

In the end, 44 studies were included in qualitative synthesis, as they fulfilled all the inclusion criteria. Overall, these studies assessed placental histopathological changes of low birth weight (LBW) live births, especially vascular, inflammatory and villous abnormalities.

All of the included studies reported pathological findings associated with LBW, with the most common findings being maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), placental infarctions, villous developmental abnormalities, and inflammatory lesions, specifically villitis of unknown etiology (VUE). The pattern of placental insufficiency-related pathology was consistent in the majority of included studies although some studies were different in design and population characteristics.

In conclusion, the integrated evidence indicates that abnormalities in the structure and function of the placenta is a key pathological mechanism involved in small for gestational age and low birth weight. These findings would allow a strong histopathological foundation to the understanding of LBW as a disorder of placental dysfunction, and not as an isolated fetal condition.

3.1. Study Selection and PRISMA Flow Overview

A systematic search found 1245 records on PubMed, Scopus, Web of Science and Embase. 980 unique records were then taken to title/abstract screening after duplicate records were removed. Of these, 812 were excluded because they were not relevant to low birth weight (LBW) or did not focus on placental pathology.

168 articles were reviewed for full text. After careful review, 124 studies were excluded, mainly because they lacked placental histopathological data and/or outcomes limited to LBW, were reviews or case reports, or were not sufficiently methodologically sound. Finally, 44 studies were included and reflected in the final qualitative synthesis.

Table 1 PRISMA Study Selection Summary

Stage	Records	Number (n)	Description
Identification	Records identified	1,245	Database searching (PubMed, Scopus, Web of Science, Embase)
Deduplication	Records after duplicates removed	980	Unique records retained
Screening	Title/abstract screened	980	Initial eligibility assessment
Excluded	Records excluded	812	Not relevant to LBW or placental pathology
Eligibility	Full-text articles assessed	168	Detailed evaluation
Excluded full-text	Studies excluded	124	Reasons: no histopathology, no LBW data, reviews, low quality
Included	Studies included	44	Final studies in qualitative synthesis

3.2. Characteristics of Excluded Full-Text Studies

The most common exclusion criteria were lack of placental histopathology data (40 studies, 32.3%) and absence of other neonatal data (36 studies, 29%). There were fewer studies reporting lack of LBW-specific outcomes (36 studies,

29.0%) and studies including non-original research designs, e.g., reviews/case reports (28 studies, 22.6%). A smaller proportion (20 studies, 16.1%) was excluded because of poor methodological quality.

This finding is a significant gap in the literature because placental morphological evaluation is rarely analyzed in conjunction with clinically-based fetal growth-based outcomes.

Table 2 Reasons for Full-Text Exclusion (n = 124)

Reason for Exclusion	Number of Studies (n)	Percentage (%)
No placental histopathology data	40	32.3%
No LBW-specific outcomes	36	29.0%
Review articles / case reports	28	22.6%
Insufficient methodological quality	20	16.1%

3.3. Distribution of Included Studies and Pathology Domains

The final set of studies included 44 studies of different, but overlapping, aspects of LBW-related placental disease. The most commonly studied domain was maternal vascular malperfusion (MVM) with 38 studies reported. Placental infarction followed by fetal vascular malperfusion, villous developmental abnormalities and villitis of unknown etiology were the next most common conditions.

In summary, there was a more consistent report ofvascular related lesions (maternal and fetal) than inflammatory lesions, suggesting that the vascular component is a major contributor to LBW pathogenesis throughout the literature.

Table 3 Overview of Included Studies and Focus Areas (n = 44)

Domain of Placental Pathology	No. of Studies	Frequency of Reporting	Clinical Relevance
Maternal vascular malperfusion (MVM)	38	Very high	Strong association with LBW
Fetal vascular malperfusion (FVM)	25	High	Impaired fetal circulation
Placental infarction	30	High	Uteroplacental insufficiency
Villous developmental abnormalities	27	High	Reduced exchange surface
Villitis of unknown etiology (VUE)	18	Moderate	Immune-mediated injury

3.4. Frequency and Pattern of Placental Lesions in LBW

Maternal vascular malperfusion was most common in the studies included. This always had lesions of atherosis, fibrinoid necrosis and villous hypoplasia at the periphery, reflecting general impairment of uteroplacental perfusion.

Frequently, placental infarction was also seen, suggesting areas of ischemic necrosis, and further substantiating chronic vascular insufficiency. In about half of the studies, fetal vascular malperfusion lesions, such as thrombotic occlusion and avascular villi, were reported, indicating a major, but secondary, role in fetal circulatory compromise.

Villous developmental abnormalities were frequently reported, mainly syncytial knotting and villous hypoplasia, which means that there was a decrease in the villous surface area for maternal-fetal exchange. Some studies showed inflammatory lesions (villitis of unknown etiology) which were less common but always present, indicating immune-mediated injury in some cases

Table 4 Summary of Key Pathological Patterns in LBW Placenta

Pathological Pattern	Histological Features	Pathophysiological Mechanism	Impact on Fetal Growth
MVM	Atherosis, fibrinoid necrosis, distal villous hypoplasia	Impaired uteroplacental perfusion	Chronic hypoxia
FVM	Thrombi, avascular villi	Fetal circulation impairment	Nutrient restriction
Infarction	Ischemic necrosis of villi	Severe vascular insufficiency	Placental failure
Villous abnormalities	Syncytial knotting, hypoplasia	Reduced exchange surface	Growth restriction
VUE	Chronic lymphocytic infiltration	Immune-mediated injury	Inflammatory damage

4. Integrated Pattern of Placental Pathology

Taken together, the reported histopathological abnormalities indicate a consistent pattern of the co-occurrence of vascular and structural abnormalities in LBW placentas. Maternal vascular malperfusion is the most consistent and most prominent lesion as observed in all studies, often in association with placental infarction and villous immaturity.

In severe LBW phenotypes, fetal vascular malperfusion lesions were frequently found, indicating correlation with the severity of the disease. Vascular lesions were not the only type observed, as inflammatory lesions, though not as common, were also frequently seen, suggesting a possible synergistic effect between inflammation and poor blood supply.

4.1. Summary of Key Findings

Analysis of 44 studies included shows a consistently high pathological signature for LBW placentas in which:

- In most studies, the predominant maternal vascular malperfusion was across most of the studies.
- Frequent placental infarction (chronic ischemic injury)
- Late onset of symptoms (usually after the first 20 weeks of gestation)
- Abnormal development of the villous lining, which is widespread, indicating impairment of the formation of exchange surfaces.
- Repeatedly and progressively inflammatory lesions that lead to immune mediated damage

Taken together, these results suggest that LBW is tightly linked to a reproducible pattern of placental vascular, structural and inflammatory abnormalities, with maternal vascular malperfusion as the central pathological axis.

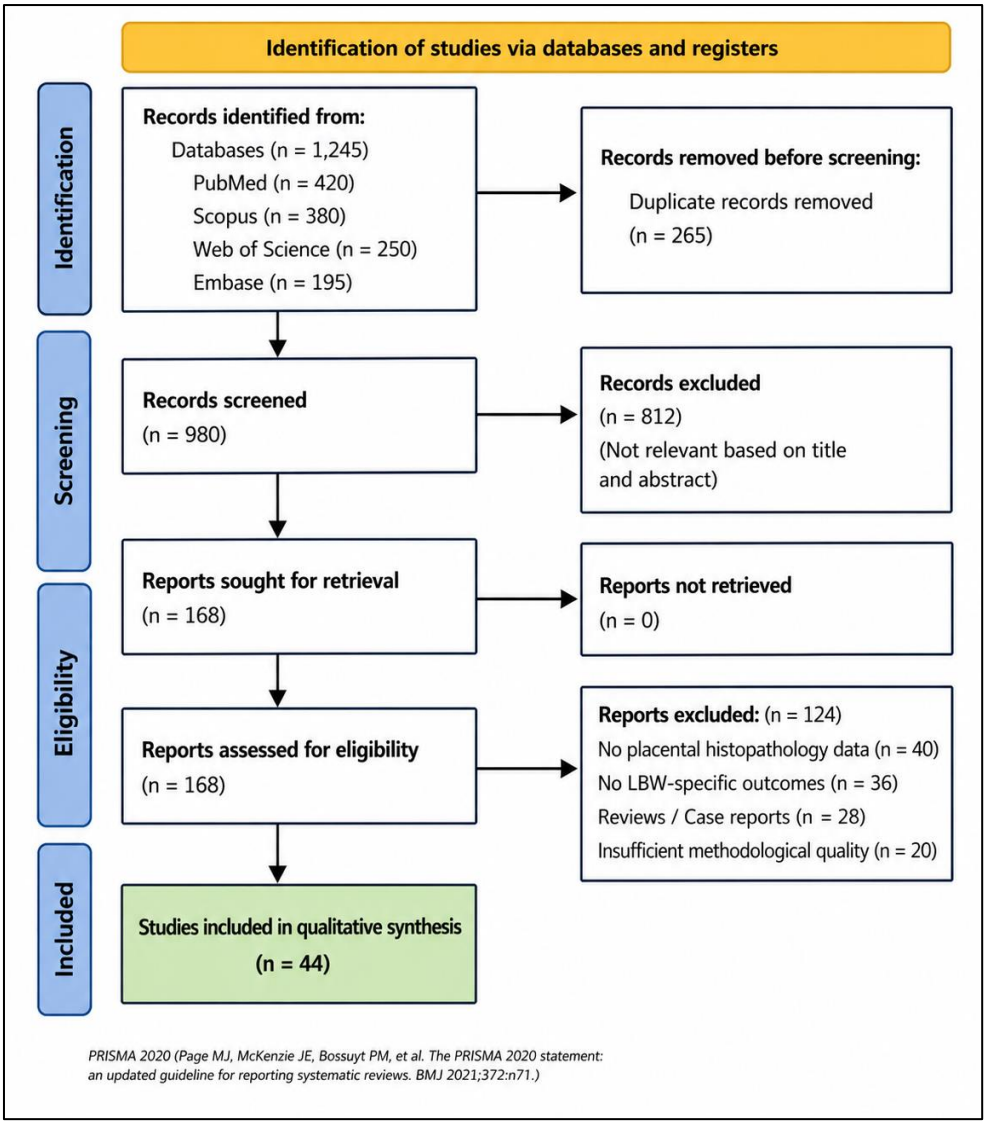

Figure 1 PRISMA 2020 flow diagram for systematic reviews

5. Mechanistic Insights

5.1. Hypoxia and Oxidative Stress

The hypoxic intrauterine environment induced by reduced uteroplacental perfusion leads to an excess production of reactive oxygen species (ROS). This oxidative stress leads to a progressive injury of the cells through lipid peroxidisation, protein modification and DNA injury, thus altering the integrity and function of the placenta.

5.2. Endothelial Dysfunction

There is strong association of placental hypoperfusion with endothelial injury, with loss of angiogenic signaling and vascular adaptation. This includes poor spiral artery remodeling, causing poor uteroplacental blood flow and causing more fetal growth restriction.

5.3. Immune Dysregulation

There is a disturbed immunological milieu, reflected by disturbed cytokine profiles. A pro-inflammatory environment/circumstance is observed, involving an increase in the expression of inflammatory mediators which perpetuates inflammation of the placenta and compromises maternal–fetal immune tolerance.

6. Clinical Implications

Histopathological changes of the placenta present a promising clinical risk stratification biomarker.

- **Diagnostic use**: May help in identifying pregnancies at high risk for complications.
- **Prognostic utility:** This is due to its contribution in predicting long-term developmental outcomes and neonatal morbidity.
- **Clinical application**: Can provide information on targeted preventive measures in the prenatal period and provide structure for postnatal surveillance of affected neonates.

7. Discussion

The results of this systematic review support the concept of placental dysfunction as a key and unifying mechanism in the pathogenesis of low birth weight (LBW). In the spectrum of placental lesions, maternal vascular malperfusion (MVM) is always the most common and always the most strongly associated pathological pattern, and therefore is the most critical factor in reducing fetoplacental perfusion. The results confirm that lack of spiral artery remodeling and subsequent chronic uteroplacental hypoperfusion are important upstream events leading to placental insufficiency and fetoplacental growth restriction [26,27].

In addition to vascular pathology, fetal and inflammatory vascular malperfusion lesions imply that LBW is a multifactorial, interdependent disease. Chronic placental inflammation and fetal vascular compromise indicate that LBW is not simply a reflection of maternal hemodynamic dysfunction, but that fetal vascular pathology, immune dysregulation and fetal disturbances of blood flow interact to produce LBW in the placenta [28]. This combined pathological environment is a response to a variety of maternal, fetal and environmental insults, shared downstream [29].

Most notably, these placental abnormalities may be the morphological culmination of parallel pathogenic mechanisms of oxidative stress, endothelial injury and immune activation [30]. Mechanistic overlap offers a biologically plausible explanation for the coexistence of multiple lesion types within the same placenta, and supports the concept of LBW as a syndrome of placental insufficiency instead of a single-etiology disorder [31,32].

In a clinical view, the constant correlation between certain placentas lesions and LBW strongly underlines the importance of detailed placental histopathological examination for diagnosis and prognosis. The identification of MVM and related lesions can help in earlier detection of high-risk pregnancies, prediction of adverse neonatal outcomes, and targeted surveillance strategies [33]. In addition, the results here provide a novel direction towards translating modulation of maternal vascular function and inflammatory pathways into prevention and/or treatment of placental insufficiency [34,35].

The overall picture drawn from the evidence included in this review confirms the validity of the “placentally mediated” paradigm and the fact that the LBW condition has several different pathological processes, which are also interrelated, thus requiring integrated maternal–fetal evaluation and multi-disciplinary clinical management.

Limitations

Although extensive evidence has been built up, there are some limitations to be noted. The first limitation is that there is a great deal of variation between studies in terms of study design, population characteristics and inclusion criteria, which can impact comparison of results. Secondly, the pathological classification of placentas is not always consistent, and reporting of lesions is not standardized meaning that patterns cannot be uniformly interpreted between various cohorts. Third, most data available are from cross-sectional or retrospective studies, so that few well designed longitudinal studies have been performed to draw inferences regarding temporal and causal links between placental lesions and the development of low birth weight.

8. Conclusion

Histopathological evaluation of the placenta is a powerful and essential tool to help understand the underlying causes of LBW. The close relationship between certain types of placental lesions and FGR further highlights the importance of placental's dysfunction in pathogenesis. But to progress towards diagnostic precision and clinical application, the use of the traditional histopathology with the new molecular and biomarker-based methods will need to be integrated.

These multi-faceted approaches offer great potential in terms of risk stratification, early detection and targeted therapeutic interventions.

Future Directions

Further research is needed to transition to a more integrated and multi-disciplinary approach to improve understanding of placental mediated foetal growth restriction. Key priorities include:

- **Combining multi-omics technologies**: Using genomics, transcriptomics, proteomics and metabolomics in addition to histopathological results to gain insight into the underlying molecular mechanisms.
- **Classification systems**: Establishment of universally accepted and reproducible criteria for classification of placental lesions for better comparability between studies.
- **Large-scale**, Development of large, well-documented cohorts to examine temporal relationships and causal pathways between placental pathology with adverse fetal/neonatal outcomes.

These combined advances should improve the degree of accuracy in diagnosis, further define the mechanistic underpinnings of low birth weight, and enable the creation of strategies tailored to individual pregnancies for prevention and/or therapy..

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