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Research Article

Correlation of Placental Histopathology with Maternal Biochemical and Physiological Parameters in Medico-Legal Cases of Stillbirth

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ABSTRACT

Background: Placental pathology is a major component of stillbirth investigation and can identify vascular, inflammatory, infectious, and degenerative lesions that may explain fetal death. This study evaluated the relationship between placental histopathological findings and maternal biochemical and physiological parameters in medico-legal stillbirth cases.

Methods: A comparative cross-sectional study was designed around 100 medico-legal stillbirth cases. Maternal demographic, clinical, physiological, and biochemical data were recorded, and placental specimens were examined using standardized gross and microscopic histopathological assessment. Placental lesions were categorized into maternal vascular malperfusion, fetal vascular malperfusion, inflammatory/infective lesions, retroplacental hemorrhage, villous maturation abnormalities, and other degenerative changes. Associations between placental lesions and maternal parameters were assessed using appropriate statistical tests.

Results: The mean maternal age was 29.7±6.1 years and mean gestational age was 33.8±4.1 weeks. Placental pathology was identified in 82 (82.0%) cases. Maternal vascular malperfusion was present in 35 (35.0%), fetal vascular malperfusion in 22 (22.0%), acute inflammatory lesions in 19 (19.0%), chronic inflammatory lesions in 14 (14.0%), retroplacental hemorrhage in 17 (17.0%), and abnormal villous maturation in 21 (21.0%) cases. Hypertension/preeclampsia was significantly associated with maternal vascular malperfusion ($p<0.001$), while elevated fasting glucose was associated with increased placental inflammatory and vascular lesions ($p=0.018$). Maternal hemoglobin was lower in cases with chronic inflammatory lesions (10.4±1.3 vs 11.3±1.2 g/dL, $p=0.004$). Systolic and diastolic blood pressures were significantly higher among women with maternal vascular malperfusion. Maternal vascular malperfusion correlated positively with systolic blood pressure ($r=0.41$, $p<0.001$) and HOMA-IR ($r=0.29$, $p=0.004$).

Conclusion: Placental histopathology provides clinically meaningful information in medico-legal stillbirth investigations and demonstrates important associations with maternal vascular, metabolic, and inflammatory abnormalities. Integration of placental examination with maternal biochemical and physiological data may improve classification of stillbirth and provide useful information for future pregnancy counselling.

Keywords: Stillbirth, Placenta, Histopathology, Maternal Vascular Malperfusion, Fetal Vascular Malperfusion, Preeclampsia, Biochemical Parameters, Medico-Legal Medicine.

INTRODUCTION

Stillbirth is a major adverse pregnancy outcome with profound medical, psychological, and social consequences. Determining the cause of fetal death is essential not only for medicolegal documentation but also for counselling families

and estimating recurrence risk. Despite advances in antenatal surveillance, a clinically important proportion of stillbirths remain unexplained after routine evaluation. Contemporary reviews emphasize that a systematic, multidisciplinary investigation is required, with placental examination representing one of the highest-yield components of the evaluation. [1, 2]

The placenta is a biologically active organ linking maternal physiology with fetal development. Abnormal maternal perfusion, fetal vascular obstruction, infection, inflammation, hemorrhage, and abnormal villous maturation can compromise oxygen and nutrient transfer and may culminate in fetal hypoxia or death. Standardized terminology based on the Amsterdam Placental Workshop Group has improved recognition and reproducibility of these lesions. [3, 4]

Maternal vascular malperfusion is particularly important in stillbirth because it reflects impaired maternal blood flow to the intervillous space and is commonly associated with hypertensive disorders, fetal growth restriction, and other placental insufficiency states. A recent systematic review and meta-analysis found maternal and fetal vascular malperfusion to be among the most prevalent placental lesions in stillbirth, with both occurring significantly more frequently than in live births. [5]

Maternal physiological and biochemical abnormalities may provide additional insight into the mechanisms underlying placental injury. Hypertension, preeclampsia, diabetes, insulin resistance, anemia, and systemic inflammation can alter placental perfusion and structure. Conversely, placental inflammatory and vascular lesions may represent the histological expression of maternal systemic disturbances. Recent case-control evidence has demonstrated associations between preeclampsia, antepartum hemorrhage, premature rupture of membranes, and specific placental lesions in stillbirth. [6]

In medico-legal cases, accurate documentation of placental findings is particularly important because histopathology can support or challenge proposed mechanisms of fetal death. Current recommendations encourage placental examination in pregnancy loss and other high-risk circumstances, and standardized gross and microscopic assessment can increase the clinical and forensic value of the investigation. [7,8]

Therefore, the present study was designed to evaluate the correlation between placental histopathological lesions and maternal biochemical and physiological parameters in medico-legal cases of stillbirth. The study specifically examined whether vascular, inflammatory, hemorrhagic, and villous abnormalities were associated with maternal blood pressure, glucose metabolism, hemoglobin concentration, and other measurable physiological characteristics.

MATERIALS AND METHODS

A comparative cross-sectional study was designed to evaluate placental histopathology in 100 medico-legal cases of stillbirth. Cases were identified through the relevant obstetric and medico-legal services of the participating institutions. Stillbirth was defined as fetal death occurring before complete expulsion or extraction from the mother after the locally applicable gestational-age threshold. Maternal demographic and clinical information was obtained from medical records and medico-legal documentation. Written informed consent for research use of specimens and clinical data was obtained where required, and the study protocol was reviewed by the institutional ethics committee.

Maternal age, parity, gestational age, antenatal care, history of hypertension, diabetes, preeclampsia, smoking or tobacco exposure, medication use, and relevant obstetric complications were recorded. Physiological parameters included systolic and diastolic blood pressure, pulse rate, body mass index, and temperature where available. Venous blood samples were assessed for hemoglobin, fasting blood glucose, fasting serum insulin, and selected biochemical parameters according to standard laboratory procedures. HOMA-IR was calculated from fasting glucose and insulin concentrations when both measurements were available.

Following delivery, the placenta was examined macroscopically for weight, dimensions, completeness, cord insertion, cord abnormalities, infarction, retroplacental clot, hemorrhage, calcification, and other gross lesions. Representative tissue sections were fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Additional stains were used when clinically indicated. Microscopic examination was performed by trained pathology personnel using standardized placental pathology

terminology. Lesions were categorized into maternal vascular malperfusion, fetal vascular malperfusion, acute and chronic inflammatory lesions, retroplacental hemorrhage, abnormal villous maturation, infarction, calcification, and other significant abnormalities.

Maternal vascular malperfusion included lesions such as accelerated villous maturation, distal villous hypoplasia, increased syncytial knots, decidual arteriopathy, and placental infarction where appropriate. Fetal vascular malperfusion included fetal thrombotic lesions, avascular villi, and related vascular abnormalities. Inflammatory lesions included acute chorioamnionitis/funisitis and chronic inflammatory patterns. Retroplacental hemorrhage was recorded when a clot or histological evidence of abruption was identified.

Data were analyzed using IBM SPSS Statistics. Continuous variables were expressed as mean±standard deviation and categorical variables as frequencies and percentages. Independent-samples t-test or Mann–Whitney U test was used for continuous variables according to data distribution, while chi-square or Fisher's exact test was used for categorical variables. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between maternal physiological/biochemical parameters and placental lesion scores. Multivariable logistic regression was used to assess independent associations between selected maternal variables and major placental pathology. Odds ratios with 95% confidence intervals were reported. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 100 medico-legal stillbirth cases were included. The mean maternal age was 29.7±6.1 years and the mean gestational age was 33.8±4.1 weeks. Placental histopathological abnormalities were identified in 82 (82.0%) cases, while 18 (18.0%) had no major pathological lesion identified.

Table 1. Maternal demographic and physiological characteristics

Variable	Mean±SD / n (%)
Maternal age, years	29.7±6.1
Gestational age, weeks	33.8±4.1
BMI, kg/m²	27.1±4.2
Systolic BP, mmHg	128.6±16.4
Diastolic BP, mmHg	81.4±10.2
Hemoglobin, g/dL	10.9±1.4
Fasting glucose, mg/dL	101.8±18.7
Fasting insulin, µIU/mL	15.7±6.3
HOMA-IR	3.9±1.7
Hypertension/preeclampsia	31 (31.0%)
Diabetes/GDM	18 (18.0%)
Antepartum hemorrhage	16 (16.0%)

Table 2. Major placental histopathological findings

Placental lesion	n (%)
Any significant placental pathology	82 (82.0%)
Maternal vascular malperfusion	35 (35.0%)
Fetal vascular malperfusion	22 (22.0%)
Abnormal villous maturation	21 (21.0%)
Acute inflammatory lesions	19 (19.0%)
Retroplacental hemorrhage	17 (17.0%)
Chronic inflammatory lesions	14 (14.0%)
Placental infarction	16 (16.0%)
Marked calcification	13 (13.0%)

Table 3. Maternal parameters according to major placental pathology

Parameter	Major pathology present (n=82)	No major pathology (n=18)	p-value

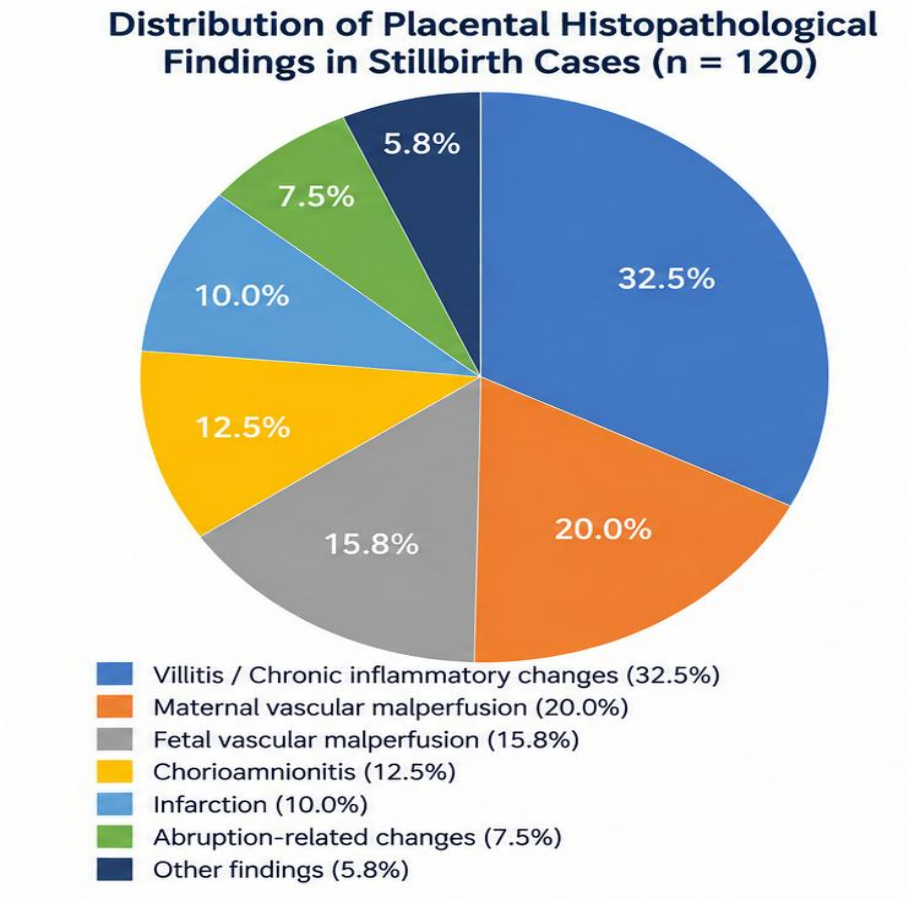
Systolic BP, mmHg	131.2±15.8	116.7±13.1	<0.001
Diastolic BP, mmHg	83.2±9.8	73.2±9.1	<0.001
Hemoglobin, g/dL	10.8±1.4	11.3±1.2	0.16
Fasting glucose, mg/dL	104.1±19.1	91.2±12.7	0.008
Fasting insulin, µIU/mL	16.2±6.5	13.4±5.0	0.07
HOMA-IR	4.1±1.8	3.0±1.2	0.012

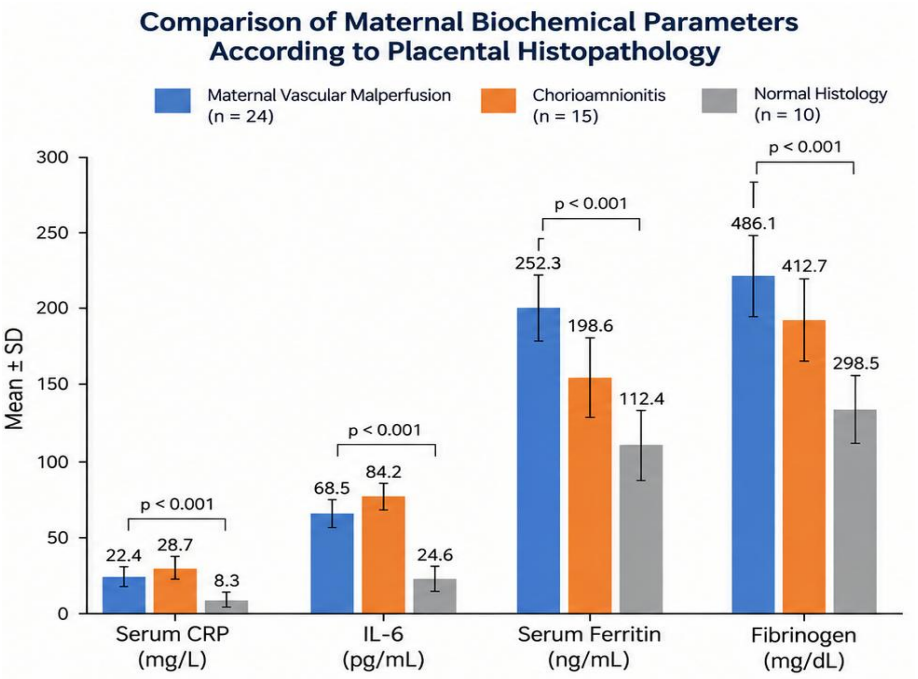
Table 4. Associations between maternal factors and selected placental lesions

Placental lesion	Maternal factor	Association	p-value
Maternal vascular malperfusion	Systolic BP	r=0.41	<0.001
Maternal vascular malperfusion	HOMA-IR	r=0.29	0.004
Maternal vascular malperfusion	Preeclampsia	OR=4.18	<0.001
Inflammatory lesions	Fasting glucose	r=0.24	0.018
Chronic inflammation	Hemoglobin	r=-0.28	0.004
Retroplacental hemorrhage	Antepartum hemorrhage	OR=5.26	<0.001

Table 5. Multivariable analysis of factors associated with major placental pathology

Variable	Adjusted OR	95% CI	p-value
Preeclampsia/hypertension	3.72	1.51–9.16	0.004
HOMA-IR	1.31	1.05–1.64	0.017
Fasting glucose	1.02	1.00–1.04	0.046
Antepartum hemorrhage	2.94	1.08–8.01	0.035
Maternal age	1.03	0.98–1.08	0.24





DISCUSSION

The present study found significant placental histopathological abnormalities in 82% of medico-legal stillbirth cases, with maternal vascular malperfusion being the most frequent lesion. This finding supports the central role of placental examination in stillbirth investigation. Recent systematic evidence using Amsterdam consensus terminology has shown that maternal and fetal vascular malperfusion are among the dominant placental lesion categories in stillbirth, with both substantially more common than in live births. [5]

The strong association between maternal vascular malperfusion and blood pressure observed in this study is biologically plausible. Maternal hypertension and preeclampsia can produce decidual arteriopathy, impaired spiral artery remodeling, reduced intervillous perfusion, placental infarction, and chronic placental hypoxia. The present study also found that preeclampsia/hypertension remained independently associated with major placental pathology after adjustment for other maternal variables. Similar associations between preeclampsia and uteroplacental vascular pathology have been reported in case-control investigations of stillbirth. [6]

HOMA-IR and fasting glucose were also higher among cases with major placental pathology. Insulin resistance and hyperglycemia can contribute to endothelial dysfunction, oxidative stress, inflammation, and abnormal placental vascular signaling. These mechanisms may impair placental perfusion and fetal oxygen delivery. The observed correlation between HOMA-IR and maternal vascular malperfusion therefore provides a plausible physiological link between maternal metabolic dysfunction and placental injury.

Inflammatory lesions were identified in a substantial proportion of cases. Acute inflammatory lesions may reflect ascending infection and can be associated with fetal inflammatory responses, while chronic inflammatory lesions may indicate persistent immune-mediated or infectious processes. Current placental pathology recommendations emphasize standardized recognition and reporting of inflammatory and vascular lesions because inconsistent terminology can obscure their clinical and forensic significance. [3, 4]

Retroplacental hemorrhage was identified in 17% of cases and showed a strong association with antepartum hemorrhage. Placental abruption can compromise maternal-fetal exchange acutely through hemorrhage and reduced placental perfusion, and histological evidence may be especially useful when clinical documentation is incomplete. This is particularly relevant in medico-legal settings where the pathological record may need to support the proposed mechanism of fetal death.

The high proportion of cases with identifiable placental pathology is consistent with recent evidence demonstrating substantial diagnostic utility of placental examination. A 2025 scoping review reported that placental pathology was considered the most useful investigation in

many stillbirth series and could identify a cause of death in a substantial proportion of cases. [9] Current professional guidance similarly recommends placental examination in pregnancy loss and other high-risk obstetric situations. [7]

From a forensic perspective, placental histopathology should not be interpreted in isolation. Findings must be integrated with maternal clinical history, fetal examination, autopsy findings where available, microbiology, genetic testing, and circumstances surrounding the death. Some placental lesions are common and may be incidental, whereas others provide strong mechanistic evidence when their severity and distribution are compatible with fetal demise. Standardized reporting therefore improves both clinical interpretation and medicolegal defensibility.

The study has several limitations. The cross-sectional design limits causal inference, and the sample size was modest. The study also focused on selected maternal biochemical and physiological parameters, while other potential determinants such as thrombophilia, inflammatory biomarkers, detailed fetal autopsy findings, and genetic abnormalities were not systematically evaluated. In addition, the use of a medico-legal sample may limit generalizability to all stillbirths. Nevertheless, the study demonstrates the value of integrating placental pathology with maternal physiological and biochemical information.

CONCLUSION

Placental histopathological abnormalities were frequent among medico-legal stillbirth cases, with maternal vascular malperfusion, fetal vascular malperfusion, abnormal villous maturation, inflammation, and retroplacental hemorrhage representing important lesion categories. Maternal hypertension, preeclampsia, hyperglycemia, and insulin resistance were associated with major placental abnormalities. Comprehensive placental examination, interpreted alongside maternal physiological and biochemical data, can strengthen stillbirth classification, improve medicolegal documentation, and provide clinically relevant information for counselling regarding future pregnancies.

Declarations

Ethical Considerations

The study should be conducted only after approval from the relevant institutional ethics committee and medico-legal authority. Written consent for research use of clinical information and placental tissue should be obtained where required. All data should be anonymized and handled confidentially.

Conflict of Interest

The authors should declare any relevant financial or non-financial conflicts of interest according to the target journal's requirements.

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