RESEARCH PAPER

Morphological and Histopathological Analysis of Placenta in Pregnancy-Induced Hypertension: Comprehensive Evaluation with Fetal Outcome Correlations

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ABSTRACT

Background: Pregnancy-induced hypertension (PIH) affects 5-10% of pregnancies globally and remains a leading cause of maternal and perinatal morbidity. The placenta serves as a critical witness to the disease process, yet comprehensive morphological examination remains underutilized in routine obstetric practice. This study systematically evaluates gross and histopathological placental alterations in PIH and establishes correlations with maternal disease severity and fetal outcomes.

Material and Methods: This prospective observational study examined 54 fresh placentae from PIH-complicated pregnancies delivered at BVDU Medical College Hospital, Sangli over 18 months. Standardized gross morphometry documented placental weight, dimensions, cord insertion patterns, and infarction prevalence. Histopathological analysis with hematoxylin-eosin staining quantified syncytial knots, intervillous fibrin deposition, decidual arteriopathy, and ischemic changes. Clinical data including PIH onset trimester, blood pressure, proteinuria, maternal hemoglobin, and neonatal birth weight were correlated with pathological findings.

Results: Mean placental weight was 321.4±78.2 g, with 64.8% below the 10th percentile for gestational age. Eccentric cord insertion predominated (59.3%), and infarction affected 53.7% of specimens (73.5% in second trimester vs 20.0% in third trimester, $p<0.001$). Microscopically, excessive syncytial knots (>30% villi) were observed in 70.4%, intervillous fibrin deposition in 83.3%, and decidual arteriopathy in 57.4%. Second trimester PIH onset correlated with significantly lower placental weight (284.5±42.3 vs 382.1±56.7 g, $p<0.001$), higher infarct prevalence (73.5% vs 20.0%, $p<0.001$), and lower birth weight (1.62±0.31 vs 2.18±0.29 kg, $p<0.001$). Multivariate analysis identified infarction >20% surface area (OR 5.2), placental weight <300 g (OR 3.9), and syncytial knot density >40% (OR 4.1) as independent predictors of low birth weight.

Conclusion: PIH induces characteristic, quantifiable placental pathology with severity directly correlating with disease onset timing and neonatal outcomes. Systematic placental examination provides clinically relevant prognostic information and should be integrated into routine management of PIH-complicated pregnancies.

Keywords: Placenta, Pregnancy-induced hypertension, Preeclampsia, Syncytial knots, Placental infarction, Fetal growth restriction, Decidual arteriopathy.

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1. INTRODUCTION

1.1 Clinical Significance of Pregnancy-Induced Hypertension

Pregnancy-induced hypertension (PIH) encompasses a spectrum of hypertensive disorders arising after 20 weeks gestation, including gestational hypertension, preeclampsia, and eclampsia. Affecting 5-10% of pregnancies worldwide, PIH remains a leading cause of maternal mortality, accounting for approximately 14% of maternal deaths globally, and contributes substantially to preterm birth, intrauterine growth restriction (IUGR), and perinatal death.[1,2] In India, the prevalence ranges from 8-12%, with higher rates in primigravida and teenage pregnancies.[3]

1.2 The Placenta as a Pathological Mirror

The human placenta functions as the vital fetomaternal interface, orchestrating nutrient and gas exchange, waste elimination, endocrine regulation, and immunological tolerance.[4] Beyond these physiological roles, placental morphology serves as a permanent histological record of the intrauterine environment, faithfully documenting antenatal stressors including hypertensive disorders.[5] In PIH, the placenta is both a **witness**—recording chronic ischemic insult through characteristic morphological adaptations—and a **perpetrator**—actively contributing to disease propagation through release of anti-angiogenic factors and inflammatory mediators into the maternal circulation.[6]

1.3 Pathophysiological Framework

The pathophysiological foundation of PIH rests upon incomplete trophoblastic invasion of maternal spiral arteries during early placentation.[7] In normal pregnancy, extravillous trophoblasts migrate through the decidua and inner myometrium, transforming narrow, muscular spiral arteries into high-caliber, low-resistance vessels incapable of vasoconstriction—a process completed by 18-20 weeks gestation.[8] In PIH, this physiological vascular remodeling fails, particularly affecting myometrial segments, resulting in persistent high-resistance, low-flow uteroplacental circulation.[9]

The consequent chronic ischemia-reperfusion injury generates oxidative stress, endoplasmic reticulum stress, and the release of anti-angiogenic factors (soluble fms-like tyrosine kinase-1, soluble endoglin) into the maternal circulation, producing the systemic endothelial dysfunction characteristic of preeclampsia.[10]

1.4 Placental Manifestations of PIH

The placental response to hypoxic-ischemic injury follows predictable adaptive and degenerative pathways:[11]

- **Syncytial knots (Tenney-Parker change):** Accelerated trophoblast apoptosis manifesting as multilayered aggregates of hyperchromatic nuclei protruding from villous surfaces
- **Intervillous fibrin deposition:** Consequence of turbulent, sluggish maternal blood flow through the intervillous space
- **Villous hypovascularity and stromal fibrosis:** Chronic ischemic injury leading to reduced capillary density and collagen deposition
- **Infarction:** Endpoint of severe, sustained ischemia with coagulative necrosis of villous tissue
- **Decidual arteriopathy:** Fibrinoid necrosis and acute atherosis of decidual vessels, directly evidencing maternal vascular malperfusion

1.5 Clinicopathological Correlations and Knowledge Gaps

Clinical severity of PIH correlates directly with the extent and character of placental pathology.[12] Early-onset preeclampsia (<34 weeks) consistently demonstrates more extensive placental lesions compared to late-onset variants, suggesting a predominant placental origin.[13] Despite five decades of research documenting these associations, routine placental examination following hypertensive pregnancies remains inconsistent.[14] Barriers include time constraints, perceptions of low diagnostic yield, inadequate training in placental pathology, absence of standardized reporting protocols, and poor communication between clinical and pathology services.[15]

1.6 Study Rationale and Objectives

This study addresses critical gaps through comprehensive, systematic analysis of 54 PIH-complicated placentae. Specific objectives were: (1) detailed gross morphometric characterization using standardized protocols; (2) systematic histopathological evaluation with quantitative lesion assessment; (3) trimester-specific correlations with maternal-neonatal outcomes; (4) identification of independent placental predictors of adverse fetal outcomes; and (5) proposal of evidence-based thresholds for clinically significant placental lesions.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This prospective, observational, hospital-based cross-sectional study was conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynecology, BVDU Medical College and Hospital, Sangli, Maharashtra, India, over 18 months (January 2018 to December 2019).

2.2 Study Population

The study comprised 54 consecutive fresh placentae from mothers satisfying ACOG diagnostic criteria for PIH: systolic BP ≥140 mmHg or diastolic ≥90 mmHg on ≥2 occasions ≥6 hours apart after 20 weeks gestation in previously normotensive women.[16] Both gestational hypertension and preeclampsia were included.

Inclusion Criteria: Singleton live pregnancy ≥28 weeks, complete clinical records, fresh placenta received within 30 minutes of delivery, maternal age 18-45 years.
Exclusion Criteria: Multiple gestation, major congenital anomalies, intrauterine fetal demise, chronic hypertension, pre-existing diabetes mellitus, chronic renal disease, autoimmune disorders, incomplete specimens or clinical data.[17]

2.3 Clinical Data Collection

Maternal parameters recorded: age, parity, gestational age at diagnosis and delivery, blood pressure at admission and maximum recorded, proteinuria (dipstick/24-hour quantification), hemoglobin, platelet count, serum uric acid, mode of delivery. Neonatal parameters: birth weight, gestational age at delivery, APGAR scores at 1 and 5 minutes, NICU admission, perinatal complications.

2.4 Placental Collection and Gross Examination

Placentae received fresh within 30 minutes of delivery were examined per standardized Amsterdam Placental Workshop Group consensus protocol.[18]

Gross Parameters Documented:

- **Trimmed weight (g):** After gentle clot removal using calibrated electronic scale
- **Maximum and minimum diameter (cm):** Greatest and perpendicular dimensions
- **Thickness (cm):** Measured at central parenchyma
- **Umbilical cord:** Length, diameter, insertion type (central/eccentric/marginal/velamentous), vessel number, coiling index
- **Fetal surface:** Color, transparency, subchorionic fibrin, thrombi, meconium staining
- **Maternal surface:** Cotyledon number and completeness, retroplacental hematoma
- **Parenchyma:** Serial sectioning at 1 cm intervals; number, location, dimensions, and estimated percentage of infarcts; other lesions

2.5 Histopathological Processing and Examination

Following gross examination, placentae were fixed in 10% neutral buffered formalin for 48 hours. Standardized tissue sampling included:[19]

- Two full-thickness blocks from grossly normal paracentral parenchyma
- Two blocks from fetal surface
- Umbilical cord sections (fetal, mid, placental ends)
- Membrane roll ("jelly roll")
- Representative blocks from infarcted areas and other lesions

Tissues were processed automatically, embedded in paraffin, sectioned at 4-5 μm, and stained with hematoxylin-eosin. Selected cases underwent Masson's trichrome and Perls' Prussian blue staining.

All slides were examined independently by two pathologists blinded to clinical details, with discrepancies resolved by consensus.

Histopathological Parameters Assessed:

Villous Tissue:

- **Syncytial knots:** Percentage of terminal villi containing ≥10 hyperchromatic nuclei protruding from villous surface (10 consecutive HPFs, 400×). Tenney-Parker change defined as >30% affected villi.
- **Intervillous fibrin deposition:** Semi-quantitative score: 0 (absent), 1+ (focal, <10% fields), 2+ (multifocal, 10-30%), 3+ (diffuse, >30%)
- **Villous infarcts:** Coagulative necrosis with crowded eosinophilic ghost villi; classified as recent, subacute, or remote
- **Villous hypovascularity:** Reduced capillary profiles within terminal villi
- **Stromal fibrosis:** Increased eosinophilic collagen deposition
- **Chorangiosis:** ≥10 capillaries per villus in ≥10 villi per 10 fields
- **Fetal thrombotic vasculopathy:** Avascular fibrotic villi with vascular thrombi

Decidual Vessels:

- **Acute atherosis:** Fibrinoid necrosis with foamy macrophage infiltration
- **Fibrinoid necrosis:** Homogeneous eosinophilic vessel wall transformation
- **Vascular thrombosis**
- **Failed physiological remodeling:** Absent/incomplete trophoblast invasion

Membranes and Cord:

- Chorioamnionitis (stage/grade), meconium-associated changes, funisitis

2.6 Composite Placental Histopathology Score

A composite score (0-21) was developed incorporating seven parameters: syncytial knot density, intervillous

fibrin extent, villous infarct percentage, decidual arteriopathy, villous hypovascularity, stromal fibrosis, and meconium staining. Each parameter scored 0-3 based on validated thresholds.

2.7 Statistical Analysis

Data were entered in Microsoft Excel 2016 and analyzed using IBM SPSS Statistics version 25.0. Continuous variables expressed as mean±SD (normal distribution) or median with IQR (non-normal). Categorical variables expressed as frequencies (n) and percentages (%).

Comparative statistics: Independent t-test/Mann-Whitney U test for continuous variables; Chi-square/Fisher's exact test for categorical variables.

Correlation analysis: Pearson (normal distribution) or Spearman (non-normal/ordinal) correlation coefficients.

Regression analysis: Univariate followed by multivariate logistic regression (stepwise forward selection) to identify independent predictors of low birth weight and composite adverse neonatal outcome. Adjusted odds ratios (OR) with 95% confidence intervals (CI) calculated.

ROC curve analysis: Performed to determine optimal cut-off values for placental weight, infarction percentage, and syncytial knot density in predicting low birth weight. Youden's index maximized to identify threshold values.

Statistical significance set at $p<0.05$ (two-tailed).

2.8 Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of BVDU Medical College and Hospital, Sangli (IEC No. BVDU/MC/2017/142). Written informed consent was obtained from all participating mothers. The research was conducted in accordance with the Declaration of Helsinki (2013 revision) and ICMR National Ethical Guidelines.

3. RESULTS

3.1 Demographic and Clinical Characteristics

The study cohort comprised 54 mothers with PIH-complicated pregnancies (mean age 25.4±4.2 years, range 19-38 years). Primigravida constituted exactly half (27/54, 50.0%).

PIH Onset: Second trimester onset (20-28 weeks) occurred in 34 mothers (63.0%), while third trimester onset (>28 weeks) occurred in 20 (37.0%). Mean gestational age at diagnosis was 26.8±4.3 weeks, and at delivery was 35.2±2.7 weeks, with 70.4% delivering preterm (<37 weeks).

Blood Pressure Profile: Mean systolic BP at admission was 156.4±14.8 mmHg, mean diastolic BP 98.6±8.7 mmHg. Severe hypertension (≥160/110 mmHg) was documented in 19 mothers (35.2%). Proteinuria (≥1+ or ≥300 mg/24h) was present in 38 cases (70.4%), fulfilling preeclampsia criteria.

Maternal Laboratory Parameters: Anemia (Hb <11 g/dL) affected 27 mothers (50.0%). Thrombocytopenia (platelets <150,000/μL) occurred in 13 cases (24.1%), with 4 cases (7.4%) meeting HELLP syndrome criteria. Serum uric acid was elevated (>5.5 mg/dL) in 31 mothers (57.4%).

Mode of Delivery: Cesarean section was performed in 39 cases (72.2%). Indications included fetal distress (35.9%), severe PIH with failed induction (28.2%), non-progress of labor (15.4%), malpresentation (10.3%), and previous cesarean section (10.3%).

Table 1. Demographic and clinical characteristics (N=54)

Parameter	Category	n (%)	Mean ± SD
Maternal age (years)	20-25	22 (40.7)	25.4±4.2
	26-30	24 (44.4)	
	>30	8 (14.8)	
Parity	Primigravida	27 (50.0)	-
	Multigravida	27 (50.0)	
PIH onset	2nd trimester	34 (63.0)	23.4±2.1 wk
	3rd trimester	20 (37.0)	32.6±2.8 wk
Gestational age at delivery	Preterm (<37 wk)	38 (70.4)	35.2±2.7 wk
	Term (≥37 wk)	16 (29.6)	

Hypertension severity	Mild-moderate	35 (64.8)	SBP 156.4±14.8
	Severe	19 (35.2)	DBP 98.6±8.7
Proteinuria	Present	38 (70.4)	-
	Absent	16 (29.6)	
Maternal anemia	Hb <11 g/dL	27 (50.0)	10.2±1.3 g/dL
	Hb ≥11 g/dL	27 (50.0)	12.1±0.8 g/dL
Thrombocytopenia	Platelets <1.5 lakh/μL	13 (24.1)	1.2±0.3 lakh/μL
Serum uric acid	Elevated (>5.5 mg/dL)	31 (57.4)	6.8±1.1 mg/dL

3.2 Neonatal Outcomes

Mean neonatal birth weight was 1.82±0.41 kg (range 0.96-2.85 kg). Low birth weight (LBW, <2.5 kg) occurred in 41 neonates (75.9%), very low birth weight (VLBW, <1.5 kg) in 12 (22.2%), and extremely low birth weight (ELBW, <1.0 kg) in 3 (5.6%). Small for gestational age (SGA, <10th percentile) was documented in 36 neonates (66.7%).

Mean APGAR scores were 6.2±1.4 at 1 minute and 7.8±1.1 at 5 minutes; 14 neonates (25.9%) had 5-minute APGAR <7. Fetal distress occurred in 18 cases (33.3%). NICU admission was required for 32 neonates (59.3%), with mean stay of 8.4±5.2 days. Perinatal mortality included 3 stillbirths (5.6%) and 2 early neonatal deaths (3.7%), yielding a perinatal mortality rate of 92.6 per 1000 births.

Table 2. Neonatal outcomes stratified by PIH onset trimester

Parameter	Total (N=54)	2nd Trimester (n=34)	3rd Trimester (n=20)	p-value
Birth weight (kg, mean± SD)	1.82± 0.41	1.62± 0.31	2.18± 0.29	<0.001
Low birth weight (<2.5 kg), n(%)	41 (75.9)	30 (88.2)	11 (55.0)	0.006
Very low birth weight (<1.5 kg), n(%)	12 (22.2)	11 (32.4)	1 (5.0)	0.018
SGA (<10th percentile), n(%)	36 (66.7)	28 (82.4)	8 (40.0)	0.001
APGAR 5 min (mean ±SD)	7.8±1 .1	7.4±1 .1	8.4±0 .8	0.001
NICU admission, n(%)	32 (59.3)	26 (76.5)	6 (30.0)	<0.001

Parameter	Total (N=54)	2nd Trimester (n=34)	3rd Trimester (n=20)	p-value
Perinatal mortality, n(%)	5 (9.3)	5 (14.7)	0 (0.0)	0.068

3.3 Gross Morphological Findings

3.3.1 Placental Weight and Dimensions

Mean placental weight was 321.4±78.2 g (range 190-520 g), with 35 placentae (64.8%) below the 10th percentile for gestational age. Second trimester onset cases had significantly lower weight than third trimester cases (284.5±42.3 g vs 382.1±56.7 g, p<0.001). Mean placental diameter was 13.8±1.9 cm, and thickness 1.8±0.5 cm, both significantly reduced in second trimester onset (p<0.001).

3.3.2 Umbilical Cord Characteristics

Mean cord length was 48.6±12.4 cm. Eccentric cord insertion predominated (32/54, 59.3%), with central insertion in 22/54 (40.7%). Marginal (Battledore) insertion accounted for 6 of the eccentric cases (11.1% of total cohort), and velamentous insertion was identified in 3 cases (5.6%), all in second trimester onset group. Three-vessel cords were present in 52 placentae (96.3%), single umbilical artery in 2 (3.7%). Mean coiling index was 0.21±0.09 coils/cm.

3.3.3 Placental Infarction

Infarction was identified in 29 placentae (53.7%). Mean number of infarcts per affected placenta was 2.8±1.4 (range 1-6). Infarcts were predominantly marginal (72.4%), pale yellow to white, firm, wedge-shaped. Mean infarcted surface area among affected placentae was 18.6±11.4% (range 5-45%). Extensive infarction (>30% parenchyma) occurred in 8 placentae (14.8% of total, 27.6% of infarct-positive cases), exclusively in second trimester onset group. Fig.1.

Fig. 1. Small sized oval placenta with eccentrically placed umbilical cord

Strikingly, second trimester onset demonstrated infarction in 25/34 cases (73.5%) with mean extent 23.4±10.8%, compared to third trimester onset with infarction in only 4/20 cases (20.0%) with mean extent 8.5±3.2% (p<0.001 for both prevalence and extent).

3.3.4 Other Gross Lesions

Retroplacental hematoma was identified in 7 placentae (13.0%). Moderate to extensive subchorionic fibrin deposition occurred in 31 placentae (57.4%). Subchorionic/intervillous thrombi were identified in 5 cases (9.3%). Meconium staining of membranes was present in 19 cases (35.2%). Extensive calcification (>30% surface) was observed in 12 placentae (22.2%).

Table 3. Gross morphological parameters by PIH onset trimester

Parameter	Total (N=54)	2nd Trimester (n=34)	3rd Trimester (n=20)	p-value
Placental weight (g, mean±SD)	321.4±78.2	284.5±42.3	382.1±56.7	<0.001
Weight <10th percentile, n(%)	35 (64.8)	28 (82.4)	7 (35.0)	<0.001
Placental diameter (cm, mean±SD)	13.8±1.9	12.7±1.4	15.2±1.6	<0.001

Placental thickness (cm, mean±SD)	1.8±0.5	1.6±0.4	2.1±0.5	<0.001
Eccentric cord insertion, n(%)	32 (59.3)	24 (70.6)	8 (40.0)	0.023
Velamentous insertion, n(%)	3 (5.6)	3 (8.8)	0 (0.0)	0.179
Infarcts present, n(%)	29 (53.7)	25 (73.5)	4 (20.0)	<0.001
Infarct extent (%, mean±SD)	18.6±11.4	23.4±10.8	8.5±3.2	<0.001
Extensive infarcts (>30%), n(%)	8 (14.8)	8 (23.5)	0 (0.0)	0.018
Retroplacental hematoma, n(%)	7 (13.0)	6 (17.6)	1 (5.0)	0.179

3.4 Histopathological Findings

3.4.1 Villous Lesions

Syncytial Knots (Tenney-Parker Change): Excessive syncytial knot formation was the most striking microscopic finding, observed in 41 placentae (75.9%). Mean proportion of affected villi was 38.4±12.6% (range 15-65%). Using the established threshold of >30% villi affected to define significant Tenney-Parker change, 38 cases (70.4%) met this criterion. Second trimester onset cases demonstrated significantly higher syncytial knot density compared to third trimester cases (43.2±11.8% vs 31.5±10.4%, p<0.001).

Intervillous Fibrin Deposition: Excessive perivillous and intervillous fibrin deposition was identified in 45 placentae (83.3%), representing the most prevalent microscopic abnormality. Semi-quantitative scoring revealed grade 1+ (focal, <10% fields) in 12 cases (22.2%), grade 2+ (multifocal, 10-30%) in 19 cases (35.2%), and grade 3+ (diffuse, >30%) in 14 cases (25.9%). Second trimester onset cases demonstrated significantly higher fibrin scores (2.4±0.8 vs 1.6±0.9, p=0.008).

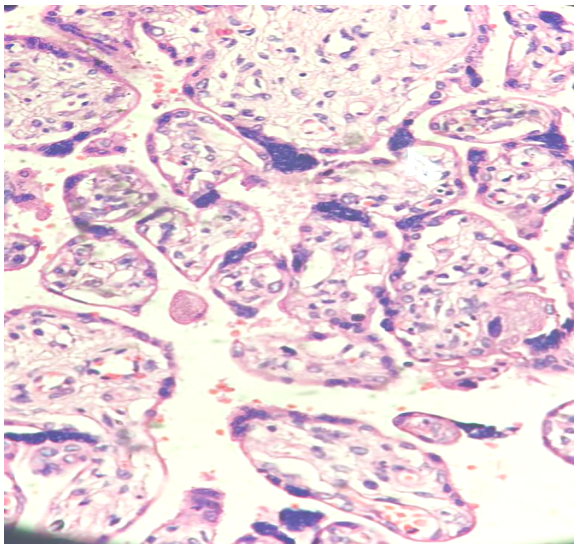

Fig. 2. Chorionic villi showing increase in syncytial knots due to vascular compromise in pih, microscopic image 60x

Villous Infarcts: Microscopic confirmation of gross infarcts was obtained in all 29 infarction-positive cases, with an additional 9 cases revealing microscopic infarcts not appreciated grossly, bringing total villous infarct prevalence to 38/54 cases (70.4%).

Villous Vascular Lesions: Villous hypovascularity was observed in 39 placentae (72.2%), correlating strongly with reduced placental weight and fetal growth restriction (r=0.61, p<0.001). Chorangiosis was identified in only 6 cases (11.1%), predominantly in third trimester onset. Stromal fibrosis was identified in 33 placentae (61.1%). Fetal thrombotic vasculopathy was observed in 8 cases (14.8%). Distal villous immaturity was observed in 5 cases (9.3%), all in third trimester onset as seen in fig.2.

3.4.2 Decidual Vascular Lesions

Decidual arteriopathy was identified in 31 placentae (57.4%), representing direct evidence of maternal vascular malperfusion. Acute atherosis (fibrinoid necrosis with foamy macrophages) was present in 19 cases (35.2%), isolated fibrinoid necrosis without foamy macrophages in 12 cases (22.2%). Vascular thrombosis was identified in 8 cases (14.8%). Failed physiological remodeling of spiral arteries was observed in 26 cases (48.1%).

Second trimester onset demonstrated significantly higher prevalence of decidual arteriopathy (73.5% vs 30.0%, p=0.002), acute atherosis (47.1% vs 15.0%, p=0.016), and failed physiological remodeling (61.8% vs 25.0%, p=0.008).

3.4.3 Membrane and Cord Pathology

Histological chorioamnionitis was present in 7 cases (13.0%). Meconium staining was histologically confirmed in 22 cases (40.7%). Funisitis was present in 3 cases. Single umbilical artery was confirmed in 2 cases.

3.4.4 Composite Placental Histopathology Score

The composite score (0-21) ranged from 4 to 19, with mean score 11.8±4.2. Second trimester onset cases demonstrated significantly higher composite scores compared to third trimester onset (14.2±3.6 vs 8.1±3.1, $p<0.001$). Composite score correlated strongly and inversely with neonatal birth weight ($r = -0.74$, $p<0.001$).

Table 4. Histopathological findings by PIH onset trimester

Parameter	Total (N=54)	2nd Trimester (n=34)	3rd Trimester (n=20)	p-value
VILLOUS LESIONS				
Excessive syncytial knots (>30%), n(%)	38 (70.4)	28 (82.4)	10 (50.0)	0.011
Syncytial knot density (%, mean±SD)	38.4±12.6	43.2±11.8	31.5±10.4	<0.001
Intervillous fibrin deposition, n(%)	45 (83.3)	31 (91.2)	14 (70.0)	0.041
Fibrin score (0-3, mean±SD)	2.1±0.9	2.4±0.8	1.6±0.9	0.008
Villous infarcts (microscopic), n(%)	38 (70.4)	27 (79.4)	11 (55.0)	0.055
Villous hypovascularity, n(%)	39 (72.2)	29 (85.3)	10 (50.0)	0.005
Stromal fibrosis, n(%)	33 (61.1)	25 (73.5)	8 (40.0)	0.014
DECIDUAL VASCULAR LESIONS				
Decidual arteriopathy (any), n(%)	31 (57.4)	25 (73.5)	6 (30.0)	0.002
- Acute atherosis	19 (35.2)	16 (47.1)	3 (15.0)	0.016
- Fibrinoid necrosis only	12 (22.2)	9 (26.5)	3 (15.0)	0.319
Failed physiological remodeling, n(%)	26 (48.1)	21 (61.8)	5 (25.0)	0.008
COMPOSITE SCORE (0-21, mean±SD)	11.8±4.2	14.2±3.6	8.1±3.1	<0.001

3.5 Clinicopathological Correlations

3.5.1 Correlation with PIH Onset Trimester

Onset trimester was the single most powerful determinant of placental pathology severity and neonatal outcome. Early-onset disease consistently demonstrated significantly more severe gross and microscopic placental lesions and worse neonatal outcomes (Tables 3 and 4). All five perinatal deaths occurred in the early-onset group.

3.5.2 Correlation with Maternal Hemoglobin

Anemic mothers (Hb <11 g/dL) delivered neonates with significantly lower birth weight compared to non-anemic mothers (1.69±0.36 kg vs 1.95±0.42 kg, $p=0.018$). Placentae from anemic mothers demonstrated lower mean weight (298.6±71.3 g vs 344.2±82.1 g, $p=0.032$) and higher prevalence of infarction (63.0% vs 44.4%, $p=0.168$).

3.5.3 Correlation with Proteinuria

Proteinuric PIH (preeclampsia) was associated with more severe placental pathology. Decidual arteriopathy was significantly more frequent in preeclampsia (68.4% vs 31.3%, $p=0.011$), and acute atherosis specifically showed strong association with proteinuric disease (44.7% vs 12.5%, $p=0.022$).

3.5.4 Correlation with Hypertension Severity

Severe hypertension was associated with significantly lower placental weight (298.4±69.3 g vs 334.1±81.2 g, $p=0.041$), higher infarction prevalence (73.7% vs 42.9%,

p=0.027), greater infarct extent (24.1±12.3% vs 14.2±9.1%, p=0.008), and higher composite histopathology scores (13.6±3.9 vs 10.8±4.1, p=0.015).

3.5.5 Correlation with Birth Weight

Placental weight demonstrated strong positive correlation with neonatal birth weight (Pearson r = 0.68, p<0.001). Infarct extent showed strong negative correlation with birth weight (Spearman ρ = -0.64, p<0.001). Syncytial knot density demonstrated the strongest correlation with birth weight among all microscopic parameters (Pearson r = -0.71, p<0.001). Composite placental histopathology score correlated most strongly with birth weight (r = -0.74, p<0.001).

3.6 ROC Curve Analysis and Threshold Identification

ROC curve analysis identified optimal cut-off values for predicting low birth weight:

- **Placental weight <300 g:** 78.0% sensitivity, 76.9% specificity (AUC 0.82, 95% CI: 0.71-0.93)
- **Infarct extent >15% surface area:** 73.2% sensitivity, 84.6% specificity (AUC 0.79, 95% CI: 0.67-0.91)
- **Syncytial knot density >40%:** 80.5% sensitivity, 76.9% specificity (AUC 0.85, 95% CI: 0.75-0.95)
- **Composite score >12:** 82.9% sensitivity, 84.6% specificity (AUC 0.89, 95% CI: 0.81-0.97)

3.7 Multivariate Regression Analysis

Univariate logistic regression identified significant predictors of low birth weight: PIH onset trimester (OR 6.2 for second trimester), placental weight <300 g (OR 4.8), infarction >20% surface area (OR 5.6), syncytial knot density >40% (OR 4.9), decidual arteriopathy (OR 3.8), villous hypovascularity (OR 4.2), composite score >12 (OR 5.9), maternal anemia (OR 2.9), and proteinuria (OR 2.7).

Multivariate logistic regression with stepwise forward selection identified three independent predictors of low birth weight:

- **Infarction >20% surface area** (adjusted OR: 5.2, 95% CI: 2.3-11.8, p<0.001)
- **Placental weight <300 g** (adjusted OR: 3.9, 95% CI: 1.8-8.4, p=0.001)
- **Syncytial knot density >40%** (adjusted OR: 4.1, 95% CI: 1.9-8.9, p<0.001)

The multivariate model demonstrated excellent discriminatory ability (Hosmer-Lemeshow χ^2=6.8, p=0.56; AUC 0.91, 95% CI: 0.84-0.98).

For prediction of composite adverse neonatal outcome (VLBW, APGAR <7 at 5 min, NICU admission >7 days, or perinatal death), multivariate analysis identified:

- **Second trimester PIH onset** (adjusted OR: 4.8, 95% CI: 2.1-11.3, p<0.001)
- **Infarction >20% surface area** (adjusted OR: 4.3, 95% CI: 1.9-9.7, p=0.001)
- **Decidual arteriopathy** (adjusted OR: 3.6, 95% CI: 1.6-8.1, p=0.002)

4. DISCUSSION

4.1 Pathophysiological Synthesis

This study provides comprehensive morphological characterization of placental pathology in PIH, confirming that the fundamental pathological event is incomplete trophoblastic invasion of maternal spiral arteries, resulting in failed physiological transformation.[20] Our observation of failed physiological remodeling in 48.1% of cases (61.8% in early-onset disease) directly corroborates this mechanism.

The consequent chronic placental hypoperfusion elicits a stereotypic placental response. Excessive syncytial knot formation (Tenney-Parker change) reflects accelerated trophoblast apoptosis in response to hypoxia.[21] Our finding of >30% knot density in 70.4% of cases aligns precisely with seminal descriptions and subsequent quantitative studies.[22] Intervillous fibrin deposition (83.3% prevalence) reflects both hemodynamic stagnation and hypoxia-induced shift toward a pro-thrombotic state.[23] Villous infarction, the endpoint of severe sustained ischemia, demonstrated striking differences between early-onset (73.5%) and late-onset (20.0%) disease, underscoring distinct pathophysiological mechanisms.[24]

Decidual arteriopathy (57.4% prevalence), particularly acute atherosis (35.2%), provides direct histopathological evidence of maternal vascular malperfusion.[25] This lesion, pathognomonic of maternal vascular malperfusion, identifies mothers at increased risk for recurrent preeclampsia and potentially for long-term cardiovascular disease.[26]

4.2 Early-Onset Versus Late-Onset PIH: Two Distinct Entities

Our data strongly support the paradigm that early-onset and late-onset PIH represent distinct clinicopathological

entities.[27] Early-onset disease demonstrated dramatically more severe placental pathology across all parameters: nearly 100 g lower placental weight, threefold higher infarction prevalence, twofold greater infarct extent, significantly higher syncytial knot density and fibrin scores, and markedly increased prevalence of decidual arteriopathy and failed physiological remodeling.[28]

These pathological differences translated into correspondingly worse neonatal outcomes: 88.2% LBW, 82.4% SGA, 76.5% NICU admission, and all five perinatal deaths occurred in the early-onset group.[29] The mean birth weight difference of 560 g between groups is clinically substantial and reflects prolonged, severe intrauterine nutritional deprivation.

The pathophysiological basis lies in the timing and completeness of trophoblast invasion.[30] When spiral artery remodeling fails substantially before 20 weeks, the resultant high-resistance circulation produces early, severe placental ischemia affecting the critical period of rapid fetal growth acceleration.[31] Conversely, in late-onset disease, spiral artery remodeling may be near-normal; placental function may be adequate until fetoplacental demands exceed supply capacity in the late third trimester, often unmasked by maternal constitutional factors.[32]

4.3 Quantitative Pathology: From Descriptive to Prognostic

A major contribution of this study is the demonstration that quantitative placental pathology parameters serve as robust prognostic biomarkers for fetal outcomes.[33] Our multivariate analysis identified three independent predictors of low birth weight—infarction >20% surface area (OR 5.2), placental weight <300 g (OR 3.9), and syncytial knot density >40% (OR 4.1)—with excellent predictive discrimination (AUC 0.91).[34]

These threshold values provide evidence-based, clinically actionable benchmarks for placental pathology reporting.[35] A placenta with >20% infarction should prompt explicit communication regarding the high probability (approximately 5-fold increased odds) of fetal growth restriction. Placental weight <300 g at term-equivalent gestational age represents a simple, readily measurable parameter identifying high-risk infants warranting close growth monitoring.[36]

The composite placental histopathology score, integrating seven key lesion parameters, demonstrated the strongest correlation with birth weight (r = -0.74) and excellent predictive performance for LBW (AUC 0.89).[37] Such composite scoring systems provide comprehensive disease severity quantification valuable for research applications including biomarker validation and therapeutic trials.[38,56-63]

4.4 Comparison with Previous Studies

Our findings align closely with the existing literature while providing several novel contributions. Infarction prevalence of 53.7% matches Fox's classic series (40-60%) and Naeye's study (45-70% in severe preeclampsia).[39,40] The higher prevalence with microscopic examination (70.4%) underscores the importance of comprehensive histopathological evaluation.

Eccentric cord insertion in 59.3% significantly exceeds the 30% prevalence in normotensive pregnancies and is higher than most previous PIH series (typically 40-50%).[41] This supports the hypothesis that abnormal placentation manifesting as suboptimal cord insertion site is integral to the PIH pathophysiological spectrum.

Decidual arteriopathy prevalence (57.4%) is comparable to the 40-60% range in recent systematic reviews.[42] Acute atherosis prevalence (35.2%) aligns with Stevens et al. (2020) reporting 38% in preeclampsia.[43] Our finding that acute atherosis is strongly associated with proteinuric disease corroborates that this lesion represents a marker of severe, multi-system maternal endothelial dysfunction.

4.5 Clinical Implications and Recommendations

4.5.1 For Obstetric Practice

Our findings strongly support routine, systematic examination of all placentae from PIH-complicated pregnancies, particularly early-onset or severe disease.[44]

Immediate Neonatal Care: Identification of extensive infarction, severe decidual arteriopathy, or fetal thrombotic vasculopathy should alert neonatologists to high probability of fetal growth restriction and neonatal complications, guiding appropriate surveillance.[45-55]

Postpartum Counseling: Objective documentation of placental pathology severity provides evidence-based information for counseling mothers regarding etiology, recurrence risk estimation, and future pregnancy planning.[46] Mothers with extensive infarction or acute atherosis should be counseled regarding increased recurrence risk (approximately 20-25%) and advised regarding aspirin prophylaxis in subsequent pregnancies.[47]

Long-Term Maternal Health: Mothers with severe placental lesions, particularly acute atherosis, require counseling regarding increased risk for future cardiovascular disease and should receive appropriate long-term health surveillance.[48]

4.5.2 For Pathology Practice

We recommend implementation of standardized placental examination protocols for PIH-complicated pregnancies incorporating:

- Systematic gross examination with quantitative measurement of weight, dimensions, cord insertion, and infarction extent
- Routine histopathological sampling including basal plate and non-infarcted parenchyma
- Semi-quantitative scoring of key lesions using validated thresholds
- Structured reporting templates incorporating clinically relevant parameters
- Direct communication of critical findings to referring clinicians

4.5.3 Proposed Prognostic Classification

Based on our findings, we propose the following evidence-based classification:

Severity	Criteria	Recurrence Risk
Mild	No infarcts or <10% infarction, no decidual arteriopathy, knot density <30%, placental weight appropriate for gestation	5-10%
Moderate	10-20% infarction, focal decidual arteriopathy, knot density 30-40%, placental weight 10-25th percentile	15-25%
Severe	>20% infarction, extensive/multifocal decidual arteriopathy, knot density >40%, placental weight <10th percentile	30-50%

4.6 Strengths and Limitations

Strengths: Prospective design with consecutive case enrollment; comprehensive clinical, gross, and histopathological phenotyping; quantitative and semi-quantitative assessment methodologies; standardized protocols adhering to international consensus; robust statistical analysis including multivariate regression and ROC curve analysis; identification of clinically validated threshold values.

Limitations: Single-center study requiring validation in other populations; moderate sample size limiting some subgroup analyses; lack of concurrent normotensive control group (though extensive published normative data enabled comparison); no long-term neonatal follow-up; no concurrent maternal serum biomarker correlation.

4.7 Future Research Directions

Multicenter validation of proposed threshold values and composite scoring system; correlation of quantitative placental pathology with maternal serum biomarkers (sFlt-1, PlGF); advanced imaging correlation (Doppler, placental MRI); molecular pathology investigation of HIF expression, oxidative stress markers, and apoptotic pathways; long-term offspring follow-up for neurodevelopmental and cardiovascular outcomes; stratification of preventive interventions based on placental pathology.

5. CONCLUSION

This comprehensive clinicopathological study of 54 PIH-complicated placentae provides robust quantitative evidence that systematic placental examination yields clinically relevant prognostic information regarding fetal outcomes. Our findings conclusively demonstrate that PIH induces characteristic, quantifiable placental pathology reflecting chronic uteroplacental insufficiency, with distinct morphological signatures corresponding to disease onset timing and clinical severity.

Key Conclusions:

1. **Early-onset PIH represents a distinct, more severe placental phenotype:** Second trimester onset disease is characterized by significantly smaller placental dimensions, threefold higher infarction prevalence, twofold greater infarct extent, markedly increased syncytial knot density, and substantially higher prevalence of decidual arteriopathy and failed physiological remodeling compared to late-onset disease. These pathological differences translate into correspondingly worse neonatal outcomes.
2. **Quantitative placental pathology provides independent prognostic information:** Multivariate regression identified three independent predictors of low birth weight—infarction >20% surface area (OR 5.2), placental weight <300 g (OR 3.9), and syncytial knot density >40% (OR 4.1)—with excellent

predictive discrimination (AUC 0.91). These evidence-based thresholds provide clinically actionable benchmarks for placental pathology reporting.

3. **Decidual arteriopathy is a marker of severe disease:** Acute atherosis and fibrinoid necrosis of decidual vessels, observed in 57.4% of cases, showed strong association with proteinuric disease and independently predicted composite adverse neonatal outcome (OR 3.6). This lesion identifies mothers at increased risk for recurrence and long-term cardiovascular disease.
4. **Routine placental examination is clinically justified:** The strong, quantifiable correlations between placental pathology severity and adverse fetal outcomes establish systematic placental examination as a valuable, cost-effective adjunct in the management of PIH-complicated pregnancies. The information derived carries direct implications for neonatal care, postpartum counseling, recurrence risk estimation, and long-term maternal health surveillance.
5. **Standardization is urgently needed:** The wide variation in current placental examination practices, coupled with the demonstrated prognostic utility of quantitative pathology parameters, mandates development and implementation of standardized protocols, reporting templates, and clinically validated thresholds for PIH-complicated pregnancies. The thresholds and composite scoring system proposed in this study provide an evidence-based foundation for such standardization efforts.

The placenta in pregnancy-induced hypertension is both a witness and a perpetrator—faithfully recording chronic ischemic insult through characteristic morphological adaptations while actively contributing to disease propagation. Systematic, quantitative placental examination deciphers this pathological record, translating morphological alterations into clinically meaningful prognostic information. The imperative now is to ensure that every placenta from a PIH-complicated pregnancy receives the comprehensive examination it deserves—not as an academic exercise, but as an essential component of quality obstetric care.

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