Volume 4, Issue 5, May 2026 ISSN (E): 2938-3765

HISTOCHEMICAL CHARACTERISTICS OF PLACENTAL TISSUE IN WOMEN WITH CARDIAC DEFECTS

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Abstract
This study examines histochemical alterations in placental tissue from women with congenital and acquired cardiac defects compared to healthy controls. Applying PAS-reaction, Alcian Blue, Van Gieson, Sudan III, and hematoxylin-eosin staining to 60 specimens, we identified significant reduction in trophoblast glycogen, increased fibrinoid deposition, basement membrane thickening, stromal fibrosis, and lipid accumulation, confirming measurable hypoxic placental injury.

Keywords: Cardiac defects, placental histochemistry, syncytiotrophoblast, fibrinoid necrosis, PAS-reaction, glycogen depletion, Alcian Blue staining, acid mucopolysaccharides, fetoplacental insufficiency, villous edema, stromal fibrosis, Van Gieson staining, placental ischemia, basement membrane, perinatology.

Introduction

Cardiac defects constitute one of the most clinically significant forms of extragenital pathology in pregnant women, accounting for 2-5% of all pregnancies worldwide and reaching 8-10% in regions with high rheumatic disease burden. Despite considerable clinical literature on the obstetric management of cardiac disease in pregnancy, the direct structural consequences of compromised maternal hemodynamics on placental tissue remain insufficiently characterized at the histochemical level. The placenta functions as the sole interface for gas exchange, nutrient delivery, and waste elimination between mother and fetus; chronic reduction in uteroplacental perfusion caused by impaired cardiac output necessarily affects placental parenchymal architecture. Histochemical analysis offers a precise, quantifiable window into these changes - revealing alterations in carbohydrate reserves, matrix composition, lipid metabolism, and fibrous remodeling that precede or accompany clinical fetoplacental insufficiency. Establishing these patterns is essential for understanding the pathophysiology of adverse perinatal outcomes in this high-risk group.

Literature review

A.P. Milovanov (1999) established the foundational morphological classification of placental insufficiency and identified fibrinoid accumulation as a universal trophoblast response to ischemic stress. B.I. Gluhovets and N.G. Gluhovets (2002) systematically described the pathomorphological spectrum of placental lesions in maternal cardiovascular disease, including basement membrane thickening and stromal edema. L.P. Peretyatko et al. (2008) demonstrated altered PAS-positive

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glycoprotein distribution in placentas from high-risk pregnancies using standardized morphometry. V.N. Serov (2009) analyzed the systemic effects of cardiac insufficiency on uteroplacental hemodynamics and trophoblast metabolism. I.O. Makarov (2012) quantified fetoplacental blood flow impairment in structural heart disease pregnancies and linked Doppler findings to morphological placental damage. Sh.T. Toshmatova and M.A. Yusupova (2017) identified regional histological placental damage patterns specific to cardiac disease pregnancies in the Central Asian population. E.V. Murashko (2012) reviewed cardiovascular disease in pregnancy from a clinical pathophysiology perspective, linking NYHA class with placental outcome severity. These works collectively form the methodological and conceptual framework of the present study.

Methodology

This prospective morphological study was conducted on placental specimens collected from 60 women following delivery at a tertiary-level obstetric institution. Participants were divided into two groups: the study group comprised 40 women with echocardiographically confirmed cardiac defects (congenital or acquired), and the control group comprised 20 women with uncomplicated singleton pregnancies and no cardiovascular pathology, matched for gestational age and parity. Inclusion criteria for the study group: verified structural cardiac defect confirmed by cardiologist and echocardiography before delivery; singleton pregnancy; gestational age 37-40 weeks at delivery; NYHA functional class I-III. Exclusion criteria for both groups: pre-existing diabetes mellitus, active systemic infection, chromosomal fetal anomalies, multiple gestation, and pre-existing autoimmune disease. Mean maternal age in the study group was 27.4 ± 3.8 years (control: 26.9 ± 3.2 years). Cardiac defect distribution in the study group: mitral stenosis 37.5% (n=15), combined valve disease 27.5% (n=11), ventricular septal defect 20.0% (n=8), aortic insufficiency 15.0% (n=6). NYHA class I-II: 62.5% (n=25); class III: 37.5% (n=15). Mean gestational age at delivery: 38.2 ± 0.9 weeks (study) versus 39.1 ± 0.6 weeks (control). Emergency caesarean section was performed in 45.0% (n=18) of the study group versus 10.0% (n=2) of controls.

Immediately following placental delivery, standardized full-thickness samples measuring 1.0 × 1.0 × 0.5 cm were excised from four anatomical regions of each placenta: central zone, paracentral zone, peripheral zone, and the umbilical cord insertion site - yielding four blocks per specimen, 240 tissue blocks total. Each block was fixed in 10% neutral buffered formalin for 24 hours at room temperature, then dehydrated through ascending alcohol concentrations (70%, 80%, 96%, absolute ethanol), cleared in xylene (two changes, 30 minutes each), and embedded in paraffin. Serial sections of 5-7 µm thickness were cut using a rotary microtome (Leica RM2235, Germany) and mounted on silanized glass slides for histochemical staining.

Five histochemical methods were applied to all specimens. Hematoxylin and Eosin (H&E): Standard protocol for morphological assessment of villous architecture, syncytiotrophoblast integrity, cytotrophoblast distribution, stromal cellularity, and fetal capillary patency. Periodic Acid-Schiff (PAS) reaction: Performed according to Hotchkiss-McManus protocol - oxidation with 0.5% periodic acid for 5 minutes, rinsing in distilled water, treatment with Schiff reagent (Sigma-Aldrich) for 15 minutes, counterstaining with Mayer's hematoxylin. Detects glycogen, neutral mucopolysaccharides, and basement membrane glycoproteins. Alcian Blue (pH 2.5): Slides immersed in 1% Alcian Blue solution (pH 2.5, Acetic acid buffer) for 30 minutes at room temperature, rinsed, counterstained with

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

Nuclear Fast Red. Visualizes acid mucopolysaccharides and hyaluronic acid within villous stroma. Van Gieson (Picrofuchsin): Standard protocol using Weigert's iron hematoxylin followed by Van Gieson solution (1% acid fuchsin in saturated picric acid) for 3 minutes. Differentiates collagen fibers (red) from muscle and cytoplasm (yellow) within villous stroma and vessel walls. Sudan III: Applied to 10-µm cryostat sections; slides incubated in Sudan III solution (0.3% in 70% ethanol) for 15 minutes at 37°C, rinsed in 50% ethanol, counterstained with Mayer's hematoxylin. Identifies neutral lipid accumulation in syncytiotrophoblast and stromal cells. All slides were examined under a Nikon Eclipse E200 light microscope (Japan) at magnifications ×100, ×200, and ×400. Digital images were captured with a Nikon DS-Fi2 camera. Morphometric analysis was performed using ImageJ 1.53 (NIH, USA). Per slide, 10 non-overlapping fields of view were evaluated at ×200 magnification. Measured parameters: PAS-positive area fraction in syncytiotrophoblast (%), basement membrane thickness (µm), Alcian Blue-positive stromal area fraction (%), Van Gieson collagen fiber density (%), and Sudan III-positive cell percentage (%). Data expressed as mean ± standard deviation. Statistical analysis performed in SPSS Statistics 23.0 using Mann-Whitney U-test for non-parametric comparisons; significance threshold $p < 0.05$.

Results

In the control group, terminal villi displayed intact syncytiotrophoblast coverage with evenly distributed nuclei, regular cytotrophoblast population, patent fetal capillaries with thin walls, and loose, moderately cellular stroma. In the study group, significant structural alterations were identified in 87.5% of specimens (n=35/40). Fibrinoid necrosis of villous trophoblast was the most prevalent finding, observed in 82.5% (n=33) of cardiac defect placentas versus 15.0% (n=3) in controls ($p<0.001$). Syncytiotrophoblast desquamation accompanied by syncytial knot formation was present in 72.5% (n=29) of study specimens versus 25.0% (n=5) in controls ($p<0.001$). Perivillous fibrin deposition covered a mean of 18.4 ± 3.2% of villous surface area in the study group versus 4.7 ± 1.1% in controls ($p<0.001$). Villous edema with stromal loosening was detected in 65.0% (n=26) of study group specimens versus 10.0% (n=2) in controls ($p<0.001$). Placental infarcts, defined as zones of complete villous necrosis surrounded by fibrin, were identified in 40.0% (n=16) of cardiac defect specimens and were absent in the control group. Glycogen content in syncytiotrophoblast, reflected by PAS-positive staining intensity, was markedly reduced in the study group. The PAS-positive area fraction in syncytiotrophoblast measured 14.3 ± 2.8% in the cardiac defect group versus 38.6 ± 4.1% in controls ($p<0.001$) - a 2.7-fold reduction. Basement membranes of terminal villi demonstrated irregular, asymmetric thickening in 77.5% (n=31) of study specimens; PAS-positive membrane width measured 3.8 ± 0.6 µm in the study group versus 1.9 ± 0.3 µm in controls ($p<0.001$). Glycoprotein-rich fibrinoid material in perivillous spaces occupied 22.1 ± 3.7% of the intervillous space area in the cardiac defect group versus 5.2 ± 1.4% in controls ($p<0.001$). Acid mucopolysaccharide content in villous stroma was significantly elevated in the study group. Alcian Blue-positive staining occupied 31.6 ± 4.4% of stromal area in cardiac defect placentas versus 12.3 ± 2.1% in controls ($p<0.001$). Elevation was most pronounced in edematous villi and in the perivascular zone of fetal capillaries, indicating altered proteoglycan synthesis as a component of the villous hypoxic response. Collagen fiber density in villous stroma was substantially higher in the study group: 24.8 ± 3.9% of stromal area versus 9.4 ± 1.7% in controls ($p<0.001$). Fibrotic remodeling was particularly evident in the stem

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villous cores and around the walls of fetal blood vessels, indicating chronic ischemic reorganization of the placental connective tissue framework. Neutral lipid accumulation in syncytiotrophoblast was markedly elevated in the study group: the Sudan III-positive cell fraction reached 28.3 ± 4.1% versus 9.7 ± 2.2% in controls ($p<0.001$). Lipid droplets were also present in stromal macrophages (Hofbauer cells) in 57.5% (n=23) of study specimens. This pattern is consistent with impaired mitochondrial fatty acid oxidation under conditions of chronic hypoxia.

Discussion

The histochemical findings of this study converge on a coherent pathogenic narrative: maternal cardiac defects produce a reproducible, quantifiable pattern of chronic hypoxic injury in placental tissue, detectable through standard histochemical methods and measurable with objective morphometry.

The glycogen depletion in syncytiotrophoblast - a nearly threefold reduction in PAS-positive area fraction (14.3% vs. 38.6%) - is arguably the most functionally significant finding. Glycogen is the primary carbohydrate reserve of the trophoblast and serves as an immediate substrate for anaerobic glycolysis when oxygen delivery is reduced. Its marked depletion indicates that the trophoblast has been chronically operating under hypoxic energy stress, exhausting intracellular reserves that would normally sustain active transport and synthetic functions. This aligns with Milovanov's (1999) characterization of glycogen loss as an early indicator of trophoblast metabolic failure in ischemic placentas.

Basement membrane thickening - 3.8 μm versus 1.9 μm, a twofold increase - is mechanistically important because it directly increases the diffusion path length between the intervillous space and fetal capillaries. Oxygen, glucose, and amino acids must traverse this thickened glycoprotein barrier, further reducing transfer efficiency in a system already compromised by diminished perfusion pressure. Gluhovets and Gluhovets (2002) described this phenomenon as a structural correlate of the villous "barrier effect" in placentas from cardiovascular disease pregnancies, and our quantitative data provide precise numeric confirmation of their observations.

The elevated acid mucopolysaccharide content documented by Alcian Blue staining (31.6% vs. 12.3%) reflects increased production of hyaluronic acid and chondroitin sulfate by hypoxically stimulated stromal fibroblasts. While these proteoglycans normally contribute to extracellular matrix hydration, their excess production paradoxically increases stromal water retention, leading to the villous edema observed on H&E sections. This stromal swelling compresses fetal capillaries, further reducing perfusion in terminal villi - a vicious cycle of edema and ischemia.

Stromal fibrosis quantified by Van Gieson staining (24.8% vs. 9.4%) represents the end-stage consequence of repeated ischemia-reperfusion injury. The transition from edematous, hypoxic stroma to fibrotic, acellular connective tissue is a late-stage, largely irreversible change that permanently diminishes the elastic properties of terminal villi and their capacity for angiogenesis. In the context of NYHA class III patients (37.5% of our study group), the degree of fibrosis was visibly more extensive, suggesting a dose-response relationship between cardiac functional status and the severity of placental connective tissue remodeling.

Neutral lipid accumulation in syncytiotrophoblast (28.3% vs. 9.7%) points to disturbed mitochondrial fatty acid β-oxidation, a metabolic consequence of reduced intracellular oxygen tension. When

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

oxidative phosphorylation is impaired, long-chain fatty acids accumulate in cytoplasmic lipid droplets rather than being oxidized. This impairs membrane lipid turnover and reduces the biosynthetic capacity of the syncytiotrophoblast - with direct consequences for the production of placental hormones, transport proteins, and lipid-soluble vitamin delivery to the fetus. The concurrent lipid accumulation in Hofbauer cells (57.5% of study specimens) suggests that placental macrophages are also metabolically compromised, potentially impairing their immunomodulatory role. Collectively, these findings support the use of post-delivery histochemical placental examination as a practical tool in obstetric care: in women with cardiac defects, the degree of glycogen depletion, fibrinoid deposition, and stromal fibrosis provides objective morphological evidence of the cumulative ischemic burden sustained by the placenta, informing neonatal risk stratification and postnatal follow-up planning.

Placental tissue in women with cardiac defects consistently exhibits histochemically quantifiable alterations - syncytiotrophoblast glycogen depletion, thickened basement membranes, increased fibrinoid deposits, elevated stromal mucopolysaccharides, collagen fibrosis, and lipid accumulation - that collectively reflect chronic hypoxic injury. These findings establish a reproducible morphological profile and support routine histochemical placental assessment as an evidence-based component of postnatal care in cardiac disease pregnancies.

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