

**PATHOLOGICAL ANATOMY AND CAUSES OF ANTENATAL DEATH:  
INSIGHTS FROM PLACENTAL HISTOLOGY**

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**Abstract.** Significant advancements in obstetric and neonatal care have led to a gradual decrease in perinatal mortality rates globally and within the Russian Federation. While this improvement is largely due to reductions in early neonatal mortality, the rising stillbirth rate has become a pressing concern, representing an increasing proportion of perinatal mortality. Despite the development of modern prenatal diagnostic techniques, biochemical marker evaluations for identifying pregnancy complications, and targeted referrals of high-risk patients for specialized ultrasound examinations, the challenge of antenatal fetal death remains inadequately addressed. In developed nations, as much as 60% of stillbirths are currently classified as unexplained, in contrast to 4.7% in the Russian Federation. This situation underscores a critical need for enhanced understanding of the mechanisms underlying antenatal fetal death, which is essential for developing effective preventive strategies and improving maternal-fetal outcomes.

**Keywords:** Antenatal fetal death, stillbirth, perinatal mortality, placental insufficiency, microRNA, prenatal diagnosis, obstetric care, neonatal outcomes, chronic inflammation, risk factors.

**Introduction.** The percentage of stillbirths in developed countries attributed to unexplained reasons varies significantly, ranging from 37.1% to 60%. Commonly ruled-out causes such as obstetric complications, fetal infections, placental insufficiency, umbilical cord abnormalities, and congenital anomalies mean that cases of stillbirth post-20 weeks of gestation occur at a rate of 1 in 200, surpassing the incidence of neonatal death, including sudden infant death syndrome. Over the last several decades, stillbirth rates have remained unchanged in developed countries. In the Russian Federation, stillbirth rates have shown a troubling trend, increasing from 5.44 % in 2019 to 5.67 % in 2020, with 4.7% of cases lacking an established cause of death. The UN estimates that if current trends persist, an additional 19 million stillbirths may occur globally by 2030.

**Relevance of the Work.** Identification of two critical points for antenatal fetal death has emerged: at 24 weeks gestation and after 39 weeks. It is particularly challenging to determine the immediate cause of death through standard histological examination in stillbirth cases occurring at term. Therefore, novel approaches are necessary to identify contributing factors to adverse pregnancy outcomes. Important processes deserving investigation include glycolysis regulation, cell differentiation, apoptosis, and hypoxia—each crucial to placental function during pregnancy. The glucose transporter protein 1 (GLUT-1), encoded by the SLC2A gene (1p34), is fundamental for glucose diffusion across the blood-brain barrier.

**Purpose.** The aim of this study is to perform a comparative histological and immunohistochemical analysis of placentas under the conditions of antenatal fetal death and live births, identifying the related pathological changes and potential risk factors contributing to antenatal fetal death at full term.

**Materials and Methods of Research.** A comparative histological and immunohistochemical analysis of placentas in cases of antenatal fetal death and live births at 37 weeks 0 days to 41 weeks 6 days of gestation was conducted among 60 patients treated across maternity institutions in the

Chelyabinsk region from 2019 to 2021. Group 1 comprised 30 patients with antenatal fetal death at term, while Group 2 involved 30 women who experienced live births.

Inclusion criteria for Group 1 included: single-fetus, spontaneously conceived pregnancies, gestation periods of 37 weeks 0 days to 41 weeks 6 days, and stillbirth of unspecified cause (intrauterine fetal death). Inclusion criteria for Group 2 included the same gestation period along with live birth. Exclusion criteria encompassed induced pregnancies, multiple pregnancies, severe maternal somatic pathologies (such as decompensated extragenital diseases, HIV, tuberculosis, and malignant tumors), and an established direct cause of antenatal fetal death.

Placental tissue samples underwent processing via a rotary microtome to obtain 5  $\mu\text{m}$  sections, which were stained with hematoxylin and eosin for histological examination.

**Results and Discussion.** Histological evaluation of placental samples from Group 1 revealed characteristics of chronic placental insufficiency in 21 samples (70%). Lymphoid-plasmacellular infiltration of chorionic structures was observed in 16 samples (53.3%), involutive-dystrophic processes in 15 (50%), along with congestion of villous capillaries in 13 (43.3%) cases. Acute chorioamnionitis with neutrophilic infiltration occurred in only 6 (20%) cases, indicative of a maternal inflammatory response. A fetal inflammatory response, represented by chorioamnionitis, was evident in merely one case (3.3%), associated with purulent-destructive chorioamnionitis, suggesting advanced inflammation.

Most exudates localized within the intervillous space consisted mainly of plasma cells, indicative of a chronic inflammatory state. Additionally, chronic forms of placental inflammation, such as basal deciduitis, were noted in 10 cases (33.3%). Signs of hypoxic damage were present in 24 samples (80%), which impacted both maternal and fetal stromovascular compartments: vascular malperfusion, accelerated villous maturation, presence of intervillous fibrin in 13 cases (43.3%), agglutinated villi and syncytial knobs in 8 cases (26.6%), and distal immaturity of villi in 3 cases (10%).

The issue of antenatal fetal protection remains inadequately resolved, as conventional clinical and laboratory methods for assessing intrauterine fetal growth are often indirect and subjective. The annual increase in perinatal morbidity and mortality, heavily influenced by stillbirth, remains significant. Notably, in the Russian Federation, a rise in stillbirth numbers was recorded from 8101 cases in 2019 (5.44 ‰) to 8192 cases in 2020 (5.67 ‰), mirroring trends observed in the Chelyabinsk region where 216 stillbirth cases were recorded in 2019 (6.28 ‰) versus 221 in 2020 (6.8 ‰).

In anticipation, it is critical to recognize that at 24 weeks of gestation, antenatal fetal death is often attributed to chromosomal anomalies, congenital malformations, and infectious diseases, whereas identifying the immediate cause of death is more challenging after 39 weeks. The ongoing demographic crisis in the past decade has not only affected the Russian Federation but extends worldwide, with stillbirth rates highest in developing countries like Pakistan (46 ‰) and Nigeria (42 ‰) while the lowest are seen in developed nations such as Singapore and Finland (2%).

Many studies have sought to explore the causes of antenatal fetal death, primarily identifying acute antenatal complications, particularly intrauterine hypoxia, as the leading cause of fetal death, with occurrence rates ranging from 80.5% to 88%. The absence of a unified international definition and classification for intrauterine fetal death continues to complicate data interpretation. The most widely utilized classification for national monitoring was developed in the UK, known as the CODAC system, which includes 94 subcategories to categorize stillbirth causes and related conditions.

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A retrospective review of antenatal fetal death cases from 37 weeks 0 days to 41 weeks 6 days of gestation, recorded in the Chelyabinsk region from 2019 to 2021, was undertaken. Participants were divided into two groups: Group 1 consisted of 158 women with antenatal death of the full-term fetus, and Group 2 included 50 women who had live full-term births. Medical records—birth history (Form No. 096u), gravidity and parity history (Form No. 111/y 20), autopsy reports, and forms from the Russian Statistics Committee—were thoroughly analyzed. Inclusion criteria for Group 1 dictated that the women had received routine medical check-ups at an antenatal clinic within the gestation range specified.

The analysis revealed that antenatal fetal deaths predominantly occurred in Group II maternity hospitals: 30 cases (65.2%) in 2019, 47 (81%) in 2020, and 41 (69.5%) in 2021, while Group I healthcare facilities recorded substantially fewer cases (4.7%, 3.4%, and 1.7%, respectively). In 2019 and 2020, antenatal deaths in Level I medical care were attributed to premature separation of normally implanted placenta in 50% of cases, with 100% attributed in 2021. Patients experiencing antenatal death of a full-term fetus were statistically more likely to be residents of Chelyabinsk and major cities in the region, have secondary vocational education, and be tobacco smokers. There was also a significant association with diseases such as hypertension, endocrine issues, and specific infections (HIV, hepatitis C, and tuberculosis).

**Conclusion.** The findings from this study underscore a complex interplay of risk factors contributing to antenatal fetal death at full term. It is paramount to elucidate these factors to develop effective strategies for prenatal care. By addressing modifiable risk factors such as hypertensive disorders, endocrine pathologies, and lifestyle choices (e.g., tobacco use), healthcare providers can improve management and outcomes for at-risk pregnancies. Preventive measures, including the selection of optimal timing and mode of delivery between 37 weeks 0 days and 38 weeks 0 days of gestation, may significantly reduce stillbirth rates and enhance overall perinatal outcomes. As research advances our understanding of the genetic and molecular underpinnings of placental function and the involvement of microRNAs in embryonic development, there lies potential for integrating these insights into clinical practice. Continuous efforts towards improved prenatal monitoring and diagnostic methods are essential in addressing this critical aspect of maternal and fetal health.

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