INTEGRATED DIGITAL ANALYSIS OF PATHOMORPHOLOGICAL CHANGES IN THE MOTHER–PLACENTA–FETUS SYSTEM: STUDY DESIGN AND DEVELOPMENT OF A PERINATAL MORTALITY RISK PREDICTION MODEL

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Abstract. The thesis presents the design of a dissertation study aimed at integrated digital analysis of pathomorphological changes in the mother–placenta–fetus system and at developing a model for predicting the risk of perinatal mortality. The study combines maternal clinical and laboratory data, standardised macroscopic and microscopic examination of the placenta according to the Amsterdam consensus, whole-slide imaging with quantitative morphometry and immunohistochemistry, and the results of fetal and neonatal autopsy. Predictors will be selected using penalised logistic regression and compared with machine-learning algorithms; the final model will be internally validated and reported in accordance with TRIPOD+AI. The expected outcome is an objective, reproducible tool for perinatal risk stratification and for verifying the thanatogenesis of perinatal death.

Keywords: perinatal mortality; stillbirth; early neonatal death; placenta; digital pathology; whole-slide imaging; morphometry; prediction model; machine learning; mother–placenta–fetus system.

Relevance

About 2.0 million stillbirths occurred worldwide in 2019, and perinatal mortality remains a key indicator of the effectiveness of obstetric and neonatal care [2]. Most existing tools for perinatal risk assessment rely on clinical and ultrasound data alone. Placental examination, although it reveals the morphological substrate of death in most stillbirths, is used mainly retrospectively and descriptively [1, 3].

The morphological picture of perinatal death is formed by interacting changes in the mother, the placenta and the fetus. Isolated, semi-quantitative assessment of each component does not capture these interactions and cannot be used directly in prognostic calculations. Digital pathology, based on whole-slide imaging and automated morphometry, makes it possible to measure placental structures objectively and

reproducibly [4]. Combining such quantitative data with maternal and fetal parameters in a statistically validated model is a promising, still insufficiently developed direction, particularly in the population of Uzbekistan, for which such data are lacking.

Aim and objectives

Aim: to develop and validate a model for predicting the risk of perinatal mortality based on an integrated digital analysis of pathomorphological changes in the mother–placenta–fetus system.

Objectives:

1. To determine the structure and frequency of placental lesions in stillbirths and early neonatal deaths, classified according to the Amsterdam consensus.
2. To establish quantitative morphometric and immunohistochemical characteristics of the placenta in perinatal death compared with live births.
3. To analyse the relationship between maternal pathology, placental lesions and morphological changes in fetal and neonatal organs.
4. To identify independent predictors of perinatal death and to build a prognostic model combining clinical and digital morphological variables.
5. To evaluate the discrimination, calibration and clinical usefulness of the model and to propose an algorithm for its use in practice.

Materials and methods

Study design. A retrospective–prospective comparative (case–control) study is planned. Cases of perinatal death at a gestational age of 22 weeks or more will be included, with deaths classified according to the WHO ICD-PM system [10]. Groups:

– Group I: antenatal and intrapartum stillbirths;
– Group II: early neonatal deaths (0–6 days of life);
– Group III (comparison): live births after complicated pregnancy (pre-eclampsia, fetal growth restriction, preterm birth) with a favourable outcome, matched by gestational age;
– Group IV (control): live births after uncomplicated term pregnancy.

Exclusion criteria are lethal congenital malformations, confirmed chromosomal abnormalities, multiple pregnancy and advanced autolysis precluding morphological assessment. The minimum sample size will be calculated according to Riley et al. for

prediction-model development, based on the expected outcome prevalence and number of candidate predictors [5].

Data on the three components of the system. Each case will be described by an integrated set of variables (Table 1).

Table 1. Variables collected for the mother–placenta–fetus system

Component	Variables	Methods
Mother	Age, parity, obstetric history, extragenital disease, pre-eclampsia, diabetes, anaemia, infections, blood tests, Doppler indices	Medical record analysis, standardised data form
Placenta (macroscopy)	Weight, placental–fetal weight ratio, dimensions, cord insertion and length, infarcts, haematomas	Examination and sampling per the Amsterdam consensus [1]
Placenta (microscopy)	MVM, FVM, acute and chronic inflammation, villous maturation, perivillous fibrin; graded by stage and severity	H&E, PAS; consensus definitions [1, 3]
Placenta (digital morphometry)	Villous area fraction, terminal villus count and diameter, capillary-to-villus ratio, syncytial knot density, fibrinoid and infarct area, inflammatory cell density	Whole-slide imaging at ×40, analysis in QuPath [4]
Placenta (immunohistochemistry)	Vascular density (CD34), angiogenic markers (VEGF), proliferation (Ki-67), apoptosis, macrophage infiltration (CD68)	Automated quantification of positive area or cells
Fetus / newborn	Body and organ weights, growth restriction, signs of chronic and acute hypoxia, infection, haemorrhages, organ maturity	Perinatal autopsy, histology of internal organs

Statistical analysis and modelling. Groups will be compared using parametric or non-parametric tests depending on data distribution. Associations between maternal, placental and fetal variables will be assessed by correlation and multivariable analysis.

Candidate predictors will be selected with LASSO-penalised logistic regression [9]. The resulting model will be compared with machine-learning algorithms (random forest, gradient boosting), and predictor contributions will be interpreted with SHAP values [11]. Internal validation will use bootstrap resampling. Performance will be assessed by discrimination (area under the ROC curve), calibration (calibration plot, slope and intercept) and clinical usefulness (decision curve analysis) [7, 8]. Development and reporting will follow the TRIPOD+AI statement [6].

Expected results and scientific novelty

- For the first time in the population of Uzbekistan, the structure of placental lesions in perinatal death will be described using the international Amsterdam classification, with stillbirths and early neonatal deaths analysed separately.
- Quantitative digital morphometric and immunohistochemical parameters of the placenta will be established that distinguish perinatal death from live births after complicated and uncomplicated pregnancy.
- The pathogenetic links "maternal pathology – placental lesion – fetal organ damage" will be reconstructed on the basis of an integrated analysis of all three components of the system.
- A prognostic model of perinatal mortality risk combining clinical and digital morphological predictors will be developed, internally validated and presented as a nomogram or calculator for practical use.

Practical significance. The proposed protocol standardises placental examination and makes it reproducible. The model can be used to stratify perinatal risk, to support the audit of perinatal deaths and to plan subsequent pregnancies in women with a history of perinatal loss.

Conclusions

1. The mother–placenta–fetus system should be studied as a single object, in which maternal disease, placental lesions and fetal organ changes form a common pathogenetic chain leading to perinatal death.
2. Whole-slide imaging and digital morphometry convert placental morphology into objective quantitative predictors suitable for statistical modelling.
3. The designed study combines standardised pathology, digital image analysis and modern methods of prediction-model development and validation. It is expected

to produce a reproducible tool for predicting perinatal mortality risk and for verifying the causes of perinatal death.

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