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Original article

Identifying risk factors for neonatal hypoglycemia in infants conceived through assisted reproductive technology: A retrospective cohort study

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Abstract. *Background and aim:* 12 million infants are born worldwide after assisted reproductive technologies (ART), yet their health remains under-researched. Evidence indicates that neonatal hypoglycemia (NG) is more prevalent in ART-conceived infants. This study aims to identify risk factors for NG and explore prediction possibilities in this population, focusing specifically on ART-conceived infants without direct comparison to naturally conceived infants. *Research design and Methods:* Our retrospective cohort study involved 120 infants born after ART. The participants met specific criteria, including being born from a successful ART program resulting in single or multiple pregnancies. Those born using donor oocytes/sperm, intrauterine insemination, or surrogacy were not included. Data for the anamnesis were gathered and analyzed using IBM SPSS Statistics 26. *Results:* ART-conceived infants were at greater risk of being born with NG in cases of multiple pregnancies (OR=14.2; 95% CI: 1.71-117.67), isthmic-cervical insufficiency (OR=10.29; 95% CI: 1.47-71.98), premature birth (OR=13.39; 95% CI: 2.61-68.84), and uterine infertility (OR=10.29; 95% CI: 1.47-71.98). ART-conceived infants had a higher incidence of NG when they were late preterm (OR=16.95; 95% CI: 3.26-88), with fetal growth restriction (OR=13.38; 95% CI: 2.42-73.8), infantile asphyxia (OR=45; 95% CI: 7.86-257.64), congenital pneumonia (OR=16.96; 95% CI: 3.45-83.3), congenital infection (OR=18; 95% CI: 2.98-108.8), respiratory distress syndrome (OR=16.09; 95% CI: 3.6-72.03), and low or very low birth weight. A regression model that exhibited statistical significance encompassed late prematurity, neonatal asphyxia, congenital infection, and maternal hormone intake before pregnancy. *Conclusions*: Our study on ART-conceived infants identified key risk factors for NG. The prognostic model we developed supports early intervention and preventive measures, enhancing care for these infants. Future studies should include a control group of naturally conceived infants to compare the risk of NG between ART-conceived and naturally conceived populations. (www.actabiomedica.it)

Key words: assisted reproductive techniques, neonatal hypoglycemia, risk factors, newborn, prediction model, infant, hypoglycemia diagnosis, pregnancy assisted, reproductive technology

Introduction

Assisted reproductive technology (ART) has become a necessity in today's world, as every 6 couple suffer from infertility. Over 12 million infants worldwide and over 40,000 infants in Kazakhstan have been born through ART (1). The development of modern reproductology in Kazakhstan dates back almost 30 years. The first ART laboratory opened in October 1995, and the first "test tube" baby in Kazakhstan was born on July 31, 1996 (2). Researchers and clinicians worldwide are focusing on the impact of ART on

child health, including the endocrine status (2–5). In Kazakhstan, in 2022, the first research was launched to study the health status of ART-conceived infants. One of the focus areas of this study was the endocrine system, specifically neonatal hypoglycemia (NH), which is significant in pediatric endocrinology. NH is a common metabolic disorder that can affect newborns and potentially cause brain damage. The definition of NH is debated. Our protocol defines it as <2.6 mmol/L. It can occur as a transient condition or due to pathological causes such as hyperinsulinism, metabolic diseases, or perinatal disorders. However, the prevalence of NH varies greatly due to the nonspecific nature of its symptoms and the lack of clear diagnostic criteria. Recent studies have shown that low blood glucose levels can significantly impact brain neurons, leading to discussions about monitoring glycemia in the first few days of a newborn's life and developing strategies for managing newborns with hypoglycemic syndrome. When carbohydrate metabolism is disrupted in the neonatal period, the brain is the first to be affected. Infants who experience NH are at increased risk of developing sensorineural impairment and neurological problems (6–8). A study by Chi-Hong Ho et al. (9) reported that twins who conceived spontaneously had a greater incidence of NH than ART-conceived twins. However, Kouhkan, A. et al. reported that the risk of NH was greater in ART-conceived infants whose mothers had a history of gestational diabetes mellitus than in naturally conceived infants (10,11). Despite the significant impact of NHs on the development of a child's nervous system, only a few studies have been conducted on this topic, especially concerning infants who were conceived through ART. Our study aimed to identify risk factors associated with the development of NH and their predictive value in ART-conceived infants with a particular emphasis on ART-conceived infants without a direct comparison to those conceived naturally.

Patients and Methods

Study design and patients

This retrospective cohort study is designed to deliver a comprehensive analysis by examining the medical records of 96 women who successfully underwent in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) procedures at three leading reproductive clinics in Almaty from 2018 to 2022. The inclusion criteria focused on women who completed one or more cycles of IVF or ICSI that resulted in a clinical pregnancy that culminated in childbirth. In contrast, the exclusion criteria were meticulously defined to ensure data integrity; these criteria included cases involving donor oocytes or sperm, embryo recipients, intrauterine insemination, and surrogacy. Furthermore, the analysis incorporated the medical records of 120 infants born to these women, thereby offering valuable insights into NG and the developmental risk factors associated with these assisted reproductive technologies.

Data collection

Anamnestic data were collected. Maternal data (smoking history, obstetric, gynecological, and somatic history) and medical history of infants (history of NG and other pathological conditions) were retrospectively abstracted from medical records. In our study, we included all cases of NH, regardless of whether they were symptomatic or asymptomatic. This decision was based on the understanding that both symptomatic and asymptomatic NH can have significant implications for neonatal health, including potential long-term neurodevelopmental outcomes. By including all cases, we aimed to provide a comprehensive assessment of NH risk factors in ART-conceived infants.

Glucose testing protocol

Glucose levels were measured within the first 24 hours after birth using capillary blood samples. All infants were tested under similar conditions, specifically in a fasting state before feeding, to ensure consistency in the timing of glucose measurements. The glucose testing protocol was standardized across all participating clinics, and the results were systematically recorded in the medical charts for further analysis. This standardized approach minimized variability in testing procedures and ensured reliable data collection for the study.

Statistical analysis

Based on previous studies and the prevalence of NH in ART-conceived infants, we estimated that a sample size of 120 infants would provide sufficient statistical power (80%) to detect significant risk factors with an odds ratio of 2.0 or higher, assuming a 10% prevalence of NH in the population.

Statistics were performed using IBM SPSS statistical software (version 26, SPSS Inc., USA). Comparisons between groups were carried out by Fisher's exact test and the χ2 test. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed for all maternal somatic, obstetric, and postnatal care history variables in the NH group of ART-conceived infants. The development of a prognostic model to assess the risk of a particular outcome was conducted utilizing the binary logistic regression method. This methodological choice was primarily influenced by the dichotomous nature of the dependent variable (e.g., presence or absence of the pathological condition), while the independent variables encompassed both categorical (nominal or ordinal) and quantitative attributes. The logistic regression model estimates the probability pp of the occurrence of the outcome under investigation and can be mathematically expressed as follows:

$$p = \frac{1}{1 + e^{-(a_0 + a_1 x_1 + a_2 x_2 + \ldots + a_n x_n)}}$$

Where:

- p is the probability of the outcome (ranging from 0 to 1).
- x_1, x_2, …, x_n represent the values of the independent variables (risk factors) measured on nominal, ordinal, or quantitative scales.
- a_0 is the intercept term.
- a_1, a_2, …, a_n are the regression coefficients corresponding to each independent variable.
- e is the base of the natural logarithm.

The stepwise forward selection method was employed for the selection of independent variables, using the Wald statistic as the criterion for exclusion. This approach ensured that only statistically significant predictors were retained in the final model. The overall statistical significance of the resultant model was evaluated using the χ^2 test.

To quantify the explanatory power of the logistic regression model, the Nagelkerke R^2 was employed. This metric indicates the proportion of variance in the dependent variable that can be explained by the independent variables included in the model. A higher Nagelkerke R^2 value suggests a better fit of the model to the data. To assess the diagnostic significance of quantitative variables in predicting the outcome (e.g., NG), the Receiver Operating Characteristic (ROC) curve analysis was applied. This methodology was used to determine the optimal threshold for classifying patients according to their risk level, achieving the best balance between sensitivity (true positive rate) and specificity (true negative rate). The quality of the prognostic model was evaluated based on the area under the ROC curve (AUC), along with its standard error and 95% confidence interval. Additionally, the level of statistical significance (p-value) was reported to confirm the robustness of the model.The limit of statistical significance was $P \leq 0.05$. Missing values were less than 1%.
Trial registration: The protocol was registered on ClinicalTrials.gov (NCT06094998) on October 17, 2023.

Ethical approval

This study complied with the Declaration of Helsinki and was approved by the local Ethics Committee of the "Scientific Center of Pediatrics and Pediatric Surgery" on April 13, 2022 (№ IRB-02-2022). Informed consent was obtained from all the legally authorized representatives of the research participants before enrolling in the trial.

Results

We selected 120 ART-conceived infants who met our inclusion criteria. According to the medical history, NH was diagnosed in 7.5% (9) ART-conceived infants.

Maternal risk factors

We compared the influence of maternal factors on the development of NH in ART-conceived infants. The results are presented in Table 1.

Table 1. Frequency of maternal factors influencing neonatal hypoglycemia in ART-conceived children.

Maternal risk factors	NH in medical history		P value	OR; 95% CI
	Presence (n=9)	Absence (n=111)		
Smoking	1(11.1)	4(3.6)	0.327	3.34; 0.33-33.55
Multiple pregnancy	8(88.9)	40(36)	0.003*	14.2; 1.71-117.67
C-section	8(88.9)	76(68.5)	0.276	3.68; 0.44-30.6
Arterial hypertension	0(0)	5(4.5)	0.990	1.02; 0.05-19.87
Thyroid disease	1(11.1)	24(21.6)	0.683	0.45; 0.05-3.8
Chronic pyelonephritis	4(44.4)	19(17.1)	0.067	3.87; 0.95-15.78
GDM	0(0)	3(2.7)	0.752	1.63; 0.08-33.99
Anemia of pregnancy	4(44.4)	35(31.5)	0.470	1.74; 0.44-6.87
Preeclampsia	2(22.2)	8(7.2)	0.164	3.68; 0.65-20.71
Insuficiencia istmicocervical	2(22.2)	3(2.7)	0.045*	10.29; 1.47-71.98
Premature delivery	7(77.8)	23(20.7)	0.001*	13.39; 2.61-68.84
ART in medical history	6(66.7)	48(43.2)	0.296	2.63; 0.63-11.03
ICSI	4(44.4)	69(62.2)	0.311	0.49; 0.12-1.92
FET	7(77.8)	84(75.7)	1.000	1.13; 0.22-5.74
Taking estrogen and progesterone before pregnancy	7(77.8)	50(45)	0.084	4.27; 0.85-21.48
Secondary infertility	3(33.3)	59(53.2)	0.312	0.44; 0.11-1.85
Tubal infertility	7(77.8)	65(58.6)	0.313	2.48; 0.49-12.47
Uterine infertility	2(22.2)	3(2.7)	0.045*	10.29; 1.47-71.98
Taking estrogen and progesterone during pregnancy	7(77.8)	58(52.3)	0.177	3.2; 0.64-16.08

Note: Data are expressed as n (%). P values were determined by using the Chi-square test or Fisher's exact test for categorical data. OR = odds ratio; CI = confidence interval. *Abbreviations:* GDM - gestational diabetes mellitus; ART - assisted reproductive technology; ICSI - intracytoplasmic sperm injection; FET - frozen embryo transfer.
* Indicates statistical significance at $p < 0.05$.

Based on the obstetric history analysis, infants born from multiple pregnancies had a 14.2-fold greater risk of NH than infants born from singleton pregnancies (95% CI: 1.71-117.67). Compared with mothers whose mothers did not have isthmic-cervical insufficiency during pregnancy, newborns whose mothers suffered from isthmic-cervical insufficiency during pregnancy had a 10.29-fold greater risk of NH (95% CI: 1.47-71.98). Furthermore, NHs are more prevalent in infants whose mothers have a preterm birth, with odds being 13.39 times greater than those in infants born at full term (95% CI: 2.61-68.84). Additionally, the odds of developing NH in ART-conceived infants increased 10.29 times in women with uterine infertility (95% CI: 1.47-71.98).

Risk factors in pediatric history

We compared the frequency of NH-related pediatric factors in ART-conceived infants (Table 2).

Based on the analysis of pediatric history data, late preterm infants born between 34 and 36 weeks of gestation had a 16.95 times greater risk of NH than full-term infants (95% CI: 3.26-88). The risk of NH in infants with *fetal growth restriction (FGR)* was 13.38 times greater than that in infants without

Table 2. Frequency of pediatric factors influencing neonatal hypoglycemia in ART-conceived children.

Pediatric risk factors	NH in medical history		P value	OR; 95% CI
	Presence (n=9)	Absence (n=111)		
Late preterm	7(77.8)	19(17.1)	<0.001*	16.95; 3.26-88
Low birth weight	5(55.6)	20(18)	0.019*	5.69; 1.4-23.09
FGR	3(33.3)	4(3.6)	0.009*	13.38; 2.42-73.8
Infantile asphyxia	5(55.6)	3(2.7)	<0.001*	45; 7.86-257.64
Congenital pneumonia	4(44.4)	5(4.5)	0.002*	16.96; 3.45-83.3
Congenital infection	3(33.3)	3(2.7)	0.005*	18; 2.98-108.8
Respiratory distress syndrome	5(55.6)	8(7.2)	0.001*	16.09; 3.6-72.03
Pathologic hyperbilirubinemia	6(66.7)	37(33.3)	0.068	4; 0.95-16.9

Note: Data are expressed as n (%). P values were determined by using the Chi-square test or Fisher's exact test for categorical data. OR = odds ratio; CI = confidence interval. *Abbreviations:* FGR - fetal growth restriction. * indicates statistical significance at $p < 0.05$.

Table 3. Comparison of birth weight groups according to neonatal hypoglycemia status among ART-conceived children.

	Classification of prematurity categorized by birth weight					
	Normal weight 2500-3999 g	High birth weight (>4000 g)	LBW	VLBW	ELBW	P value
NH(n=9)	3 (33.3)	1 (11.1)	4 (44.4)	1 (11.1)	0 (0)	0.029* p_{1-3}=0.045* p_{1-4}=0.013*

Note: Data are expressed as n (%). P values were determined by using the Chi-square test or Fisher's exact test for categorical data. *Abbreviations:* LBW - low birth weight (<2500 g = 1500–2499 g); VLBW - very low birth weight (<1500 = 1000–1499 g); ELBW - extremely low birth weight (<1000 g). * Indicates statistical significance at $p < 0.05$.

FGR (95% CI: 2.42-73.8). NH occurred 5.69 times statistically significantly more often in the group of infants with low birth weight (95% CI: 1.4-23.09). Additionally, infants with neonatal asphyxia were at a greater risk of NH, with odds increasing 45-fold (95% CI: 7.86-257.64). The risk of developing NH was 16.96 times greater in infants with congenital pneumonia (95% CI: 3.45-83.3). Similarly, infants with a history of congenital infection were 18 times more likely to develop NH (95% CI: 2.98–108.8). Furthermore, infants with neonatal respiratory distress syndrome were 16.09 times more likely to develop NH (95% CI: 3.6-72.03). However, the study did not find any significant association between pathological hyperbilirubinemia and NH in ART-conceived infants. Table 3 compares the frequency of NHs among ART-conceived infants in different birth weight groups.

After comparing groups based on birth weight and the frequency of NHs among ART-conceived infants, it was found that there were statistically significant differences ($p = 0.029$). The differences were explained by a greater incidence of NH among infants with low birth weight ($p = 0.045$) and very low birth weight ($p = 0.013$) than among infants with normal weight.

Development of a prediction model for NH in infants with ART-conceived infants.

We created a prediction model using binary logistic regression to estimate the probability of NH in ART-conceived infants. It was based on risk factors identified from the medical history. The relationship observed is defined by equation (1):

$$P = 1 / (1 + e^{-z}) * 100\%$$

$$z = -6{,}79 + 3{,}15 * X_{LP} + 3{,}63 * X_{IA} + 2{,}5 * X_{CI} + 3{,}25 * X_{E+P} \quad (1)$$

where P – the probability of NH in ART-conceived infants (%), X_{LP} –late preterm (0 – absence, 1 – presence), X_{IA} – neonatal asphyxia (0 – absence, 1 – presence), X_{CI} –congenital infection (0 – absence, 1 – presence), X_{E+P} –taking estrogen and progesterone before pregnancy (0 – absence, 1 – presence).

The resulting regression model was statistically significant (p<0.001). Based on the Nigelkirk coefficient of determination, the model explained 60.6% of the observed variance in the presence of NH in ART-conceived infants. According to the regression coefficients, certain factors, such as late preterm birth, infantile asphyxia, congenital infection, and a history of taking estrogen and progesterone before pregnancy, were found to be directly associated with the probability of NH in ART-conceived infants. The characteristics of each factor are presented in Table 4.

Figure 1 compares the values of the adjusted odds ratios with 95% CIs for the studied factors included in model (1).

The cutoff value of the logistic function P was determined using the ROC curve analysis. The resulting curve is shown in Figure 2.

The area under the ROC curve was 0.9±0.09 (95% CI: 0.74–1). The threshold value of the logistic function (1) at the cutoff point was 25%. P values

Table 4. Relationship between predictors of model (1) and the probability of NG in ART-conceived children.

	Unadjusted		Adjusted	
Predictors	**COR; 95% CI**	**p**	**AOR; 95% CI**	**p**
Late preterm	16.95; 3.26-88	<0.001*	23.38; 2.04-267.81	0.011*
Infantile asphyxia	45; 7.86-257.64	<0.001*	37.88; 1.49-963.68	0.028*
Congenital infection	18; 2.98-108.8	0.005*	12.16; 0.82-180.83	0.070
Taking estrogen and progesterone before pregnancy	4.27; 0.85-21.48	0.084	25.66; 1.41-465.921	0.028*

Note: P values were determined by using the Chi-square test or Fisher's exact test for categorical data. *Abbreviations:* COR – crude odds ratio; AOR – adjusted odds ratio; CI - confidence interval. * Indicates statistical significance at p < 0.05.

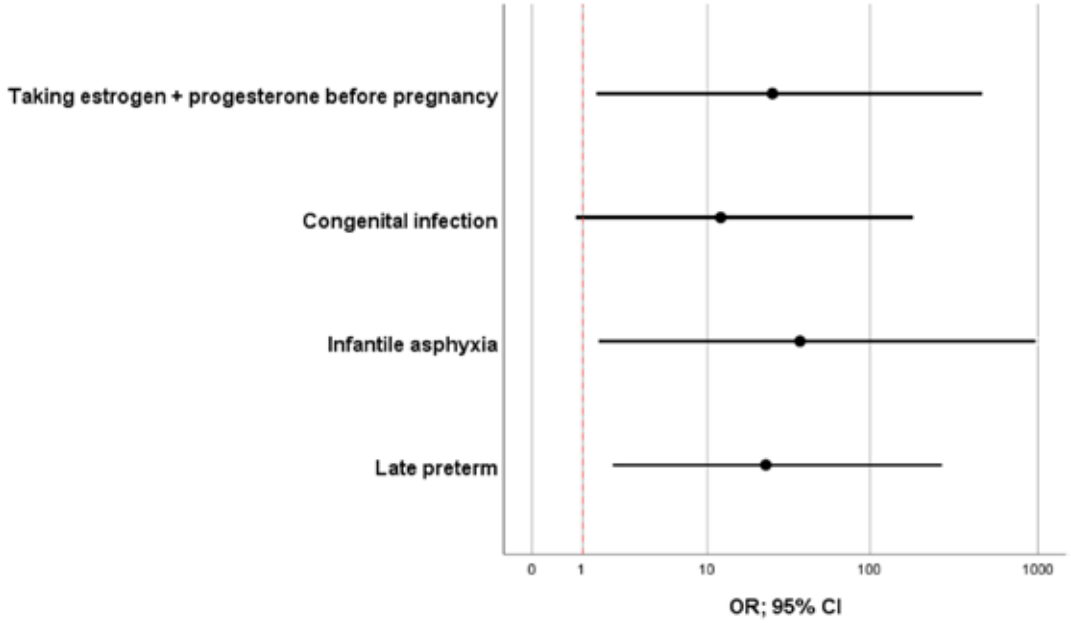

Figure 1. Forest plot showing Ors with 95% CI for the predictors of NG in ART-conceived infants.

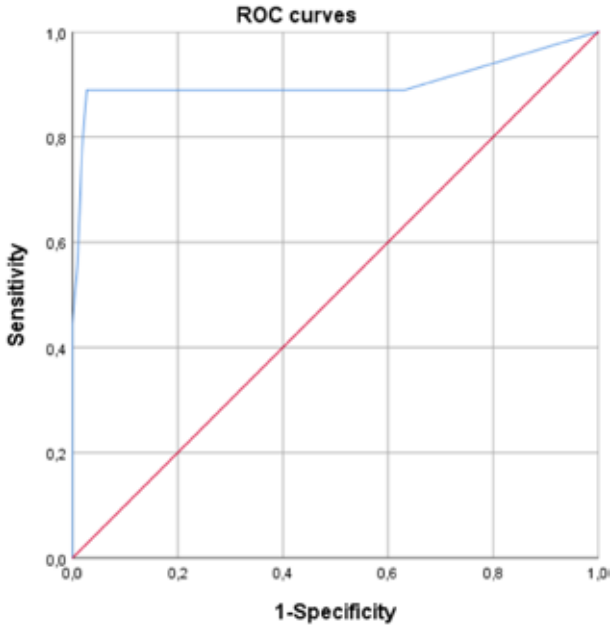

Figure 2. ROC-curve characterizing the dependence of NG in ART-conceived infants on the values of P function (1).

greater than or equal to 25% indicated a high risk of NH in ART-conceived infants, and P values <25% indicated a low risk of NH in ART-conceived infants. The sensitivity and specificity of this model (1) at this threshold were 88.9% and 97.3%, respectively.

Discussion

The key findings of this study are as follows: (i) based on the history of maternal risk factors, ART-conceived infants were at greater risk for NH in cases of multiple pregnancies, isthmic-cervical insufficiency, premature birth, and uterine infertility; (ii) based on the history of pediatric risk factors, the risk of NH in ART-conceived infants was greater in the case of late prematurity of infants, FGR, neonatal asphyxia, congenital pneumonia, congenital infection, respiratory distress syndrome of newborns, and low and very low birth weight; (iii) when constructing a statistically significant regression model taking into account all statistically significant risk factors, it was found that late preterm birth, infantile asphyxia, congenital infection and a history of taking estrogen and progesterone before pregnancy were directly associated with the probability of NH in ART-conceived infants and may help predict the development of this condition. The inclusion of both symptomatic and asymptomatic cases of NH in our study has important implications. While symptomatic NH is often more readily identified and treated, asymptomatic NH can also pose significant risks, including potential long-term neurodevelopmental consequences if left undetected. By including all cases, our study provides a more comprehensive understanding of NH in ART-conceived infants, highlighting the need for vigilant monitoring and early intervention, even in the absence of overt symptoms. This approach underscores the importance of universal screening for NH in high-risk populations, such as ART-conceived infants, to ensure timely identification and management of both symptomatic and asymptomatic cases. When analyzing maternal risk factors in ART-conceived infants with NH, multiple pregnancies (95% CI: 4.25-118.16), isthmic-cervical insufficiency (95% CI: 1.47-71.98), preterm birth (95% CI: 1.56-27.99), and uterine infertility (95% CI: 1.47-71.98) had significant influences. Several previous studies have confirmed that multiple pregnancies and preterm births are associated with a high incidence of NH (12–16). The presence of isthmic-cervical insufficiency usually has a direct connection with premature birth, which is associated with NH. In addition, a role for uterine infertility has been discovered, but further study is needed to better understand this relationship. Interestingly, in our study, maternal gestational diabetes was not a risk factor for NH in infants. When analyzing pediatric risk factors, it was found that the odds of NH were 16.95 times greater among late preterm infants born between 34 and 36 weeks of gestation than among full-term infants (95% CI: 3.26-88). Additionally, the risk of NHs with a history of FGR increased by 13.38 times (95% CI: 2.42-73.8), neonatal asphyxia by 45 times (95% CI: 7.86-257.64), congenital pneumonia by 16.96 times (95% CI: 3.45-83.3), congenital infection by 18 times (95% CI: 2.98-108.8), respiratory distress syndrome by 16.09 times (95% CI: 3.6-72.03). Additionally, NHs were more common in low birth weight (p=0.045) and very low birth weight (p=0.013) infants than in normal-weight infants. This assertion holds true for all individuals, including those conceived spontaneously; however, these

conditions are more prevalent among ART-conceived infants. Consequently, this may increase the likelihood of NG within the ART population. Previous studies have also revealed the influence of prematurity, low birth weight, neonatal respiratory distress syndrome, and neonatal asphyxia on NH (17–19). In addition, some studies have noted that infants with FGR have a high risk of NH (20–22). According to the regression model, the most significant factors were late prematurity [aOR: 23,38 (2,04-267,81)], neonatal asphyxia [aOR: 37,88 (1,49-963,68)], and congenital infection [aOR: 12,16 (0,82-180,83)]. Additionally, the history of taking estrogen and progesterone before pregnancy was also identified as a statistically significant risk factor [aOR:25,66 (1,41-465,921)]. It is important to note that placental progesterone and estrogens play a crucial role in controlling insulin sensitivity during pregnancy. These steroid hormones can lead to pancreatic hypertrophy, with progesterone reducing insulin-stimulated glucose uptake and stimulating appetite and fat deposition, while estrogen increases systemic insulin sensitivity (23). Progesterone may have toxic effects on pancreatic βcells by triggering apoptosis through an oxidative stress-dependent mechanism (24). Furthermore, abnormal levels of steroid hormones during pregnancy have been strongly linked to the development of GDM (25). Therefore, it is reasonable to conclude that there is a logical correlation between mothers' use of estrogen and progesterone before pregnancy and the increased risk of NH in ART-conceived infants. In our study, maternal GDM was not identified as a significant risk factor for NG among infants conceived via ART. This observation may be attributed to the limited sample size of mothers diagnosed with GDM within our cohort, consisting of only three out of 120 mothers. Furthermore, it is plausible that the management strategies employed for GDM in these cases—such as dietary modifications, insulin therapy, or vigilant monitoring—may have alleviated the risk of NG in their offspring. We recommend that future research with larger sample sizes investigate the relationship between GDM and NG in ART-conceived infants to enhance the understanding of the potential implications of GDM on neonatal outcomes in this demographic. Multiple births, premature births, and low birth weight in infants have been shown to increase the risk of NH. These risk factors are commonly observed in ART-conceived infants. Consequently, it is logical to observe a higher prevalence of NH in ART-conceived infants, which aligns with the findings of previous studies (10,11). Today, the use of ART allows for the identification and management of these risks, enabling healthcare professionals to provide appropriate counseling for women and pediatric care for their offspring. However, further research is essential to evaluate these findings and develop effective preventive strategies.

Limitations

Several limitations of our study should be considered. First, because there are no registries of ART infants in Kazakhstan, the size of this cohort could not have been representative of the wider population. Second, our study is limited by a short follow-up period due to the complexity and cost of longitudinal studies, which makes it impossible to assess the long-term effects of NH on the nervous system of ART-conceived infants. Third, we recognize that the retrospective nature of this study limits our ability to control for certain variables, such as the exact timing of glucose testing or the type of feeding (e.g., breast milk, formula, or dextrose) prior to testing. While the glucose testing protocol was consistent across all participating clinics, the lack of precise control over these variables may introduce some degree of variability in the results. Future prospective studies with standardized protocols for glucose testing and feeding schedules would help address these limitations and provide more robust data on NG in ART-conceived infants. Fourth, we assessed only some of the risk factors; however, infertility itself, drugs used for ovulation induction, pathology of the placenta, and other diseases may influence the incidence of NH in offspring. Fifth, this study included only a sample from Kazakhstan. It is necessary to expand the geography of studies to increase the sample size and increase the applicability of findings to other ethnic groups. Sixth, the majority of risk factors are applicable to both infants conceived via ART and those conceived naturally, and preventive measures would again come down to proper antenatal care and prevention of prematurity; however, these conditions are observed with greater frequency among ART-conceived

infants. Consequently, this may increase the likelihood of NG within the ART population. Seventh, we acknowledge that the inclusion of a control group of naturally conceived infants would have strengthened the study by allowing for a direct comparison of NG risk between ART-conceived and naturally conceived infants. However, due to the retrospective nature of the study and the lack of a registry for naturally conceived infants in Kazakhstan, we were unable to include such a control group. This limitation restricts our ability to generalize the findings to the broader population and highlights the need for future prospective studies that include both ART-conceived and naturally conceived infants to better understand the differences in NG risk between these groups. Additionally, the sample size may not be large enough to detect smaller effect sizes or less common risk factors, which could be important in understanding the full spectrum of NH in ART-conceived infants. The generalizability of our findings may be limited due to the relatively small sample size and the specific population studied (infants born in Kazakhstan). The lack of diversity in the study population, including variations in ethnic, socioeconomic, and healthcare access factors, may restrict the applicability of our findings to other regions or populations. Future studies with larger, more diverse cohorts are needed to validate our findings and further explore the risk factors for NH in ART-conceived infants across different settings. We recommend that future studies validate the model in different populations to assess its broader applicability.

Conclusions

In conclusion, while research on the risk factors for NH in ART-conceived infants is limited, our study emphasizes the importance of addressing this specific group. Our retrospective study of ART-conceived infants allowed us to identify significant risk factors for NH, including late prematurity, neonatal asphyxia, congenital infection, and maternal estrogen and progesterone intake before pregnancy. The developed prognostic model allows us to predict the probability of NH, providing an opportunity for early intervention and appropriate preventive measures. With ART becoming an increasingly utilized tool, it is essential to consider prognostic risks and intervene promptly to address potential health concerns in infants. The findings from this study are valuable for reproductologists, neonatologists, and pediatricians because they provide valuable insights that can improve the care of ART-conceived infants. Further research in this field has the potential to improve pregnancy and birth outcomes, as well as reduce the occurrence of newborn complications.

Ethic Approval: This study complied with the Declaration of Helsinki and was approved by the local Ethics Committee of the "Scientific Center of Pediatrics and Pediatric Surgery" on April 13, 2022 (№ IRB-02-2022). The informed consent was obtained from all legally authorized representatives of research participants before enrolment in the trial.

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Authors' Contribution: ZN: Data Curation, Formal analysis, Investigation, Writing - Review & Editing. SI: Data Curation, Formal analysis, Investigation, Writing - Original Draft. VL: Conceptualization, Methodology, Data Curation, Resources, Writing - Review & Editing, Supervision. LM: Methodology, Project administration, Writing - Review & Editing, Funding acquisition, Resources. RS: Writing - Review & Editing.

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