Gansu Provincial Maternity and Childcare Hospital

Statistical Analysis Plan (SAP)

Project name: A cohort study on the effects of gestational blood sugar management and postnatal nurturing environment on delayed language development in children

Project source: National Clinical Medical Research Center for Child Health and Disease

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According to the implementation plan of the "Western Baby Plan" queue, 1.5-2.5-year-old offspring children who have entered the "Western Baby Plan" queue as research objects were be surveyed. The language development and family nurturing environment of 2-year-old children using the "Language Development Evaluation S-S Method, Gesell Infant and Toddler Development Scale, and 0-6 Year Old Family Nurturing Environment Evaluation Scale" were be evaluated. We investigated the results of blood sugar screening during pregnancy of children's mothers using retrospective cohort study methods, and follow up the blood sugar management effect of pregnant women with abnormal blood sugar before delivery. At the same time, pregnant women diagnosed with abnormal blood sugar during pregnancy are used as research objects to conduct prospective cohort studies: collect standardized epidemiological survey data of the "Western Baby Plan" queue (mainly including general conditions, diet, exercise, environmental factor investigations, etc.), follow up blood sugar control methods at 36-40 weeks of pregnancy, record pre-pregnancy blood sugar control results and neonatal outcomes, collect peripheral blood and umbilical blood during delivery and store them in the mother-infant biological sample library. The study would follow up the growth and development of offspring, and evaluate the language development and family nurturing environment of 2-year-old children using the "Language Development Evaluation S-S Method, Gesell Infant and Toddler Development Scale, and 0-6 Year Old Family Nurturing Environment Evaluation Scale".

Sample size estimation: Referring to delayed language development in children as the disease outcome, the incidence rate (p1) of delayed language development in the group exposed to high prenatal sugar is 15%, and the relative risk (RR) is 2.0, with a desired significance level (a) of 0.05 and a desired power (1-b) of 0.90. By plugging in these values into

the formula, it is determined that both the exposed group and the control group require 160 individuals. Considering the possibility of loss to follow-up, the sample size is increased by 10%. The final estimated sample size for the cohort is 356 cases, with a planned investigation of 360 individuals in the blood sugar abnormality specialized disease cohort.

The sample calculation formula for the cohort study collects data information through the electronic medical record system and the Western Children's Health and Disease Cohort Platform, with dual data entry into an Excel database. Differences in the distribution of general conditions of pregnant women are compared using statistical methods such as the chi-square test or Fisher's exact probability test for categorical data (Socio demographic profile, menstrual and reproductive history, indoor environment Environmental factors, Scale indicators etc.), and statistical methods such as the t-test or ANOVA test for continuous data (Check labs (e.g., fasting blood glucose, glycosylated hemoglobin, lipids, liver and kidney function, etc.). After further controlling for confounding factors, logistic regression analysis is used to explore the impact of poor blood sugar management (high prenatal sugar exposure) on delayed language development around 1-2 years of age.

The combined effect of GDM and postnatal environment of the offspring was analyzed using an EXCEL spreadsheet developed by Andersson et al. The additive interaction was evaluated using three indices: relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S). If the 95% confidence intervals (CI) of RERI and AP included 0, and the 95% CI of S included 1, it indicated no additive interaction; otherwise, there was an additive interaction.

The regression models were used to screen the effect of maternal GDM and related factors on the delayed language development (DLD) in

offspring. The binomial logistics regression model and the lasso regression model were constructed by using the "rms" and "glmnet" package to analyse risk factors. The nomogram, which based on proportionally converting each regression coefficient to a zero to one-hundred-point scale, was used to screen the effect of maternal GDM and related factors on the DLD. The effect of the variable with the highest β coefficient was assigned one hundred points. The points were added across independent variables to derive total points, which were converted to predicted probabilities. The total scores of each patient were calculated based on the nomogram for clinical prediction. We used the predictive performance of the nomogram was measured by concordance index (C index). Prediction models were validated by plotting calibration curves and using bootstrap method with one thousand replicate samples. The clinical validity of the prediction model was evaluated using decision curve analysis (DCA).

All analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA, version 21.0) and R version (4.1.3, http://www.r-project.org/). The significance level for statistical tests is set at a value of 0.05, the selection criterion for the regression equation is set at a level of 0.05, and the exclusion level is set at 0.10. Missing values are handled according to the default method in SPSS, which means that observations with missing values in the test variables are excluded from the analysis. A p-value of <0.05 indicates a statistically significant difference.