eRegQual analysis

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# Introduction

This document presents the methods used to analyze the adverse pregnancy outcome data for the eRegQual trial and presents the corresponding results.

# Methods

Because outcome data were missing for about a third of participants (see results), we used Little's tests (Little 1988) of the null hypotheses that missing values of the constituent outcomes were jointly missing completely at random (MCAR) and covariate-dependent missing (CDM). We then used multiple imputation via chained equations (van Buuren 2007) to create and analyze 50 multiply-imputed datasets. We imputed each of the constituent outcomes using the auxiliary variables age, BMI, years of education, average monthly household income (transformed to the log scale due to the skewed distribution of income), and variables that indicated whether a laboratory or ultrasound were available at the clinics; the variables included in the analysis described below were also included. We were not able to include auxiliary variables that indicated previous pregnancy with pre-eclampsia or previous history of GDM due to collinearity. We evaluated the convergence of the imputation algorithm by inspecting trace plots and evaluated imputed data by inspecting kernel density and bar plots comparing the distributions of imputed and complete case data.

For each imputed data set, we computed the composite outcome from the imputed constituent outcome data. An adverse pregnancy outcome was defined to have occurred if at least one of the constituent outcomes occurred, and not to have occurred if none of the constituent outcomes occurred. For each imputed data set and outcome, we estimated a risk ratio to compare treatment to control, adjusted for the stratification variable as a fixed effect, and used generalized estimating equations (GEE; binomial errors and log link) to account for the cluster design. We combined estimates for each outcome using Rubin's rules (Rubin 2004). For comparison, we also performed a complete case analysis under the MCAR assumption. We estimated the intraclass correlation coefficient (ICC) using the complete cases.

We followed the intention-to-treat principle: participants were analyzed in the arms to which they were randomized and — with the exception of the complete case analyses — all participants were included in the analyses. We computed 95% confidence intervals and used the significance criterion P<0.05 throughout. Statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, Texas, USA).

# Results

Outcome data were missing for between 11.8% and 35.5% of the constituent outcomes, and 33.8% of the composite outcome. We were unable to reject the MCAR and CDM hypotheses (P=0.15 and P=0.64, respectively). Distributions of the original and the first five imputed data sets are shown in the Appendix. Table 1 shows the result of the adverse pregnancy outcome analysis. The risk ratio was estimated to be 1.01 (95% CI 0.92 to 1.11, P = 0.87). This compares to the complete case risk ratio of 0.99 (95% CI 0.91 to 1.08, P = 0.85). Tables 2–6 show results for the constituent outcomes. The ICC was estimated to be close to zero and no greater than 0.007 (upper bound of 95% CI).

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| Table 1. Adverse pregnancy outcome (multiply-imputed result) | | | | | | |
| y | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.01 | 0.05 | 0.16 | 0.87 | 0.92 | 1.11 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.10 | 0.09 | 1.27 | 0.20 | 0.95 | 1.29 |
| 9d5ed6 | 0.93 | 0.10 | -0.68 | 0.50 | 0.75 | 1.15 |
| e1e1d3 | 1.08 | 0.09 | 0.99 | 0.32 | 0.92 | 1.27 |
| ff4457 | 1.15 | 0.09 | 1.79 | 0.07 | 0.99 | 1.34 |
|  |  |  |  |  |  |  |
| \_cons | 0.23 | 0.02 | -20.65 | 0.00 | 0.20 | 0.27 |

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| Table 2. Anemia at birth (multiply-imputed result) | | | | | | |
| y1 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.17 | 0.27 | 0.67 | 0.51 | 0.74 | 1.85 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.38 | 0.61 | 0.73 | 0.47 | 0.58 | 3.27 |
| 9d5ed6 | 1.54 | 0.88 | 0.75 | 0.45 | 0.50 | 4.75 |
| e1e1d3 | 1.90 | 0.82 | 1.50 | 0.13 | 0.82 | 4.42 |
| ff4457 | 1.77 | 0.74 | 1.38 | 0.17 | 0.78 | 4.00 |
|  |  |  |  |  |  |  |
| \_cons | 0.01 | 0.00 | -11.61 | 0.00 | 0.00 | 0.02 |

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| Table 3. Severe hypertension at birth (multiply-imputed result) | | | | | | |
| y2 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.52 | 0.60 | 1.08 | 0.28 | 0.70 | 3.29 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.17 | 0.99 | 0.19 | 0.85 | 0.22 | 6.12 |
| 9d5ed6 | 0.99 | 1.19 | -0.01 | 0.99 | 0.09 | 10.45 |
| e1e1d3 | 1.79 | 1.48 | 0.70 | 0.48 | 0.35 | 9.12 |
| ff4457 | 4.34 | 3.25 | 1.96 | 0.05 | 1.00 | 18.87 |
|  |  |  |  |  |  |  |
| \_cons | 0.00 | 0.00 | -8.02 | 0.00 | 0.00 | 0.01 |

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| Table 4. SGA undetected at birth (multiply-imputed result) | | | | | | |
| y3 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.02 | 0.11 | 0.16 | 0.88 | 0.82 | 1.26 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 0.86 | 0.15 | -0.88 | 0.38 | 0.61 | 1.21 |
| 9d5ed6 | 0.67 | 0.18 | -1.53 | 0.13 | 0.40 | 1.12 |
| e1e1d3 | 0.93 | 0.16 | -0.44 | 0.66 | 0.66 | 1.31 |
| ff4457 | 0.93 | 0.16 | -0.41 | 0.68 | 0.67 | 1.30 |
|  |  |  |  |  |  |  |
| \_cons | 0.09 | 0.01 | -16.27 | 0.00 | 0.07 | 0.12 |

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| Table 5. Malpresentation undetected at birth (multiply-imputed result) | | | | | | |
| y4 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.10 | 0.17 | 0.59 | 0.55 | 0.81 | 1.49 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.25 | 0.39 | 0.72 | 0.47 | 0.68 | 2.29 |
| 9d5ed6 | 0.75 | 0.36 | -0.60 | 0.55 | 0.29 | 1.91 |
| e1e1d3 | 1.88 | 0.55 | 2.17 | 0.03 | 1.06 | 3.34 |
| ff4457 | 1.63 | 0.49 | 1.63 | 0.10 | 0.91 | 2.93 |
|  |  |  |  |  |  |  |
| \_cons | 0.02 | 0.01 | -14.24 | 0.00 | 0.01 | 0.04 |

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| Table 6. Large for gestational age (multiply-imputed result) | | | | | | |
| y5 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 0.93 | 0.07 | -1.00 | 0.32 | 0.81 | 1.07 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.18 | 0.14 | 1.40 | 0.16 | 0.94 | 1.48 |
| 9d5ed6 | 1.12 | 0.17 | 0.72 | 0.47 | 0.83 | 1.51 |
| e1e1d3 | 1.00 | 0.13 | -0.02 | 0.98 | 0.78 | 1.28 |
| ff4457 | 1.14 | 0.14 | 1.05 | 0.29 | 0.90 | 1.44 |
|  |  |  |  |  |  |  |
| \_cons | 0.12 | 0.01 | -19.87 | 0.00 | 0.10 | 0.15 |

# References

van Buuren, S. (2007). Multiple imputation of discrete and continuous data by fully conditional specification. Statistical methods in medical research, 16(3), 219-242.

Little, R. J. (1988). A test of missing completely at random for multivariate data with missing values. Journal of the American statistical Association, 83(404), 1198-1202.

Rubin, D. B. (2004). Multiple imputation for nonresponse in surveys (Vol. 81). John Wiley & Sons.

# Appendix

The following figures show the distributions of the original and a selection of the imputed data.  
  
  
  
  
  
  
  
  
