A likelihood model that accounts for censoring due to fetal loss can accurately test the effects of maternal and fetal genotype on the probability of miscarriage

Colin I. O'Donnell[1], Charles J. Glueck[2], Tasha E. Fingerlin[1], and Deborah H. Glueck[1]

[1]Department of Preventive Medicine and Biometrics, University of Colorado at Denver and Health Sciences
Center, Denver, Colorado 80262
[2]The Cholesterol Center, Jewish Hospital, Cincinnati, Ohio 45229.

Objective: Heritable maternal and fetal thrombophilia and/or hypofibrinolysis are important causes of miscarriage. Under the constraint that fetal genotype is observed only after a live birth, estimating risk is complicated. Censoring prevents use of published statistical methodology. We propose techniques to determine whether increases in miscarriage are due to the fetal genotype, maternal genotype, or both.

Methods: We propose a study to estimate the risk of miscarriage contributed by an allele, expressed in either dominant or recessive fashion. Using a multinomial likelihood, we derive maximum likelihood estimates of risk for different genotype groups. We describe likelihood ratio tests and a planned hypothesis testing strategy.

Results: Parameter estimation is accurate (bias<0.0011, root mean squared error<0.0780, N=500). We used simulation to estimate power for studies of three gene mutations: the 4G hypofibrinolytic mutation in the plasminogen activator inhibitor gene (PAI-1), the prothrombin G20210A mutation, and the Factor V Leiden mutation. With 500 families, our methods have approximately 90% power to detect an increase in the miscarriage rate of 0.2, above a background rate of 0.2.

Conclusion: Our statistical method can determine whether increases in miscarriage are due to fetal genotype, maternal genotype, or both despite censoring.