Causal Effects on Birth Defects with Missing by Terathanasia

Andrew Ying

University of California
E-mail: anying@ucsd.edu

Abstract: We investigate the causal effects of etanercept (trade name Enbrel) on birth defects, a pharmaceutical that treats autoimmune diseases and recently went through the US FDA revised labeling for use in pregnancy, as the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. An outstanding problem, which was not addressed in the data analysis leading up to the FDA relabeling, is the missing birth defect outcomes due to spontaneous abortion since in accepted standard practice an infant or a fetus is assumed not to be malformed unless a defect is found. This led to likely bias (and missing not at random) because, according to the theory of "terathanasia", a defected fetus is more likely to be spontaneously aborted. In addition, the previous analysis stratified on live birth against spontaneous abortion, which was itself a post-exposure variable showing a higher rate of spontaneous abortion in the unexposed women, hence did not lead to a causal interpretation of the stratified results. In this paper, we aim to estimate and provide inference for the causal parameters of scientific interest, including the principal effects, making use of the missing data mechanism informed by terathanasia. During the process, we also deal with complications in the data including left truncation, observational nature, and rare events. We report our findings which not only provide a more in-depth analysis than previously done on etanercept, but also shed light on how similar studies on causal effects of medication (or vaccine, other substances etc.) during pregnancy may be analyzed.