Statistics and Its Interface Volume 11 (2018) 397–399

Challenges in analyzing time to live birth

Hongying Kuang, Hao Huang, Haizhu Tan,
Allen R. Kunselman, and Heping Zhang*

Live birth is recommended as the primary clinical outcome in studies of infertility. Although it is commonly treated as a dichotomous response, namely live birth or not, time to live birth is also of important clinical interest. In this call-for-attention essay, we present the subtlety in characterizing the time to live birth, but not to offer a solution.

The Practice Committee of American Society for Reproductive Medicine operationally defines infertility as the inability to conceive within 1 year of unprotected intercourse [1]. It is estimated to affect between 8 and 12% of reproductive-aged couples or 186 million people worldwide [2]. Infertility is of both public health and social significance. Efforts have been devoted to standardize the reporting of clinical studies that are designed to evaluate treatment effectiveness for infertility, especially in selecting the primary outcome. In fact, there is a consensus in that live birth is the most desirable endpoint [3], although some authors believe the duration of delivering a live birth make it disadvantageous as the primary outcome in a clinical study as compared to the use of ongoing pregnancy [4]. However, this ongoing debate is not the topic of this essay. Instead, given the clinical interest in live birth as the primary endpoint, we present the issues in statistical analysis of live birth that rarely have been discussed and yet have major consequences in the interpretation of the data.

If we treat live birth as a dichotomous response (yes or no), the definition of this response is clear cut; however, time to live birth is also of great interest [5–10]. Without offering our preference or a solution, we present some options and encourage readers to assess those and perhaps other options.

When a live birth is delivered, the end date is determined from when the baby(ies) is born. In order to calculate the time to live birth, we still need to define the starting date. In clinical trials, the starting date is typically the day when the treatment(s) is provided. If we follow this definition of the starting date, it is a common knowledge that women have menstrual cycles, and in general, they ovulate once in about a month. A pregnancy occurs only after ovulation. Consequently, if a woman fails to get pregnant in a menstrual cycle, she has to wait until the next cycle to have another chance. Thus, two women can end up with the same time to live birth but with totally different paths and implications. One woman can get pregnant in the first cycle following the treatment and deliver a live birth after a 9-month pregnancy, giving rise to a total of, say, 10 months for the time to live birth. Another woman can get pregnant in the second cycle following the treatment and deliver a live birth after an 8-month pregnancy, also giving rise to a total of 10 months for the time to live birth.

A reasonable solution to avoid this complication is to start the time from when a pregnancy is detected. This eliminates part of the complications, but complications remain. First, we cannot ignore what happened prior to the pregnancy. In fact, there is a well-established literature on how to model time-to-pregnancy, which we will discuss briefly. Second, we still need to deal with whatever complications that we face from pregnancy to live birth. For example, unlike time to death where a longer survival time is the desirable outcome, time to live birth is ideal only when the pregnancy is carried for about 40 weeks. Much shorter or longer is not ideal. Therefore, a shorter or longer time to live birth is not necessarily better, depending on how it occurs.

Fully non-parametric, parametric, and semi-parametric models are available for analysis of time-to-pregnancy data [11]. By a nonparametric approach, we can examine the cumulative success probability for the first k cycles by multiplying the probability of being pregnant at a given cycle conditional on not successful in prior cycles. This is essentially equivalent to the computation of Kaplan-Meier curves in survival analysis as illustrated in Figure 1. The parametric, beta-geometric model assumes that each couple has an inherent fecundability, which refer to the ability of conceiving a pregnancy per menstrual cycle. Then, for each couple, the time to pregnancy is geometrically distributed. These approaches treat each cycle as a separate experiment for a given couple [12]. A model based on a day-specific probability of pregnancy is proposed in [13]. This probability depends on a few factors. The first one is a cycle viability parameter, say A, that measures the biologic capacity for conception in a cycle and irrelevant to the timing of intercourse. The second one is the number, say k, of days relative to the day of ovulation, which is counted as negative before the ovulation and positive after the ovulation. The last one is the event of intercourse. Then, the probability of conception for a couple in cycle j is $A(1-\prod_k(1-p_k)^{X_{jk}})$, where p_k is the probability of conception on the k-th day relative

*Corresponding author.

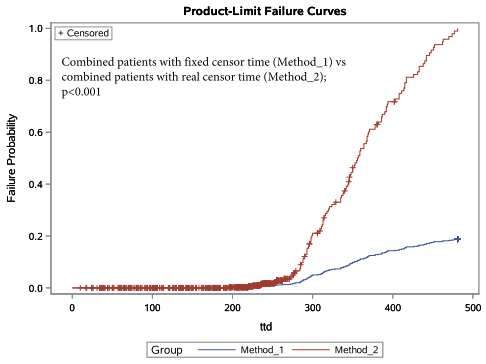

Figure 1. Kaplan-Meier curves based on two approaches of defining the censoring time. Method 1 censors all unobserved times to the end of study, and method 2 censors at the last observed times. The x-axis is the number of days to live birth (ttd).

to the day of ovulation in the cycle, and X_{jk} is the indicator for whether intercourse(s) occurs on the specific day.

Having presented complications and different approaches to modeling time to live birth, we now illustrate the consequences of different choices in a synthetic example. The data are not real but were generated based on real data. As displayed in Figure 1, seemingly reasonable but different methods of defining censoring time may have a profound impact in the resulting Kaplan-Meier curves. This impact can also lead to different conclusions and interpretation of the data. For example, a group difference in time to live birth between two arms may or may not be statistically significant ($p \leq 0.05$) depending on how the censoring time is defined (Figure 2).

In summary, time to live birth is an important endpoint in infertility studies, this essay is to point out that modeling time to live birth involves complexities and is underdeveloped.

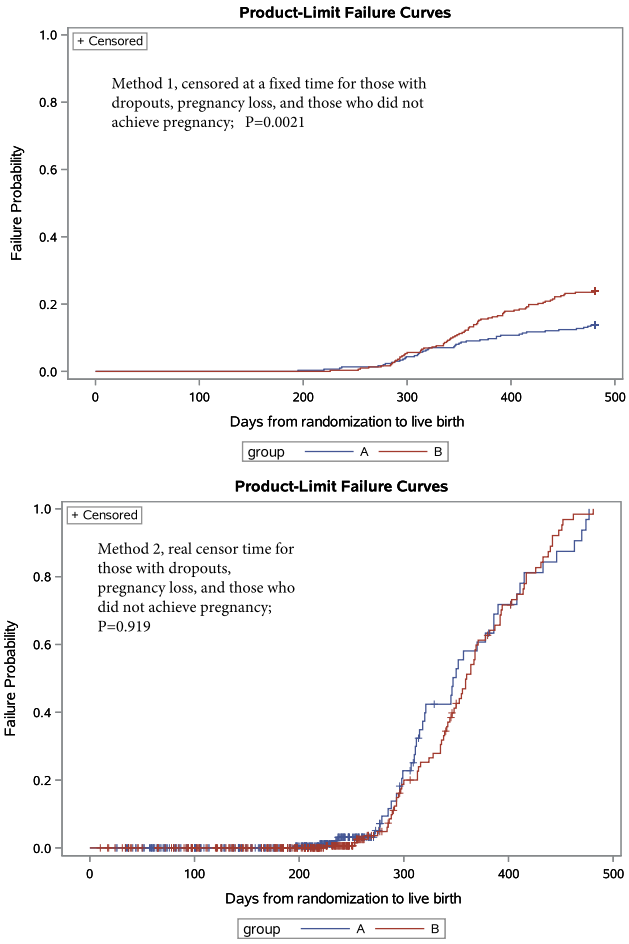

Figure 2. Kaplan-Meier curves based on two approaches of defining the censoring time, and a comparison of two hypothetical treatment arms. Method 1 censors all unobserved times to the end of study, and method 2 censors at the last observed times. Groups A and B refer to two hypothetical treatment groups. The log-rank test was used for the two-group comparisons.

REFERENCES

[1] Practice Committee of American Society for Reproductive Medicine (2013). Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertility and sterility.* **99**: 63.

[2] Inhorn, M.C., Patrizio, P. (2015). Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. *Hum Reprod.* **21**: 411–426.

[3] Harbin Consensus Conference Workshop Group (2014). Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement. *Fertility and sterility.* **102**: 952–959 e915.

[4] Gadalla, M.A., Wang, R., Van Wely, M., Mol, B.W.J. (2018). How should we report outcomes in reproductive medicine? *Ultrasound Obstet Gynecol.* **51**: 7–9.

[5] Chen, Z.J., Shi, Y. et al., Zhang, H., and Legro, R.S. (2016) Fresh versus frozen embryos for infertility in polycystic ovary syndrome. *The New England Journal of Medicine* **375**: 523–533.

[6] Diamond, M.P., Legro, R.S. et al., Zhang, H., and for the NICHD Reproductive Medicine Network. (2015) Letrozole, gonadotropins, and clomiphene citrate for unexplained infertility. *The New England Journal of Medicine* **373**: 1230–1240.

[7] Legro, R.S., Barnhart, H.X., Schlaff, W.D., Carr, B.R., Diamond, M.P., Carson, S.A., Steinkampf, M.P., Coutifaris, C., McGovern, P.G., Cataldo, N.A., Gosman, G.G., Nestler, J.E., Giudice, L.C., Leppert, P.C., Mysers, E.R., and Cooperative Multicenter Reproductive Medicine Network. (2007) Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N. Engl. J. Med.* **356**: 551–566.

[8] Legro, R.S., Diamond, M.P. et al., Zhang, H.P., and for the NICHD Reproductive Medicine Network. (2014) Letrozole versus clomiphene for infertility in polycystic ovary syndrome. *The New England Journal of Medicine* **371**: 119–129.

[9] Wu, X., Stener-Victorin, E., Kuang, H. et al., Zhang, H., and for PCOSAct Study Group. (2017) Effect of acupuncture and clomiphene on Chinese women with polycystic ovary syndrome: a randomized clinical trial. *JAMA* **317**: 2502–2514.

[10] Zhang, H., Legro, R.S., Zhang, J. et al. (2010) Decision trees for identifying predictors of treatment effectiveness in clinical trials and its application to ovulation in a study of women with polycystic ovary syndrome. *Human Reproduction* **25**: 2612–2621.

[11] Weinberg, C.R., Baird, D.D., and Wilcox, A.J. (1994) Sources of bias in studies of time to pregnancy. *Statistics in Medicine* **13**: 671–681.
[12] Scheike, T.H., Jensen, T.K. (1997) A discrete survival model with random effects: an application to time to pregnancy. *Biometrics* **53**: 349–60.
[13] Stanford, J.B. and Dunson, D.B. (2006) Effects of Sexual Intercourse Patterns in Time to Pregnancy Studies. *American Journal of Epidemiology* **165**: 1088–1095.

Hongying Kuang
Department of Obstetrics and Gynecology
First Affiliated Hospital Heilongjiang University of Chinese Medicine
Harbin 150040
China
E-mail address: hyk20042@sina.com

Hao Huang
Department of Biostatistics
Yale University School of Public Health
New Haven, CT 06520-8034
USA
E-mail address: hao.huang@yale.edu

Haizhu Tan
Department of Physics and Computer Applications
Shantou University Medical College
Shantou
China
E-mail address: linnanqia@126.com

Allen R. Kunselman
Department Public Health Sciences
College of Medicine
Hershey, PA 17033
USA
E-mail address: akunselm@phs.psu.edu

Heping Zhang
Department of Biostatistics
Yale University School of Public Health
New Haven, CT 06520-8034
USA
E-mail address: heping.zhang@yale.edu