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Appendix 1

**This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Chambers GM, Paul R, Harris K, et al. Assisted reproductive technology in Australia and New Zealand: cumulative live birth rates as measures of success. *Med J Aust* 2017; 207: 114-118. doi: 10.5694/mja16.01435.

Cumulative live-birth rates after repeated assisted reproduction technology treatment cycles in Australian and New Zealand.

Appendix 1: Prognostic adjusted cumulative live birth rates.

Rationale and methods

A sensitivity analysis was performed by varying assumptions about the probability of future treatment success in women who discontinued treatment. Prognostic adjusted rates have been used in ART studies previously (1), and attempt to account for any relationship between treatment discontinuation and probability of future success.

A recent systematic review (2) found that 38% (95% CI: 24-54%) of women discontinue because of poor prognosis. As a censoring mechanism poor prognosis is clearly informative, and so these women are unlikely to have achieved recorded cycle specific delivery rates. This motivates the use of prognostic adjusted rates which assume (i) poor prognosis women had zero probability of a future live delivery and the remaining proportion of women follow standard Kaplan-Meier assumptions (ii) poor prognosis women discontinue treatment at an even rate throughout the study.

For each ART cycle $t = 1, 2, \ldots$ we observe n_t the number of women starting that cycle and x_t the number of live deliveries. The cycle specific live delivery rate $\hat{p}_t$ can then be calculated as $\hat{p}_t = \frac{x_t}{n_t}$ and the cycle specific non-progression rate, or proportion of unsuccessful women who discontinue treatment, as $\hat{c}_t = \frac{n_t - x_t - n_{t-1}}{n_t - x_t}$. In order to perform prognostic adjustment we also introduce

$$\phi_t = \phi_{t-1}(1 - \hat{p}_{t-1})(1 - r\hat{c}_{t-1})$$

and a prognostic adjusted survival function

$$\hat{S}_r(t) = \hat{S}_r(t-1)\left[1 - \frac{\phi_t}{\hat{S}_r(t-1)}\hat{p}_t\right]$$

with $\hat{S}_r(0) = 1, \phi_0 = 1, \hat{p}_0 = 0$ and $\hat{c}_0 = 0$.

Here r is the prognostic adjustment parameter that treats $100r\%$ of women who discontinue treatment on a given cycle as having zero future probability of a live birth, i.e. poor prognosis. For the remaining $100(1-r)\%$ of women who discontinue treatment there is assumed to be no relationship between future probability of a live birth and censoring. From the survival function $\hat{S}_r(t)$ we can then calculate the prognostic adjusted cumulative live birth rate as $\hat{F}_r(t) = 1 - \hat{S}_r(t)$.

References

1. Smith AC, Tilling K, Nelson SM, Lawlor DA. Live-birth rate associated with repeat in vitro fertilization treatment cycles. JAMA. 2015;314(24):2654-62.
2. Gameiro S, Boivin J, Peronace L, Verhaak CM. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. Hum Reprod Update. 2012;18(6):652-69.

Results

Figure 1. Prognostic adjusted cumulative live-birth rates (CLBR) by female age at commencement of first complete assisted reproductive technology (ART) cycle for women (A) of all ages (B) less than 30 years (C) 30-34 years (D) 35-39 years (E) 40-44 years (F) greater than 44 years. Women who commenced ART treatment in 2009-2012, Australia and New Zealand.