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Estimating cumulative live-birth rates after IVF treatment with Kaplan–Meier and competing risk methods

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ABSTRACT

Objective(s): To explore the use of competing risk (CR) as compared to the commonly used Kaplan–Meier (KM) methodology in estimating the cumulative live-birth rate (CLBR) after IVF Treatment in a context of high dropout rates and informative censoring.
Study design: We compare the KM and CR methodologies for estimating 2-year CLBR in a retrospective cohort of 2779 patients undergoing 5002 embryo transfers over a period of 9 years, from 2000 to 2008, at KKIVF Centre.
Results: We observed a total of 1105 LB (39.8%), and a dropout rate of 44.2% (1228 patients). The overall CLBR is lower with CR compared with KM method (39% vs 52%) after up to nine embryo-transfer cycles over a period of two years. The highest CLBR was achieved for ovulation disorders (57% vs 49%, KM vs CR) followed by male factors (54% vs 43%, KM vs CR), with poorer outcomes from patients with decreased ovarian reserve (37% vs 16%, KM vs CR) and endometriosis (36% vs 25%, KM vs CR). As dropouts in our cohort are generally older and more likely to have poorer ovarian reserves, the CR method, which accounted for these dropouts, is likely to give more meaningful estimation of IVF success rates.
Conclusion(s): The CR method should be considered as a useful alternative in deriving CLBR for IVF treatment where dropout rates are high and when informative censoring is involved.

Introduction

In vitro fertilisation (IVF) live birth (LB) rates have stagnated over the past couple of decades at around 26–32% [1–4]. Thus multiple treatment cycles are generally required to achieve a live-birth (LB) [5]. Hence there had been increasing efforts to report IVF success rates as cumulative live-birth rates (CLBR) to guide more relevant prognostication and meaningful counselling [6]. Initial studies utilised cross-sectional data, which does not account for the effect of time on IVF outcomes [7–10]. Increasingly, longitudinal analyses of individual women considering all their treatment cycles are providing a more meaningful estimation [1,11].

Currently, life table methods and the Kaplan–Meier (KM) product-limit estimates [12] are the most commonly used statistical tools to estimate success rates, being adopted in the 1970s to study crude pregnancy rates [13]. However, high dropout rates are common in most IVF cohorts [14,15], which leads to a tendency of these approaches to overestimate the success rates because of the method used to treat information on dropouts. Indeed, in KM methodology, patients who dropout provide information up to the point they were last seen and then censored from the analysis in subsequent time intervals [6,16,17]. Censoring

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indicates that information about the event (LB in this case) is not known due to the dropout. Thus, KM method assumes that censoring has no impact on a patient's chance of a LB, which is not the case, as those who continue with treatment have an increased chance of a LB over no treatment [18].

The use of a competing risk (CR) methodology may overcome some of the shortcoming associated with the use of life-table and KM analyses [19,20]. In contrast to the KM method, the CR method regards 'dropout' as an event itself and is not censored in the analysis. Instead both events (LB and dropout, as a competing risk) are included in the calculation of the CLBR estimates, as opposed to dropout, which is considered as a censored observation in the KM method. Thus, under the CR framework, only women who remained in the trial till the end of the study period but did not experience any of the events, a LB or a dropout in this case, contribute to the censored observations.

The objective of this paper is to argue for the wider use of the CR methodology in presenting the results of IVF studies. Here, we analysed the fertility potential of the transfer of all embryos derived from up to three consecutive stimulated IVF treatment cycles at a single centre by estimating the 2-year CLBR using both KM and CR methodologies.

Materials and methods

Patients

This study was approved by our institutional ethics board (centralised institutional review board). All patients, referred to KKIVF Centre at the KK Women's and Children's Hospital, for their first IVF/ICSI cycle, from January 2000 to December 2008, were included. We analysed the outcome of live-births resulting from the transfer of all embryos (fresh and frozen) derived from a maximum of three stimulated IVF/ICSI cycles. Cancelled cycles due to either a cancellation of the oocyte retrieval or embryo transfer (ET), were included in the analysis. Patients were followed-up until a live-birth (LB), discontinuation of treatment (dropout), the transfer of all embryos derived from a maximum of three stimulated cycles, or the end of the study period.

The primary outcome was a LB, with women not achieving a LB after transferring both fresh and frozen embryos being eligible for inclusion in subsequent cycles. Indeed, as per our Centre's policy, patients can only proceed for a subsequent stimulated cycle when all the embryos from the previous cycle have been utilised. For women who stopped treatment before achieving a LB despite being eligible for another cycle, the hospital appointment system was consulted for records on infertility clinic visits. If no clinic data were captured within 2 years after the last treatment date or before the study closure, the patient would be considered as having dropped-out. The dropout reason was not captured. Patients who achieved a pregnancy within the last nine months of the study period were followed-up for LB until September 2009.

IVF/ICSI treatment protocol

Both long agonist and the short antagonist IVF protocols were used. A mid-luteal GnRH agonist (leuprolide acetate, 10 IU s/c, Abbott Laboratories PL, USA) mediated down-regulation over 14–21 days followed by controlled ovarian hyperstimulation (COH) with either urinary purified urofollitropin (Metrodin, Serono Laboratories Inc., Germany) or recombinant FSH (rFSH, Puregon, MSD, USA) for 10–14 days. In short antagonist cycles, COH was initiated on Day 2 of menses and a GnRH antagonist was added from Day 5–6 of stimulation. In both protocols, final oocyte maturation triggered with hCG (s/c 10,000u; Pregnyl, MSD, USA) before transvaginal oocyte recovery and fertilisation via IVF or ICSI, and ET performed on Day 2 or 3. Two embryos were transferred in accordance to national guidelines and luteal phase support instituted for 4 weeks.

Frozen embryo transfer

Frozen ET was performed after an interval of 2–3 months after a failed fresh or frozen ET, or when requested by patients. Natural cycle ET was performed 2 or 3 days after the ovulation, or after priming the endometrium with estradiol and progesterone in artificial cycle. Luteal-phase support was provided with progesterone (Cyclogest, Dumex-Alpharma ApS). Frozen ET was treated as unique treatment events.

Statistical methods

The CLBR is defined as the probability of achieving a LB after transfers of embryos resulting from a maximum of three stimulated IVF cycles (up to 9 fresh or frozen ET). Our primary endpoint is a LB, and we estimated the CLBR using: (i) KM procedure [12], (ii) CR method [19,21–23]. Events such as miscarriages, ectopic pregnancies and still-births do not prevent patients from achieving a LB in a subsequent cycle, but rather, they may delay the time taken to achieve a LB. Therefore, based on the CR methodology, the CLBR was estimated by accounting only for dropout as a competing event. The competing risk method and its formula were previously described by Tai et al. (2001). Based on the competing risks approach, differences in CLBR between cycles or age groups for example, may be compared using the Gray's test.

In the analysis of CLBR using Kaplan–Meier (KM) method, LB is considered to be the only event that is operating, and dropouts are censored at the time of occurrence. Patients who did not experience any LB or dropout had their observation also censored, but at either at the end of the study date or on the date of completion of 3 stimulated cycles, whichever was earlier. Furthermore, the CLBR derived from KM method is meaningful only when the event of interest (LB) and the competing risk (dropout) are independent while CR method is applicable regardless of whether LB and competing risk are independent.

For this study, we chose the *time-scale* for both methods to be based on the difference in calendar time between the date of event (or censoring) and date of entry. We also perform our CLBR analysis at 2-year since majority of couples would have completed their 3 stimulated cycles within 2 years.

Results

The majority underwent a long agonist protocol (92%), with a total of 2779 patients undergoing up to three fresh ovarian stimulations followed by the transfer of all embryos derived from them. This resulted in a maximum of nine embryo transfer procedures per patient. Overall, patients under 35 years old accounted for 57.5% ($n = 1597$) of the cohort, with 8.8% ($n = 247$) being older than 40 years old. The cohort comprises 71.8% Chinese, 12.3% Indians, 8.5% Malays and 7.4% other races, broadly representative of the multi-ethnic mix in Singapore. The majority of the cohort was nulliparous (91.3%) at the start of the first treatment cycle. Only 8.5% of patients had diminished ovarian reserves (FSH $\geq$ 10 IU/L), and the most common cause of infertility was male factor (48.7%) followed by multiple factors (24.1%) (summarised in Table 1).

Crude cycle outcomes

We observed a total of 1105 LB (39.8%), and a high dropout rate of 44.2% (1228 patients). In addition, 446 (16.0%) patients had their