Life table (survival) analysis to generate cumulative pregnancy rates in assisted reproduction: an alternative method of calculating the cumulative pregnancy rate in assisted reproduction technology

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The current method of calculating cumulative pregnancy rate can lead to an overestimation of treatment efficacy, especially over many cycles of assisted reproduction treatment. The choice of scale of passage of time should be dependent upon the types of treatment to be evaluated. The number of treatment cycles to which patients’ effort and commitment is directly related may be appropriate where the chance of pregnancy is expected to be significantly higher than non-treatment for them. Limiting the calculation of cumulative pregnancy rate only to the second or third cycle within 1 or 2 years will ensure that most patients are included in the calculation. More research is needed to assess different methods and develop better variables for assessing the efficacy of infertility treatment that can be informative for patients over the course of their treatment.

Key words: assisted reproduction treatment/cumulative pregnancy rates/life table analysis

The current method of using life table analysis to calculate cumulative pregnancy rate can lead to an overestimation of the treatment efficacy, especially over many cycles of treatment (Daya, 2005). There is a need to improve the method of calculating to minimize the overestimation and provide more reliable results to the patients and clinicians. Indeed, infertile patients often undergo a course of multiple treatment cycles; therefore they want to know their overall chance of achieving a successful pregnancy over the course of their treatment. Providing them such information may also encourage patients to accept single embryo transfer. Randomized clinical trials showed that there was a lower pregnancy rate following single embryo transfer compared with double embryo transfer and no difference for cumulative pregnancy rate following another fresh cycle (Lukassen et al., 2005) or overall pregnancy rate following one frozen embryo transfer cycle (Thurin et al., 2004). In a recent debate started in Human Reproduction, Daya has summarized the history of life table analysis, or survival analysis, the method commonly used to calculate cumulative pregnancy rate, and discussed the pros and cons of using it in assisted reproduction (Daya, 2005). He also suggested ways to improve the calculation to minimize the overestimation apart from some alternative variables to express the treatment efficacy.

There are large variations in the reported cumulative pregnancy rate. The variation of cumulative pregnancy rate is dependent on many factors, including intrinsic factors such as patient age, aetiology of infertility, response to hyperstimulation and the number of embryos transferred (Tadokoro et al., 1997; Croucher et al., 1998; Lass et al., 1998; Engmann et al., 1999). In addition to these factors, some methodological variations, such as the definition of outcome events, the patient discontinuation (censoring) pattern and how the censored patients are used in calculation, can have a significant effect on the cumulative pregnancy rate (Doody, 1993; Roest et al., 1998). The scale of passage of time is another factor that may impact on the calculation of cumulative pregnancy rate using life table analysis. The scale of measuring the passage of time in infertility research is often the cycle of treatment, usually an effective treatment cycle, such as an oocyte retrieval cycle or an embryo transfer cycle. Treatment cycles should be used in assisted reproduction treatment where the chance of pregnancy is expected to be much higher than the untreated pregnancy rate. The chance of achieving a pregnancy or having a live birth without treatment is low in adequately investigated and defined infertile patients (Collins et al., 1995). Although using cycle as a scale of the passage of time is not conventional for survival analysis, it does represent the actual time for the occurrence of an event. In traditional survival analysis, many events, such as death, can occur at any time, so absolute time has been used as the proper scale of time. There are situations where a combination of actual time, say a limitation of 2 years, and cycle, say a minimum of three cycles, may be appropriate, such as in natural IVF cycles, and low dose stimulation with or without insemination and donor insemination cycle. Thus only patients who have received a certain minimum level of treatment over an acceptable treatment period are included in calculation.
A long time-interval over many cycles of treatment above a certain age may also mean a significant fall in the chances of achieving pregnancy even with infertility treatment (Piette et al., 1990).

Below I would like to propose an alternative measurement of cumulative pregnancy rate: cumulative pregnancy rate based on patients with two or three completed cycles for a limited period of 1–2 years.

Although many patients pursue a live birth through infertility treatment over a long treatment course, sometimes up to 10 or more cycles of treatment, financial and other personal costs often limit most patients to only two or three cycles of treatment. Based on our analysis of patients in a large assisted reproduction clinic over a 5 year period (1994–1999), 36% of the initial patients withdrew after one cycle of IVF, including <2% failing to reach oocyte retrieval stage, 20% after failing to achieve a pregnancy and 14% after achieving an ongoing pregnancy. A further 28% withdrew after second oocyte retrieval cycle, including 13% with an ongoing pregnancy. Using ongoing pregnancy as the outcome event for the analysis, the calculation of cumulative pregnancy rate with two treatment cycles will include 78% of the initial patient population and with three cycles will include 63% of them. Including such a large proportion of patients may minimize the potential bias resulting from exclusion of the patients withdrawn from the analysis. Since only 37% of the patient population receive four or more cycles of treatment, it may be not unreasonable to calculate the cumulative pregnancy rate up to three cycles only. That means the cumulative pregnancy rate of two or three cycles will be usable by almost two-thirds to 80% patients. On the other hand, using only patients who completed two or three cycles of treatment can reduce the possible overestimation caused by informative censoring in some patients. In the first two or three cycles patients may have a lower financial burden or mental stresses and possibly a more optimistic view of their chance of pregnancy. Also doctors may not make specific recommendation due to the uncertainty of outcomes from further treatment.

One study reported a very low rate of active censoring for poor prognosis in the first and second cycles, 5.6 and 4.6% respectively (Smeenk et al., 2004). Another study showed that a majority of discontinuations were due to psychological stress or other reasons and only 25% due to a poor prognosis (Olivius et al., 2004). With fewer cycles, this method also requires a short data collection period, such as 1 or 2 years. This will also reduce the chance of introducing bias caused by either ageing patients or the presence of a secular trend. One study found no difference in performance of their first or second cycles between patients who continued treatment and those who dropped out (Roest et al., 1998). Given the rapid development of assisted reproduction treatment and the sharp decline in chance of pregnancy in many infertile women after their mid-30s, calculating cumulative pregnancy rate over two or three cycles carried out in a relatively short period will provide more accurate information for most patients. It is also clear from Daya’s (2005) hypothetical example that the overestimation increased progressively with the consecutive cycles.

In summary, there is a need to improve the method of calculating cumulative pregnancy rate to minimize the overestimation and provide more reliable results to patients and clinicians. The choice of scale of passage of time should be dependent upon the types of treatment to be evaluated. In assisted reproduction treatment, the scale needs to be treatment cycle where the chance of pregnancy is expected to be much higher than the untreated menstrual cycles. Furthermore, under the circumstances of assisted reproduction treatment, patients’ effort and commitment is more directly related to the number of treatment cycles than time per se. Informative censoring cannot be totally avoided since patients can decide whether to continue their treatment based on information that they are entitled to receive. Calculating cumulative pregnancy rate only to the second or third cycle within a reasonably short period of 1–2 years may ensure that most patients are included in the calculation while minimizing the impact of informative censoring.

References

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