How effective is in vitro fertilization, and how can it be improved?

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Objective: To measure IVF effectiveness, which is defined as the cumulative incidence of live delivery over real time in women after commencing IVF treatment.
Design: Population-based retrospective cohort study.
Setting: IVF clinics in Western Australia (WA).
Patient(s): All women ages 20–44 years inclusive at start of treatment, commencing IVF in 1982–1992 and 1993–2002 at clinics in WA (n = 8,275).
Intervention(s): Data on IVF cycles were extracted from hospital records and a statutory reproductive technology register and linked to records of births.
Main Outcome Measure(s): Cumulative incidence of an IVF-attributed live delivery and cumulative incidence of an IVF-attributed or IVF treatment-independent live delivery.
Result(s): IVF effectiveness in the 1993–2002 cohort was 47% overall. It was highest in women ages 20–29 years at the start of treatment, measuring 58%; and 79% with the inclusion of IVF treatment-independent deliveries, and declined to 22% and 33%, respectively, in women ages 40–44 years. Couples underwent, on average, only three cycles, even though the cumulative probability of a live delivery increased with each successive cycle for at least the first five cycles.
Conclusion(s): IVF effectiveness could be improved if women, particularly those over 35, underwent more cycles. (Fertil Steril® 2011;95:1677–83. ©2011 by American Society for Reproductive Medicine.)

Key Words: Cohort studies, fertilization in vitro, life tables, live birth, maternal age, probability

Two useful measures of any treatment are its efficacy and its effectiveness. Efficacy relates to how successful a treatment could be under ideal circumstances, while effectiveness relates to how successful a treatment really is under usual conditions. When a couple asks, "What is the probability that we will one day take home a baby?" they can be asking, "How efficacious is IVF?" or "How effective is IVF?"

If the couple knows in advance that they will undertake up to, for example, six cycles if necessary, then their probability of success can been predicted to be 51%–72% (1). This is a measure of efficacy.

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If, on the other hand, the couple does not know how many cycles they will undertake, because this decision is rarely made in advance but rather evolves as treatment progresses, then their probability of success can only be predicted based on the number of cycles undertaken by those who have gone before them. This is effectiveness, and it is a measure highly relevant to couples at the start of IVF treatment when they do not know how many cycles they will undergo. IVF efficacy has been well documented in the literature (1–6), but effectiveness to date has not, although it is an approach that is now attracting increasing interest (7).

The aim of this study was to determine IVF effectiveness by measuring the probability of a live delivery over real time in a population-based cohort of women undergoing IVF treatment at clinics in Western Australia (WA).

Live deliveries after IVF also include IVF treatment-independent deliveries. If the couple's question is, "What is the probability that we will one day take home a baby?" then IVF treatment-independent deliveries cannot be ignored. Therefore, in this study, separate analyses that included IVF treatment-independent deliveries were also conducted.

MATERIALS AND METHODS

Study Population

The study population comprised all women commencing IVF treatment between January 1, 1982, and December 31, 2002, at clinics in WA. Two separate analyses were conducted. The first analysis focused on women commencing treatment between 1982 and 1992. The second focused on women commencing IVF treatment between 1993 and 2002. The two time

periods were chosen to create two groups covering a similar time span and comprising a similar number of participants.

Data Sources

The WA Data Linkage System brings together records for the same individual from many different data collections (8). This study used data from five data collections. Information on IVF cycles was obtained from the Hospital Morbidity Data Collection, which records inpatient episodes in WA, and the Reproductive Technology Register, which was established by statute in 1993 to record and collate information on all IVF treatment cycles carried out in WA. Records of IVF cycles in the two data sets were extensively cross-checked against one another.

Information on births was obtained from the Midwives Notification System. Information on deaths was sourced from the WA Death Registry. Women who were known to have moved out of WA during follow-up were identified from the WA Electoral Roll. Women with an interstate address in either the hospital or Reproductive Technology Register data sets were also identified. To ensure the study was based on a geographically contained population and to reduce loss to follow-up, these women were excluded from the final study population.

Identification of IVF Cycles

All IVF cycles were counted; intracytoplasmic sperm injection and donor cycles were included. One cycle could be egg collection plus ET, egg collection without ET, frozen ET, or a cancelled cycle. None of the cycles involved preimplantation genetic diagnosis or preimplantation genetic screening.

Identification of Births

The outcome of interest was the live delivery of at least one infant. Multiple births were counted once, as a single delivery. Only first live deliveries after IVF treatment were included. Births before IVF treatment were not included in the analysis, nor were subsequent births after the first live delivery.

Births after IVF treatment were further subdivided into two categories: IVF-attributed deliveries (those occurring within 44 weeks of the last IVF cycle) and all first deliveries after the commencement of IVF treatment (IVF-attributed plus IVF treatment-independent deliveries). The time period of 44 weeks was chosen to allow for pregnancies of up to 42 weeks from the cycle start date plus uncertainty in the date of delivery: for reasons of data confidentiality, only month of birth (not actual date) was supplied: this gave a 2-week margin of error. Deliveries occurring more than 44 weeks after the last IVF cycle were considered to be IVF treatment-independent deliveries.

Follow-up

Women were followed from the date of commencement of their first IVF treatment cycle until their first live delivery. If they did not deliver a live baby, follow-up ceased on the censor date of December 31, 2007. If the woman died during follow-up, then follow-up ceased on the date of death.

Data Analysis

Survival curves were plotted using the life table method. Two sets of curves were produced. The first set of curves plotted the probability of live delivery against the time from commencement of treatment. The second set plotted the probability of live delivery according to the number of cycles attempted. "Optimistic" and "conservative" survival curves were generated following principles described by previous investigators (1, 9) and according to the following assumptions:

1. that women who dropped out of treatment had the same probability of success as those who continued (optimistic analysis); or
2. that women who dropped out of treatment had zero probability of success (conservative analysis).

Data were analyzed using SPSS, version 17 (Chicago).

Institutional Review Board Approval

This study received Institutional Review Board approval from The University of WA Human Research Ethics Committee and the Department of Health WA Human Research Ethics Committee.

RESULTS

Characteristics of the Study Population

Number of women In total, 8,543 women ages 20–44 years inclusive commenced IVF treatment between January 1, 1982, and December 31, 2002 in WA. Of these, 268 had an interstate address on their hospital or reproductive technology register records or a movement into or out of the state on the Electoral Roll and were excluded from further analysis. The final study population therefore comprised a total of 8,275 women: 3,158 commenced IVF in 1982—1992, and 5,117 commenced IVF in 1993–2002 (Table 1).

Number of deaths Some 80 women died after commencing IVF treatment and before the study censor date of December 31, 2007. Of these, 29 had at least one live delivery and 51 did not deliver a live baby.

Number of cycles In 1993–2002, women undertook a mean of 3.0 cycles; a median of two and mode of one cycle (Table 1). The majority of women (80%) attempted four cycles or fewer. There was little variation between age groups in the mean number of cycles undertaken. In every age group, the median was two. Women for whom IVF was successful undertook, on average, slightly fewer cycles than women who did not achieve a live birth after IVF (2.7 $\pm$ 2.2 cycles compared with 3.3 $\pm$ 2.7 cycles).

Women commencing IVF treatment in 1982–1992 undertook slightly fewer cycles: an average of 2.6 cycles (Table 1).

Mean number of oocytes retrieved The mean number of oocytes retrieved, averaged across all of a woman's collection cycles, was calculated for women commencing IVF between 1993 and 2002. It was greater in women who gave birth after IVF (11.8 $\pm$ 7.7) than in those who did not (9.6 $\pm$ 7.0; mean $\pm$ SD). It was highest in the youngest age group and lowest in the oldest age group. For women ages 20–29 who gave birth after IVF, the mean number of oocytes retrieved was 13.7 $\pm$ 8.0, compared with 12.4 $\pm$ 7.2 in women who did not give birth; in women ages 40–44, it was 7.8 $\pm$ 6.1 in women who gave birth and 6.4 $\pm$ 5.6 in women who did not.

Number of deliveries Out of a total of 5,117 women commencing IVF in 1993–2002, 2,266 delivered an IVF baby (Table 1). An additional 902 women delivered an IVF treatment-independent baby. A very small proportion of these deliveries occurred after further infertility treatment after the last IVF cycle: we identified 11 women in the 1993–2002 cohort who had in-hospital treatment associated with a diagnosis of endometriosis after ceasing IVF treatment and subsequently delivered a baby. Births occurring after the censor date of December 31, 2007, were not included.

The Probability of a Live Delivery: Cohort Analysis

The cumulative incidence (an estimate of probability) of a live delivery in women after commencement of IVF treatment was analyzed using life table survival analysis. The two time periods 1982–1992 and 1993–2002 were analyzed separately. Summary results for the two time periods are presented in Table 2. The