Cumulative live birth rates in more than 3,000 patients with poor ovarian response: a 15-year survey of final in vitro fertilization outcome

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Objective: To estimate the cumulative live birth rates (CLBRs) in women with poor ovarian response (POR) diagnosed according to the Bologna criteria.
Design: A 15-year population-based observational cohort study.
Setting: Teaching hospital.
Patient(s): Between 2002 and 2016 a total of 3,391 women with POR were followed from their first fresh, nondonor IVF cycle until they had a live birth or discontinued treatment. All IVF and intracytoplasmic sperm injection (ICSI) cycles and cryocycles were included.
Intervention(s): None.
Main Outcome Measure(s): Live birth rates per initiated cycle, the conservative and optimistic CLBR for multiple IVF cycles.
Result(s): The CLBRs after six IVF cycles were 14.9% for the conservative and 35.3% for the optimistic estimate. The CLBR decreased from 22% for women ≤30 years to 18.3% for women aged 31–34 years, 17.2% for 35–37 years, 13.5% for 38–40 years, 10.5% for 41–43 years, and 4.4% among women >43 years in the conservative analysis. There was a significant decreased CLBR starting at age 38 years compared with women <35 years. After adjusting for age, antral follicle count, basal FSH level, and IVF cycle number, natural cycles were associated with the lowest CLBR among all the protocols, and this difference was significant compared with the other protocols.
Conclusion(s): For women with POR, the CLBR declined with increasing age. Women with advanced age (≥38 years) achieved a significantly lower CLBR than young poor responders (<35 years). Very low CLBR was associated with women aged >43 years old. Natural cycle IVF is of no benefit for these patients. (Fertil Steril® 2018;109:1051–9. ©2018 by American Society for Reproductive Medicine.)
Key Words: Bologna criteria, cumulative live birth rate, in vitro fertilization, ovarian stimulation, poor ovarian response

Since the delivery of the first IVF baby nearly 40 years ago, great steps forward have been made in the area of assisted reproductive technology (ART). Traditionally, the success of IVF has been reported based on the outcome per treatment cycle. Thanks to refined cryopreservation technology, the numbers of thawed frozen ETs have greatly increased and have become an integral part of IVF (1, 2). We therefore propose that IVF treatment success rates should not only incorporate outcomes associated with fresh ETs but also those resulting frozen thawed ETs. More specifically, the cumulative live birth rate (CLBR) per woman, a new outcome reporting method to provide an all-inclusive success rate (3), has been used by national registries in Australia, Belgium, Germany, New Zealand, the United Kingdom, and the United States (4–8). Reporting CLBR undergoing any number of ART cycles is meaningful for clinicians and patients and has been gaining increasing attention in modern reproductive medicine.

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In IVF treatment, poor ovarian response (POR) is a condition of utmost clinical and scientific relevance because of its great negative influence on the patient. The treatment of women suffering from POR has been one of the most difficult challenges in assisted reproductive medicine (9). Reporting CLBR in women with POR is of particular importance for two reasons: due to the poor treatment results of this population, most subfertile couples undergo more than one treatment cycle before attaining a live delivery; and to explore the most suitable treatment for those POR patients, several different protocols have been tried during the past 20 years, resulting in confusing and apparently conflicting literature. For some new methods, such as luteal phase ovarian stimulation, all embryos had to be cryopreserved for subsequent frozen ET because of the asynchronous stages of the embryo and the endometrium of the patient (10). Meanwhile, a "freeze-all embryo" strategy has also been proposed by some investigators in the use of minimal stimulation protocol (11). Recently a new approach has been proposed by accumulating vitrified embryos during several stimulation cycles to increase the success rates in patients with POR (12, 13). For these new protocols, reporting IVF outcomes in the traditional manner has limited usefulness for patients with POR and their physicians as they are more interested in the chance of a live birth for the individual couple versus an entire IVF program. Therefore CLBR, an estimate of final ART success rates, appears to be a much better indicator of quality and success in IVF programs for this specific group of patients. In addition, it most probably allows for better comparisons between different treatment regimens.

Here we report a 15-year survey to provide estimates of the final success in women with poor response presenting for IVF through repeated observations. The CLBRs were reported in >3,000 patients with POR, diagnosed according to the Bologna criteria, who underwent multiple IVF cycles including all IVF, intracytoplasmic sperm injection (ICSI), and cycles with cryopreserved embryos in a single large center. This study also quantified cumulative live birth rates in women with POR as a function of the treatment protocol, to compare success rate of the different ovarian stimulation regimens.

MATERIALS AND METHODS

Study Participants

This was a noninterventional, retrospective, single-center cohort study. All patients admitted at the Tongji hospital between January 1, 2002 and January 1, 2016 (with follow-up until January 1, 2017) who had POR, according to the Bologna criteria, were included in the analysis. We followed women for at least 1 year after their first IVF cycle, until they either delivered a live infant or discontinued their treatment, whichever occurred first. Donor recipient cycles were excluded. Women already with a live birth after IVF treatment re-entered the analysis as a "new patient" if they underwent additional ART. A total of 3,391 patients undergoing autologous IVF/ICSI treatment were enrolled. Women with POR were classified with at least two of the three following criteria: advanced maternal age (≥40 years) or any other risk factor for POR; a previous POR (≤3 oocytes with a conventional ovarian stimulation protocol); and an abnormal ovarian reserve test: antral follicle count (AFC) <5–7 follicles, according to the Bologna criteria (14). The study conformed to the Declaration of Helsinki for Medical Research involving Human Subjects. Also, approval was obtained from the Ethical Committee of Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology. Each of the patients had given written authorization at the time of treatment for the future use of their clinical data.

GnRH Agonist Long Protocol

In the GnRH agonist (GnRH-a) long protocol, pituitary suppression was achieved by SC injection of 0.1 mg triptorelin acetate (Decapeptyl; Ferring) daily, starting in the midluteal phase of the preceding cycle, which was reduced to 0.05 mg once the down-regulation was achieved when complete pituitary desensitization was confirmed by a low plasma E_2 level of ≤30 pg/mL and an LH level of ≤2 mIU/mL, after which ovarian stimulation was started with IM administration of 150–225 IU/d recombinant FSH (Gonal-F; Merck-Serono) and 75–150 IU of highly purified urinary gonadotropin (hMG, Lizhu). Recombinant hCG (250 mg; Ovidrel; Merck-Serono) was given to trigger ovulation when the leading follicles reached a mean diameter of 18 mm.

In the depot GnRH-a long protocol, patients received single dose SC injection of 3.75 mg long-acting triptorelin acetate on day 2 of the cycle after the ultrasound scan to confirm ovarian quiescence and the presence of a thin endometrium (<5 mm). When complete pituitary desensitization was achieved (28 days after the initiation of GnRH-a), measured as described, ovarian stimulation was started with administration of FSH and hMG.

GnRH-a Short Protocol

For the short GnRH-a regimen, treatment was initiated by SC injection of 0.1 mg triptorelin acetate daily on day 2 or 3 of the cycle after the ultrasound scan to confirm ovarian quiescence and the presence of a thin endometrium. Controlled ovarian hyperstimulation (COH) was commenced with FSH and hMG as 1 day later. The GnRH-a administration was continued until the day of hCG administration.

GnRH Antagonist Protocol

In the GnRH antagonist protocol, ovarian stimulation was carried out with FSH and hMG from day 2 or 3 of the cycle. Daily injections of the GnRH antagonist Cetrotide (0.25 mg SC; Merck-Serono) were administered to prevent premature ovulation if at least one of the following criteria was met: the presence of at least one follicle measuring >14 mm; E_2 serum levels >300 pg/mL; or LH serum levels >10 IU/L. Recombinant hCG was given to trigger ovulation when the leading follicles reached a mean diameter of 18 mm. The GnRH antagonist administration was continued up to and including the day of hCG administration.