ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Live-birth rates in very poor prognosis patients, who are defined as poor responders under the Bologna criteria, with nonelective single embryo, two-embryo, and three or more embryo transfers

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Objective: To determine live-birth rates (LBRs) at various ages in very poor prognosis patients, who are defined as poor responders under the Bologna criteria.
Design: Retrospective cohort study.
Setting: Academically affiliated private fertility center.
Patient(s): Among 483 patients, who under the Bologna criteria (three or fewer oocytes, >40 years of age, and/or antimüllerian hormone [AMH] <1.1 ng/mL [2/3 criteria minimum]) were poor responders, 278 (381 fresh IVF cycles) qualified for the study because they had at least one embryo on day 3 for transfer.
Intervention(s): IVF cycles in women with low functional ovarian reserve, involving androgen and CoQ10 supplementation and ovarian stimulation with daily gonadotropin dosages of 300–450 IU of FSH and 150 IU of hMG in microdose agonist cycles.
Main Outcome Measure(s): Age-specific LBRs per ET.
Result(s): Ages did not differ between nonelective (ne) single ET (SET), ne2-ET, and ne≥3-ET cycles (41.3 ± 3.9, 41.7 ± 3.1, and 42.4 ± 2.1 years, respectively). Patients with neSETs demonstrated significantly lower AMH and higher FSH levels and required higher gonadotropin dosages than ne2-ET and ne≥3-ET patients. LBRs declined with age. Above age 42, three or more embryos are required to achieve reasonable LBRs and two or more to avoid futility under American Society for Reproductive Medicine (ASRM) guidelines.

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Conclusion(s): Very poor prognosis patients can still achieve acceptable pregnancy rates at least till their mid-40s if they reach ET. The degree to which egg donation is emphasized as the only treatment option in such patients, therefore, requires reconsideration. Above age 42, at least two, and preferably three embryos, are however required to exceed futility, as defined by ASRM. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Poor prognosis patients, poor responders in vitro fertilization (IVF), live birth rates, futility

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Where the line should be drawn and women with low pregnancy chances should no longer be offered access to IVF with use of their own oocytes has remained undetermined among medical professionals (1, 2) as well as among the lay public (3). Our center has advocated a policy of almost brutal directness in discussing pregnancy and live-birth chances but at the same time has offered patients an almost unrestricted right of self-determination in choosing poor chances with own eggs over better pregnancy and live-birth chances with young donor oocytes after detailed informed consent (4, 5).

The American Society for Reproductive Medicine (ASRM) tried to offer some guidance on this issue by defining "futility" as a $\leq$1% and "very poor prognosis" as >1% to $\leq$5% chance of achieving live birth per cycle of treatment and suggested that practitioners had no obligation to treat patients with outcome chances they considered inadequate. The Society, however, in such cases also recommended that patients be offered referrals to practitioners who do offer such treatments (6).

In the United States, poor-prognosis patients with low functional ovarian reserve (LFOR) only rarely receive open access to IVF. This can be deduced from annual national Centers for Disease Control and Prevention (CDC) reports, which demonstrate that women above age 42 still represent only a minute fraction of IVF cycles (7). More specifically, U.S. 2013 CDC data (the latest year available) report that only 6.6% of fresh nondonor IVF cycles were performed in women $\geq$43 years and only 16.8% in women $\geq$41 years (http://www.cdc.2015). Society for Assisted Reproduction (SART) data are almost identical (6.6% for $\geq$43 years; 17.0% for $\geq$41 years; http://www.sartcorsonline.com). European Society for Reproductive Medicine and Embryology data are only available for 2010 and report 17.1% of cycles in women $\geq$40 years of age (8).

Restrictions on the access of poor-prognosis patients are also not always very obvious. We previously reported that some IVF centers to significant degrees exclude such patients from national reporting (9). More recent CDC reports counterintuitively and against all expectations demonstrate that in the United States, embryo cryopreservation increases with advancing female age (10). This again suggests that poor-prognosis patients are only incompletely represented in national center-specific outcome statistics since, as they do not reach ET, many, if not most, remain invisible in national IVF outcome statistics published by CDC and SART.

In Europe, the tendency to deny treatment to poor-prognosis patients is maybe even more pronounced, and certainly more "open." Especially in Scandinavian countries, women above age 40–41 are automatically excluded from national insurance coverage with the argument that national cost-effectiveness strategies do not warrant expenditures on a procedure with such minimal expectation of success (11). Since even the private market usually refuses treatment to older women, their only remaining option is often cross-border treatment (5). After considerable public opposition, the government of the Canadian province Quebec, which had proposed to outlaw IVF above female age 42, recently retracted the proposal (12).

The right of self-determination is, however, not the only reason why our center strongly supports free treatment choices for well-educated poor-prognosis patients. In the early years of IVF, success rates for what now are considered "best-" prognosis patients barely exceeded the pregnancy and delivery chances of today's poor-prognosis patients. Since then, IVF has continued to dare to reach for new horizons and to serve patients of older ages and lower functional ovarian reserve (FOR). These efforts, until only a few short years ago, led to continuous improvements in worldwide IVF outcomes.

At some point, the professional IVF community, however, convinced itself that treatment beyond age 42 was no longer worthwhile. As rapidly rising numbers of donor egg IVF cycles in the United States witness (7), the use of donor eggs, therefore, became the primary IVF treatment not only for older women but also for younger women with LFOR, (also called occult primary ovarian insufficiency or premature ovarian aging), even with FSH levels that were clearly still premenopausal.

The relative ease of achieving indisputably better pregnancy success in donor egg than in autologous IVF cycles in women with LFOR strongly supports the use of egg donation and discourages the use of autologous oocytes in poor-prognosis patients. The professional community's hesitancy to treat poor-prognosis patients with LFOR with autologous oocytes is, therefore, understandable. As the evolution of IVF in its early stages, however, well demonstrated, unless IVF continues to dare to reach for new horizons, the field will stagnate.

To obtain the ability to judge potential progress in IVF outcomes, the baseline from which such progress is expected has to be defined first. This is the principal purpose of this