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Poor ovarian response as a predictor for live birth in older women undergoing IVF

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KEY MESSAGE

Poor response to stimulation in the first IVF cycle has a limited predictive value for the outcomes of subsequent cycles in women over 40 years. Poor response, defined by number of oocytes retrieved, and not by number of dominant follicles, is an independent predictor for births for women over 40.

A B S T R A C T

Women of advanced age present a major challenge for fertility treatments. This study was designed to assess whether poor ovarian response (POR) according to the Bologna criteria is a significant predictor for live birth in women over 40. The outcomes of subsequent IVF cycles were also studied. The results of 1870 fresh IVF cycles in 1212 women were retrospectively analysed. The live birth per cycle was 3.3 times higher (11.61% versus 3.54%, $P < 0.001$) in good responders with more than three oocytes collected compared with women with less. Ovarian response defined by oocytes collected, but not by the number of follicles, was independently associated with live birth (odds ratio, 2.0; 95% confidence interval, 1.18 to 3.54; $P = 0.009$). The occurrence of POR in subsequent IVF cycles was only 55%. No differences in live births were found in persistent POR compared with women with at least one good response. A single episode of POR in a first IVF cycle in older women has a limited predictive value for the outcomes of subsequent cycles. POR in women aged 40–43 years, defined by the number of oocytes retrieved, is a predictor for live birth in IVF.

Introduction

As more women delay childbearing, women at the age of 40 and over present a major challenge for fertility treatments. Spontaneous live birth rate decreases dramatically in this age group and, even with IVF, the live birth rate for this subgroup of patients is around 10% (Crawford et al., 2017; Sunderam et al., 2017). Earlier single-centre studies reported a live birth rate of 2.0–13.9% for women between the ages of 40 and 43 (Klipstein

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et al., 2005; Lass et al., 1998; Serour et al., 2010; Tsafrir et al., 2007).

The decline in fertility in older women over 40 is caused both by reduced ovarian reserve caused by accelerated follicular loss (Faddy et al., 1992), as well as by a higher rate of chromosomal abnormalities and cytoplasmic dysfunction, such as mitochondrial dysfunction (Hassold and Hunt, 2009; Miao et al., 2009). These destructive mechanisms will ultimately lead to lower pregnancy rates and higher pregnancy losses. Poor ovarian response (POR) to ovarian stimulation is defined either by ovarian reserve tests such as Day 3 FSH, antral follicle count (AFC), the number of growing follicles during controlled ovarian stimulation or, alternatively, following ovum pickup, by the number of oocytes retrieved. Since 2011, the accepted definition for women with POR is the Bologna criteria (Ferraretti et al., 2011).

The success rate of IVF is correlated with the ovarian response and the number of oocytes retrieved (Sunkara et al., 2011). Nevertheless, few studies have evaluated the outcome of IVF in women over 40 according to their ovarian response. Biljan et al. (2000) used sonographic criteria to define poor response and indicated a higher but not statistically significant live birth rate per cycle in those with more than three follicles (15.7% versus 4.2%). Yih et al. (2005) found a higher clinical pregnancy rate in women above 40 when five or more oocytes were retrieved. The Bologna criteria for poor responders (Ferraretti et al., 2011) standardizes the definition of POR. Women aged 40 and over need only one additional criteria to meet the definition of POR, including either previous POR (≤3 oocytes with conventional stimulation) or an abnormal ovarian test reserve.

Although one may assume that older women with good response carry a better prognosis for live birth, the effect of lower oocyte quality cannot be ignored. The aim of this study was to assess ovarian response based on the number of oocytes retrieved in accordance with the Bologna criteria and the number of dominant follicles, as significant predictors for live birth rate in women aged 40–43.

Materials and methods

Patient population

This was a retrospective study conducted at a university hospital reproductive centre. The computerized database of the IVF unit for the years 2010 to 2015 was retrospectively analysed. The analysis included women who were 40–43 years of age, undergoing a non-donor IVF cycle. Pre-implantation genetic diagnosis (PGD), oocyte donation, in-vitro maturation (IVM) and natural IVF cycles were excluded. Women older than 43 were not treated, according to clinic policy. The study received Institutional Review Board approval on 16 May 2013 (reference number 13-053-SDR).

IVF was publicly funded during the study period. According to the clinic policy, all patients with at least one follicle underwent ovum pickup. The outcome measures were calculated for women with at least one oocyte collected (per oocyte pickup). We analysed the primary outcome measures according to two accepted definitions for POR to stimulation: the first complies with the Bologna criteria – ≤ 3 oocytes retrieved and age 40 and above (Ferraretti et al., 2011); the second is based on ultrasonographic findings of ≤3 dominant follicles (>14 mm in diameter) imaged 24–48 h prior to human chorionic gonadotrophin (HCG) administration (potential POR) (Biljan et al., 2000; Fridström et al., 1997).

The primary outcome measure was live birth. Secondary outcome measures included IVF protocol parameters, embryo development and baseline ovarian reserve test results. A second analysis was conducted for women over 40 undergoing their first IVF cycle. In addition, we searched for the outcome of poor responders in their first cycle with one or more subsequent IVF cycles. Those who had ≤3 oocytes in all subsequent cycles were defined as persistent poor responders and were compared with women with at least one subsequent cycle with good response. The outcome of women with cryopreserved embryos that underwent cryopreserved embryo transfer was also analysed.

Ovarian stimulation protocol

Ovarian stimulation was performed by means of one of the following protocols: microdose-flare protocol, fixed gonadotrophin-releasing hormone (GnRH) antagonist protocol and mid-luteal long GnRH agonist protocol. Briefly, ovarian stimulation was performed with gonadotrophins (Gonal-F, EMD-Serono Inc., Canada; Puregon, Merck Inc., Canada; Menopur, Ferring Pharmaceuticals Inc., Canada), ovulation was suppressed with GnRH antagonist (Cetrotide, EMD-Serono Inc.; Orgalutran, Merck Inc.) or GnRH agonist (Superfact, Sanofi-Aventis Inc., Canada). No standard stimulation protocol is used for patients with POR in our clinic; protocol and gonadotrophin dose were based on AFC, Day 3 FSH and the results of previous IVF cycles. Gonadotrophin dose was ≥300 IU FSH per day. After 5–7 days of stimulation, FSH dose was adjusted based on ultrasound scan and serum oestradiol level. The maximal dose of FSH was 600 IU. When ideally two follicles attained a mean diameter of 17 mm, 250 µg of human recombinant chorionic gonadotrophin was administered (Ovidrel, EMD-Serono Inc.). Oocyte retrieval by an ultrasound guided transvaginal approach was scheduled 36–38 h later.

Embryo culture

Oocytes were fertilized by either conventional IVF or intracytoplasmic sperm injection (ICSI), according to the clinical indication. Fertilization was assessed 16–18 h after insemination for the appearance of two distinct pronuclei and two polar bodies. The zygotes were cultured in cleavage medium (Cook Medical, Sydney, Australia). Embryonic development was assessed daily. Embryos were cultured to the blastocyst stage in the blastocyst medium (Cook Medical). According to our IVF laboratory protocol, if there were at least three good-quality embryos on Day 3, the embryo culture was extended to the blastocyst stage and the embryos were transferred on Day 5. Cleavage embryos were defined as good quality (Grade 1 or 2) if they had four cells on Day 2 and/or seven or eight cells on Day 3, contained <20% fragmentation and exhibited no apparent morphological abnormalities. Poor-quality embryos included fair quality (Grade 3) embryos, which had only two cells on Day 2, three to five cells on Day 3 and/or 20–50% fragmentation, and Grade 4 embryos with <3 cells by Day 3 and >50% fragmentation. For women with fewer than three good-quality embryos, embryo transfer was at Day 2–3. Supernumerary good-quality embryos were cryopreserved (Zhang et al., 2011). The number of embryos transferred was determined according to the provincial guidelines at that time: up to two or three embryos and never more than three.

Outcome measures

The primary outcome was live birth rate per oocyte pickup. Live birth was defined as delivery of a live fetus ≥24 weeks of pregnancy. A

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