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# Live birth rates in various subgroups of poor ovarian responders fulfilling the Bologna criteria

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**KEY MESSAGE**

Patients fulfilling Bologna criteria might not be homogenous with regard to number of oocytes harvested and live birth rate. Younger poor ovarian responders may have a better outcome if they reach the embryo transfer stage. Each additional oocyte retrieved lowers the risk of cycle cancellation and enhances live birth rate.

A B S T R A C T

The European Society of Human Reproduction and Embryology published Bologna criteria to generate a definition of poor ovarian responders (PORs). However, there are few data on whether PORs are homogenous for ovarian response or live birth rates (LBRs). In this retrospective study, 821 patients fulfilling Bologna criteria and undergoing intracytoplasmic sperm injection were stratified into four groups: Group A: female age ≥40 with a previous poor response (cycle cancelled or ≤3 oocytes) (105 patients, 123 cycles); Group B: female age ≥40 with an antral follicle count (AFC) < 7 (159 patients, 253 cycles); Group C: AFC <7 with a previous poor response (350 patients, 575 cycles); and Group D: female age ≥40 with an AFC <7 and previous poor response (207 patients, 306 cycles). Cluster data analysis was performed. Although median number of oocytes was higher in Group B ($P < 0.001$), higher implantation ($P = 0.024$) and LBR per embryo transfer ($P < 0.001$) or cycle ($P = 0.001$) were noted in Group C. We conclude that, once a patient fulfils Bologna criteria, prognosis is poor, with fewer than 10% recorded LBRs per cycle. However, the LBRs are not homogenous and 'young proven' PORs have the most favourable pregnancy outcome.



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## Introduction

Poor ovarian response is encountered in 9–25% of patients undergoing IVF (Venetis et al., 2010). There had been great diversity in the definition of poor ovarian responders (PORs) until the introduction of the European Society of Human Reproduction and Embryology (ESHRE) consensus, known as the Bologna criteria (Ferraretti et al., 2011). According to the ESHRE Bologna criteria (Ferraretti et al., 2011), at least two of the following three features must be fulfilled for POR classification: (i) advanced maternal age (≥40 years) or any other risk factor, (ii) a previous poor ovarian response (cycles cancelled or ≤3 oocytes with a conventional protocol), (iii) an abnormal ovarian reserve test (ORT) [with a maximum bilateral antral follicle count (AFC) of between 5 and 7 or anti-Müllerian hormone level of 0.5–1.3 ng/ml]. In the absence of advanced maternal age or abnormal ORT, two previous episodes of poor ovarian response after maximal stimulation are sufficient to define a patient as a POR (Ferraretti et al., 2011). Although the Bologna criteria have provided a useful criteria set for the definition of PORs, there has been criticism of the criteria regarding the lack of definition of risk factors (Younis et al., 2015), the threshold points chosen (Sallam et al., 2012) and, most importantly, the lack of homogeneity of pregnancy outcomes of various subgroups fulfilling the Bologna criteria (Papathanasiou, 2014).

There is a paucity of data on the live birth rates (LBRs) of various subgroups of PORs fulfilling the Bologna criteria and undergoing IVF (Papathanasiou, 2014). To our knowledge, there are only two studies reporting the IVF performance of various subgroups of PORs fulfilling the Bologna criteria, both reporting similar LBRs (Busnelli et al., 2015; La Marca et al., 2015). Obviously, these results should be validated in larger sample size studies. The main goal of this study was to evaluate whether various subgroups of PORs fulfilling the Bologna criteria have comparable prognoses regarding cycle cancellation and LBRs at intracytoplasmic sperm injection (ICSI) and embryo transfer cycles.

## Materials and methods

The database containing detailed clinical and laboratory information on all ICSI treatment cycles performed at the Anatolia IVF and Women's Health Center during the period between August 2005 and August 2014 ($n$ = 14,709 cycles) was analysed. In the current retrospective cohort study, all the data per cycle were entered into the database prospectively. All the patient files, as well as cycle characteristics, were scrutinized manually and those cycles fulfilling the Bologna criteria were identified. The null hypothesis was that different subgroups of PORs fulfilling Bologna criteria have similar LBRs.

The exclusion criteria included: azoospermia necessitating surgical retrieval of spermatozoa ($n$ = 1095), structural or numerical chromosomal errors necessitating pre-implantation genetic diagnosis or screening ($n$ = 121) and frozen embryo transfer cycles ($n$ = 373). Since the ovarian reserve testing, as well as starting dose of FSH and number of oocytes harvested in those ICSI cycles performed elsewhere could not be precisely validated based on the couple's medical history, only those first and subsequent cycles that were performed at our centre were included. In other words, those couples with a history of a prior IVF/ICSI attempt(s) elsewhere were excluded from the current analysis.

Because AFC performed in the early follicular phase is the primary tool for the assessment of the ORT at our clinic, no anti-Müllerian hormone (AMH) data were included in the current analysis. All women underwent AFC assessment at the second or third day of menses immediately before starting ovarian stimulation. Every round or oval structure within the margin of 2 to 10 mm was considered to be an antral follicle. The threshold for normalcy for AFC was taken as 7.

Women underwent IVF/ICSI cycles using microdose flare-up (Lucrin, Abbott, Istanbul, Turkey) or multi-dose flexible GnRH antagonist (Cetrotide, Merck, Istanbul, Turkey) protocol, based on the physician's preference and in the manner described elsewhere (Yarali et al., 2009). All women with expected or proven poor ovarian response underwent ovarian stimulation with a starting gonadotrophin dose of ≥300 IU/day (300–450 IU/day). Ovarian stimulation was performed with the use of recombinant FSH (Gonal-F, Merck) and/or HP-HMG (Menopur, Ferring, Istanbul, Turkey), based on the physician's preference. Ovarian response was monitored with frequent serum oestradiol measurements and transvaginal ultrasounds. The criterion for HCG (Ovitrelle, Merck or Pregnyl, MSD, Istanbul, Turkey) administration was the presence of at least one follicle exceeding 17 mm in diameter.

Oocyte retrieval was carried out under general anaesthesia using vaginal ultrasound-guided puncture of follicles 34 to 36 h after HCG administration. Standard procedures were followed for gamete–embryo handling and ICSI. Embryo transfer was performed in all cases using a soft catheter under ultrasound guidance. Daily vaginal progesterone gel (Crinone, Merck) was administered for luteal phase support, starting 1 day after oocyte retrieval and continued until fetal cardiac activity was confirmed.

Four distinct subgroups of patients fulfilling the Bologna criteria were generated: Group A: female age ≥40 with a previous poor ovarian response (cycle cancelled or ≤3 oocytes) (105 patients; 123 cycles); Group B: female age ≥40 with AFC <7 (159 patients; 253 cycles); Group C: AFC <7 with a previous poor ovarian response (350 patients; 575 cycles); and Group D: female age ≥40 with AFC <7 and a previous poor ovarian response (207 patients; 306 cycles). All comparisons between these four groups were made on a per-cycle basis.

Clinical pregnancy was defined as visualization of a gestational sac with fetal cardiac activity at ultrasonography and/or confirmation of chorionic villi at the pathology specimen. Live birth was defined as a birth of a live baby exceeding 24 weeks of gestation. Pregnancy rates were given as per cycle commenced and per embryo transfer attempt. We calculated the implantation rate for a given patient (individual implantation rate) by dividing the number of sacs with fetal cardiac activity by the number of embryos transferred, as reported (Ben-Shlomo et al., 1997). We then summed the individual implantation rates and divided by the number of embryo transfer attempts in each group.

Normally distributed parametric variables confirmed by the Kolmogorov–Smirnov and Shapiro–Wilk tests were compared by analysis of variance (ANOVA) with the Bonferroni method for post hoc analysis by using Statistics Package for Social Sciences (ver. 21.0; SPSS Inc., Chicago). Non-normally distributed metric variables were analysed by the Kruskal–Wallis and Mann–Whitney U-tests. The chi-squared test was used to analyse nominal variables in the form of frequency tables. Binary logistic regression analysis with the forward conditional method was used to delineate the independent variable(s) for live birth. $P < 0.05$ was considered statistically significant. Values were expressed as medians (minimum–maximum), unless otherwise stated.



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