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ARTICLE

Reproductive outcome in European and Middle Eastern/North African patients

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Abstract The aim of this retrospective cohort study was to assess differences in infertility-related baseline characteristics and IVF outcome between European and Middle Eastern/North African (MENA) patients. Of 2703 patients undergoing their first IVF cycle, 2485 were Caucasian of European descent and 218 originated from the MENA region. MENA patients were significantly younger (30.6 versus 34.0 years, $P < 0.001$), less likely smokers, with higher body mass indexes. Infertility duration was longer in MENA patients ($P < 0.001$), their male partners were younger ($P < 0.001$) and smoked more often than European male patients ($P = 0.005$). Male factor infertility ($P = 0.017$) and polycystic ovary syndrome (PCOS; $P = 0.032$) was more prevalent in MENA patients, showed significantly higher basal FSH concentrations ($P = 0.012$) and significantly fewer oocytes retrieved (RR 0.83, 95% CI 0.74–0.93, $P = 0.001$). Clinical pregnancy rates were comparable (22.4% [European] versus 22.9% [MENA]). Fewer MENA patients had surplus embryos cryopreserved (OR 0.41, 95% CI 0.22–0.76, $P = 0.004$). Despite younger age and higher prevalence of PCOS, MENA patients had significantly lower oocyte yields than their European counterparts ($P = 0.001$). These findings suggest a more rapid decline in ovarian function in women of MENA descent.

KEYWORDS: ethnicity, IVF/ICSI outcome, male infertility, MENA, ovarian reserve

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Introduction

The literature suggests an impact of ethnicity on pregnancy potential in the course of IVF (Wellons et al., 2012). American studies revealed significant differences in IVF/intracytoplasmic sperm injection (ICSI) outcome between patients of Caucasian, Black American, Asian and Latino descent (Fujimoto et al., 2010; McQueen et al., 2015). However, Europe-based studies on ethnicity are rare (Dhillon et al., 2015; Iglesias et al., 2014; Jayaprakasan et al., 2014). To date no study focused on infertility-related differences of patients originating from the Middle Eastern and North African (MENA) region. This region has one of the highest infertility prevalences worldwide (Mascarenhas et al., 2012). Possible causes include environmental, psychological and genetic factors. Smoking, caffeine consumption, environmental toxins, obesity-linked polycystic ovary syndrome (PCOS) and high consanguinity prevalence in the MENA region are likely to contribute to this phenomenon (Curtis et al., 1997; Inhorn and Patrizio, 2015; Inhorn et al., 2008, 2009; Zlotogora, 1997).

Furthermore, people immigrating from MENA countries to Europe represent the biggest immigrant group from outside the European Union (Eurostat, 2015). These facts and the lack of sufficient studies on fertility in Middle Eastern minorities underline the need for thorough investigations in this field (Bosdou et al., 2016; Read et al., 2005).

In addition to lifestyle and environmental factors, various studies suggest that accelerated ovarian ageing patterns may contribute to higher infertility rates in certain ethnic groups (Gleicher et al., 2012; Seifer et al., 2009). For instance, Black Americans, Asian Americans and Latino patients showed a higher risk of prematurely declining ovarian function compared with Caucasians (Gleicher et al., 2007, 2012; Seifer et al., 2009). However, data on ovarian reserve parameters are lacking in MENA patients. Therefore, the aim of the present study was to investigate differences in population characteristics and IVF/ICSI outcomes of European and MENA patients.

Materials and methods

This retrospective database study included 2703 patients undergoing their first IVF/ICSI cycle at the Wunschbaby Institut Feichtinger (WIF) between January 2000 and December 2011. This study was approved by the ethics committee of the Medical University of Vienna on 12 May 2015 (reference number 1258/2015). Two thousand four hundred eighty five (91.9%) of these patients were Caucasians of European descent, 218 (8.1%) patients originated from Middle Eastern (including Turkey) and North African countries (MENA-Region). Patients' baseline characteristics, such as ethnicity, age at menarche, duration of infertility, height, weight, smoking status and number of previous pregnancies were assessed at initial presentation. All patients underwent ovarian reserve testing by serum baseline FSH assessment on cycle day 2 or 3 as previously reported (Weghofer et al., 2005).

Ovarian stimulation was performed with standard gonadotrophin-releasing hormone (GnRH) agonist or antagonist stimulation. Stimulation protocol was chosen according to female age, baseline FSH and body mass index (BMI) (Grow et al., 2014). In the antagonist protocol, ovarian stimulation was initiated on day three of the menstrual cycle with a starting dose of 150 IU of human-derived FSH (Fostimon, IBSA, Vienna, Austria) in women <36 years and 225 IU in patients ≥36 years, expected lower ovarian reserve or higher BMI. On day 6 of stimulation, GnRH antagonist treatment (i.e. 0.25 mg of ganirelix, Orgalutran, MSD, Vienna, Austria) was initiated. If necessary, gonadotrophin dosage was adjusted according to ovarian response.

In the agonist protocol pituitary desensitization was started on day 21 of the cycle preceding the stimulation using 0.5 mg of buserelin (Suprefact, Sanofi, Vienna, Austria) subcutaneously. Ovarian stimulation was started using 75 IU of human-derived FSH (Fostimon, IBSA) for patients <36 years and 150 IU for patients ≥36 years, expected lower ovarian reserve or higher BMI levels and 75 IU of human-derived menotrophin (Merional, IBSA) subcutaneously. Gonadotrophin dosage adjustments occurred if necessary.

If at least one follicle reached a diameter of 18 mm, ovulation was triggered with 5000 IU or 10,000 IU of human chorionic gonadotrophin (HCG)(Pregnyl, MSD, Vienna, Austria). Thirty-two to thirty-six hours later transvaginal oocyte pickup was performed. Surplus embryos of good quality were cryopreserved and used for transfer in subsequent cycles (Moragianni and Penzias, 2010). Serum HCG concentrations were measured two weeks after oocyte retrieval. Clinical pregnancy was defined by the presence of fetal heartbeat(s) at eight weeks of gestation.

Statistical analysis

Clinical pregnancy per cycle initiated was set as primary outcome measure. Secondary outcome measures were defined as biochemical pregnancy per cycle start, number of retrieved, mature and fertilized oocytes and probability of embryo transfer. Categorical variables were summarized by counts and percentages. Continuous scaled variables were summarized by means ± standard deviations (SD). Group specific differences were assessed by using Student's *t*-test or the chi-squared test for univariable analysis, respectively. To assess the impact of ethnicity on binary outcomes (clinical pregnancy, biochemical pregnancy, embryo transfer), binary logistic regression models were used to adjust for co-variables like age (metric-scaled, years), BMI (metric scaled, kg/m^2) and stimulation protocol (binary, agonist/antagonist). The results are presented as odds ratio (OR) and 95% confidence interval (95% CI).

Count data (i.e. number of retrieved, mature or fertilized oocytes) were expressed as median and interquartile range. The impact of ethnicity on these variables was assessed by univariable as well as covariable adjusted Poisson regression (accounting for overdispersion), whereby the effects of these models were expressed as rate ratios (RR). The impact of ethnicity on FSH concentrations was assessed using linear regression models.

The functional form of age in multivariable analyses was modelled by multivariable fractional polynomials according to Sauerbrei *et al.* (Sauerbrei and Royston, 1999) to allow a flexible model fit of non-linear functions or associations, such as between age and FSH. Statistical analysis was performed with SPSS version 21 (IBM Corp., USA) and R (version 3.2.2) (R-Core-Team, 2015). The two-sided significance level was set

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