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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

to 0.05. However, *P*-values were interpreted in an explorative manner and there was no adjustment for multiplicity.

The association between number of (retrieved, mature and fertilized) oocytes as well as the chance of biochemical or clinical pregnancy and female age was shown to be curve linear, particularly decreasing at 30–35 years. This was accounted for in multivariable analysis, with additionally including BMI and stimulation protocol as further covariables.

Results

Patient characteristics

As shown in Table 1, MENA patients that presented for fertility treatment were significantly younger than controls (30.6 versus 34.0 years, $P < 0.001$). Additionally, MENA women had a longer duration of infertility (6.5 versus 4.6 years, $P < 0.001$), were less likely to be nulligravida (55.6% versus 63.7%, $P = 0.039$) and were less likely smokers (19.9% versus 27.0%, $P = 0.037$). Moreover, higher rates were observed of overweight (BMI ≥25) (42.1% versus 21.8%, $P < 0.001$) and obesity (BMI ≥30) (20.5% versus 7.2%, $P < 0.001$) in MENA patients. Male partners of MENA patients were significantly younger (34.7 versus 36.9 years, $P < 0.001$) and showed higher smoking rates than European patients (44.4% versus 33.7%, $P = 0.005$). After adjustment for age and smoking status of the male partner, MENA partners were more likely to suffer from male factor infertility (OR 1.62, 95% CI 1.09–2.41, $P = 0.017$).

Baseline FSH concentrations were significantly higher in MENA patients compared with European patients after adjusting for age and BMI (adjusted mean difference: 0.60, 95% CI 0.13–1.07, $P = 0.012$). These results remained significant when the specific functional form of the association between age and FSH was modelled by multivariable fractional polynomials ($P = 0.041$). In the study group, women were less likely to suffer from tubal factor and more likely to present with PCOS (Table 1).

IVF/ICSI cycle outcome

Univariate analysis of IVF/ICSI cycle outcome is presented in Table 2. To further evaluate the impact of ethnicity on IVF/ICSI cycle outcome, multivariate logistic regression models correcting for age, BMI and stimulation protocol have been applied.

Analyses from this study demonstrated that MENA patients showed 17% fewer retrieved oocytes (RR 0.83, 95% CI 0.74–0.93, $P = 0.001$) as compared with the indigenous population. Comparable results were observed when only mature oocytes (RR 0.86, 95% CI 0.76–0.97, $P = 0.017$) or fertilized oocytes (RR 0.82, 95% CI 0.72–0.94, $P < 0.005$) were analysed, respectively.

A sensitivity analysis was performed on FSH values and oocytes excluding PCOS patients. The results were similar to those of the overall group.

Multivariable logistic regression analysis revealed that the risk of cycle cancellation due to poor ovarian response or fertilization failure was considerably increased in MENA women (OR 2.02, 95% CI 1.28–3.10, $P = 0.002$). In a minority of patients (i.e. $n = 40$ in European and $n = 8$ in MENA patients), a

Table 1 Patient characteristics with univariate analysis.

Parameter	*Indigenous (2485)*		*MENA (218)*		P-*value*
	n	*Values*	n	*Values*	
Women's age	$n = 2485$	34.0 ± 5.2	218	30.6 ± 6.1	<0.001
Men's age	$n = 2478$	36.9 ± 6.7	218	34.7 ± 7.4	<0.001
Infertility duration years	$n = 800$	4.6 ± 3.2	57	6.5 ± 4.0	<0.001
Menarche	$n = 2085$	13.1 ± 1.4	178	13.0 ± 1.3	NS
Nulligravida *n* (%)	$n = 2024$	1289 (63.7)	162	90 (55.6)	0.039
BMI	$n = 2102$	23.0 ± 4.2	171	25.8 ± 6.0	<0.001
Overweight (BMI ≥25) *n* (%)	$n = 2102$	459 (21.8)	171	72 (42.1)	<0.001
Obesity (BMI ≥30) *n* (%)	$n = 2102$	152 (7.2)	171	35 (20.5)	<0.001
Smoking women *n* (%)	$n = 2197$	593 (27.0)	181	36 (19.9)	0.037
Smoking men *n* (%)	$n = 2104$	709 (33.7)	169	75 (44.4)	0.005
Tubal Factor *n* (%)	$n = 2485$	431 (17.3)	218	25 (11.5)	0.026
Endometriosis *n* (%)	$n = 2485$	101 (4.1)	218	5 (2.3)	NS
PCO *n* (%)	$n = 2485$	88 (3.5)	218	14 (6.4)	0.032
Idiopathic Infertility *n* (%)	$n = 2485$	63 (2.5)	218	3 (1.4)	NS
Male Factor *n* (%)	$n = 2485$	1802 (72.5)	218	171 (78.4)	NS
Antagonist *n* (%)	$n = 2485$	1415 (56.9)	218	104 (47.7)	0.008
Agonist *n* (%)	$n = 2485$	1070 (43.1)	218	114 (52.3)	0.008
IVF *n* (%)	$n = 2154$	379 (17.6)	172	25 (14.5)	NS
ICSI *n* (%)	$n = 2154$	1775 (82.4)	172	147 (85.5)	NS

Data are presented as mean ± standard deviation or number (%) with *n* representing the number of total available data for the appropriate variable.
BMI = body mass index; ICSI = intracytoplasmic sperm injection; MENA = Middle Eastern/North African; NS = not statistically significant; PCO = polycystic ovary.

Table 2 Clinical outcomes with univariate analysis.

Parameter	*(2485) Indigenous*	*(218) MENA*	*P-value*
Peak endometrial thickness	11.26 ± 1.88	11.34 ± 1.80	NS
Oocytes	7 (4–10)	6 (3–10)	0.043
Mature oocytes	5 (3–8)	5 (3–8)	NS
Fertilized oocytes	3 (2–6)	3 (1–6)	0.042
Transferred embryos	2 (2)	2 (1–2)	NS
Biochemical pregnancy *n* (%)[a]	772 (31.6)	72 (34.3)	NS
Clinical pregnancy *n* (%) [a]	548 (22.4)	48 (22.9)	NS
No transfer *n* (%) [a]	284 (11.6)	37 (17.6)	0.015

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).
MENA = Middle Eastern/North African; NS = not statistically significant.
[a]Excluding 'freeze-all' patients (indigenous $n = 40$, MENA $n = 8$).

'freeze all' strategy had to be applied, mainly due to ovarian hyperstimulation syndrome (OHSS). These patients were excluded from further analyses.

The biochemical (OR 0.91, 95% CI 0.64–1.30) and clinical (OR 0.81, 95% CI 0.53–1.20) pregnancy rates, adjusted for covariables, were comparable among the groups. Fewer MENA patients had surplus embryos cryopreserved compared with European patients (OR 0.41, 95% CI 0.22–0.76, $P = 0.004$). Results were controlled for female age, BMI and stimulation protocol.

Discussion

In the present study distinctive differences in patient characteristics and cycle outcome between fertility patients of European and MENA descent could be shown. MENA women accessed fertility treatment at a younger age despite significantly longer periods of infertility. Infertility is a multifactorial phenomenon – ethnical, cultural, religious and socioeconomic factors play a central role in the perception of infertility and response to infertility treatment (Jain, 2006; Missmer et al., 2011). Women of various ethnocultural backgrounds experience the burden of infertility differently. It was shown that infertile Muslim immigrant women experience high social pressure and impaired health-related quality of life (Schmid et al., 2004; Vanderlinden, 2009). Taking these results into consideration, one would assume a shorter duration of infertility in MENA patients seeking fertility treatment. However, some evidence suggests that lack of information and different social taboos could finally result in a longer period of infertility (Missmer et al., 2011). These findings are in agreement with previous studies reporting that patients from minority groups tend to have a longer duration of infertility before seeking professional care (Dhillon et al., 2015; Jain, 2006).

Since minority patients tend to have a higher risk of an underprivileged social background (Jain, 2006), one may also assume that access to assisted reproduction may be limited (Feinberg et al., 2006). In the USA, Arab Americans where shown to face unequal access to infertility care similar to African Americans (Inhorn and Fakih, 2006). In contrast, Austria provides broad coverage of fertility treatment. We were therefore able to investigate a representative sample of an infertile population; a major strength of this study.

Few studies were conducted to assess health disparities between Middle Eastern immigrants and European or American white indigenous people (Inhorn and Serour, 2011). American studies on Middle Eastern immigrants showed that these patients had a high prevalence of smoking in men and women (Islam and Johnson, 2003; Rice and Kulwicki, 1992). In this study, female MENA patients were less likely to smoke than their European counterparts, while more male MENA patients smoked when compared with European males. Patients from the MENA region showed a significantly higher BMI compared with European women. Likewise rates of overweight (BMI ≥25) and obesity (BMI ≥30) were higher in the MENA group. Ethnic minorities seem to have different prevalences of overweight and obesity with specific implications on reproductive outcome for these minorities (Luke et al., 2011).

Various studies described different ethnicity-related causes of infertility (Fujimoto et al., 2010; Kjerulff et al., 1993;). In this study, some of the differences in assisted reproduction treatment indications are explainable by distinctive differences in population characteristics. Higher rates of tubal factor infertility in Europeans may be attributable to the higher prevalence of smoking, to differences in the number of sexual partners and subsequent risk of genital infections and to the fact that European women were older than MENA patients (Ghazal-Aswad et al., 2004). In contrast, higher frequencies of PCOS-related infertility in the Middle Eastern group could be explained by higher BMI and younger age. The Middle Eastern region is believed to have the highest prevalence of male factor infertility worldwide (Agarwal et al., 2015; Inhorn, 2004, 2012). This study could confirm this trend, even though partners of MENA patients were younger than their European counterparts. These results may be attributable to environmental factors, such as smoking status, to consanguinity and family clustering (Inhorn et al., 2009; Kobeissi et al., 2008). Overall, differences in age, BMI, FSH concentrations and indications for fertility treatment accounted for the differences observed in stimulation protocol application between the two groups. Although a relatively large sample size was analysed in this study, some sub-analyses might not be representative. To minimize potential selection biases, only the first treatment cycle of a large, unselected patient cohort were included.

When IVF/ICSI cycle outcome was compared among MENA patients and European, MENA women produced significantly fewer oocytes. This finding is of particular interest, as MENA women were significantly younger and presented with a significantly higher prevalence of PCOS, a diagnosis that is closely related to excessive oocyte yield (Ludwig et al., 1999). These results strongly suggest ethnicity-related differences in ovarian function between MENA women and Europeans. Indeed, baseline serum FSH concentrations before ovarian stimulation were significantly higher in this group suggesting a possible lower ovarian reserve in MENA patients (Luna et al., 2007). Although pregnancy chances after fresh embryo transfer were comparable between the groups, it is tempting to speculate that lower oocyte numbers and significantly fewer frozen embryos, as could be demonstrated, will eventually result in lower cumulative pregnancy rates in MENA patients.

Differences in ovarian reserve markers between ethnic groups have been observed among patients of various ethnicities (Bleil et al., 2014; Gleicher et al., 2007; Iglesias et al., 2014). Bide *et al.*, in contrast, reported no differences in ovarian reserve among different ethnic groups in Great Britain (Bhide et al., 2015). These conflicting reports raise the question whether differences observed are genetic or environmental in nature. One recent study investigating ovarian reserve markers in Bangladeshi women raised in Bangladesh compared with Bangladeshi women raised in Great Britain and British women pointed out the importance of childhood development over ethnicity (Begum et al., 2016). On the other hand, consistent reports on ethnic disparities in ovarian function in the USA may emphasize a genetic component (Schuh-Huerta et al., 2012).

To our knowledge this is the first study to investigate specific differences between European and MENA patient characteristics and IVF cycle outcome. Although a relatively large sample size was analysed in this study, some sub-analyses might not be representative. Future studies should aim to further investigate the role of impaired ovarian reserve in MENA patients using additional ovarian reserve markers like anti-Müllerian hormone or antral follicle count that could not be investigated in the present study.

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