Arabian Peninsula ethnicity is associated with lower ovarian reserve and ovarian response in women undergoing fresh ICSI cycles

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Received: 18 August 2017 / Accepted: 13 October 2017 / Published online: 23 October 2017
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Abstract

Purpose Recent studies have demonstrated that ethnicity can be an independent determinant of assisted reproductive technology (ART) outcomes. In this context, we investigate whether ART outcomes differ between Arabian Peninsula and Caucasian women.

Methods This is a retrospective cohort study of women undergoing fresh intracytoplasmic sperm injection (ICSI)-embryo transfer (ET) cycles for male factor infertility. The study cohort was divided into 2 groups based on ethnicity—Arabian Peninsula or Caucasian. Ovarian reserve, ovarian response, and pregnancy outcomes were compared between the groups. A sub-analysis was performed between individual Arabian Peninsula nationalities for the same outcomes. A multiple linear regression model was used to assess the independent effect of ethnicity on ovarian response.

Results Seven hundred sixty-three patients were included—217 (28.4%) Arabian Peninsula and 546 (71.6%) Caucasian. There was no difference in the mean age of the two groups; however, the former had a higher body mass index (28.5 ± 7.5 vs. 23.3 ± 5.7 ; $P < 0.001$). Although follicle stimulating hormone (FSH) levels and antral follicle counts (AFC) were within the normal range in both groups, Arabian Peninsula women had higher FSH levels (5.7 ± 2.5 vs. 4.9 ± 2.8 ; $P = 0.001$) and lower AFC (13.9 ± 4.7 vs. 16.5 ± 4.3 ; $P < 0.001$) when

compared to Caucasian women. Women from the Arabian Peninsula also had a statistically lower number of mature oocytes retrieved (15.6 ± 6.8 vs. 14.1 ± 8.4 ; $P = 0.01$), despite requiring higher gonadotropin doses. Multiple linear regression revealed that Arabian Peninsula women had 2.5 (95% CI 2.1–3.9) less mature oocytes, even after controlling for confounders. A sub-analysis within the Arab cohort demonstrated that Qatari women had a higher yield of mature oocytes when compared to Emirati, Kuwaiti, and Saudi women. There was no difference in the rates of implantation, clinical pregnancy, or live birth when comparing individual Arabian Peninsula nationalities with each other or to Caucasians.

Conclusions Arabian Peninsula ethnicity is associated with lower ovarian reserve and ovarian response parameters in women undergoing their first ICSI-ET cycle.

Keywords Intracytoplasmic sperm injection · Assisted reproductive technologies · Ovarian response · Ethnicity · Disparities · Arabian Peninsula

Introduction

Assisted reproductive technology (ART), specifically in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), is commonly used for the treatment of infertile couples. The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) reported that 4,461,309 ART cycles were initiated between 2008 and 2010 globally, resulting in the birth of 1,144,858 newborns [1]. Their data also suggested that there are variations in ART success rates from region to region. For example, the overall live birth rate per ART cycle in Asia was 8.9%, compared to 33.9% in North America during the study period [1]. Although much of this variation can be attributed to

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differences in patient populations, infertility diagnoses, ovarian stimulation protocols, and laboratory facilities, recent studies have also shown that other independent variables may contribute to such variation.

One such plausible variable contributing to the difference in ART success rates is ethnicity [2]. Several prior studies have compared the ART outcomes of different ethnicities to a referent population of white or Caucasian women. For example, an analysis of 139,027 ART cycles between 2004 and 2006 from the Society for Assisted Reproductive Technology database revealed that the odds for live birth were reduced for Asian, black, and Hispanic women when compared to white women [3]. A recent study conducted in the UK and Ireland investigated the outcomes of 13,473 first IVF cycles among the Centers for Assisted Reproduction (CARE) clinics between 2008 and 2012 [4]. This study also reported that south Asian and black women had lower odds of live birth when compared to white women.

Currently, there is very limited knowledge about ART outcomes in the Arab or Middle Eastern population, despite a high prevalence of primary infertility in this population [5]. Although the ART outcomes of Middle Eastern patients are covered by most ICMART reports, these data are generated from very few countries and omit countries located in the main Arabian Peninsula, except Saudi Arabia [1, 6, 7]. Sporadic studies of ART outcomes in the Middle Eastern population also combine women of Middle Eastern and North African ethnicities together [8, 9]. Due to these limitations, we sought to investigate the ART outcomes of couples from the Arabian Peninsula undergoing treatment at our center.

Materials and methods

Inclusion and exclusion criteria

All couples undergoing their first ICSI cycle with fresh day-3 embryo transfer (ET) for male factor infertility with ejaculated or surgically retrieved sperm at our center between 2010 and 2015 were assessed for inclusion. From this cohort, patients were divided into two groups based on self-reported ethnicity—Arabian Peninsula and Caucasian. In this study, patients with Arabian Peninsula ethnicity primarily originated from the countries of the main Arabian Peninsula, i.e., Qatar, the United Arab Emirates (UAE), Kuwait, and Saudi Arabia [10]. As most patients from the Arabian Peninsula are referred to our center for the treatment of male factor infertility, we compared the outcomes of fresh ICSI-ET cycles for male factor infertility between the patients and Caucasians. Patients with other infertility diagnoses and those utilizing cryopreserved embryos, donor oocytes, or donor sperm were excluded. Additional exclusion criteria include female age > 40 years, cycle day-2/3 follicle stimulating hormone

(FSH) level > 12 mIU/mL and cycle day-2/3 anti-müllerian hormone (AMH) level < 1 ng/mL. Our retrospective study was approved by the Institutional Review Board.

Clinical and laboratory protocols

Protocols for ovarian stimulation, human chorionic gonadotropin (hCG) trigger, oocyte retrieval, sperm preparation, and embryo transfer have been described previously [11, 12]. All patients underwent a thorough evaluation of the uterine cavity via saline infusion sonography, hysterosalpingography, or hysteroscopy prior to treatment. Ovarian stimulation was carried out with gonadotropins (Menopur, Ferring Pharmaceuticals Inc., Parsippany, NJ, USA; and, Gonal-F, EMD-Serono Inc., Rockland, MA, USA, or Follistim, Merck, Kenilworth, NJ, USA). Gonadotropin dosing was based on antral follicle count, AMH level and body mass index (BMI, kg/m²). Suppression of ovulation during ovarian stimulation was achieved with gonadotropin releasing hormone-antagonist (GnRH-ant), which was initiated based on a previously described flexible protocol [12]. hCG (Pregnyl, Merck, Kenilworth, NJ, USA) was administered when the two lead follicles attained a mean diameter > 17 mm. A sliding scale for hCG administration based on estradiol (E_2 , pg/mL) levels was utilized, i.e., 10,000 IU for E_2 < 1500 pg/mL, 5000 IU for E_2 1501–2500 pg/mL, 4000 IU for E_2 2501–3000 pg/mL, and 3300 IU for E_2 > 3001 pg/mL [13]. Oocyte retrieval was performed under conscious sedation approximately 34–35 h after hCG administration. All patients received intramuscular progesterone (50 mg daily) for luteal support after the oocyte retrieval.

Ejaculated or surgically retrieved sperm samples were processed based on established in-house protocols [14, 15]. Oocytes were exposed to 40 IU recombinant hyaluronidase (Cumulase, Halozyme Therapeutics, Inc. San Diego, CA, USA) to remove the surrounding cumulus cell layer [14]. Microinjection of metaphase-II (M-II) oocytes was performed after selection and immobilization of spermatozoa. The injected oocytes were examined 14–18 h after microinjection for normal fertilization and the resulting embryos were cultured until the cleavage stage using in-house culture media [16]. Fresh embryos were transferred with Wallace catheters (Smiths Medical Inc., Norwell, MA, USA) approximately 1 cm less than the uterine depth identified at prior trial transfer.

Study variables

Baseline demographics recorded for each patient included age (years), BMI (kg/m²) and self-reported ethnicity (Arabian Peninsula vs. Caucasian). Ovarian stimulation parameters recorded were cycle day-2/3 FSH (mIU/mL), cycle day-2/3 AMH (ng/mL), cycle day-2/3 antral follicle counts (AFC),

duration of ovarian stimulation (days), total dosage of gonadotropins administered (IU), E_2 on the day of trigger, and mature oocytes retrieved. The number of mature oocytes retrieved per unit of AMH (mature oocyte to AMH ratio) and AFC (mature oocyte to AFC ratio) was also calculated. ICSI outcomes analyzed were fertilization rate (%) and number of day-3 embryos transferred. Fresh ET outcomes included implantation rate, clinical pregnancy rate, and live birth rate. The number of supernumerary embryos cryopreserved per patient was also noted. Implantation rate was defined as the number of sacs seen via ultrasonography divided by the number of embryos transferred for each patient. Clinical pregnancy rate was defined as the number of intrauterine gestations with fetal cardiac activity per ICSI cycle. Any birth after 24 weeks of gestation was considered a live birth.

Statistical analyses

Standard descriptive statistics were used to characterize the study cohort. Categorical variables were expressed as number of cases (n) with percentage of occurrence (%). Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), depending on the normality of the data. The study cohort was divided into two main groups based on ethnicity—Arabian Peninsula or Caucasian. Statistical comparison of study variables between these groups was performed using the two-sample t test or nonparametric Wilcoxon rank-sum test, as appropriate. Categorical variables of interest were compared using the chi-square test or Fisher's exact test. Odds ratios (OR) with 95% confidence intervals (CI) for implantation, clinical pregnancy, and live birth rates were also estimated. A multiple linear regression model was used to assess the independent effect of ethnicity on specific outcomes of interest, after controlling for confounding variables. A separate sub-comparison of baseline demographics, ovarian stimulation parameters, ICSI outcomes, and fresh ET outcomes was performed between individual Arabian Peninsula nationalities. The Analysis of Variance (ANOVA) test with Bonferroni multiple comparisons correction or chi-square test was used for this sub-comparison. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using STATA version 14.0 (College Station, TX; StataCorp LP).

Results

A total of 763 patients were included—217 (28.4%) Arabian Peninsula and 546 (71.6%) Caucasian. Table 1 compares the baseline demographics and ovarian stimulation parameters of the two groups. While there was no difference in mean age, Arabian Peninsula women had a higher BMI compared to Caucasian women (28.5 ± 7.5 vs. 23.3 ± 5.7 ; $P < 0.001$).

These women also had a statistically higher FSH level, lower AMH level, and lower AFC when compared to Caucasian women. No difference was noted in the duration of ovarian stimulation or E_2 level on the day of trigger; however, the total dosage of gonadotropins administered was higher in the Arabian Peninsula group (2769.2 ± 1550.1 vs. 2129.9 ± 1003.1 ; $P < 0.001$). Compared to Caucasians, women from the Arabian Peninsula had a statistically lower number of mature oocytes (15.6 ± 6.8 vs. 14.1 ± 8.4 ; $P = 0.01$). Furthermore, the ratio of mature oocytes to AMH and mature oocytes to AFC was lower in Arabian Peninsula women when compared to Caucasian women. Table 2 summarizes the multiple linear regression analysis exploring the association between ethnicity and number of mature oocytes. When compared to Caucasians (referent group), Arabian Peninsula women were noted to have 2.5 (95% CI 2.1–3.9) less mature oocytes, even after controlling for age, BMI, AMH, AFC, total dosage of gonadotropins administered, and E_2 level on the day of trigger.

Sixty-two (28.6%) and 55 (10.1%) of treatment cycles were canceled in Arabian Peninsula and Caucasian women, respectively due to absence of sperm in the ejaculate or surgically retrieved samples. However, as seen in Table 3, when sperm was found, there was no statistical difference in ICSI fertilization rates between Arabian Peninsula ($52.9 \pm 9.4\%$) and Caucasian ($53.8 \pm 8.7\%$) women. There was also no difference in the mean day-3 embryos transferred—Arabian Peninsula (1.67 ± 0.4) vs. Caucasian (1.61 ± 0.5) women. Furthermore, the odds of implantation (OR 0.99, 95% CI 0.57–1.74), clinical pregnancy (OR 0.86, 95% CI 0.62–1.18), and live birth (OR 0.92, 95% CI 0.67–1.28) were similar between the two groups per ET cycle. The number of supernumerary embryos cryopreserved in the Arabian Peninsula and Caucasian groups was comparable.

Table 4 compares the baseline demographics and ovarian stimulation parameters of individual nationalities within the Arabian Peninsula cohort. No difference was noted in the mean age, BMI, FSH level, AMH level, AFC, duration of ovarian stimulation, total dosage of gonadotropins, or E_2 level on the day of trigger when comparing Qatari, Emirati, Kuwaiti, or Saudi women. However, compared to other Arabian Peninsula nationalities, Qatari women had a statistically higher yield of mature oocytes (Table 4). There was no difference in the rates of clinical pregnancy or live birth when comparing individual Arabian Peninsula nationalities to the referent Caucasian group.

Discussion

The results of the current study suggest that Arabian Peninsula ethnicity is associated with lower ovarian reserve and ovarian response parameters in women undergoing ICSI-ET cycles.

Table 1 Comparison of baseline demographics and ovarian stimulation parameters of the study cohort ($n = 763$)

Parameter	Arab ($n = 217$)	Caucasian ($n = 546$)	<i>P</i>
Baseline demographics			
Age (years)	31.6 (± 3.3)	31.9 (± 3.4)	0.27
BMI (kg/m^2)	28.5 (± 7.5)	23.3 (± 5.7)	< 0.001
Ovarian stimulation parameters			
Cycle day 2/3 FSH (mIU/mL)	5.66 (± 2.5)	4.93 (± 2.8)	0.001
Cycle day-2/3 AMH (ng/mL)	2.16 (1.09–4.35)	2.50 (1.62–4.51)	< 0.001
Cycle day-2/3 AFC (number)	13.9 (± 4.7)	16.5 (± 4.3)	< 0.001
Duration of ovarian stimulation (days)	9.50 (± 2.5)	9.52 (± 1.9)	0.91
Total gonadotropins administered (IU)	2769.2 (± 1550.1)	2129.9 (± 1003.1)	< 0.001
E_2 at trigger (pg/mL)	2119.2 (± 997.2)	1971.4 (± 795.5)	0.08
Mature oocytes retrieved (number)	14.1 (± 8.4)	15.6 (± 6.8)	0.01
Mature oocytes to AMH ratio	5.04 (± 5.3)	6.17 (± 4.1)	0.001
Mature oocytes to AFC ratio	0.76 (± 0.71)	1.07 (± 0.72)	< 0.001

Data are presented as mean $\pm$ standard deviation or median (IQR)

BMI body mass index, FSH follicle stimulating hormone, AMH anti-müllerian hormone, AFC antral follicle count, E_2 , estradiol

Specifically, women from the Arabian Peninsula were found to have higher FSH, lower AMH and lower AFC, as well as a lower yield of mature oocytes when compared to Caucasians. The lower yield of mature oocytes remained true, even after controlling for confounders of interest. A sub-analysis within the Arabian Peninsula cohort demonstrated that Qatari women had a higher yield of mature oocytes when compared to Emirati, Kuwaiti, and Saudi women, though all had a lower yield of mature oocytes when compared to Caucasians. Despite these differences, no difference was noted in the rates of implantation, clinical pregnancy, or live birth when comparing individual Arabian Peninsula nationalities with each other or to the referent Caucasian group.

Very few studies to date have reported ART outcomes in the Arabian Peninsula population. In one study, Feichtinger et al. [8] compared the outcomes of 218 Middle Eastern/North African (MENA) patients to 2485 Caucasian patients of European descent undergoing their first IVF cycle. MENA patients were younger and had a higher BMI compared to their Caucasian counterparts. In addition, MENA patients had a longer duration of infertility, higher prevalence of male factor

infertility and polycystic ovarian syndrome (PCOS). MENA patients also had higher basal FSH levels (adjusted mean difference 0.60, 95% CI 0.13–1.07) and significantly lower number of oocytes retrieved (relative risk 0.83, 95% CI 0.74–0.93) when compared to Caucasian patients. The clinical pregnancy rates were comparable between the groups. Despite a younger age and higher prevalence PCOS, MENA patients had lower oocyte yields; thus, the authors concluded that MENA patients likely had a more rapid decline in ovarian function when compared to Caucasian patients. In a more recent study, Salem et al. [9] compared the outcomes of 190 MENA and 200 Caucasian patients undergoing their first IVF cycle. Like the study by Feichtinger et al. [8], the authors found that MENA patients were younger and had a higher prevalence of male factor infertility. Although ovarian response parameters were similar between the groups, including the number of mature oocytes, MENA patients had lower live birth rates per blastocyst transfer (OR 0.55, 95% CI 0.35–0.85) and higher odds of miscarriage (OR 2.55, 95% CI 1.04–6.27).

It is interesting to note that the results of our study are consistent with some findings reported by the above studies,

Table 2 Multiple linear regression to explore the association between Caucasian vs. Arab ethnicity and number of mature oocytes

Parameter	Coefficient	95% confidence intervals	<i>P</i>
Caucasian vs. Arab (referent)	2.5	2.1,3.9	< 0.001
Age (years)	− 0.5	− 0.7, 0.4	0.26
BMI (kg/m^2)	− 0.2	− 0.4,0.3	0.91
Cycle day-2/3 AMH (ng/mL)	0.1	− 0.2,0.6	0.84
Cycle day-2/3 AFC (number)	0.4	− 0.1,0.7	0.67
Total gonadotropins administered (IU)	0.1	− 0.1,0.5	0.54
E_2 at trigger (pg/mL)	0.2	− 0.4,0.8	0.57

BMI body mass index, AMH anti-müllerian hormone, AFC antral follicle count, E_2 estradiol

Table 3 Comparison of ICSI-ET cycle outcomes of the study cohort ($n = 763$)

Parameter	Arab ($n = 217$)	Caucasian ($n = 546$)	<i>P</i>
Fertilization rate (%)	52.9 (± 9.4)	53.8 (± 8.7)	0.21
Number of day-3 embryos transferred	1.67 (± 0.4)	1.61 (± 0.5)	0.12
Implantation rate per ET cycle (%)	42.9%	43.1%	0.98
Clinical pregnancy rate per ET cycle (%)	71/155 (45.8%)	262/491 (53.4%)	0.35
Live birth rate per ET cycle (%)	66/155 (42.6%)	226/491 (46.0%)	0.64
Supernumerary embryos cryopreserved	0.73 (± 0.4)	0.71 (± 0.3)	0.45

Data are presented as mean $\pm$ standard deviation or number (%)

ET embryo transfer

namely higher BMI, higher basal FSH levels, and lower oocyte yields in the Arabian Peninsula population. However, the biologic or environmental factors underpinning these trends remain poorly understood. Previous studies have consistently reported higher rates of male factor infertility in the Arab or MENA population [8, 9, 17], with smoking, consanguinity, and family clustering being identified as putative risk factors [18, 19]. Other studies have also reported that ethnic minorities may have a higher prevalence of women who are overweight and obese, which can be detrimental to oocyte yields and pregnancy rates [20]. Furthermore, genome-wide association studies have identified some candidate genes that may be associated with lower ovarian reserve parameters in certain ethnic groups [21].

A unique environmental factor that could influence ART outcomes in the Arabian Peninsula population is vitamin D deficiency [22]. Its prevalence is estimated to be $> 50\%$ in most of the Arabian Peninsula, with rates as high as 85–90% in Saudi Arabia [23, 24]. Scientific investigations in the mouse-model have suggested that the lack of vitamin D signaling impairs folliculogenesis [25]. In vitro studies of human cell-lines have also shown that vitamin D stimulates steroidogenesis in the ovary [26, 27]. Thus, the ethnic variations in ovarian reserve and ovarian response parameters, as in the case of women from the Arabian Peninsula, could be mediated

by differential levels of vitamin D [26]. In addition, previous studies have also suggested that lower vitamin D levels can impair IVF pregnancy rates [28, 29].

The major strength of the current study is the inclusion of a homogenous patient population from the mainland Arabian Peninsula undergoing ICSI-ET cycles during a 5-year duration at the same center. Previous studies have either omitted this patient population or pooled them in the MENA population. Furthermore, the inclusion of ICSI-ET cycles for only male factor infertility also eliminates the impact that other female-factor infertility diagnoses may have on ART outcomes [30, 31]. It is important to note that prior studies have suggested that ICSI cycles utilizing spermatozoa with severe defects or those from non-obstructed azoospermic men result in lower fertilization rates, with lower development to the blastocyst stage and lower blastocyst implantation rates [32, 33]. Our current study cohort consisted of couples undergoing ICSI for male factor infertility with ejaculated and surgically retrieved sperm samples. Thus, to mitigate the risk of lower blastocyst development or implantation, our center most often performs day-3 ET in such couples. Supernumerary blastocysts are subsequently cryopreserved.

Our study also has some limitations. First, the sample size of Arabian Peninsula cohort as well as the individual Arabian Peninsula nationalities was small, thereby limiting the

Table 4 Comparison of baseline demographics and ovarian stimulation parameters within the Arab cohort ($n = 217$)

Parameter	Qatar ($n = 35$)	U.A.E. ($n = 31$)	Kuwait ($n = 124$)	Saudi Arabia ($n = 27$)	<i>P</i>
Age (years)	31.9 (± 4.0)	32.4 (± 3.3)	31.2 (± 3.0)	31.9 (± 3.2)	0.40
BMI (kg/m^2)	28.9 (± 6.4)	30.2 (± 7.4)	29.1 (± 8.0)	26.3 (± 4.0)	0.22
Cycle day 2/3 FSH (mIU/mL)	6.3 (± 2.0)	5.6 (± 1.9)	5.5 (± 2.5)	6.6 (± 3.2)	0.14
Cycle day-2/3 AMH (ng/mL)	2.2 (± 2.2)	2.2 (± 1.3)	2.4 (± 1.8)	2.1 (± 1.4)	0.86
Cycle day-2/3 AFC (number)	13.7 (± 4.6)	12.3 (± 4.8)	13.9 (± 3.8)	14.3 (± 4.8)	0.25
Duration of ovarian stimulation (days)	9.5 (± 2.4)	10.0 (± 2.1)	8.9 (± 3.5)	9.7 (± 2.2)	0.35
Total gonadotropins administered (IU)	3027.1 (± 1544.6)	2787.5 (± 1348.2)	2838.8 (± 1016.2)	2753.9 (± 1727.7)	0.87
E_2 at trigger (pg/mL)	2000.2 (± 686.4)	1887.1 (± 1057.4)	2161.5 (± 919.3)	2164.6 (± 1042.8)	0.54
Mature oocytes retrieved (number)	14.8 (± 4.4)	12.3 (± 4.7)	13.5 (± 5.2)	12.9 (± 5.1)	0.02

Data are presented as mean $\pm$ standard deviation or median (IQR)

BMI body mass index, FSH follicle stimulating hormone, AMH anti-müllerian hormone, AFC antral follicle count, E_2 estradiol

generalizability of our results. Second, while a statistical difference in the ovarian reserve and oocyte yield of Arabian Peninsula women and Caucasian women was noted, the clinical significance of these results may seem limited, especially in the context of equivalent implantation, clinical pregnancy, and live birth rates between the two groups. However, we deem that these preliminary findings do merit further investigation in a larger prospective setting. Third, vitamin D deficiency was posited as a key factor for ICSI-ET outcomes in the Arabian Peninsula population. However, recent studies have shown no association between vitamin D levels and ovarian reserve, ovarian response, or pregnancy rates [34–36]. Finally, although BMI was controlled for in our study, it is possible for obesity to be an independent mediator of lower ovarian reserve, ovarian response, and pregnancy rates in ICSI-ET cycles [37–39].

In conclusion, the current study demonstrates that Arabian Peninsula ethnicity is associated with lower ovarian reserve and ovarian response parameters in women undergoing their first ICSI-ET cycle. In addition, the yield of mature oocytes was lower in Arabian Peninsula women when compared to Caucasians, even after accounting for confounders of interest. Despite these differences, the rates of implantation, clinical pregnancy, and live birth were similar between the two groups. While obesity and vitamin D deficiency may contribute to some of the observed differences, further large-scale studies are required to identify the biologic or environmental mechanisms central to ethnicity-based variations in ART outcomes.

Compliance with ethical standards

Our retrospective study was approved by the Institutional Review Board.

Conflict of interest The authors declare that they have no conflict of interest.

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