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Ethnical and sociocultural differences causing infertility are poorly understood—insights from the Arabian perspective

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Abstract
Infertility is acknowledged worldwide as a major health concern. Although global levels of primary and secondary infertility have hardly changed between 1990 and 2010, significant regional differences have been reported. The prevalence of infertility in women has been estimated to be one in every seven couples in the western world and one in every four couples in developing countries. Male infertility may be under-reported in some regions due to an unwillingness of the male partner to undergo fertility investigations. Geographical, sociocultural/religious and ethnical dissimilarities contribute to these global variations in infertility prevalence. Infertility has a major impact on family stability in many cultures, especially in developing countries, where childlessness can impact sociocultural status. Moreover, it is important to realise that most fertility treatment protocols are based on studies performed in Caucasian population. The purpose of this opinion paper is to critically appraise the existing evidence regarding the association between infertility and relevant sociocultural factors in Middle East countries focusing on aspects such as parental consanguinity, obesity and vitamin D deficiency. There may be reason to believe that in addition to the current standard evaluation of infertile couples, region-specific counselling and treatment modalities are required.

Keywords Infertility · Middle East · Consanguinity · Vitamin D deficiency · Obesity · Ethnical difference · Research

Opinion paper

Infertility affects approximately one in every four couples in developing countries and according to the WHO definition and data, infertility has been defined as a “disease” which generates disability and is ranked the fifth highest serious global disability (http://www.who.int/reproductivehealth/topics/infertility/definitions/en/). Due to the lack of a standardised worldwide reporting system, reported prevalence rates vary between many countries and the available information may not be reflective of the true incidence. Whereas infertility/subfertility occurs in all countries, the aetiologies of infertility may differ in different parts of the world.

Infertility takes a significant psychological toll on most affected couples, the extent of which depends not only on the social and cultural background of the couple but also on their geographical location. Access to reproductive units differs largely worldwide and infertility treatment may not be affordable particularly in the absence of insurance coverage [1], with both factors likely to exacerbate the already existing physical and emotional burden of infertility.

The MENA region (Middle East/North Africa) extents from Western Asia to Egypt, comprises 17 countries with multiple ethnicities (http://worldpopulationreview.com/continents/the-middle-east-population/) and has one of the highest infertility rates in the world [2]. Infertility may have a potentially adverse effect on the sexual and marital relationship of the affected couple which is not strictly population or culturally specific [3]. However, the Arabian culture is a pro-family society in which bearing children is considered essential for women. Therefore, women who do not conceive are susceptible to pressure exerted not only from their immediate family but from society in general. In this context, the diagnosis of infertility itself is stigmatising and the secrecy which surrounds infertility and the required treatment may lead to even greater pressure [4]. As divorce and

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polygamy are accepted resorts to infertility, women fear being divorced from their husbands or the possibility that their husbands will marry a second wife because of their inability to conceive [5]. Consequently, infertility has a significant negative impact on the quality of life of the affected women, especially in the case of women above 30 years of age and women in a polygamous marriage with a diagnosis of female factor infertility [5].

Despite the fact that the underlying aetiology of infertility can be attributed to either partner or may be multifactorial, in regions like Northern Africa or the Middle East, the female partner is often blamed for the couple inability to conceive. Exact numbers of infertile male in this region are unknown as male partners do not always agree to undergo fertility evaluation which subsequently may lead to under-reporting of male infertility in those regions. It is estimated in the Middle East region that the percentage of couples in which male factor is included as one of multiple factors attributed to the couples' difficulty to conceive is approximately 60–70% [6]. Interestingly, racial differences have been demonstrated in semen parameters of infertile men [7–9], and data from Qatar [10] revealed significantly lower semen quality parameters in infertile patients from the MENA region compared to non-MENA regions. In pro-natalist societies of the Middle East, an important part of manhood is the ability to father a child and therefore the inability to do so is generally considered to be a potentially emasculating condition [11]. This may lead to stigma of the affected male resulting in higher rates of depression compared to infertile males in Western countries [12].

Extensive research in all areas of reproductive medicine has resulted in significant advancements and improved treatment outcomes in ART (assisted reproductive techniques) [13]. Research suggests that both the underlying causes of female infertility and individual treatment prognosis differ by ethnicity [14]. Infertility causes in the Arab ethnicity are distinct from common "western" causes, not only due to social, cultural and religious peculiarities, but also to different genetic influences. Despite this knowledge, the impact of ethnical differences is not sufficiently addressed in research.

One of the key players in successful ART outcome is the number of oocytes retrieved for IVF/ICSI [15]. Recently published retrospective studies compared patients of MENA origin with Caucasian patients in terms of response to ovarian stimulation. Despite a younger age and a higher incidence of patients with polycystic ovarian syndrome (PCOS) which would normally be expected to favourably impact affect oocyte yield, a reduced ovarian reserve and a lower number of retrieved oocytes was identified in the MENA population [8, 16]. This finding highlights the significant influence of ethnicity on the stimulation outcome. The identified reduced ovarian reserve in this ethnical group despite being of younger age and a higher prevalence of PCOS may be related to sociocultural, environmental as well as to genetic factors.

Many Arab countries have high rates of consanguineous marriages, with reported rates in the Middle East of 20–50% generally but in certain regions rates as high as 80% are reported. The term "consanguinity" is derived from the two Latin words "con" (= common) and "sanguineus" (= blood) and refers to a relationship between two people who share a common ancestor or blood. Therefore, consanguine couples are biologically related individuals. Among Arabs, consanguine marriages include couples who are double first cousins, first cousins, first cousins once removed and second cousins. Sharing a common pool of genes not only increases the risk of homozygotes for autosomal recessive genetic disorders in the offspring [17] but also appears to have an adverse impact on ovarian reserve in the female descendants of consanguine couples. An observational study [18] in infertility patients in Kuwait demonstrated that consanguinity was strongly associated with a significant and sustained reduction in antral follicle count (AFC). The finding that daughters of first-degree cousins, who share 1/8 of their genes have a significantly higher risk of developing a low AFC compared to daughters of second-degree cousins, highlights a possible genetic influence via a homozygous expression of (as yet unidentified) recessive genes determining ovarian reserve [18].

Consanguinity also has a potentially adverse effect on male fertility leading to rare genetic sperm-defect syndromes which involve predominantly the sperm head or sperm tail [19, 20], and among men born into consanguineous families, male factor infertility is increased with a pattern of familial clustering [21].

Complementary to genetics, environmental components contribute to infertility and a clear division between these two factors may not be possible. One of these factors, involving environmental as well as genetic factors, is the highly controversial influence of vitamin D deficiency on ovarian reserve. Vitamin D deficiency is the most common vitamin deficiency worldwide with an estimated 1 billion people being vitamin D–deficient and deficiencies can be found in all ethnicities and age groups [22]. Exposure of the skin to sunlight is the most important source of vitamin D for humans. Vitamin D production following sun exposure is subject to factors such as age, skin colour, degree of exposed skin, length of time exposed to sunlight, geographical location, time of year, time of day, extent of cloud cover and the presence of smog, dust or haze. Different factors contribute to low sun exposure and low vitamin D levels in women of reproductive age residing in the MENA region [23].

Due to sociocultural and religious habits, women in the MENA region are expected to adhere to a strict dress-code which covers most of the skin [24]. The concealing dress code has been found to be an independent adverse prognostic factor of vitamin D deficiency in Lebanese women confirming the importance of sunlight exposure in vitamin D synthesis [25]. Differences observed in vitamin D deficiency rates between

Christian and Muslim women in the Middle East highlight the adverse effect of a concealing dress code on vitamin D synthesis [26].

Whereas in Europe, the number of sunshine hours vary between 1.400/year (UK) to more than 2.800/year (Spain, Portugal), most countries of the Middle East have approximately 2.500 to 3.500 h of sunshine per year (https://en.wikipedia.org/wiki/List_of_cities_by_sunshine_duration). Despite this sunshine climate, the highest prevalence of vitamin D deficiency in the world are found in the MENA region, ranging from 67% in Iran, 55–83% in Jordan, 84% in Lebanon and up to 90% in Saudi Arabia [27].

Several recent studies evaluated the influence of vitamin D on ovarian reserve with conflicting results. The studies of Fabris et al. [28], Drakopoulos et al. [29] and Shapiro et al. [30] did not find a correlation between vitamin D deficiency and ovarian reserve. In those studies, Caucasians represented either 95% [28] or the "vast majority" [29] of the study population and the study of Shapiro et al. [30] did not state the race and ethnicity of the included patients. However, it can be assumed that most patients in those studies were not expected to be subjected to concealing dress due to their sociocultural backgrounds. In contrast to these study findings, the study of Arefi et al. [31] was conducted in a society in which women wear concealing clothing and this dress-code is imposed from an early age. In this study, women diagnosed as severely vitamin D–deficient demonstrated a clear correlation between vitamin D deficiency and a reduced ovarian reserve. This data indicates that severe and prolonged vitamin D deficiency caused by inadequate sun-exposure to the skin could be a cause for or at the very least contributing to a reduced ovarian reserve. The discrepancy in the findings of the above-mentioned studies also highlights the fact that data from one ethnicity cannot be applied without caution to other ethnicities. Whereas in western societies, the influence of vitamin D levels on ART outcomes has been demonstrated by two studies [32, 33], surprisingly, no comparable data for the Middle East population has been published to date.

In recent years, life style and work environments have changed dramatically in the Middle East due to a pronounced increase in wealth. In addition, a more sedentary life style has been adopted and a change of eating habits has been noted due to the increased availability of fast food, resulting in a dramatic increase in obesity rates in these countries [34]. Obesity is a health issue worldwide and the MENA region has one of the highest prevalences of obesity with reported ranges according to BMI (Body-Mass-Index) calculations, varying from 74 to 86% in women and 69 to 77% in men (http://www.emro.who.int/health-topics/obesity/). BMI calculation provides a quick estimate of adiposity and is now universally considered to be a marker of wellness and disease risk. The current WHO (World Health Organisation) guidelines for the definition of overweight and obesity are based on European ancestry populations [35]; however, ethnical differences in body composition might systemically bias BMI as an indicator of excess adiposity across populations [36]. Therefore, the number of women in the MENA region classified as overweight/obese may not be correct and may even underestimate the extent of existing obesity. Obesity has a broadly described adverse effect on the female reproductive system [37], the extent of which depends not only on BMI but also on ethnicity [38]. In males, obesity leads to hypogonadotropic, hyperestrogenic hypogonadism and has been linked to altered semen parameters and increased sperm DNA damage. As a consequence of the specific body habitus in overweight/obese males and the association of obesity with inactivity, testicular temperature is increased and may lead to impaired spermatogenesis [39]. Resorts to reduce obesity include weight loss, physical activity, diet and bariatric surgery and existing data points towards the fact that weight reduction may improve fertility [40]. Further investigation is required to determine if the anticipated beneficial effect of weight loss may differ according to the ethnical background of the patient.

Obesity and polycystic ovarian syndrome (PCOS) are closely associated [41]. Despite extensive research, the aetiology of PCOS remains unclear. Familial aggregation of PCOS and twin studies suggest that genetic factors play an important role in the pathogenesis [42]. The role of genetic factors as a contributory cause of PCOS is reinforced by consanguinity. A study in a Pakistani population, in which consanguine marriages are common, confirmed the role of intra-family marriages in the increased incidence of PCOS and inheritance of insulin-resistance [43]. Despite the fact that Pakistani and Arab populations are distinct, it can be assumed that the genetic influence on the prevalence of PCOS in the Arab population is aggravated by consanguinity and therefore plays an important factor in infertility in this population.

The prevalence of PCOS worldwide is reported in several studies as being 3 to 10% [44, 45]. However, the prevalence of PCOS varies according to the definition used, with approximately 6% according to NIH (National Institute of Health) and 10% according to the Rotterdam criteria and the Androgen excess society guidelines [46]. Due to the variability of the symptoms or the lack of knowledge of the health care provider, these numbers may be an underestimate, not representative of the true incidence of women affected by PCOS worldwide. Recently published meta-analyses [46, 47] studying the geographical prevalence of PCOS as determined by race and ethnicity regrettably did not include any data pertaining to the Arab ethnicity. A recently published study in an unselected Qatari population demonstrated a prevalence of PCOS in this population of 12.1%, using the NIH guidelines and this may translate into 20% using either the Rotterdam or Androgen Excess Society criteria, which is distinctly higher compared to other females from other continents and ethnicities.

Conclusion

Infertility in both genders is often multi-factorial. Genetic and environmental factors contribute to infertility to different extents and both factors may differ based on ethnicity and sociocultural background. Unfortunately, until now, ethnic peculiarities are not sufficiently represented or recognised in research.

According to current data, consanguinity has a negative impact on both male and female infertility by reducing ovarian reserve in females and leading to an impairment of the semen parameters in males. Further research is required to determine the possible underlying pathophysiological and genetic mechanism causing this adverse effect on the fertility status of both genders. Despite a climate of abundant sunshine, vitamin D deficiency is endemic in the Middle East countries and contrary to the findings in Caucasian population, vitamin D deficiency due to a lack of sun exposure to the skin might impact ovarian reserve negatively. Reproduction is negatively influenced by obesity and the Middle East has one of the highest prevalence rates of obesity in the world. Future research will have to clarify whether the strategies employed for weight loss in Caucasian population will have the same benefits in other populations and ethnicities.

The differences identified in studies between different ethnicities highlight the importance of interpreting studies carefully and not routinely transferring a study's findings in one ethnicity to another ethnicity without due caution. As a consequence of this knowledge, future research should investigate ethnical differences in more detail.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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