Journal of Reproductive Immunology 141 (2020) 103173

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

Review article

# Potential causes of male and female infertility in Qatar

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ARTICLE INFO

*Keywords:*
Infertility
Qatar
Consanguinity
Assisted reproductive techniques
Diabetes
Obesity
Smoking
Environmental factors

ABSTRACT

A steady decline in the fertility rate has been observed in Qatar during the past fifty years. Therefore, infertility is considered a national priority in Qatar, a pronatalist society. This review article summarises the potential causes of infertility that are

particularly prevalent in the Qatari population. The high rate of consanguinity leading to genetic abnormalities, the high incidence of metabolic disease, environmental contamination due to the rapid urbanization and oil and natural gas extraction procedures are discussed. In addition, the particular lifestyle of the Qatari population and the influence of religion and culture on sexual and reproductive behavior in an Arab/Islamic society are considered. The active response of the state of Qatar in implementing ways to mitigate the effects of these factors to protect fertility are also presented.

## 1. Introduction

Infertility, is defined as the inability to conceive after a year or more of trying, resulting in involuntary childlessness. Estimating global infertility prevalence rates is difficult due to the presence of both male and female factors. In addition, most estimates only address the woman and an outcome of a pregnancy diagnosis or live birth. A steady decline in the fertility rate, expressed as the number of children born per women, has been observed in Qatar during the past 55 years (Anon, 2020a, Fig. 1).

While the decline in fertility rates in Qatar can be partially explained by the higher educational attainment of Qatari women and increased labor force participation (Anon, 2020b), preference of career to marriage and childbearing, and the reluctance of young people from early marriage, a recent report showed that 16 percent of couples in Qatar are infertile (Anon, 2020c). Therefore, infertility is considered a national priority in Qatar, a pronatalist society.

No information is available in reference to the incidence of female infertility rate in Qatar. Regarding male infertility, it has been reported that the incidence of primary infertility in Qatar is approximately 30 % (Anon, 2020d; Al-Ansari et al., 2009; Bener et al., 2009; Arafa et al., 2017a). Interestingly, 35 % of infertile men in Qatar were affected by type 2 diabetes (T2DM) (Bener et al., 2009). Infertility was more frequently observed in men between 31 and 40 years old (Al-Ansari et al., 2009). In 22 % of males the cause of infertility was not determined (idiopathic infertility) (8). In this line, around 7000 male patients seek medical help at the infertility unit at the Hamad Medical Corporation's Urology Department in Doha every year (Anon, 2020e). Male infertility might be particularly problematic for men in an Arabic Islamic society like Qatar where virility and fertility are directly associated with manhood. Male infertility in Qatar and other Islamic countries could be seen as an emasculating condition surrounded by secrecy and stigma (Inhorn, 2004). Therefore, the incidence of male infertility might be underestimated. In addition, a considerable number of couples might seek medical treatment abroad.

In this review article, we will discuss the specific and characteristic infertility risk factors in the Qatari population that can contribute to the high number of couples undergoing artificial reproductive techniques (ART).

## 2. Consanguinity – genetic disorders

In many Middle Eastern countries such as Qatar, consanguineous marriages are culturally favored with longstanding traditions (Ben-Omran et al., 2020). The rate of consanguinity in Qatar is approximately 54 %, which are mainly first cousins' marriages (Ben-Omran et al., 2020; Bener and Hussain, 2006; Bener et al., 2019). Previous studies showed that consanguinity increases the prevalence of birth defects and other genetic disorders. Genetic abnormalities were identified as causes of infertility in 5–10 % of men in Qatar (Bener et al., 2009; Arafa et al., 2017a). Whole exome sequencing (WES) was used to identify several disease-causing genes in consanguineous families in Qatar (Fahiminiya et al., 2014). Multiple mutations in the cystathionine beta-synthase (CBS) and methylene tetra hydrofolate reductase

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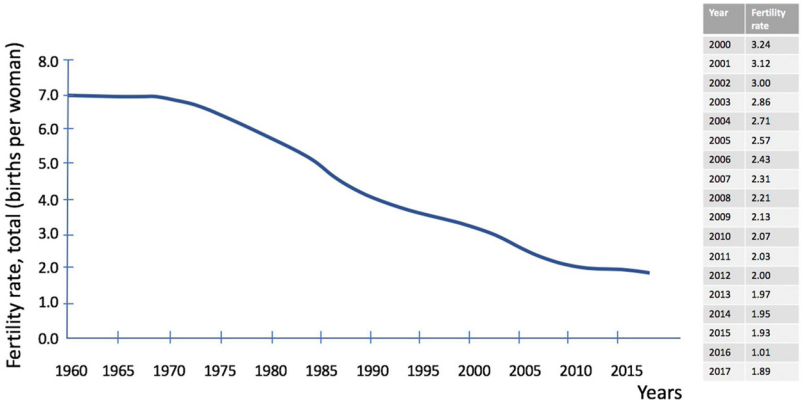
https://doi.org/10.1016/j.jri.2020.103173
Received 17 May 2020; Received in revised form 14 June 2020; Accepted 22 June 2020
Available online 28 June 2020




| Year | Fertility rate |
|---|---|
| 2000 | 3.24 |
| 2001 | 3.12 |
| 2002 | 3.00 |
| 2003 | 2.86 |
| 2004 | 2.71 |
| 2005 | 2.57 |
| 2006 | 2.43 |
| 2007 | 2.31 |
| 2008 | 2.21 |
| 2009 | 2.13 |
| 2010 | 2.07 |
| 2011 | 2.03 |
| 2012 | 2.00 |
| 2013 | 1.97 |
| 2014 | 1.95 |
| 2015 | 1.93 |
| 2016 | 1.01 |
| 2017 | 1.89 |

**Fig. 1.** Remarkable decline in fertility rate in Qatar. Modified from https://www.indexmundi.com/facts/qatar/indicator/SP.DYN.TFRT.IN.

(MTHFR) gene have been documented in Qatar, resulting in an exceptionally high prevalence of hyperhomocysteinemia (HHcys) (Al-Sadeq and Nasrallah, 2020). HHcys concentrations are involved not only in cardiovascular disease but also in pathophysiological processes in reproductive health in men and women. A relationship between HHcys and gonadal abnormalities, such as altered spermatogenesis and impaired ovarian reserve, has been documented (Forges et al., 2007). HHcys is a risk factor for endothelial dysfunction. Considering that the penis is a richly vascularized organ, erectile dysfunction (ED) can be classified predominately as a vascular disease. Therefore, it has been suggested that HHcys can increase the risk of vasculogenic ED (Lee et al., 2014). In this line, ED is observed in one in six infertile men (Lotti and Maggi, 2018). Furthermore, a dose-dependent association between HHcys and ED has been demonstrated (Giovannone et al., 2015). Provocatively, HHcys also has deleterious effects on female reproductive function, increasing the risk for early miscarriages and congenital birth defects (Guzmán et al., 2006).

Thalassemias, inherited disorders of hemoglobin synthesis, are common diseases in Mediterranean and Middle East countries, including Qatar (Nashwan, 2018). β-thalassaemia is associated with common reproductive health disorders such as hypo-gonadotrophic hypogonadism, infertility, delayed or absent sexual development, and pregnancy complications (preeclampsia and placenta previa). Iron overload and ineffective erythropoiesis can play a role in the impaired reproductive health observed in women with β-thalassaemia (Nourollahpour et al., 2020).

Consanguinity in Qatar is also associated with a higher risk for diseases such as diabetes mellitus, heart diseases, asthma and hypertension (Bener and Hussain, 2006). An association between infertility and these diseases has also been reported and will be discussed later.

A significant correlation between consanguineous recurrent pregnancy loss and chromosomal abnormalities have been reported; around 5 % of recurrent miscarriages are caused by chromosomal abnormality (Franssen et al., 2006; Christiansen et al., 2008; Warburton and Strobino, 1987; Gillerot et al., 1988; Stern et al., 1999; Nicol et al., 2000). Abnormal chromosomal numbers, structure and allelic polymorphisms of some pro-thrombophilic genes (Factor V Leiden and Prothrombin) have been reported among the causes of recurrent miscarriages (Franssen et al., 2006; Christiansen et al., 2008).

Beyond chromosomal changes, single genes mutations may also affect early pregnancy development leading to spontaneous abortion (Lockwood, 2002; Turki et al., 2016). Fareed et al. assessed almost a thousand families in the Muslim population in India to investigate the deleterious effects of consanguinity on reproduction and found an association between increased numbers of miscarriages and infant mortality rate and a high degree of inbreeding (Fareed et al., 2017).

In females, several gene mutations have been associated with infertility. Seven different mutations in the primate gene *TUBB8* were shown to cause oocytes meiosis arrest with a serious impact on fertility (Feng et al., 2016). Another gene mutation associated with infertility is the one in the *ZP1* gene, which causes the lack of the ZP1 glycoprotein expression distorting the formation of the zona pellucida around the oocyte (Huang et al., 2014; Nishimura et al., 2019). Mutations in *STAG3* that encodes a meiosis-specific protein were associated with particular premature ovarian failure leading to women infertility (Caburet et al., 2014). Sharing a common pool of genes also has a negative impact on ovarian reserve in the female descendants of consanguine couples (Vander Borght and Wynsa, 2018; Bosdou et al., 2016). Leukemia inhibitory factor (LIF) plays a critical role in embryo development and implantation, hence LIF gene polymorphisms has been associated with female infertility (Olubunmi et al., 2019). In this line, patients with unexplained infertility have been shown to have lower endometrial LIF concentrations (Aghajanova, 2004; Kralickova et al., 2006). Therefore, inbreeding in the Qatari society can contribute to the propagation of these mutations leading to impaired female fertility.

Consanguinity can also affect male fertility. Male factor infertility is increased in consanguineous families with a pattern of familial clustering (Lawrenz et al., 2019). STAG3 has been shown to be a strong candidate gene for male infertility as well (van der Bijl et al., 2019).

Interestingly, some studies found a positive association between consanguinity and fertility. Increased fertility rate, number of pregnancies and livebirths were found in consanguinity marriages compared to outbred marriages (Fuster, 2003; Helgason et al., 2008; Weller and Santos, 2013).

Varicocele is the pathological dilation of the pampiniform plexus of veins of the spermatic cord. Increased oxidative stress is directly related to varicocele, adversely affecting sperm structure and function and reducing overall sperm quality leading to impaired fertility. Varicocele is much more frequent in consanguineous patients. The global incidence of varicocele is about 35 %–50 % in men with primary infertility. In this line, Al-Ansari et al. reported that varicocele was the most common cause of infertility found in almost 30 % of infertile men in Qatar (Al-Ansari et al., 2009). In a retrospective study, Elbardisi et al reported that varicocele was clinically diagnosed in 43 % of the men attending the male Infertility Unit of Hamad Medical Corporation in Doha but no differences were found between Qatari and non Qatari patients (ElBardisi et al., 2017).

Within the genetic abnormalities identified as causes of male infertility in Qatar, Klinefelter syndrome (KS) was the most frequent one (Arafa et al., 2017a; Yones et al., 2009). KS, also known as 47, XXY, is the set of symptoms that results from the presence of two or more X chromosomes in males. The primary features of KS are testicular dysfunction, abnormal spermatogenesis, and hypergonadotrophic hypogonadism resulting in infertility. KS is a well established cause of

azoospermia (Selice et al., 2010).

The pathogenesis of non-obstructive azoospermia (NOA), caused by meiotic arrest, is also associated with genetic factors (Ghieh et al., 2019). Five candidate genes for NOA, TEX14, SPO11, NANOS2, WNK3 and CCDC155, were identified by WES in a study performed in eight multiplexed families from the Middle East (Fakhro et al., 2019).

Arafa et al. performed a retrospective study to evaluate the incidence of chromosomal abnormalities in infertile men with azoospermia and severe oligozoospermia in Qatar (Arafa et al., 2017b). The chromosomal abnormalities rate was 10.6 % in Qatari and 9.0 % in non Qatari men. In the intracytoplasmic sperm injection (ICSI) procedure, men with chromosomal abnormalities had a significantly lower total sperm retrieval rate, surgical sperm retrieval, and lower clinical pregnancy rate when compared to the idiopathic infertility group (Arafa et al., 2017b).

The above information suggests that the high rate of consanguinity in the Qatari population contributing to genetic abnormalities could be an additional risk factor for male and female infertility as well as for recurrent early pregnancy failure. Given the high rate of consanguineous marriages in Qatar, systematic cytogenetic investigation and genetic counseling should be performed at premarital stage or during early pregnancy phase through preimplantation genetic diagnosis.

## 3. Vitamin D deficiency

Vitamin D insufficiency affects almost 50 % of the population worldwide. In this line, a very high prevalence of vitamin D insufficiency/deficiency has been found in Qatar (Badawi et al., 2012). Hypovitaminosis D can be attributed to many factors within the Qatari and Gulf region population. While diet is an important source of vitamin D, exposure to sunlight is the limiting factor. Environmental factors such as pollution, observed in Qatar due to the highly industrialization and rapid urbanization, can reduce exposure to sunlight, required for ultraviolet-B (UVB)-induced vitamin D production in the epidermis. Socio-cultural factors play a crucial role in the development of hypovitaminosis D in Qatar. In order to maintain a fair complexion, women in particular avoid sun exposure. In addition, the particular dressing code in Qatar contribute to limiting the direct contact of the skin with sunlight. Clothing laws in Qatar forbid wearing clothes considered revealing or indecent and favor the use of thawbs, or thobes, over loose pants by men and abayas, long black robes by women. In addition, men and women wear a headdress, ghutra and hijab respectively. Even more, some Qatari women wear a burqa to cover up their faces. These traditional garments significantly reduce exposure of the skin to sunlight. In addition, a particular lifestyle with reduced outdoor activities is prevalent in the Qatari population. Genetic factors, favored by consanguineous marriage, and skin pigmentation might also account for the diminished vitamin D synthesis in Qatari people. The high prevalence of obesity and diabetes observed in Qatar and other Gulf areas might also be associated with vitamin D deficiency (Haj Bakri, 2013a). Excessive adipose tissue has been associated with a diminished release of endogenously synthesized vitamin D into the circulation (Danield et al., 2015). Vitamin D deficiency is common in Qatari young population and very prevalent in people suffering from diabetes. In addition, it has been suggested that vitamin D supplementation might be an effective strategy to reduce the risk of diabetes (Kwiecinksi et al., 1989).

Studies in laboratory animals have shown a reduced mating success in vitamin D deficient females. Vitamin D-deficient diet was associated with a reduction of up to 70 % in the ability to conceive and a significant reduction in the number of viable pups in rats. Provocatively, fertility was restored with 125-Dihydroxyvitamin D3 supplementation (Chambon, 1951). It has been demonstrated that vitamin D acts synergistically with progesterone in ovum implantation (Rojansky et al., 1992). While a calcium dependent mechanism might account for this, direct effects of vitamin D on the ovaries and the hypothalamic–pituitary axis, including brain neurotransmitters such as serotonin and dopamine have also been described.

Interestingly, significant correlations between fertility, seasonal changes and geographical locations have been observed. It is tempting to speculate that this is caused by changes in vitamin D-levels dependent on exposure to UV light (Chu et al., 2018).

In this line, a recent systematic review highlighted the association between vitamin D levels and fertility. A significant correlation was found between serum vitamin D levels and live birth rates in women undergoing ART (Kwiecinski et al., 1989). Therefore, vitamin D supplementation could be a potential therapeutic tool in women with compromised fertility considering ART.

The male reproductive tract is also affected by vitamin D. It is established that vitamin D receptor activating and inactivating enzymes are expressed in the human testis, epididymis, seminal vesicle, prostate and spermatozoa (Alzoubi et al., 2017). Abnormal spermatogenesis, oligoasthenospermia and infertility have been found in vitamin D insufficient males (Kinuta et al., 2000; Breitbart, 2002).

A role of vitamin D in conception, implantation and placental development has also been described. In this line, vitamin D receptor (VDR) and vitamin D activating enzymes can be found in decidua and placenta early in pregnancy (Panda et al., 2001; Aghajafari et al., 2013). Vitamin D binding to VDR upregulates crucial genes for endometrial development, uterine receptivity and implantation such as *HoxA10* (Akbari et al., 2018). Vitamin D may also favor implantation and placentation indirectly via its immunomodulatory actions. Vitamin D is an important factor in preventing maternal immune responses to the paternal genes-carrying embryo that could result in poor implantation and embryo demise (Tamblyn et al., 2015). It has been shown that vitamin D synthesis in the decidua modulates inflammatory cells such as uterine natural killer cells, macrophages, dendritic cells and T cells leading to immune tolerance and protected pregnancies (Cyprian et al., 2019).

## 4. Polycystic Ovarian syndrome (PCOS)

PCOS is the primary cause of hyperandrogenism and oligo-anovulation leading to infertility (Azziz et al., 2004). This endocrine and reproductive disorder has a prevalence of 10 % in women of reproductive age worldwide. A recent study showed that the prevalence of PCOS in Qatar is 18.3 % (Wang and Alvero, 2013). In agreement with this, among the 100 women that visit the Infertility and Gynecology Clinic at Hamad Hospital in Qatar weekly, 50 percent are diagnosed with PCOS (Sharif et al., 2017). A recent study confirmed the high incidence of PCOS in women of reproductive age in Qatar (Anon, 2020f). In a study performed at Qatar Biobank (QBB), PCOS was found in 20 % of the women (Anon, 2020f). It has been reported that 60 % of PCOS women have insulin resistance, up to 40 % have impaired glucose tolerance and 10 % may develop type 2 diabetes (Dargham et al., 2017; Bozdag et al., 2016). In addition, obesity is frequently seen in women with PCOS (Dumesic et al., 2016; Kahal et al., 2013). Therefore, the deleterious effects of diabetes and obesity on women's reproductive function can also contribute to PCOS-associated impaired fertility.

## 5. Hypothyroidism

While the incidence and prevalence of hypothyroidism in Qatar is not known, a systematic review of thyroid disorders in the Arab world in 2016 reported a high prevalence of hypothyroidism ranging from 6.18 %–47.34 % (Al Shahrani et al., 2016). Hypothyroidism in the Gulf area is certainly more prevalent compared to the United Kingdom where 1.9 % of women and 0.1 % of men develop this condition (Tunbridge et al., 1977). In this line, the Thyroid Unit at Hamad General Hospital reported a growing number of patients with thyroid disorders. Thyroid nodules are seen in around 70 percent of male and

female patients with thyroid abnormalities attending this unit (Anon, 2020g).

Normal thyroid function is required for fertility, pregnancy and maintenance of pregnancy. Hypothyroidism can affect fertility in many ways. If undiagnosed or untreated it can lead to anovulatory cycles, luteal phase defect, high prolactin levels, and sex hormone imbalances. Therefore, it is recommended that thyroid evaluation is performed in any woman who is planning a pregnancy with family history of thyroid problem, irregular menstrual cycle, difficulty to conceive and/or miscarriages. In addition, the presence of thyroid antibodies doubles the risk of recurrent miscarriages (Poppe et al., 2008; Poppe and Velkeniers, 2003).

In males, thyroid hormone plays an important role in testicular development and function. Hypothyroidism decreases steroidogenesis and by decreasing sex hormone-binding globulin concentrations and serum testosterone level, it may impair spermatogenesis. Triiodothyronine (T3) modulates Sertoli cells proliferation and functional maturation as well as postnatal Leydig cells differentiation, highlighting the role of thyroid hormones as essential regulators of male reproductive functions. In addition, nuclear thyroid hormone receptors are expressed in fetal and adult Sertoli cells, suggesting genomics effects of thyroid hormones play vital roles in male gonadal development (Wagner et al., 2008). Thyroid insufficiency for a long period in childhood or puberty may also induce erectile dysfunction, delayed ejaculation, lower libido and semen quality deterioration. During T3 deficiency, decreased diameter of seminiferous tubules and net weight of testicles, epididymis and prostate gland have been observed leading to impaired sperm development, sperm motility, and their transport through the epididymis (Alahmar et al., 2019).

Hypothyroidism has been associated with testicular oxidative stress affecting sperm vitality and increasing the incidence of teratozoospermia. In this line, the measurement of thyroid hormones is recommended in patients with sperm abnormalities and erectile dysfunction (Nikoobakht et al., 2012).

## 6. Sexually transmitted diseases & microbiota

More than 1 million sexually transmitted infections (STIs) are acquired every day worldwide (Anon, 2020h). While most STDs affect both men and women, the associated health problems, in particular fertility problems, can be more frequently seen in women.

Several STDs, including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, have been widely associated with infertility (Tsevat et al., 2016). Additionally, other pathogens such as *Mycoplasma genitalium* and *Trichomonas vaginalis,* may also contribute to infertility (Tsevat et al., 2016). Tubal factor infertility (TFI) is one of the most common causes of infertility. Most cases of TFI are due to salpingitis, an inflammation of the fallopian tubes, and subsequent development of pelvic-peritoneal adhesions, mostly caused by previous or persistent infections.

Epidemiological data related to STDs remain scarce in the Arabian Gulf area due to its limited research capacity and sociocultural sensitivity around STDs. However, among the few studies in the region, Al Thani et al. showed a prevalence of *Chlamydia trachomatis* infection among general population women in Doha, Qatar higher than expected (Al-Thani et al., 2013). In this study, the prevalence of *C trachomatis* infection in Pap smears was 5.3 % among Qatari women and 5.5 % among non-Qatari women, with no statistically significant difference between both groups (Al-Thani et al., 2013).

In addition, certain vaginal/endometrial microbiomes has been associated with infertility (Moreno and Simon, 2018). The role of endometrial microbiota at the embryo-maternal interface during implantation is of crucial value to reproductive medicine (Hyman et al., 2012). Infection-associated inflammation and immune response are well known risk factors for infertility with deleterious effects on embryo adhesion and implantation. It has been demonstrated that certain uterine flora such as *E coli* and *Klebsiella* are associated with poor IVF outcomes (Franasiak et al., 2016). On the other hand, increased implantation and pregnancy rates are observed in association with microbiomes rich in *Lactobacillus spp* (Franasiak et al., 2016). The roles of different STD pathogens, co-infections including their individual vaginal/uterine microbiome, may all affect a woman's subsequent ability to conceive.

STDs might also impact male fertility. A recent study showed that the most abundant species of bacteria in semen of infertile men in Iran were *Chlamydia trachomatis* (12.5 %) followed by *Neisseria gonorrhoeae* (11 %) (Ahmadi et al., 2015). The presence of *N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium, Haemophilus,* and *Klebsiella* was significantly associated with sperm abnormality and decreased fertility (Ahmadi et al., 2015).

## 7. Diabetes

Type 2 diabetes (T2DM) is becoming more and more prevalent worldwide. Following this increasing global trend, Qatar has a significantly high incidence of diabetes. Around 17 % of the adult population in Qatar suffers from T2DM (Anon, 2020i). A novel mathematical modelling approach showed that T2DM prevalence in Qatar will increase to at least 24.0 % by 2050 (Awad et al., 2018). In addition, type 1 diabetes (T1DM) is also observed in a high proportion of the Qatari population. A recent study showed a relatively higher incidence of T1DM in Qatar compared to the rest of the world (Alyafei et al., 2018). Even more, the incidence rate increased significantly compared to previous periods (Alyafei et al., 2018). As previously discussed, the higher incidence of T1DM and T2DM can be caused by consanguinity (Sandridge et al., 2010). T1DM and T2DM cause long-term injury, dysfunction, and failure of various organs including those in the male and female reproductive tract and have been associated with infertility. T1DM affects female fertility, even before is diagnosed. Hyperglycemia and insulin deficiency can result in decreased fertility by inducing hypogonadism and hyperandrogenism (Lin et al., 2018). Numerous cohort studies have shown that women with type 1 DM have fewer offspring (Jonasson et al., 2007; Sjöberg et al., 2013).

Although the association between infertility and T1DM and T2DM in males is well known, the mechanisms by which diabetes causes infertility are not completely understood. Pathogenic mechanisms at the pre-testicular, testicular, and post-testicular level have been proposed. Abnormal sperm parameters have been reported in T1DM and T2DM patients. An inflammatory response leading to increased oxidative stress resulting in diminished sperm vitality and increased sperm DNA fragmentation has been demonstrated in T2DM. In T1DM, epididymal changes causing a diminished ejaculate volume and mitochondrial injury resulting in asthenospermia have been observed (Condorelli et al., 2018). Glucose metabolism is not only a crucial event during spermatogenesis but is also necessary for sperm cells motility after epididymal maturation. In addition, glucose is needed for fertilization ability in mature sperm.

Epigenetic changes such as DNA methylation, histone modifications, remodeling of nucleosomes and chromatin reorganization are crucial events during spermatogenesis. If epigenetic modifications occur during embryonic gonadal development, and germline differentiation, they may become permanent in the germ line epigenome and impact subsequent generations through epigenetic transgenerational inheritance including an increased risk of diabetes and associated infertility in the offspring (Ding et al., 2015). Aberrant epigenetic changes induced by hyperglycemia/diabetes during spermatogenesis could result in abnormal sperm account and motility leading to infertility (Capra et al., 2019). In addition, advanced glycosylated end products (AGE) through interaction with their receptors in the testis activate mitogen-activated protein kinase signaling resulting in altered sperm function and contributing to male infertility in diabetic rats (Omolaoye and Du Plessis, 2020).

Considering the high incidence of diabetes among women and men in Qatar, and the deleterious effects of diabetes on fertility, it is tempting to speculate that diabetes might play a crucial role in the impaired fertility observed in Qatari couples. Prevention of diabetes could certainly prevent fertility decline in men and women.

## 8. Cardiovascular disease – hypertension

Cardiovascular disease (CVD), is very common in Qatar. In this line, ischemic heart disease, characterized by endothelial dysfunction, is the leading cause of death in Qatar (Anon, 2020j).

Erectile dysfunction (ED) is predominately a vascular disease (Capogrosso et al., 2013). Therefore, cardiovascular conditions that compromise the endothelial function might have an impact on erectile function. In this line, risk factors for CVD, including hypercholesterolemia, hypertension, diabetes mellitus (DM), and smoking are also harmful to erectile function (Kendirci et al., 2005). In addition, treatments used for these conditions are known to constitute major causes of ED (Anon, 2020k).

Several epidemiologic studies have shown a high incidence and prevalence of ED worldwide, affecting up to 150 million men (Shaeer and Shaeer, 2011; Landripet and Štulhofer, 2015). In 2014, a study was conducted to investigate the prevalence of ED in Qatar and to determine the risk factors associated with it (Al Naimi et al., 2014). This study showed a ED prevalence rate of 54.5 % in Qatar, comparable to other studies in the MENA region (Shaeer et al., 2003; Berrada et al., 2003). Among the main risk factors associated with ED, hypertension, diabetes mellitus and coronary artery disease were the most prevalent.

Nowadays, 1.2 billion men are hypertensive worldwide, and several studies showed an association between hypertension and infertility. A study by Guo et al. showed a direct correlation between hypertension and impaired semen quality. Men diagnosed with hypertension have a lower semen volume, sperm motility and total sperm count compared to non-hypertensive men (Guo et al., 2017).

Animal studies also demonstrated an association between hypertension and abnormal sperm quality. Studies in rats showed that high blood pressure affects sperm quality and functional characteristics (Colli et al., 2019). Among these effects, DNA fragmentation, changes in acrosome integrity, changes in mitochondrial activity and increased reactive oxygen species production were observed in sperm in hypertensive rats (Colli et al., 2019).

In addition to the extensively described effects of elevated blood pressure on cardiovascular health, preconceptional hypertension can also affect reproductive health in women (Nobles et al., 2018). Inflammation, oxidative stress and endothelial dysfunction, pathways involved in hypertension, may also affect ovulation, implantation, and vascularization of the placenta leading to adverse reproductive outcomes (Parikh et al., 2012).

Studies in mice showed an inverse relationship between hypertension and fertility (Kennedy et al., 1999). Lipid mediators such as prostaglandins (PGs) have numerous physiologic activities, including modulation of inflammation, ovulation and arterial blood pressure. Mice deficient in PGs receptor EP2 have reduced litters and showed hypertension that became more severe with high salt diet (Kennedy et al., 1999). Smaller litters in EP2 deficient mice were caused by preimplantation defects, impaired ovulation and reduced fertilization (Kennedy et al., 1999). Chronic hypertension has also been associated with pregnancy complications such as miscarriages, preeclampsia, stillbirth, small for gestational age and preterm birth (Panaitescu et al., 2017). Provocatively, increased incidence of cardiovascular diseases have been reported after pregnancy in women that were normotensive prior to pregnancy but developed hypertensive disorders while pregnant (Bellamy et al., 2007).

## 9. Asthma

A high prevalence rate (19.8 %) of asthma is observed in the Qatari population (Janahi et al., 2006). A link between asthma and infertility has been reported in women. In males, this link has not been explored. Considering that both infertility and asthma might be caused by an overreactive immune system, it is not surprising that women with asthma experience difficulties to conceive and have higher incidence of miscarriages (Turkeltaub et al., 2019; Wasilewska and Małgorzewicz, 2019). Interestingly, a retrospective study showed a high prevalence of asthma among women undergoing IVF, compared to the general population (Esfandiari et al., 2020).

T cells, members of the adaptive immunity, are responsible for the tolerance required during implantation and pregnancy to prevent the rejection of the embryo and placenta that contains allogeneic paternal genes. Allergies and reproductive failure share a common immune mechanism, characterized by an excessive T cell Th2 response.

Interestingly, common medications for asthma might also affect fertility, delaying conception (Grzeskowiak et al., 2018). In an Australian cohort, reduced fertility was associated with asthma but the biggest association was observed in women receiving short-acting β-agonists (Grzeskowiak et al., 2018).

Asthma and infertility can also have a common mediator or trigger, air pollution. This will be discussed later.

## 10. Factors associated with lifestyle

Evidence have shown a significant impact of potentially modifiable lifestyle factors on reproductive performance. Lifestyle factors including psychological stress, smoking, exposure to environmental pollutants, sports, weight and caffeine and alcohol consumption might impact fertility. In this line, it has been suggested that lifestyle modification can assist couples to conceive spontaneously or increase conception chances with assisted reproductive technology (Sharma et al., 2013).

### *10.1. Stress*

The family unit is considered as the cornerstone for the health and equilibrium in the Muslim society and as such in Qatar (Doi, 1984). Marriage forms the sole basis for sexual relations and parenthood. Therefore, married couples are expected to conceive as soon as possible. Qatar's interest in increasing its population is evidenced by the generous subsidies and numerous social welfare programs, most of them meant to encourage marriages and large families, that Qatari citizens receive. Evenmore, family allowances increase according to the number of children per couple. The sociocultural/religious landscape in an Arab/Islamic society certainly increases the pressure on couples to procreate quickly. Living in a small country like Qatar with a small population in need of growth can add significant stress to couples. The "family pressure" on a couple to conceive also needs to be considered as an extra source of stress (Inhorn, 2004). infertile men might find themselves in a particularly stressful situation in Arabic countries, where manhood is measured by the number of heirs. Arab women, are under a lot of pressure to conceive as well. For women living in the Arab world having children is the ultimate role as a married woman (Inhorn, 2004). While some women in Qatar attain higher education and prefer a career to marriage and childbearing, the religious and social pressure to reproduce is still on them. Arranged marriages are common and even when free consent of both the bride and groom is respected, parental coercion can be strong. In addition, there is a social stigma associated with disclosing infertility in Qatar for both female and males.

Frequently, the woman may be blamed for infertility within a marriage and face considerable stigma even when it is male factor infertility.

Couples undergoing IVF after being diagnosed with subfertility or infertility are under an extra amount of pressure to conceive and usually undergo treatment in total secrecy. If the couple remains infertile, infertility causes aggravated stress as time passes. Stressor factors include the couple's isolation, unrealized potential being childless and disruption of their life during infertility evaluation and treatment.

It is not completely understood if stress is the cause or the consequence of infertility. However, animal studies clearly show that stress may disrupt fertility (Nakamura et al., 2008). In nature, animals shut down reproductive functioning in times of scarce resources and other stresses. In humans, stress generates biological responses leading to suppression of reproductive functions (Genazzani et al., 2006). The biological interaction between stress and infertility could be caused by the effects of stress hormones (adrenalin, nonadrenaline and dopamine) at the brain level, especially on hypothalamic-pituitary-adrenal axis affecting the release of gonadotropin releasing hormone, prolactin, luteinizing hormone and follicle-stimulating hormone, responsible for normal ovulatory cycles. In this line, hypothalamic amenorrhea condition in which menstruation stops without endocrine or systemic cause is known to be triggered by physical or psychological stress (Genazzani et al., 2006; Frisch and McArthur, 1974). It has been shown that high levels of stress has been not only associated with ovarian dysfunction but also with adverse pregnancy outcomes such as preterm birth and low birth weight (Barnea and Tal, 2001). Stress can also cause individuals to smoke or acquire habits that might negatively affect fertility. While the enormous variability in people's responses to stress makes measuring the relationship between stress and infertility very difficult, it is important to recognize the stress exerted by Arabic /Islamic society values and practices on couples during their reproductive ages.

### 10.2. Smoking

It has been estimated that over one third of all men globally smoke some form of tobacco. About 22 percent of women in developed countries and 9 percent of women in developing countries smoke tobacco as well (Anon, 2020l). In Qatar, the Global Adult Tobacco Survey, performed in 2014 revealed that among Qataris, 21.3 % of men and 0.65 % of women smoke tobacco while 19.6 % men and 4.6 % women non-Qataris smoke tobacco (Anon, 2020m). An alarming increase in the number of smoker was observed in a Global Youth Tobacco Survey in the 13–15 age group in Qatar. In this age group 9.8 % were smokers (Anon, 2020n). Smoking has been linked to many adverse health outcomes, including cardiovascular disease, respiratory disease, and several forms of cancer. More recently, a relationship between cigarette smoking and impaired reproductive health has been suggested (Kovac et al., 2015). A meta-analysis including twenty studies regarding smoking and male infertility showed that cigarette smoking negatively affects semen parameters, in particular sperm count (Sharma et al., 2016). A dose response was observed, with a more severe deterioration of the semen quality in heavy smokers.

The adverse effects of smoking may be due to the toxins found in cigarette smoke but studies in animal models suggest that nicotine might also play a role (Oyeyipo et al., 2011). An association between higher cotinine concentrations in the seminal plasma and abnormal sperm morphology has also been reported (Wong et al., 2000).

In a recent study by Elbardisi et al., lower semen quality was found in male infertile patients from the Middle East and North Africa (MENA) region compared to non-MENA regions (Elbardisi et al., 2018). The authors suggest that smoking can be one of the factors responsible for sperm DNA fragmentation and diminished motility and number (Elbardisi et al., 2018). Smoking was also associated with an increased risk for erectile dysfunction (Cao et al., 2013).

Cigarette smoking also affects women's fertility. Prolonged and dose-dependent adverse effect of smoking on ovarian function has been reported (Van Voorhis et al., 1996). Compared with nonsmokers, smokers have reduced gonadotropin-stimulated ovarian function. Tobacco exposure was associated with decreasing serum estradiol concentrations, numbers of retrieved oocytes, and numbers of embryos in patients undergoing in vitro fertilization (Van Voorhis et al., 1996).

Water-pipe (WP) (also known as narghile, hookah, and shisha) smoking is a very wide spread tobacco consumption method used by men and women in the MENA region (Alzaabi et al., 2017). There is a general misperception about WP being less harmful than cigarettes. It is now known that hookah users are exposed to the same toxic compounds and by-products as cigarette users. Even more, it has been demonstrated that WP-users are exposed to higher levels of toxins leading to more severe negative health effects (Qasim et al., 2019). This allows as to speculate that smoking cigarettes and the popular use of waterpipes may have negative effects on male and female fertility in Qatar. In addition, WP smoking showed deleterious effects in pregnancy. Low birth weight was observed in WP smokers compared to nonsmokers in southern Iran (Nematollahi et al., 2018).

### 10.3. Environmental factors

Environmental factors are important contributors to infertility. Within environmental factors the role of air pollution, heavy metals, petroleum hydrocarbons and excessive heat will be discussed.

#### 10.3.1. Air pollution

Air pollution is a cause of concern for human health in particular regarding respiratory disorders. However, it has been suggested that air pollutants could act as endocrine disruptors, leading to reproductive failure. In a systematic review of the literature, Carré et al. concluded that both animal and human epidemiological studies provide evidence that air pollutants cause defects during gametogenesis leading to impaired fertility (Carré et al., 2017).

Whether air pollution affects female infertility is under debate. A recent systematic review evaluating the impact of air pollution on female fertility found that in the IVF population, increased levels of nitrogen dioxide and ozone were associated with a reduced live birth rate. In addition, an association between sulfur dioxide, carbon monoxide and nitrogen dioxide content and the incidence of miscarriage and stillbirths was also described (Conforti et al., 2018). A correlation between particulate matter and reduced fertility was also reported (Carré et al., 2017).

Changes in sperm number and motility have been associated to continuous exposure to environmental chemicals. In this line, it has been suggested that functional abnormalities in the male reproductive system might be a good sensitive marker of environmental hazards (Hauser and Sokol, 2008). Air pollution may contribute to impaired reproductive health in men by inducing gonadal endocrine disruption or by direct negative effect on spermatogenesis (Hammoud et al., 2010a).

From the environmental aspect, the MENA region is characterized by deterioration of the water quality, contamination of groundwater aquifers, high temperature, reduced precipitation, and salinization of agricultural land (Brauch, 2012). In addition, the MENA region has high energy and carbon concentrations. A recent report published in 2013 found high $CO_2$ emissions in the MENA region compared to non-MENA areas (Goel et al., 2013). Therefore, the population in this region is highly exposed to environmental pollutants and faces increasing temperatures due to the global warming effect, which in turn largely affect the male reproductive system (Fisch et al., 2003).

In Qatar, the rapid population growth in parallel with the associated increase in the construction of buildings during the last two decades, has significantly contributed to air pollution (Lanouar et al., 2016). In this line, Qatar has had the highest per-capita carbon dioxide emissions in the world, at 49.1 metric tons per person in 2008. In 2014, the World Health Organization ranked Qatar as the second most polluted country in the world.

#### 10.3.2. Heavy metals

Evidence indicates that exposure to lead (Pb), mercury (Hg) and cadmium (Cd) could adversely affect the male and female reproductive system and fertility (Fisch et al., 2003). It has been shown that there is a direct association between urinary heavy metal excretion and infertility in women (Gerhard et al., 1998). Even more, a reduction in heavy metal body load showed to improve the spontaneous conception chances in infertile women (Gerhard et al., 1998). A study performed in China suggested that the concentrations of Pb and arsenic were significantly higher in the blood of infertile women than in that of pregnant women. Chinese herbal medicine was suspected to be the source of the high concentrations of heavy metals (Lei et al., 2015). Another study, showed increased infertility associated with elevated Hg levels in Taiwanese women, probably caused by highly contaminated seafood consumption (Ho and Wei, 2013). Interestingly, infertile subjects with unexplained infertility have higher levels of Hg in hair, blood and urine compared to fertile ones (Gerhard et al., 1998). In females, increased Hg levels were associated with a higher incidence of menstrual and hormonal disorders and increased rates of infertility (Gerhard et al., 1998).

In men, exposure to heavy metals can affect the sperm quality with serious consequences on fertility. Patients with low-quality semen showed significantly higher Cd, Pb and Barium concentrations in the seminal fluid than patients with normal-quality semen (Sukhn et al., 2018).

Heavy metals may induce infertility by causing endocrine disruption, adversely affecting male hormones concentration, testicular enzyme activities and sperm parameters (Benoff et al., 2000). In male, exposure to Hg induces sperm DNA damage and abnormal sperm morphology and motility.

Industrialization, rapid urbanization and military activities in particular geographic locations are sources of soil pollution with toxic metals in many parts of the world including Qatar (Peng et al., 2016). In a recent study mapping the toxic metal accumulation in Qatar after many years of mining and industrialization, variable content of toxic metal content was found in association with different intensity levels of agriculture, urbanization and industrialization. Pb, Zinc and Copper were measured in very high concentration around the Doha City area (Al-Naimi et al., 2015). In addition, heavy metal pollution is frequently observed in the marine and coastal environment (Wang and Chen, 2000). This is caused by the high adsorption capacity of marine sediments leading to the accumulation of high amounts of heavy metals (Malins, 1984).

#### 10.3.3. Petroleum hydrocarbons

The effects of petroleum derivates on reproduction are well documented (Xu et al., 1998; Balise et al., 2016). Petroleum hydrocarbons increase the risk of miscarriages in exposed women and affect semen quality in exposed men (Xu et al., 1998; Balise et al., 2016). Chinese hamster V79 cells incubated with diesel exhaust particles showed significant chromosomal aberrations in a dose-dependent manner (Hasegawa et al., 1988). Petroleum hydrocarbons were found in Qatari air, waters, and sediments (Dahab and Al MAdfa, 1993; Javed et al., 2019). Tar pollution has also been reported in Qatar (Al-Madfa et al., 1999). This can be caused by oil and natural gas extraction activities, such as drilling, hydraulic fracturing, extraction, processing, transportation and disposal of wastewater. The impact of the oil and gas extraction process on human fertility was investigated in a study by Balise et al. Exposure to oil and gas extraction activities had adverse effects on human reproduction measured by increased risk of miscarriage, birth defects, and decreased semen quality (Balise et al., 2016). Groundwater pollution by petroleum hydrocarbons can also cause human exposure leading to toxicity (La-Raoush et al., 2018).

The many environmental contaminants found in Qatar and their potential contribution to male and female infertility is of particular concern.

#### 10.3.4. Excessive heat

Qatar lies in the desert zone and therefore is characterized by a hot arid climate with scarce rainfall. This peninsular nation can reach very extreme temperatures as high as 122 °F (50 °C) during the summer months. It is known that elevated temperatures can result in spermatic damage leading to infertility (Karaca, 2002). Oxidative stress is the main factor responsible for testicular damage caused by heat stress (Karaca, 2002). Decreased motility and morphological changes have been found in ejaculated sperm after heat stress (Karaca, 2002). Reinforcing the inverse association between heat and sperm quality, abnormal semen quality has been observed in men with occupational heat exposure (Bonde, 1992; Thonneau et al., 1998).

## 11. Sports

#### 11.0.1. Horse riding

Testicular trauma is a frequent acquired cause of infertility. Accidents, work injuries and sport activities are the most common causes of testicular traumas. About 7 % of testicular injuries are due to equestrian sports. Qatar is famous for Arabian horses breeding and the tradition of equestrian sports (Turgut et al., 2005).

#### 11.0.2. Cycling

The construction of the Olympic Cycling Lane that opened in February 2020 in Doha, show the growing interest of the Qatari population in cycling. While controversial, certain studies described an association between biking and reduced male fertility. Men that participated in a 16-week low-to-intensive cycling training, showed increased levels of proinflammatory cytokines in the seminal fluid, changes in sperm morphology and a diminution in the number of spermatozoa. This study suggests that cycling training may have deleterious consequences for spermatozoa and hence may lead to impaired fertility in male cyclists (Hajizadeh Maleki and Tartibian, 2015).

Another study in men attending an IVF clinic showed no overall association between regular physical activity and semen quality, but an association between bicycling, more than 5 h per week, and lower sperm concentration and diminished motility was reported (Wise et al., 2011).

### 11.1. Weight

Both being overweight/obese or underweight might impact fertility. Chronic low energy availability in underweight women can impair the hypothalamic-pituitary-gonadal (HPG) axis leading to anovulation and impaired fertility. In addition, the energy deficiency observed in athletes undergoing excessive training is associated with menstrual dysfunction and anovulation. Excessive weight loss observed in lipodystrophies, malnutrition and starvation is also associated with decreased fertility (Boutari et al., 2020). Conversely, overweight can also have a negative impact on fertility. Obesity has reached epidemic proportions globally. The incidence of obesity in Qatar is increasing at an alarming rate. In Qatar more than 70 % of the adults are overweight and obese. The Stepwise survey conducted by the Supreme Council of Health (SCH) showed that 28.7 % of Qatari were overweight (25.1 % men and 32.2 % women), and 41.1 % were obese (43.2 % men and 39.5 % women) (Haj Bakri, 2013b).

There is a clear association between obesity and infertility. Indeed, a larger portion of women who are seeking ART are obese. It has been reported that the risk of infertility is three times higher in obese women compared to non-obese women. Interestingly, the probability of pregnancy is reduced by 5 % per unit of body mass index (BMI) in excess of 29 $kg/m^2$ (Van der Steeg et al., 2008).

In ancient Greece, Hippocrates recognized the negative impact of obesity on women's and men's reproductive health. He attributed this

to sedentary lives in women and in men with lack of desire for intercourse, probably suggesting erectile dysfunction (Tsiompanou and Marketos, 2013). Since then, the association of obesity with a decline in the reproductive health of women and men has continued to be extensively documented.

Regarding the causes of obesity-associated infertility, an association between obesity and menstrual abnormalities was identified as early as 1952 (Rogers and Mitchell, 1952). In obese women, increased peripheral aromatization of androgens to estrogens leads to abnormal gonadotropin secretion (Parihar, 2003).

Insulin resistance and hyperinsulinemia, frequently observed in obese women, result in hyperandrogenemia. In addition, diminished sex hormone-binding globulin, growth hormone, and insulin-like growth factor binding proteins and increased leptin levels impair the neuroregulation of the HPG axis leading to abnormal ovulatory function and reproductive health (Dağ and Dilbaz, 2015).

In addition, infertility in obese women may be caused by an abnormal endometrial environment. Chronic inflammation, characterized by increased release of cytokines and chemokines from the adipocytes, is observed in obesity (Trayhurn and Wood, 2004) and this might affect endometrial receptivity.

Numerous studies demonstrate a link between obesity in men and infertility (Kahn and Brannigan, 2017). In support of this, the decline in semen parameters currently observed worldwide parallels the increasing prevalence of obesity. Although the cause is not exactly known, endocrine derangements and impaired spermatogenesis seem to play a role in obesity-induced male infertility. In addition to abnormal semen quality, sexual dysfunction, endocrinopathy, aromatization activity and psychological effects might also contribute to impaired fertility observed in obese men. Inflammatory and obstructive elements of epididymitis pathology have also observed in obese infertile men (Katib, 2015).

Obesity-induced epigenetic changes in the sperm can also account for impaired fertility and if conception takes place, infertility may be directly transmitted to the offspring through the sperm. Therefore, the next generation may also suffer from fertility problems (Craig et al., 2017).

Evidence suggests that adiposity may influence DNA methylation in the testes, organs that grow rapidly and therefore are more susceptible to epigenetic changes and damage (Wahl et al., 2017). Hypermethylations of testes and epididymis-specific promoters have been reported to be associated with poor semen parameters or male infertility (Rajender et al., 2011). Among the epigenetically regulated genes relevant for spermatogenesis and male fertility, hypermethylation of the X-linked gene family of reproductive homeobox genes on the X chromosome (RHOX) has been implicated in the pathogenesis of male infertility and may serve as a biomarker for male idiopathic infertility (Richardson et al., 2014). Several epigenetic changes can result in male infertility observed in obesity/diabetes.

Histone–protamine replacement is another important epigenetic change in sperm. It leads to increased motility and confers protection from oxidative stress in the female reproductive tracts. Protamines are the major nuclear sperm proteins.

Patients with a protamine 1/protamine 2 ratio < 0.8 present abnormal sperm motility, structure and counts (Carrell and Liu, 2001)

Increased methylation of the germ line regulator *DAZL* gene could also result in male gametogenic defects resulting in oligoasthenoteratozoospermia. In this line, several genes whose epigenetic modifications are related to abnormal semen parameters and infertility have been identified. Hammoud et al. correlated DNA hypermethylation patterns of seven imprinted loci *LIT1*, *MEST*, *SNRPN*,

*PLAGL1*, *PEG3*, *H19*, and *IGF2*) with abnormal protamine levels in oligozoospermic patients (Hammoud et al., 2010b). On the other hand, hypomethylation of the *IGF2/H19* imprinting control region 1 (ICR1) has been demonstrated in patients with low concentration and sperm motility (Rajender et al., 2011; Hammoud et al., 2010b; Marques et al., 2008)

The high incidence of obesity in Qatar is likely to contribute to female and male infertility through the aforementioned mechanisms.

### *11.2. Alcohol and caffeine consumption*

#### *11.2.1. Alcohol*

Social and cultural factors play a significant role in alcohol use behaviors. In comparison to different western societies, religious and sociocultural values negatively influence alcohol consumption within Arabic-Islamic societies (Almarri and Oei, 2009). In Qatar drinking alcohol is forbidden as stated in the Holy Quran and Al-Hadith, the two major resources for Islamic rules (Tarighat-Esfanjani and Namazi, 2016). Therefore, sociocultural and religious factors may affect the reporting of alcohol consumption among infertile couples.

Alcohol use has serious effects on reproductive health, including having a child with fetal alcohol spectrum disorder, increased risk of miscarriages, and decreased chance of live birth (Van Heertum and Rossi, 2017). However, the effects of alcohol on fertility has not been fully characterized.

A Danish cohort study found that women with moderate and heavy alcohol consumption had a decreased chance of achieving a clinical pregnancy (Jensen et al., 1998). A Swedish study also found a dose-response relationship between the amount of alcohol consumed and the need of IVF treatment (Eggert et al., 2004). High alcohol consumers were more likely to seek fertility treatment than moderate drinkers (Jensen et al., 1998). Another study from Denmark found a significant correlation between alcohol intake and infertility (Tolstrup et al., 2003). In regards to the mechanism behind the deleterious effects of alcohol on fertility, heavy alcohol use diminishes ovarian reserve, a measure of a woman's reproductive potential (American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and Farrell, 2015; Hawkins Bressler et al., 2016). There is also evidence that alcoholic women may experience menopause at an earlier age compared to non-alcoholic women (Gavaler, 1985).

Alcohol consumption in men can also affect fertility. Heavy alcohol use has been associated with reduced gonadotropin release, testicular atrophy, and decreased testosterone and sperm production (Grover et al., 2014). Alcoholism can also cause liver damage/dysfunction, which can affect hormones metabolism resulting in further hormonal disturbances. Decreased quality of semen parameters and even azoospermia have been documented in heavy alcohol consumers (Condorelli et al., 2015). Alcohol abuse and heavy consumption may also cause sexual dysfunction, changes in arousal and desire, as well as ED and ejaculatory dysfunction leading to difficulties conceiving (Guthauser et al., 2014).

While alcohol consumption has been associated with impaired fertility in men and women worldwide, the low consumption of alcoholic beverages due to social and religious factors in Qatar suggests that alcohol might not be a significant factor in the overall decline of fertility observed in the region.

#### *11.2.2. Caffeine*

Caffeine (1,3,7-trimethylpurine-2,6-dione) can be found in coffee beans, tea leaves, and cocoa beans. While alcohol consumption is not well accepted in Qatar, caffeine in the form of coffee and tea is widely consumed. Qatar is one of the world's emerging coffee markets. Coffee is an integral part of the Middle Eastern culture. Arabic coffee, locally referred to as the 'gahwa', is a rooted tradition within the Qatari society.

Studies on the association between caffeine intake and female fecundity has resulted in inconsistent findings (Bolumar et al., 1997; Hatch and Bracken, 1993; Christianson et al., 1989; Caan et al., 1998; Lyngsø et al., 2017). However, a relationship between caffeine and adverse pregnancy outcomes has been reported. Increased risk of spontaneous abortion, low birth weight and stillbirth was found in

meta-analyses investigating the association of caffeine intake during pregnancy and pregnancy outcomes (Wisborg et al., 2003; Greenwood et al., 2014).

The literature suggests that caffeine consumption may have a negative effect on the male reproductive function as well. However, epidemiological studies in males are also inconsistent and inconclusive. A study analyzing 28 papers reporting observational information on coffee/caffeine intake and reproductive outcomes showed that caffeine intake did not affect semen parameters (Ricci et al., 2017). However, a negative effect of cola-containing beverages and caffeine-containing soft drinks was observed on the volume, count and concentration of the semen (Ricci et al., 2017). In addition, caffeine intake was associated with aneuploidy and DNA breaks. Finally, some studies showed a prolonged time to pregnancy in male coffee drinkers compared to men that did not consume coffee (Ricci et al., 2017). On the other hand, a prospective cohort study reported that male caffeine consumption had no effect on fertilization, pregnancy or live birth delivery in ART. Interestingly, caffeine represented a risk factor for multiple gestations (Klonoff-Cohen et al., 2002).

Though the findings are inconsistent, women and men seeking treatment for infertility should be encouraged to avoid excessive caffeine consumption to prevent its potential negative impact in their ability to conceive.

## 12. Conclusion

While Qatar population growth is significant, primarily due to the continued large influx of foreign workers (Anon, 2020o), the fertility rate in the Qatari population has diminished significantly in the last 20 years. Despite the fact that this rate is based on data on registered live births from vital registration systems, the considerable number of factors with detrimental effects on fertility found in the Qatari population and environment (Fig. 2) suggest that impaired fertility may play a crucial role in the diminished number of births per women. That infertility is a growing concern for Qatari couples is reflected in the substantial number of couples undergoing artificial reproductive techniques.

Qatar displays one of the highest rates of consanguineous marriages in the world, and specifically first cousin marriages. Parental consanguinity by increasing the prevalence of chromosomal abnormalities might affect fertility and the incidence of genetic disorders in the offspring. Therefore, the state of Qatar has implemented ways to mitigate the impact of genetic disease in the Qatari society. In this line, the newborn screening (NBS) program was implemented in December 2003 (Al-Dewik et al., 2018). In addition, the National Premarital Genetic Screening program was launched in 2009 as a mandatory step for all couples planning to get married in Qatar (Bener et al., 2019; Practice Committee of the American Society for Reproductive Medicine (ASRM), 2006). The aim of this program is to provide preconception reproductive options, improve pregnancy outcomes and identify

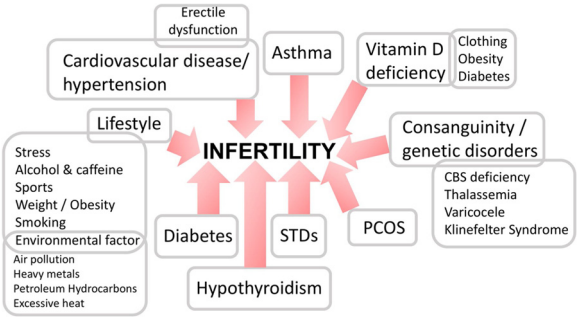



**Fig. 2.** Potential causes of infertility in Qatar.
CBS: cystathionine $\beta$-synthase, PCOS: polycystic ovary syndrome, STDs: sexually transmitted diseases.

reproductive choices in order to reduce perinatal morbidity and mortality while respecting the psychosocial, religious and cultural values.

Endometriosis, characterized by the appearance of endometrial tissue outside the uterus can influence fertility in several ways (Practice Committee of the American Society for Reproductive Medicine (ASRM), 2006). Adhesions and scars in the fallopian tubes, endocrine and ovulatory disorders and an exacerbated inflammatory response leading to impaired fertilization and implantation might contribute to infertility (Missmer et al., 2004). The incidence of endometriosis among women of reproductive age in Qatar has not been reported. However, that 25–50 % of infertile women have endometriosis and 30–50 % of women with endometriosis are infertile worldwide (Verkauf, 1987), allows us to speculate that endometriosis might also contribute to female infertility in Qatar.

Considering the high prevalence of diabetes and obesity among the Qatari population and the impact of these conditions on cardiovascular health and fertility, prevention, treatment and control of metabolic syndrome may improve reproductive health. Halting or reversing the expanding obesity/diabetes epidemic is a national priority in Qatar (Awad et al., 2019).

Regarding sexual transmitted diseases (STDs), screening and treatment efforts for *C. trachomatis* and *N. gonorrhoeae* should be implemented to reduce the incidence of pelvic inflammatory disease and subsequent infertility. In this line, development of programs for sexual health and STDs for both women and men can certainly improve reproductive health.

Air quality has an impact on overall health as well as on the reproductive function, so increased awareness of environmental protection issues is needed among the general public and the authorities in Qatar. A considerable reduction of emissions should be considered to minimize the public health risks associated with air pollution including impaired fertility. In this line, several economic policies have been proposed in order to reduce the level of air pollution in Qatar without reducing the economic growth.

Prevention, early diagnosis and treatment of hypertension as indicated in the Qatar Ministry of Public Health care map could also have a significant effect in improving reproductive health in particular for men (Anon, 2020p).

Lifestyle modifications can also assist couples to conceive spontaneously or optimize their chances of conception with ART treatment. Smoking has deleterious effects on global health including fertility. To decrease tobacco use, the Qatar government has endorsed the Framework Convention on Tobacco Control (WHO FCTC) and has implemented several tobacco control activities (El Hajj et al., 2017). Regulations for the prevention of water-pipe smoking aiming at increasing men and women's knowledge and awareness regarding the health consequences of water-pipe smoking have been proposed. Women and men should quit smoking before attempting to conceive. Nutritional counseling may also improve reproductive outcomes.

By preventing the aforementioned risk factors, the Qatari population might improve their health and in particular their reproductive health contributing to the population growth, a Qatar national priority.

## Author contributions

GZK and GG reviewed the literature and wrote the review article.
The publication of this article was funded by the Qatar National Library.

## Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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