



## Review

## Fertility and infertility: Definition and epidemiology

Mélodie Vander Borght<sup>b</sup>, Christine Wyns<sup>a,b,\*</sup><sup>a</sup> Gynecology-Andrology Unit, Medical School, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, 1200 Brussels, Belgium<sup>b</sup> Department of Gynecology-Andrology, Cliniques Universitaires Saint-Luc, 1200 Brussels, Belgium

## ARTICLE INFO

## Keywords:

Fertility  
Epidemiology  
Female infertility  
Male infertility

## ABSTRACT

Infertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse. It is estimated to affect between 8 and 12% of reproductive-aged couples worldwide. Males are found to be solely responsible for 20–30% of infertility cases but contribute to 50% of cases overall. Secondary infertility is the most common form of female infertility around the globe, often due to reproductive tract infections. The three major factors influencing the spontaneous probability of conception are the time of unwanted non-conception, the age of the female partner and the disease-related infertility. The chance of becoming spontaneously pregnant declines with the duration before conception. The fertility decline in female already starts around 25–30 years of age and the median age at last birth is 40–41 years in most studied populations experiencing natural fertility. The disease-related infertility may affect both genders or be specific to one gender. The factors affecting both genders' fertility are hypogonadotropic hypogonadism, hyperprolactinemia, disorders of ciliary function, cystic fibrosis, infections, systemic diseases and lifestyle related factors/diseases. Premature ovarian insufficiency, polycystic ovary syndrome, endometriosis, uterine fibroids and endometrial polyps may play a role in female infertility. Male infertility may be due to testicular and post-testicular deficiencies. Semen decline that has been observed over the years, endocrine disrupting chemicals and consanguinity are other factors that may be involved.

## 1. Introduction

Fertility is the capacity to establish a clinical pregnancy [1]. The term infertility is used by some clinicians interchangeably with subfertility. Formal definitions are, however, very important for appropriate management of reproductive disorders.

Worldwide > 186 million people suffer from infertility, the majority being residents of developing countries [2]. While the most powerful negative predictive factor of fertility is increasing women's age at conception [3], other factors including lifestyle and environmental factors are believed to play an increasing role. Factors influencing fertility will be presented as gender specific or not.

## 2. Infertility, subfertility and sterility: what are the differences?

Based on the latest international glossary on infertility and fertility care, *infertility* is defined as a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce, either as an individual or with his/her partner. Regular sexual intercourse is an important determinant for the occurrence of

pregnancy. According to the latest definition by the WHO, infertility is a disease which generates disability as an impairment of function [1].

*Subfertility* is a term that could be used interchangeably with infertility [1]. It was also defined as any form or grade of reduced fertility in couples unsuccessfully trying to conceive [4].

While the definition of infertility relies on a restricted time period, *sterility* is a permanent state of infertility [1].

Infertility is further categorized as primary or secondary. The primary infertile female is a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as having infertility. Secondary female infertility applies to a woman unable to establish a clinical pregnancy but who has previously been diagnosed with a clinical pregnancy [1]. The same categorisation might be applicable to the male regarding his participation in the initiation of a pregnancy.

## 3. Epidemiology of infertility around the world

The prevalence of infertility in reproductive-aged women has been estimated to be one in every seven couples in the western world and one in every four couples in developing countries. In some regions of the

\* Corresponding author at: Av. Hippocrate 10 – 1200 Woluwe-Saint-Lambert, Belgium.  
E-mail address: [christine.wyns@uclouvain.be](mailto:christine.wyns@uclouvain.be) (C. Wyns).

world, including South Asia, some countries of sub-Saharan Africa, the Middle East and North Africa, Central and Eastern Europe and Central Asia infertility rates may reach 30% [5].

Males are found to be solely responsible for 20–30% of infertility cases but contribute to 50% of cases overall. However, these figures do not accurately represent all regions of the world. The study of Agarwal et al. showed that male infertility rates were highest in Africa and Central/Eastern Europe, whereas corresponding rates for North America, Australia, and Central and Eastern Europe varied from 4.5–6%, 9%, and 8–12%, respectively [6].

In summary, infertility is estimated to affect between 8 and 12% of reproductive-aged couples worldwide [7].

Secondary infertility is the most common form of female infertility around the globe [8] [9]. Secondary infertility is most common in regions of the world with high rates of unsafe abortion and poor maternity care, leading to post-abortive and postpartum infections [2].

#### 4. Impact of infertility on demographics

Fertility, infertility, and more precisely fertility rates as being the average number of live births per woman [1] [10] have an impact on population growth or decline.

World regions differ widely in their demographic trends, with rapid population growth and high fertility rates in the poorest countries, particularly in some countries of sub-Saharan Africa, while population decline, ageing and very low fertility rates are a matter of concern in many developed countries [10].

**Fig. 1** shows worldwide prospects of fertility rates. It presents estimates from 1950 to 2010 and projections to 2050, as measured by the average number of births over a woman's lifetime. In the 1950s, while the total fertility rates in less developed regions and least developed countries (Asia, Latin America, and Africa) were high and virtually stable at around six births per woman on average, average fertility rates in more developed regions (North America and Europe) reached relatively low levels. In the late 1960s, a rapid decline in fertility started nearly simultaneously in less developed regions (Asia and Latin America). By contrast, Africa has experienced only limited reproductive changes during the same period [11].

Replacement fertility represents the level at which each generation exactly replaces the previous one, thus leading to zero population

growth (in the absence of mortality change and migration) [11]. United Nations projections for the developing world assume that the total fertility rate will eventually reach and then fall slightly below the so-called replacement level of just above 2 births per woman in all regions. For regions that have already achieved below-replacement fertility, a small rise is expected. Below-replacement fertility produces, in the long run, population decline. The total fertility rates in Asia and Latin America are now very close to the replacement level, but Africa is on a much slower trajectory toward replacement fertility. High fertility therefore remains a key cause of future population growth in Africa. In contrast, the already low fertility of Europe and North America is expected to remain below replacement and is the main cause of population decline in a few countries.

#### 5. Factors that may influence the spontaneous fertility of couples

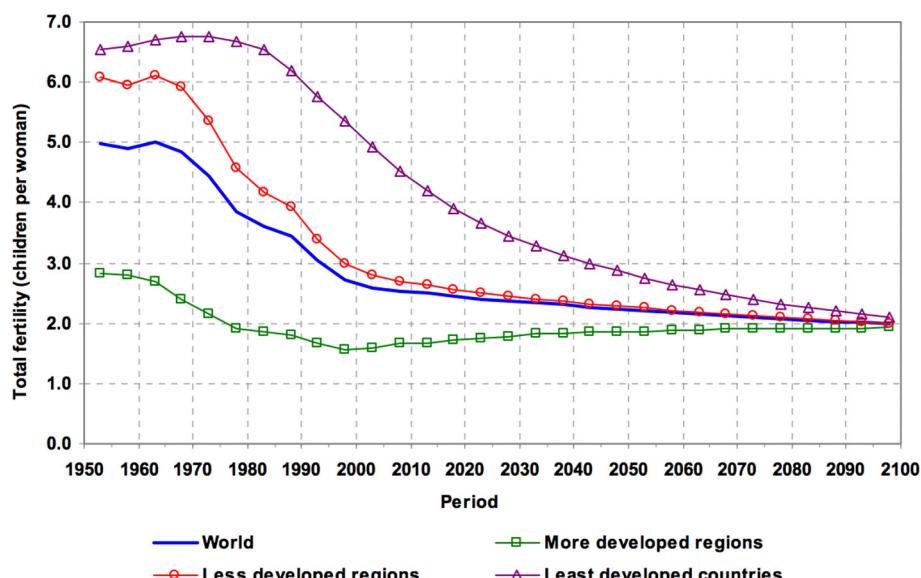
The three major factors affecting the spontaneous probability of conception are (a) time of unwanted non-conception (b) age of the female partner and (c) disease-related infertility [12]. Semen decline that has been observed over time, endocrine disrupting chemicals and consanguinity are other factors that may be involved.

##### 5.1. Time of unwanted non-conception

The major factor affecting the individual spontaneous pregnancy prospect is the time of unwanted non-conception, which determines the severity of subfertility. Eighty percent of the pregnancies occur in the first six cycles with regular intercourse in the fertile period. Using timed intercourse during the fertile window of the menstrual cycle proved to enhance the likelihood of spontaneous pregnancy. One out of two couples of the residual 20% couples without conception will conceive spontaneously in the next six cycles. After 12 unsuccessful cycles, 10% of the couples are defined as infertile but spontaneous live birth rates among them will reach nearly 55% in the next 36 months. After 48 months, 5% of the couples are definitively infertile with a nearly zero chance of becoming spontaneously pregnant [12].

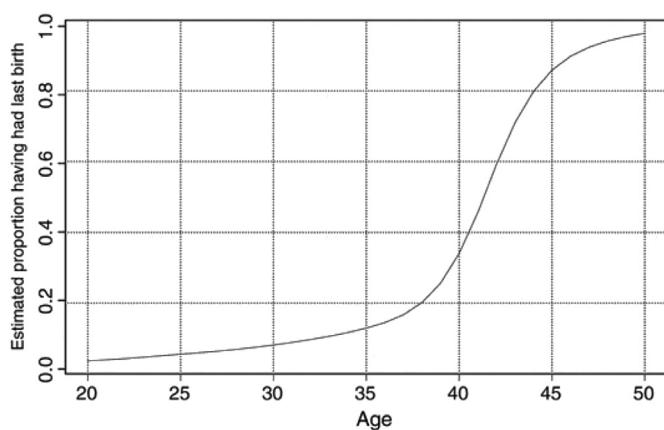
##### 5.2. Female age related fertility decline

Since the sixties, motherhood has become an issue of personal



**Fig. 1.** Fertility estimates (1950–2010) and projections (2010–2050) by region

[11] (United Nations, D.o.E.a.S.A., Population Division, *World Population Prospects: The 2012 Revision*. United Nations, New York, 2013: p. Paper No. ESA/P/WP.228).



**Fig. 2.** The biological age at last birth curve [15] (Eijkemans, M.J., et al., Too old to have children? Lessons from natural fertility populations. *Hum Reprod*, 2014. 29(6): p. 1304–12).

preferences instead of biology [13]. Women could decide to continue schooling and acquire a profession before thinking of having children with as a consequence a significant postponement of childbearing in Western societies [14]. Currently, the mean maternal age at first birth is approaching 30 years in several European countries and many women deliver their first child at age 35 or older [15].

The problem arising with delayed child wish is that the fertility decline already starts around 25–30 years of age. Furthermore, the median age at last birth for females is 40–41 years in most natural fertility populations [15]. This suggests that there is a fairly universal pattern of age-related fertility decline. Fig. 2 shows the age-related loss of fertility. Eijkemans et al. [15] analysed the distribution of female age at last birth in a natural fertility population and showed that the age-related loss of fertility slowly increases from 4.5% at age 25 years, 7% at age 30 years, 12% at age 35 years and 20% at age 38 years. Thereafter, it rises rapidly to about 50% at age 41, almost 90% at age 45 years and approaching 100% at age 50 years. The prevailing concept of fertility decline assumes that the age-dependent loss of fertility is determined by the continuous depletion of oocytes stored in both ovaries during fetal life, leading first to a decreased fertility and then to its subsequent expiration a decade later at the onset of menopause [16]. In addition, it is well established that oocyte quality also deteriorates with advancing reproductive age besides premature recruitment of follicles, increasing ovulatory disorders, reduced ovulatory frequency and impaired luteal phase, all leading to reduced conception rates [3].

Several studies show that most women are not aware of the fact that delaying childbearing increases the risk of infertility [17]. Moreover, many women believe erroneously that infertility care such as In Vitro Fertilization (IVF) can address the fertility decline associated with advancing age [18].

### 5.3. Disease-related infertility

The disease-related infertility may affect both genders or be specific to one gender as summarized in Table 1.

#### 5.3.1. Factors affecting both genders' fertility

**5.3.1.1. Hypogonadotropic hypogonadism.** Hypogonadotropic hypogonadism leads to insufficient gonadal stimulation by Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH), either due to insufficient/absent secretion of hypothalamic Gonadotropin-Releasing Hormone (GnRH) or a compromised pituitary. The main cause of GnRH insufficiency is the failure of migration of the GnRH secretory neurons to the forebrain. It may be associated with anosmia (Kallmann syndrome; KS) or not (normosmic idiopathic hypothalamic hypogonadism) [3]. Genetic central hypogonadism is more frequently

encountered in males than in females; in particular, Kallmann syndrome has a prevalence of 1/5000 with a clear male predominance [19].

**5.3.1.2. Hyperprolactinemia.** Prolactin inhibits gonadotrophin secretion leading to anovulation [3]. In men, hyperprolactinemia causes low serum testosterone levels, infertility and sexual dysfunction [20].

In a large series of 1607 patients with medically treated hyperprolactinemia, the calculated prevalence was approximately 10 per 100,000 in men and 30 per 100,000 in women, with peak prevalence for women aged 25–34 years [21]. The reported population prevalence of symptomatic prolactinoma ranges from 6 to 10 per 100,000 to approximately 50 per 100,000 [22].

In their study, Souter et al. [23] conclude that hyperprolactinemia is rare among asymptomatic women with infertility (approximately 5%). The prevalence in a population of infertile men is, as far as we know, unknown.

**5.3.1.3. Disorders of ciliary function.** The fallopian tube as a conduit for sperm and embryos transport relies on effective ciliary activity. While the fallopian tube cilia can be damaged by pathogens or inflammation, a primary disorder of ciliary structure and function (Primary Ciliary Dyskinesia (PCD)) will also impair tubal transport and predispose to ectopic implantation of the gestational sac and subfertility [3].

Most men with PCD have infertility secondary to sperm immobility as a result of defective sperm-flagella movement. PCD is a rare, autosomal recessive disorder with an estimated prevalence of approximately 1 in 10,000 to 40,000 live births. Certain geographically isolated communities or ethnic groups may have a higher PDC prevalence due to consanguinity, such as the Volendam population in the Netherlands, the British Asian population, and the Amish and Mennonite communities in the United States [24].

**5.3.1.4. Cystic fibrosis.** Mutations in the CF Transmembrane Conductance Regulator (CFTR) gene affect both male and female fertility. Cystic Fibrosis (CF) is a condition characterized by abnormal mucus secretion. This disease affects populations across the globe, but is more common in northern European whites (approximately 1 in 2500 individuals) and in Ashkenazi Jews (approximately 1 in 2270) [25]. CF is associated with female subfertility due to a direct effect on the epithelial cells of the reproductive tract. The thick cervical mucus impairs sperm penetration. The effect on the uterine cavity and the fallopian tube function is less significant, although the influence on bicarbonate metabolism may lead to problems with sperm capacitation within the fallopian tube [26]. Men suffering from cystic fibrosis usually present with congenital absence of the vas deferens. Hypoplasia or aplasia of the vas deferens and seminal vesicles may occur either bilaterally or unilaterally. Testicular development and spermatogenesis are generally not impaired [27].

**5.3.1.5. Infection.** Infectious agents have different modes of fertility impairment. In men, they can organ damage, cell damage via mediators of inflammation, create an obstruction or bind to spermatozoa [28]. In women, they can cause pelvic inflammatory disease and tubal obstruction [3]. As evidenced by IVF success rates, embryonic implantation potential is decreased in the presence of hydrosalpinges [29].

The most common infectious agent causing infertility is *Chlamydia trachomatis*, with the highest incidence in Hispanics (33.3%) [30]. Epidemiological data suggest an association of a past *Chlamydia trachomatis* infection and subfertility both in men and women [31] although the influence of *Chlamydia trachomatis* on male fertility is controversial [32], probably because of methodological issues in reported studies.

*Neisseria gonorrhoea* is another pathogen that may affect the Fallopian tube [33]. In 2008, the World Health Organization estimated

**Table 1**  
Disease-related infertility.

5.3.1. Both genders
5.3.1.1. Hypogonadotrophic hypogonadism
5.3.1.2. Hyperprolactinemia
5.3.1.3. Disorders of ciliary function
5.3.1.4. Cystic fibrosis
5.3.1.5. Infection
5.3.1.6. Systemic diseases
5.3.1.7. Lifestyle related factors/diseases
5.3.2. Female
5.3.2.1. Premature ovarian insufficiency
5.3.2.2. Polycystic ovary syndrome
5.3.2.3. Endometriosis
5.3.2.4. Uterine fibroids
5.3.2.5. Endometrial polyps
5.3.3. Male
5.3.3.1. Testicular deficiency
5.3.3.2. Post-testicular impairment

the highest incidence of gonorrhoea to be in the Western Pacific Region (42.0 million cases), South-East Asia Region (25.4 million) and Africa Region (21.1 million). In the European Region (53 countries), 3.4 million cases of gonorrhoea were estimated [34]. Gonorrhoea may also impair male fertility by inducing urethral strictures, a problem that appears not to be very relevant in European countries [28].

**5.3.1.6. Systemic diseases.** It is generally believed that severe systemic illness, such as sepsis or severe renal disease, will prevent embryonic implantation. A number of diseases such as unstable diabetes [3], uncontrolled celiac disease which is five times more prevalent in women experiencing unexplained infertility or recurrent miscarriage than in the general population [35], vitamin D insufficiency, active autoimmune conditions and subclinical hypothyroidism also appear to be associated with a reduced chance of conception [3].

Poor diabetic control ( $\text{HbA1c} \geq 7\%$ ) was significantly associated with impaired sperm motility (reduced progressive motility) and sperm abnormal morphology (double head, round and elongated spermatids and cytoplasmic mid- and tail pieces). Metabolic syndrome is a complex disorder consisting of multiple interrelated factors including insulin resistance, central adiposity, dyslipidemia, endothelial dysfunction, atherosclerotic disease, and low-grade inflammation. Ultimately, this may lead to a low sperm count, impaired motility, and abnormality of sperm morphology. It is known that hypertension can cause erectile dysfunction, either directly or as a side effect of medication [36].

The presence of thyroid antibodies in a woman with normal thyroid function is believed to be associated with difficulty to conceive, recurrent implantation failure of embryos and early pregnancy loss, potentially due to an unrecognized thyroid hormone deficiency or an autoimmune cause [37].

Autoimmune diseases may influence the reproductive life and fertility of both genders [38]. Chronic kidney failure is also been known to

detrimentally influence fertility [3] [39].

#### 5.3.1.7. Lifestyle related factors/diseases

**5.3.1.7.1. Frequency of coitus.** Regular sexual intercourse, two to three times per week beginning soon after menses, is an important determinant for the occurrence of pregnancy [40–43].

**5.3.1.7.2. Dietary restriction and over-exercise.** It is well established that calorie restriction and excessive exercise lead to a reduction in the frequency of ovulation, poor endometrial development and amenorrhea. Subfertility may even be observed at recreational levels of activity which induce abnormalities of gonadotrophin secretion and ovulatory disorders without inducing amenorrhea [3].

There is also evidence that sports' practice affects semen quality. In recreational athletes, exercise seems to be mainly associated with positive or neutral effects. By contrast, professionals should be aware of potential risks of infertility as intense training reduces sperm concentration, percentage of motile spermatozoa, and percentage of morphologically normal spermatozoa [44]. Moreover, some men practicing sport may take anabolic steroids which inhibit the hypothalamic–pituitary–gonadal axis and lead to hypogonadotropic hypogonadism, resulting in partial or complete inhibition of spermatogenesis [45].

**5.3.1.7.3. Stress.** Gaskin et al. [46] demonstrated, in a nurse population, that working longer hours (over 40 h/week) is associated with increased time to conceive, suggesting a relation of tiredness or stress with reduced fecundity.

Mental stress in men affects the quality of semen. Indeed, severe depression appears to be associated with decreased levels of testosterone, thus affecting testicular paracrine interactions and spermatogenesis [47].

**5.3.1.7.4. Obesity.** Thirteen percent of men and 21% of women in the world are classified as obese according to their body mass index (BMI) [48].

Women who are overweight are less likely to ovulate and to conceive spontaneously even after infertility care. Upon conception, they have also an increased risk of miscarriage and are predisposed to an adverse pregnancy outcome [49].

Obesity may adversely affect male reproduction by endocrine, thermal [49], genetic [50] and sexual mechanisms [49].

**5.3.1.7.5. Cigarette smoking.** Cigarette smoking has a well known effect on fertility in both male and female. For a cigarette smoking woman, each stage of reproductive function, folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and uterine myometrium are impaired, as the smoke contains heavy metals, polycyclic hydrocarbons, nitrosamines, and aromatic amines [51]. In males, smoking negatively affects sperm production, motility and morphology and is associated with an increased risk of DNA damage [52].

**5.3.1.7.6. Marijuana consumption.** In women, a disturbed menstrual cycle, a reduced number of oocytes harvested during in vitro fertilization, and a higher risk of prematurity have been observed [53].

In men, consuming cannabis several times a week for 5 years causes a reduction in the ejaculated seminal volume, number of spermatozoa as well as changes in morphology and motility with sperm hyperactivity and reduction in their fertilization capacity [54].

**5.3.1.7.7. Alcohol intake.** While alcohol is a known teratogen and should be avoided during pregnancy; its effect on fertility is less clear. Potential mechanisms through which alcohol may impair fertility include an alcohol-related rise in estrogens leading to decreased follicle stimulating hormone secretion and impaired ovulation [55].

Most studies that included alcohol as a point of investigation have failed to show a significant impact on sperm counts, at least among those with moderate alcohol consumption. In contrast, in chronic alcohol consumers, there is good evidence for impairment of spermatogenesis and reduction in sperm counts and testosterone levels [56].

### 5.3.2. Factors affecting female fertility

**5.3.2.1. Premature ovarian insufficiency.** Premature ovarian insufficiency (POI) occurs in about 1% of women. It is defined as the cessation of menstrual cycles under 40 years of age in the presence of an elevated serum FSH measured on two separate occasions. The causes may be genetic, environmental, infectious (e.g. subsequent to mumps infection), associated with autoimmune conditions, metabolic (due to biochemical damage in the presence of galactosemia) and subsequent to cancer therapy or surgery. However, in the majority of cases, the origin remains undetermined.

Possibly the most common genetic cause of POI is Turner syndrome. Another common genetic cause of POI is due to the fragile X mental retardation premutation. While the full mutation (> 200 CGG repeats) causes mental retardation and autism, the presence of 55 to 200 triplet repeats results in premature ovarian failure [3].

POI is characterized by a decrease in the number of antral follicles. The measurement of circulating anti-Mullerian hormone (AMH) appears to reflect the number of antral and pre-antral follicles present in the ovaries and is released from the granulosa cells. Its serum concentration is therefore proportional to the number of developing follicles in the ovaries, so that AMH was considered as a marker for the process of ovarian ageing. However, inter-individual variability of AMH measurements is high, mainly due to the very high variability in the number of antral follicles within groups of subjects of similar age [57]. Moreover, ethnic variations, with African-American and Hispanic women having lower serum AMH levels than those found in Caucasian women, have also been observed [58].

**5.3.2.2. Polycystic ovary syndrome.** The polycystic ovary syndrome (PCOS), a heterogeneous condition, is the most prevalent endocrine disorder in women, affecting 5–10% of the female population [59]. Besides ovulation impairment and as evidenced by IVF success rates,

embryonic implantation potential is decreased in the presence of PCOS [3].

PCOS is classically described by the Rotterdam criteria [60] as a syndrome consisting of two of the following three criteria i.e. infrequent or absent ovulation (oligospaniomenorrhea), a morphological description of the ovaries by ultrasound assessment and hyperandrogenism.

Women with PCOS show also markedly raised AMH levels due to both the increased number of small antral follicles and intrinsic characteristics of their granulosa cells, which may contribute to anovulation [61].

Obesity has been associated to exacerbated metabolic and ovulatory dysfunction related to PCOS, and weight loss has been found to restore ovulation and reduce hyperandrogenism [62]. In addition, racial/ethnic variation in phenotypes further suggests that lifestyle and cultural factors are likely to play a role in the metabolic consequences of PCOS [63].

There is also some evidence that low socioeconomic status is more closely linked to PCOS phenotypes characterized by metabolic dysfunction [64] and that the socioeconomic status-PCOS association is more pronounced among obese women [64] [65].

**5.3.2.3. Endometriosis.** Endometriosis is a pathological pelvic inflammatory process associated with infertility. The mechanisms involved in endometriosis related infertility range from anatomical distortions due to adhesions and fibrosis to endocrine abnormalities and immunological disturbances [66]. As evidenced by IVF success rates, embryonic implantation potential is decreased in the presence of endometriosis [67].

The true prevalence of endometriosis in women of reproductive age remains uncertain. The estimated overall prevalence of endometriosis in population-based studies varies from 0.8% to 6%; however, in subfertile women the prevalence seems to be considerably higher, ranging from 20% to 50%, but with significant variations over time periods and with the age of patients [66]. Some but not all studies have found a higher prevalence of endometriosis among Asian women [68].

**5.3.2.4. Uterine fibroids.** Leiomyomas are the commonest benign tumors in the female reproductive tract. Even though their role on infertility is still questionable, evidence to date suggests that the anatomic location may be related to reproductive outcomes. Several possible mechanisms have been reported on how leiomyomas may affect fertility such as anatomical distortion of endometrial cavity, abnormal uterine contractility, reduced blood supply to the endometrium and altered endometrial receptivity [69].

Uterine fibroids are more prevalent in black women and black women may have larger and higher numbers of fibroids [68].

**5.3.2.5. Endometrial polyps.** Decreased embryonic implantation potential and early pregnancy loss were both reported in the presence of endometrial polyps [3]. They have been associated with decreased mid-secretory concentrations of IGFBP-1, TNF $\alpha$  and osteopontin, as markers of implantation, which were shown to be reversed following surgical polypectomy [70].

### 5.3.3. Factors affecting male fertility

**5.3.3.1. Testicular deficiency.** Testicular dysfunction is the most frequent cause of disturbed spermatogenesis [71].

Testicular dysfunction can be further subdivided into congenital, acquired, or idiopathic testicular failure.

Congenital failure can manifest as anorchia, testicular dysgenesis and cryptorchidism. Genetic abnormalities can also cause congenital failure. Some studies have reported that white males have a significantly higher risk of cryptorchidism than black males; other studies have not reported differences [72].

The two most frequent genetic abnormalities are Klinefelter syndrome (47 XXY) and Y chromosome microdeletions.

The prevalence of Klinefelter syndrome is approximately 1 in 1000 to 1 in 500 males [73]. The adult Klinefelter patients are characterized by hypergonadotropic hypogonadism as evidenced by low to low-normal levels of testosterone, high FSH and LH levels, and undetectable levels of serum inhibin B in most of the patients. The Klinefelter subjects are traditionally described as infertile because of a complete absence of germ cells. Although semen analysis most often reveals azoospermia, some Klinefelter men may have single-residual foci with spermatogenesis. It is believed that some spermatogonia in Klinefelter subjects are capable of completing the spermatogenic process leading to the formation of mature spermatozoa. The underlying mechanisms of testicular degeneration are poorly understood. The different hypotheses concerning Leydig-cell insufficiency, impaired somatic environment of the testes, a dysfunctional communication between somatic and germ cells, incomplete X-chromosome inactivation as well as disturbed apoptotic activity of Leydig cells and Sertoli cells have been described. Increased expression of genes located on the X chromosome that escape inactivation may play an important role [74].

Microdeletions in the AZF region of the Y chromosome have been associated with altered sperm parameters and testicular histological characteristics which range from Sertoli cell only syndrome (SCOS) to hypospermatogenesis [75]. While the male sex-determining region (SRY) is located on the short arm of the Y chromosome (Yp11) [76] important genes involved in spermatogenesis are located on the proximal part of its long arm (Yq11) recognized as the azoospermia factor (AZF) region which is divided into the AZFa, AZFb and AZFc sub regions. Y-chromosome microdeletions are reported in 5–10% of infertile men [77]. The most common microdeletion is seen in the AZFc sub region and is accompanied by DAZ gene deletion and moderate to severe oligozoospermia, while microdeletions in the AZFa and AZFb sub regions have been correlated with azoospermia [78].

Acquired testicular failure can result from trauma, testicular torsion, orchitis, exogenous factors (e.g., medications), endogenous factors (e.g., systemic diseases, varicocele) or surgery that may damage the testicular vascular anatomy.

Varicoceles are present in 11.7% of men with normal semen analysis and in 25.4% of men with abnormal semen [71]. The precise mechanism by which varicocele might cause infertility is still unknown. No single factor is believed to be responsible for the negative testicular effects. In this complex pathophysiological network, oxidative stress seems to have a central role [79]. Indeed, it can harm germ cells directly or indirectly through influencing non-spermatogenic cells and the basal lamina of the seminiferous tubules resulting in induction of apoptosis. The reactive oxygen species and total antioxidant capacity balance shift leads to oxidation of fatty acids in spermatozoa membranes causing changes in sperm morphology, motility, and fertilizing capabilities [80]. Other possible pathophysiological mechanisms involved in varicocele-induced male infertility include scrotal hyperthermia, hypoxia, reflux of renal and adrenal metabolites, hormonal imbalances, and the formation of antisperm antibodies [79].

**5.3.3.2. Post-testicular impairment.** Post-testicular deficiency is due to either ejaculatory dysfunction or obstruction to sperm delivery. The obstruction can be located in the epididymis, vas deferens, or ejaculatory duct and can be acquired or congenital [81].

Epididymal obstruction is the most common cause of post-testicular deficiency. Among the acquired forms, those secondary to epididymal infection are considered to be the most frequent. Vas deferens acquired obstruction can be the result of an infection, a vasectomy or a hernia repair [71].

Congenital bilateral absence of vas deferens (CBAVD) is found in 1 in 1600 men and in most men with cystic fibrosis (CF) [82]. Young syndrome, also referred to as sinusitis-infertility syndrome, is a rare combination of symptoms such as bronchiectasis, rhinosinusitis, and azoospermia because of functional obstruction of sperm transport down the genital tract [83].

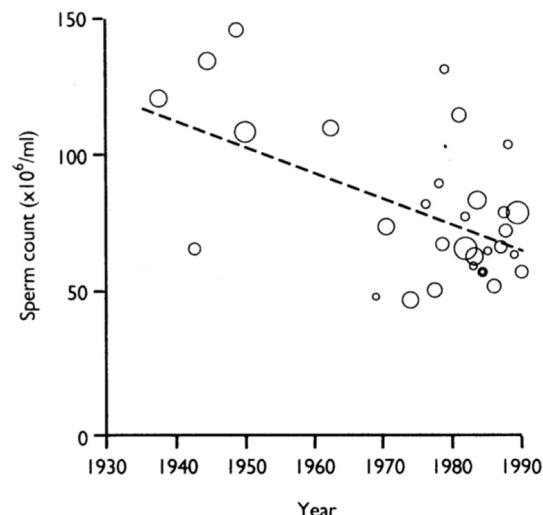
Ejaculatory duct obstruction is found in 1–3% of cases of post-testicular deficiency [84]. These obstructions can be classified as cystic or postinflammatory. Cystic obstructions are usually congenital (Müllerian duct cyst or urogenital sinus/utricle cysts) and are located medially in the prostate between the ejaculatory ducts [85]. Postinflammatory obstruction of the ejaculatory duct is usually secondary to urethral prostatitis. Congenital or acquired complete obstructions of the ejaculatory ducts or of the seminal vesicles are commonly associated with low semen volume, decreased or absent seminal fructose, and acid pH of the seminal fluid [71].

#### 5.4. Sperm quality

In 2010, the World Health Organization has defined lower reference limits for human semen characteristics based on men whose partners had a time-to-pregnancy of  $\leq 12$  months [86]: semen volume, 1.5 mL; total sperm number, 39 million per ejaculate; sperm concentration, 15 million per mL; vitality, 58% live; progressive motility, 32%; total (progressive + non progressive) motility, 40%; morphologically normal forms, 4.0%. Semen quality of this reference population was superior to that of men from the general population (a mixed population of men of unknown fertility) and normozoospermic men (according to the 1999 WHO criteria with unknown fertility or attending an infertility clinic). A possible decline of the sperm quality has been reported in a number of studies.

A systematic review [87] evaluated 61 studies published between 1938 and 1990 analysing sperm concentrations in fertile men and in men of unknown fertility. The authors showed a significant decrease in mean sperm concentrations (from 113 million/mL to 66 million/mL) and in semen volume (from 3.40 mL to 2.75 mL) over the timespan as illustrated in Fig. 3, triggering a worldwide debate regarding a possible decline in male fertility. It was argued that changing laboratory methods, statistical issues, and population heterogeneity might have induced biases and that other factors such as age, abstinence period or inherent variability of sperm counts might also have affected the results.

Springart et al. [88] also studied the evolution of semen quality over time in 1114 fertile candidates for sperm donation between 1976 and 2009. They did not find a decline in semen volume, whereas they observed a significant decrease in total sperm count (from 443.2 to 300.2 million), motility (from 64% to 49%) and vitality (from 88% to 80%). Moreover, a significant decline, from 67% to 26% of sperm with normal morphology was noted between 1976 and 1997 with a steady rise in the



**Fig. 3.** Linear regression of mean sperm density [87] (Carlsen, E., et al., *Evidence for decreasing quality of semen during past 50 years*. BMJ, 1992. 305(6854): p. 609–13).

multiple abnormalities index between 1998 and 2009 (from 1.19 to 1.65). Although this study revealed various degrees of decline in semen parameters over a period of 34 years, it involved, however, a population of fertile men from a restricted area.

Geographical differences in the evolution of sperm quality have also been reported. Indeed, Swan et al. [89] found significant declines in sperm density in North America and Europe after controlling for abstinence time, age, percent of men with proven fertility, and specimen collection method. The declines in sperm density in North America and Europe were somewhat greater than the average decline reported by Carlsen et al. of approximately 1%/year [87]. However, they did not find a decline in sperm density in non-Western countries although such data were very limited.

Furthermore, Redmon et al. [90] found significant differences in semen parameters among men of different race/ethnicity as black men in their cohort had mean values for semen volume, sperm concentration, total sperm count and total motile sperm count that were significantly lower than White or Hispanic/Latino men.

Most studies examined the potential impact of environmental exposure to dioxins on sperm parameters. The study of Faure and al [91] provided suggestive evidence of an association between dioxins and alteration of sperm quality. The association between dioxins pollution and altered sperm morphology and motility suggests that the exposure effects are present in adulthood besides those of a perinatal exposure described by other authors [92–94].

A gene-environment interaction has been proposed to explain the differential impact of the exposure to persistent organohalogen pollutants that could impair male reproductive function. Indeed, a study indicated that the androgen receptor CAG repeat length might modify the susceptibility of an individual to the adverse effects of persistent organohalogen pollutant exposure on semen quality [95].

### 5.5. Endocrine disrupting chemicals

Endocrine Disrupting Compounds (EDCs) are exogenous chemicals or mixture of chemicals that interfere with any aspect of hormone action [96].

The main EDCs are bisphenol A (BPA, a synthetic chemical widely used in the manufacture of plastics and resins), phthalates and their esters (plasticizers to provide flexibility to materials), the pesticide atrazine (used in commercial crop growing), the polychlorinated biphenyls (PCBs, banned in 1979) and DDT/DDE (an insecticide) [3].

There is extensive evidence from animal studies of a negative influence of environmental chemicals on many aspects of female fertility: follicular number, ovulation, meiosis, and embryo implantation. However, in humans the evidence of such negative associations is often lacking or contradictory [3] [97]. Further epidemiological studies should help in the clarification of these associations.

Research on the influence of EDCs on male reproductive capacity is suggestive of links between exposure and a range of disorders that include developmental abnormalities such as cryptorchidism and hypospadias, poor semen quality, and increased risk of testicular cancer. However, drawing direct links and determining which EDCs may play causal roles in these aspects has not been possible in humans [96].

### 5.6. Consanguinity

Consanguineous marriage is usually defined as marriage between a man and a woman who are related as second cousins or closer [98]. More than half of the world's population lives in areas where consanguineous marriage is widespread (North Africa, Middel East, Western and Central Asia, India, South America). By contrast, consanguineous marriage is rare in Europe, Russia, North America and Australia considering the population as a whole, although it is practiced within some ethnic and religious minorities [99].

The association between reproductive outcome and degree of

partner's consanguinity has been the focus of several studies. The fertility pattern of women descending from consanguineous parents was reported in an observational study [100] showing that parental consanguinity is associated with female infertility and prematurely reduced ovarian reserve. To the best of our knowledge, such link has not been reported in the male.

Consanguineous marriages significantly increase the incidence of inherited recessive disorders and affect some reproductive and developmental health parameters such as infertility rates and recurrent miscarriages [101].

## 6. Conclusion

This report describes current knowledge about the definition and epidemiology of fertility and infertility and presents its main etiological factors on both the female and the male's side.

We expect that this collated evidence can be used as background information for the medical world.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of interests

None.

## References

- [1] F. Zegers-Hochschild, et al., The international glossary on infertility and fertility care, 2017, *Fertil. Steril.* 108 (3) (2017) 393–406.
- [2] M.C. Inhorn, P. Patrizio, Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century, *Hum. Reprod. Update* 21 (4) (2015) 411–426.
- [3] R.J. Hart, Physiological aspects of female fertility: role of the environment, modern lifestyle, and genetics, *Physiol. Rev.* 96 (3) (2016) 873–909.
- [4] J. Jenkins, et al., European classification of infertility taskforce (ECIT) response to Habbema et al., 'Towards less confusing terminology in reproductive medicine: a proposal', *Hum. Reprod.* 19 (12) (2004) 2687–2688.
- [5] M.N. Mascarenhas, et al., National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys, *PLoS Med.* 9 (12) (2012) e1001356.
- [6] A. Agarwal, et al., A unique view on male infertility around the globe, *Reprod. Biol. Endocrinol.* 13 (2015) 37.
- [7] W. Ombelet, et al., Infertility and the provision of infertility medical services in developing countries, *Hum. Reprod. Update* 14 (6) (2008) 605–621.
- [8] R.D. Nachtigall, International disparities in access to infertility services, *Fertil. Steril.* 85 (4) (2006) 871–875.
- [9] S.O. Rutstein, S.I. Infertility, infertility, and childlessness in developing countries. DHS Comparative Reports No. 9, World Health Organization, Geneva, Switzerland, 2004.
- [10] J. Bongaarts, Global fertility and population trends, *Semin. Reprod. Med.* 33 (1) (2015) 5–10.
- [11] United Nations, D.o.E.a.S.A., Population Division, World Population Prospects: The 2012 Revision, (2013) United Nations. New York p. Paper No. ESA/P/WP.228.
- [12] C. Gnoth, et al., Definition and prevalence of subfertility and infertility, *Hum. Reprod.* 20 (5) (2005) 1144–1147.
- [13] D.J. Van de Kaa, Europe's second demographic transition, *Popul Bull* 42 (1) (1987) 1–59.
- [14] W. Lutz, B.C. O'Neill, S. Scherbov, Demographics. Europe's population at a turning point, *Science* 299 (5615) (2003) 1991–1992.
- [15] M.J. Eijkemans, et al., Too old to have children? Lessons from natural fertility populations, *Hum. Reprod.* 29 (6) (2014) 1304–1312.
- [16] E.R. Te Velde, P.L. Pears, The variability of female reproductive ageing, *Hum. Reprod. Update* 8 (2002) 141–154.
- [17] L. Schmidt, Should men and women be encouraged to start childbearing at a younger age? *Expert Rev. Obstet. Gynecol.* 5 (2010) 145–147.
- [18] A. Maheshwari, M. P, A. Shetty, S. Bhattacharya, Women's awareness and perceptions of delay in childbearing, *Fertil. Steril.* 90 (2008) 1036–1042.
- [19] H. Valdes-Socin, et al., Reproduction, smell, and neurodevelopmental disorders: genetic defects in different hypogonadotropic hypogonadal syndromes, *Front Endocrinol (Lausanne)* 5 (2014) 109.
- [20] M. De Rosa, et al., Hyperprolactinemia in men: clinical and biochemical features and response to treatment, *Endocrine* 20 (1–2) (2003) 75–82.

- [21] M. Kars, et al., Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia, *J. Clin. Endocrinol. Metab.* 94 (8) (2009) 2729–2734.
- [22] A. Fernandez, N. Karavitaki, J.A. Wass, Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK), *Clin. Endocrinol.* 72 (3) (2010) 377–382.
- [23] I. Souter, et al., Prevalence of hyperprolactinemia and abnormal magnetic resonance imaging findings in a population with infertility, *Fertil. Steril.* 94 (3) (2010) 1159–1162.
- [24] N. Damseh, et al., Primary ciliary dyskinesia: mechanisms and management, *Appl. Clin. Genet.* 10 (2017) 67–74.
- [25] I. Schrijver, Mutation distribution in expanded screening for cystic fibrosis: making up the balance in a context of ethnic diversity, *Clin. Chem.* 57 (6) (2011) 799–801.
- [26] A. Ahmad, A. Ahmed, P. Patrizio, Cystic fibrosis and fertility, *Curr. Opin. Obstet. Gynecol.* 25 (3) (2013) 167–172.
- [27] T. Ong, et al., Cystic fibrosis and congenital absence of the vas deferens, in: M.P. Adam, et al. (Eds.), *GeneReviews(R)*, Editors, Seattle (WA), 1993.
- [28] F.R. Ochsendorf, Sexually transmitted infections: impact on male fertility, *Andrologia* 40 (2) (2008) 72–75.
- [29] A. Strandell, et al., Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF, *Hum. Reprod.* 14 (11) (1999) 2762–2769.
- [30] P.B. Smith, et al., Predominant sexually transmitted diseases among different age and ethnic groups of indigent sexually active adolescents attending a family planning clinic, *J. Adolesc. Health Care* 9 (4) (1988) 291–295.
- [31] L. Karinen, et al., Association between chlamydia trachomatis antibodies and subfertility in the northern Finland birth cohort 1966 (NFB 1966), at the age of 31 years, *Epidemiol. Infect.* 132 (5) (2004) 977–984.
- [32] A. Eley, et al., Can chlamydia trachomatis directly damage your sperm? *Lancet Infect. Dis.* 5 (1) (2005) 53–57.
- [33] C. Mitchell, M. Prabhu, Pelvic inflammatory disease: current concepts in pathogenesis, diagnosis and treatment, *Infect. Dis. Clin. N. Am.* 27 (4) (2013) 793–809.
- [34] World Health Organization, Global incidence and prevalence of selected curable sexually transmitted infections - 2008, (2012).
- [35] C. Tersigni, et al., Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms, *Hum. Reprod. Update* 20 (4) (2014) 582–593.
- [36] A.E. Omu, Sperm parameters: paradigmatic index of good health and longevity, *Med. Princ. Pract.* 22 (Suppl. 1) (2013) 30–42.
- [37] R. Vissenberg, et al., Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction, *Hum. Reprod. Update* 21 (3) (2015) 378–387.
- [38] H.J. Carp, C. Selmi, Y. Shoenfeld, The autoimmune bases of infertility and pregnancy loss, *J. Autoimmun.* 38 (2–3) (2012) J266–J74.
- [39] P. Iglesias, J.J. Carrero, J.J. Diez, Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options, *J. Nephrol.* 25 (1) (2012) 31–42.
- [40] A.J. Wilcox, C.R. Weinberg, D.D. Baird, Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby, *N. Engl. J. Med.* 333 (23) (1995) 1517–1521.
- [41] J.B. Stanford, K.R. Smith, D.B. Dunson, Vulvar mucus observations and the probability of pregnancy, *Obstet. Gynecol.* 101 (6) (2003) 1285–1293.
- [42] S. Elzanaty, J. Malm, A. Giwercman, Duration of sexual abstinence: epididymal and accessory sex gland secretions and their relationship to sperm motility, *Hum. Reprod.* 20 (1) (2005) 221–225.
- [43] E. Levitas, et al., Relationship between the duration of sexual abstinence and semen quality: analysis of 9,489 semen samples, *Fertil. Steril.* 83 (6) (2005) 1680–1686.
- [44] P. Jozkow, M. Rossato, The impact of intense exercise on semen quality, *Am. J. Mens Health* 11 (3) (2017) 654–662.
- [45] M. Semet, et al., The impact of drugs on male fertility: a review, *Andrology* 5 (4) (2017) 640–663.
- [46] A.J. Gaskins, et al., Work schedule and physical factors in relation to fecundity in nurses, *Occup. Environ. Med.* 72 (11) (2015) 777–783.
- [47] P. Jozkow, M. Medras, Psychological stress and the function of male gonads, *Endokrynol. Pol.* 63 (1) (2012) 44–49.
- [48] K. Smurthwaite, N. Bagheri, Using geographical convergence of obesity, cardiovascular disease, and type 2 diabetes at the neighborhood level to inform policy and practice, *Prev. Chronic Dis.* 14 (2017) E91.
- [49] D. Best, S. Bhattacharya, Obesity and fertility, *Horm. Mol. Biol. Clin. Invest.* 24 (1) (2015) 5–10.
- [50] A. Hammoud, et al., An aromatase polymorphism modulates the relationship between weight and estradiol levels in obese men, *Fertil. Steril.* 94 (5) (2010) 1734–1738.
- [51] C. Dechanet, et al., Effects of cigarette smoking on reproduction, *Hum. Reprod. Update* 17 (1) (2011) 76–95.
- [52] R. Kunzle, et al., Semen quality of male smokers and nonsmokers in infertile couples, *Fertil. Steril.* 79 (2) (2003) 287–291.
- [53] H. Wang, S.K. Dey, M. Maccarrone, Jekyll and hyde: two faces of cannabinoid signaling in male and female fertility, *Endocr. Rev.* 27 (5) (2006) 427–448.
- [54] S. Alvarez, Do some addictions interfere with fertility? *Fertil. Steril.* 103 (1) (2015) 22–26.
- [55] B.V. Rossi, M. Abusief, S.A. Missmer, Modifiable risk factors and infertility: what are the connections? *Am. J. Lifestyle Med.* 10 (4) (2014) 220–231.
- [56] R.M. Sharpe, Environmental/lifestyle effects on spermatogenesis, *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 365 (1546) (2010) 1697–1712.
- [57] D. Dewailly, et al., The physiology and clinical utility of anti-Mullerian hormone in women, *Hum. Reprod. Update* 20 (3) (2014) 370–385.
- [58] D.B. Seifer, et al., Variations in serum mullerian inhibiting substance between white, black, and Hispanic women, *Fertil. Steril.* 92 (5) (2009) 1674–1678.
- [59] S. Franks, Polycystic ovary syndrome in adolescents, *Int. J. Obes.* 32 (7) (2008) 1035–1041.
- [60] E.A.-S.P.C.W.G. Rotterdam, Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, *Fertil. Steril.* 81 (1) (2004) 19–25.
- [61] D. Dewailly, Diagnostic criteria for PCOS: is there a need for a rethink? *Best Pract. Res. Clin. Obstet. Gynaecol.* 37 (2016) 5–11.
- [62] P.G. Crosignani, et al., Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet, *Hum. Reprod.* 18 (9) (2003) 1928–1932.
- [63] S.S. Merkin, et al., Environmental determinants of polycystic ovary syndrome, *Fertil. Steril.* 106 (1) (2016) 16–24.
- [64] G. Di Fede, et al., Influence of sociocultural factors on the ovulatory status of polycystic ovary syndrome, *Fertil. Steril.* 91 (5) (2009) 1853–1856.
- [65] S.S. Merkin, et al., Socioeconomic status and polycystic ovary syndrome, *J. Women's Health (Larchmt)* 20 (3) (2011) 413–419.
- [66] T. Tanbo, P. Fedorcsak, Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options, *Acta Obstet. Gynecol. Scand.* 96 (6) (2017) 659–667.
- [67] K. Barnhart, R. Dunsmoor-Su, C. Coutifaris, Effect of endometriosis on in vitro fertilization, *Fertil. Steril.* 77 (6) (2002) 1148–1155.
- [68] V.L. Jacoby, et al., Racial and ethnic disparities in benign gynecologic conditions and associated surgeries, *Am. J. Obstet. Gynecol.* 202 (6) (2010) 514–521.
- [69] C. Siristatidis, et al., Leiomyomas and infertility, *Minerva Ginecol.* 68 (3) (2016) 283–296.
- [70] J. Ben-Nagi, et al., The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings, *Reprod. BioMed. Online* 19 (5) (2009) 737–744.
- [71] A. Jungwirth, et al., European Association of Urology guidelines on male infertility: the 2012 update, *Eur. Urol.* 62 (2) (2012) 324–332.
- [72] K.A. McGlynn, et al., Risk factors for cryptorchism among populations at differing risks of testicular cancer, *Int. J. Epidemiol.* 35 (3) (2006) 787–795.
- [73] A. Bojesen, S. Juul, C.H. Gravholt, Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study, *J. Clin. Endocrinol. Metab.* 88 (2) (2003) 622–626.
- [74] L. Akslaaet, et al., Natural history of seminiferous tubule degeneration in Klinefelter syndrome, *Hum. Reprod. Update* 12 (1) (2006) 39–48.
- [75] C. Foresta, E. Moro, A. Ferlin, Y chromosome microdeletions and alterations of spermatogenesis, *Endocr. Rev.* 22 (2) (2001) 226–239.
- [76] F. Raicu, et al., Screening for microdeletions in human Y chromosome–AZF candidate genes and male infertility, *J. Cell. Mol. Med.* 7 (1) (2003) 43–48.
- [77] H. Sadeghi-Nejad, F. Farrokhi, Genetics of azoospermia: current knowledge, clinical implications, and future directions. Part II: Y chromosome microdeletions, *Urol. J.* 4 (4) (2007) 192–206.
- [78] F. Asadi, et al., The prevalence of Y chromosome microdeletions in Iranian infertile men with azoospermia and severe Oligospermia, *Cell J.* 19 (1) (2017) 27–33.
- [79] C.F.S. Jensen, et al., Varicocele and male infertility, *Nat. Rev. Urol.* 14 (9) (2017) 523–533.
- [80] C. Romeo, G. Santoro, Free radicals in adolescent varicocele testis, *Oxidative Med. Cell. Longev.* 2014 (2014) 912878.
- [81] H.S. Lee, J.T. Seo, Advances in surgical treatment of male infertility, *World J. Mens Health* 30 (2) (2012) 108–113.
- [82] R.D. Oates, J.A. Amos, The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis, *J. Androl.* 15 (1) (1994) 1–8.
- [83] D.J. Handelsman, et al., Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections, *N. Engl. J. Med.* 310 (1) (1984) 3–9.
- [84] R.B. Meacham, D.K. Hellerstein, L.I. Lipshultz, Evaluation and treatment of ejaculatory duct obstruction in the infertile male, *Fertil. Steril.* 59 (2) (1993) 393–397.
- [85] J.P. Pryor, W.F. Hendry, Ejaculatory duct obstruction in subfertile males: analysis of 87 patients, *Fertil. Steril.* 56 (4) (1991) 725–730.
- [86] T.G. Cooper, et al., World Health Organization reference values for human semen characteristics, *Hum. Reprod. Update* 16 (3) (2010) 231–245.
- [87] E. Carlsen, et al., Evidence for decreasing quality of semen during past 50 years, *BMJ* 305 (6854) (1992) 609–613.
- [88] C. Splingart, et al., Semen variation in a population of fertile donors: evaluation in a French Centre over a 34-year period, *Int. J. Androl.* 35 (3) (2012) 467–474.
- [89] S.H. Swan, E.P. Elkin, L. Fenster, The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996, *Environ. Health Perspect.* 108 (10) (2000) 961–966.
- [90] J.B. Redmon, et al., Semen parameters in fertile US men: the study for future families, *Andrology* 1 (6) (2013) 806–814.
- [91] A.C. Faure, et al., Evolution of sperm quality in men living in the vicinity of a municipal solid waste incinerator possibly correlated with decreasing dioxins

- emission levels, *Andrologia* 46 (7) (2014) 744–752.
- [92] P. Mocarelli, et al., Perinatal exposure to low doses of dioxin can permanently impair human semen quality, *Environ. Health Perspect.* 119 (5) (2011) 713–718.
- [93] P.C. Hsu, et al., Sperm changes in men exposed to polychlorinated biphenyls and dibenzofurans, *JAMA* 289 (22) (2003) 2943–2944.
- [94] Y.L. Guo, et al., Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans, *Lancet* 356 (9237) (2000) 1240–1241.
- [95] A. Giwercman, et al., Androgen receptor gene CAG repeat length as a modifier of the association between persistent organohalogen pollutant exposure markers and semen characteristics, *Pharmacogenet. Genomics* 17 (6) (2007) 391–401.
- [96] A.C. Gore, et al., EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals, *Endocr. Rev.* 36 (6) (2015) E1–E150.
- [97] S. Sifakis, et al., Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems, *Environ. Toxicol. Pharmacol.* 51 (2017) 56–70.
- [98] A.H. Bittles, M.L. Black, The impact of consanguinity on neonatal and infant health, *Early Hum. Dev.* 86 (11) (2010) 737–741.
- [99] C. Stoltenberg, Commentary: of the same blood, *Int. J. Epidemiol.* 38 (6) (2009) 1442–1447.
- [100] T. Seher, et al., Is parental consanguinity associated with reduced ovarian reserve? *Reprod. BioMed. Online* 31 (3) (2015) 427–433.
- [101] R.F. Turki, et al., Associations of recurrent miscarriages with chromosomal abnormalities, thrombophilia allelic polymorphisms and/or consanguinity in Saudi Arabia, *BMC Med. Genet.* 17 (Suppl. 1) (2016) 69.