International Journal of Gynecology and Obstetrics 123 (2013) S31–S35

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

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

MANAGEMENT OF INFERTILITY TODAY

The conventional management of male infertility

Eberhard Nieschlag [a,c,*], Andrea Lenzi [b]

[a] Center for Reproductive Medicine and Andrology, University of Münster, Germany
[b] Department of Experimental Medicine, Sapienza University of Rome, Italy
[c] Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia

ARTICLE INFO

Keywords:
Clinical treatments
Maldescended testes
Male infertility
Semen analysis, Sexually transmitted diseases

ABSTRACT

Although the male reproductive function is impaired in about half of infertile couples, the evaluation of male infertility is underrated or neglected even today. In addition to a physical examination and imaging techniques, semen analysis as well as endocrine and genetic analyses should be part of the routine investigation. Few disorders have become subjects of rational treatment of the infertile male, even though, as examples, hypogonadotropic hypogonadism is treatable by gonadotropins and obstructive azoospermia by reconstructive surgery. Early treatment of maldescended testes and sexually transmitted diseases can prevent infertility. Similar pregnancy rates from patients with varicocele following surgery or counseling demonstrate the important role of the physician in the treatment of infertility. In the age of evidence-based medicine, most empirical treatments have been demonstrated to be ineffective. Instead, symptomatic treatment by assisted reproductive techniques has become a central tool to overcome otherwise untreatable male infertility.

1. The role of andrology in reproductive medicine

Procreation is the basis for the existence of humankind, as it compensates for the inevitable death of each individual and ascertains the continuity of human life. In 90% of couples intending to have a child, pregnancy occurs spontaneously during natural intercourse. The remaining 10%, however, require medical advice and assistance to fulfill their wish for a child. The woman's role in the success or failure of procreation has always been obvious because she carries out the pregnancy, but the man's role is often underestimated, especially in cases of failure.

A disorder of the male reproductive function can be detected in about 50% of the male partners of infertile couples, and it is most often combined with a coexisting female problem. Generally, when a disorder is detected in one of the partners, a disorder also becomes evident in the other partner—a disorder so mild, however, that it would remain unnoticed if the other partner had normal reproductive functions. The interdependence of the female and male reproductive functions is the reason why the male partner of an infertile woman must be investigated right from her first consultations for infertility (Fig. 1). In many cases, only the reproductive problem of one partner can be treated, which may be sufficient to compensate for the problem of the other.

Consequently, when a couple consults for infertility, it is not sufficient that the woman consult a gynecologist. The man must also consult an andrologist, preferably from the same center for reproductive medicine. Andrology, however, is still a young field, underdeveloped in many countries, and it may be difficult for couples to find professional care for the man.

2. Causes of male infertility

The scope of the present article does not allow a detailed description of the pathophysiology and classification of male infertility disorders, and the reader is referred to appropriate textbooks [1]. Here, only a few topical issues that may highlight current knowledge shall be discussed. Further disorders are mentioned in the context of diagnosis (Section 3) and treatment (Section 4).

2.1. Sperm crisis: real or perceived?

A postulated decline in human male fertility has received a good deal of attention in both scientific literature and the popular press, especially in high-income countries. Early work at the beginning of the 1970s did not recognize a possible risk to the general male population.

Environmental deterioration [2] is the most accredited possible cause. In particular, pollution by xenobiotic agents with estrogen-like activity—i.e., endocrine disruptors—is suspected to cause various andrologic conditions. Examples are testicular cancer [3], but also hypospadias, cryptorchidism [4], and reduced spermatogenesis via a reduction of the numbers of Sertoli cells during fetal life [5]. It is difficult to demonstrate a cause-and-effect link between pollution and these conditions, and case-control studies have not shown clear results in different populations of workers [6]. At the same time, there have been improvements in nutrition and hygiene and advances in prevention, in part owing to the field of pediatric andrology.

* Corresponding author at: Center for Reproductive Medicine and Andrology, University of Münster, D-48129 Münster, Germany. Tel.: +49 251 8352047; fax: +49 251 8354800.
E-mail address: eberhard.nieschlag@ukmuenster.de (E. Nieschlag).

0020-7292/$ – see front matter
http://dx.doi.org/10.1016/j.ijgo.2013.09.001

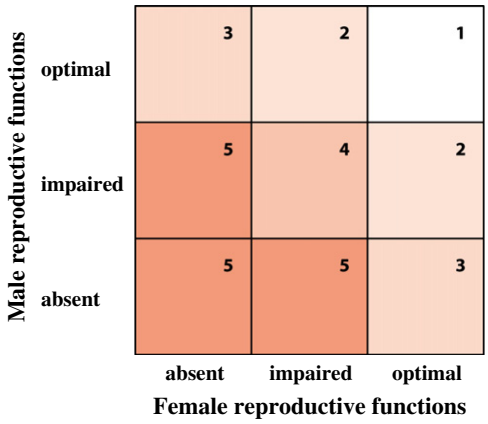

Fig. 1. Interdependence of the male and female reproductive functions [1]. In group 1, both partners have optimal reproductive function and will not consult a physician because of childlessness. In group 2, the suboptimal function of a partner will probably be compensated for by the optimal function of the other partner. These couples are probably more prevalent in the general population than their representation in fertility clinics may suggest. In group 3, only 1 partner will be treated by the gynecologist or andrologist. In groups 4 and 5, both partners require treatment. Therapeutic success, i.e., pregnancy, will be achieved more rapidly if the partners are treated at a center for reproductive medicine, where physicians have both gynecological and andrologic training.

In 1992, a review of 61 studies by Carlsen et al. [7] indicated a significant decrease in sperm concentration from 1938 to 1990. This review has attracted ongoing public interest despite the criticism that the publications were heterogeneous regarding study design, study populations, methods of semen analysis, geographic location, and ethnicity [8–12]. The review triggered 27 major studies that took into account both ethnic and geographic differences. A 2008 review by Fisch [10] reports that 16 of these 27 studies found no differences over time in sperm concentration, motility, or morphology; 5 yielded ambiguous results; and 6 found a decline regarding semen concentration and quality. The author concludes that "Far from being a worldwide and well-proved phenomenon, declines in semen quality are, at best, a highly local phenomenon with an unknown cause and, at worst, a collective artifact" [10].

In response to the criticisms of their review, Carlsen et al. [12] carried out their own longitudinal study from 1996 to 2010, analyzing semen samples annually from about 350 young men screened for military service in Denmark. The mean ± standard deviation for sperm concentration was 45 million cells per milliliter in these men, and the concentration did not vary over time, even as a trend. The study will be continuing for an undetermined period [12].

2.2. The impact of age on reproduction

The effect of age on the female reproductive function is well documented. While it is optimal in women between 20 and 30 years of age, it declines considerably after 35 years and generally ceases at 50 years [13]. Despite these physiological facts, more and more women postpone childbearing to a phase of life when chances for conception and live birth have significantly decreased. In high-income countries, where birth rates are declining, women giving birth after the age of 40 years are the only growing population willing to become pregnant. These women, however, increasingly require medical help to overcome fertility problems and many turn to assisted reproductive technology (ART), not always successfully.

As the ages of the man and the woman tend to be similar in a couple, the age of men intending to become fathers also tends to increase. A crucial question, then, is whether age-related female infertility is paralleled by age-related male infertility. In contrast to the ovarian cycle, spermatogenesis continues throughout life and sperm can be found in very old men. However, sperm motility, an important predictor of fertility, decreases with age [14–17]. Time to pregnancy significantly increases when the male partner is older than 40 years [18]. Moreover, the rate of spontaneous abortion increases [19] and the rate of live birth decreases with the age of the male partner [20], which contributes to a lower birth rate. In addition, the rates of chromosomal abnormalities and genetic autosomal dominant diseases are higher among children of aging fathers [21].

In conclusion, not only does the female reproductive function decline with age but men's chances for begetting offspring also decline, whereas the risks of genetic diseases in the offspring increase. As the reproductive function declines later in men than in women, it may not be of great importance for a given couple's fecundity. Yet, it should be borne in mind if childbearing is long postponed [22].

3. Diagnosis of male infertility

3.1. History taking and physical examination

Any factors that may affect fertility must be considered. These include prior fertility or difficulty with conception, diseases during childhood and puberty, surgical treatments, genital trauma, and infectious disease; abnormal physical and/or sexual development; social and sexual habits and problems; exposure to gonadotoxic agents; recent fever or exposure to heat; current or recent pharmacological treatment; and a family history of birth defects, mental retardation, reproductive failure, or cystic fibrosis.

The physical examination should record the aspects of the secondary sexual characteristics and the body mass index, and note the presence or absence of obesity, gynecomastia, lymphadenopathy, penile curvature, and phimosis or paraphimosis, as well as the location of the urinary meatus. A testicular examination should focus on testicular size, symmetry, consistency, and presence or absence of masses. The epididymides should be carefully examined. Palpation of the spermatic cord, with special attention to the presence or absence of the vas deferens and/or varicoceles, is important. Men with varicocele should be examined via Valsalva maneuver. The congenital bilateral absence of the vas deferens, often associated with congenital cystic fibrosis, represents a small but significant predictor of male infertility due to azoospermia. Finally, rectal examination of the prostate is performed.

3.2. Imaging diagnostics

A scrotal ultrasound is part of any infertility investigation, as it permits detection of nodules, microcalcifications, and other testicular and epididymal lesions. On high sensitivity, it detects scrotal abnormalities and differentiates testicular from paratesticular lesions. The main indication for color Doppler ultrasound is the assessment of acute scrotal symptoms, such as pain or swelling, especially when testicular torsion is suspected.

A transrectal ultrasound is recommended in cases of low semen volume (<1.0 mL), abnormal findings on digital rectal examination, and ejaculatory disorders such as anejaculation, hematospermia, and painful ejaculation. Magnetic resonance imaging is performed to rule out intracranial disorders from hormonal disturbances.

3.3. Endocrine laboratory diagnosis

Basic endocrine evaluation includes measuring levels of follicle-stimulating hormone (FSH) and total and calculated levels of testosterone (T). Elevated serum FSH is usually indicative of severe germ cell epithelium damage and results from impaired secretion of inhibin B. When associated with low-normal or below normal T levels, an FSH level greater than 2 to 3 times the upper limit of normal suggests diffuse testicular failure from a congenital (e.g., Klinefelter syndrome) or acquired cause. Luteinizing hormone (LH) stimulates the Leydig cells and hence T production. Isolated LH abnormalities are very rare.

Concomitant low levels of FSH, LH, and T are indicative of hypogonadotropic hypogonadism. Puberty may have been delayed, and affected men may present with poorly developed secondary sexual characteristics and small testes. Hyperprolactinemia is rarely a cause of infertility in men. Levels of serum estrogen, testicular cancer markers, and adrenal steroids should be determined in those presenting with gynecomastia.

3.4. Semen analysis

Semen analysis is indispensable and provides a prognosis for fertility [23]. All patients should have at least 2 semen analyses done, as wide variability may exist in the same individual. The 2 semen samples should be collected at least 2 weeks apart, each after 2 to 5 days of sexual abstinence, into a sterile container and preferably at the laboratory site. For psychological reasons, it can also be collected at home and delivered within 60 minutes of ejaculation. Seminal analysis must include the volume and pH of the ejaculate, its appearance, viscosity, and liquefaction time; sperm concentration in million per milliliter, total sperm count, sperm motility and morphology, sperm agglutination; presence of leukocytes, red blood cells, immature germ cells, epithelial cells, prostatic corpuscles; and biochemical seminal markers. To coordinate semen analysis globally, the World Health Organization has published 5 editions of a handbook for semen analysis since 1970 [24].

3.5. Sperm function tests

There has been extensive research to establish sperm function tests. However, apart from determining the presence or absence of antisperm antibody (ASA), none of the tests developed, including sperm DNA fragmentation, has become part of routine testing. Risk factors for ASA formation include genital infection, testicular trauma or biopsy, cryptorchidism, testicular damage secondary to excessive heat exposure, and obstruction of the extratesticular ductal system (e.g., from vasectomy). The presence of ASA can reduce motility, affect sperm penetration of cervical mucus, and impair the fertilization process at the levels of acrosome reaction, zona pellucida recognition and penetration, and sperm-vitellus interaction.

3.6. Cytogenetic and molecular genetics investigations

The identification of genetic conditions such as Klinefelter syndrome, microdeletions in the Y chromosome, and congenital absence of the vas deferens due to cystic fibrosis has serious implications for the offspring as well. Following the identification of any genetic condition during a routine evaluation of male infertility, the couple needs to be counseled regarding the transmission of these conditions to their offspring. The male children of men with microdeletions in the AZF region of the Y chromosome, for example, can be expected to have the same deletions as their fathers and are likely to be infertile themselves [25].

Chromosomal aberrations are assessed through G-band karyotyping. Sex chromosomal aneuploidy, also called Klinefelter syndrome or 47,XXY karyotype, is the most frequent chromosomal disorder affecting infertile men.

A mutation of the cystic fibrosis gene, which is located on the long arm of chromosome 7, is also a relatively common genetic disorder. Depending on the mutation length, cystic fibrosis can manifest as its full clinical presentation or as a mild form, which affects approximately 1.3% of infertile men with congenital bilateral absence of the vas deferens.

3.7. Testicular biopsy and histology

As spermatogenesis can be greatly reduced in men with nonobstructive azoospermia, a biopsy should be performed, if possible, in an assisted reproduction center to allow for sperm cryopreservation and thus avoid repeated procedures. For intracytoplasmic sperm injection (ICSI), sperm may be removed from the epididymis by microsurgical epididymal sperm aspiration or extracted from a testicular biopsy sample.

4. Treatment of male infertility

A number of male fertility disorders can be treated rationally and effectively. For other disorders, no rational treatments are available. Infertility is idiopathic for approximately one-third of infertile men. Since the cause is not known, a rational treatment cannot exist for these men. Consequently, some specialists propose assisted reproduction. Intrauterine insemination, in vitro fertilization (IVF), and fertilization by means of ICSI open possibilities for paternity when rational treatments are not available. Often, early preventive treatment, long before paternity is considered, is the most effective way to preserve fertility (Table 1).

4.1. Rational treatment

While there are no effective treatments to improve fertility in men with primary hypogonadism, treatment with gonadotropin-releasing hormone (GnRH) and/or gonadotropins can induce and maintain spermatogenesis in men with secondary hypogonadism. Men with hypothalamic disturbances, such as Kallman syndrome or other idiopathic hypogonadotropic hypogonadism, can undergo pulsatile GnRH treatment or gonadotropin treatment, whereas those with pituitary insufficiency can only be treated with gonadotropins. Since this stimulatory treatment also stimulates endogenous testosterone production by Leydig cells, testosterone substitution is interrupted. Once paternity has been achieved, treatment is switched back to testosterone substitution. Pituitary prolactinomas can be effectively treated with dopamine agonists.

Table 1
Therapeutic possibilities for male infertility.

Disorder	Treatment
Rational treatment	
IHH and Kallman syndrome	GnRH or gonadotropins
Pituitary insufficiency	Gonadotropins
Prolactinomas	Dopamine agonists
Infections	Antibiotics
Chronic general disease (e.g., renal insufficiency and diabetes mellitus)	Treatment of the basic disease
Drugs/toxins	Elimination
Obstructive azoospermia	Epididymovasostomy
Retrograde ejaculation	Imipramin
Preventive treatment	
Testicular maldescent	GnRH/hCG/orchidopexy
Delayed puberty	Testosterone/GnRH/hCG
Infections	Early antibiotics
Exogenous factors (radiation, drugs, toxins)	Elimination
Malignancies	Gonadal protection Cryopreservation of sperm
No treatment	
Bilateral anorchia	
Complete Sertoli-cell-only syndrome	
Gonadal dysgenesis	
Empirical treatment	
Varicocele	Surgical or radiologic occlusion
Immunological infertility	Immunosuppression
Idiopathic infertility	Various drugs
Symptomatic treatment	
Hypospadias	IUI
Oligoasthenoteratozoospermia	IUI, ART
Globozoospermia	ART
Immotile cilia	ART
Congenital bilateral absence of the vas deferens	ART
Other forms of obstructive azoospermia	ART
Nonobstructive azoospermia with incomplete spermatogenetic failure	ART
Klinefelter syndrome	ART

Abbreviations: ART, assisted reproductive technology; GnRH, gonadotropin-releasing hormone; hCG, human choriogonadotropin; IUI, intrauterine insemination.

Sexually transmitted diseases, even in subclinical forms, have become a major cause of male and female infertility. Other than HIV, the most common are chlamydia, gonorrhea, syphilis, genital herpes, human papilloma virus, hepatitis B, trichomoniasis, and bacterial vaginosis. These diseases can be prevented by refraining from sexual activity, at least with infected partners, and by using condoms. However, although condoms act as barriers to infectious agents, disease transmission may occur in some cases. Early antibiotic treatment is the treatment of choice. Before the introduction of antibiotics, and in regions where antibiotics are not readily available, obstruction of the seminal ducts and azoospermia were and are common consequences of sexually transmitted diseases, especially gonorrhea.

Once obstruction of the seminal ducts has caused azoospermia, refertilization can be attempted by microsurgical epididymovasostomy or vasovasostomy. These techniques can also be used to reverse the contraceptive effect of vasectomy. Although these operations allow sperm to reappear in semen in about 50% of cases, pregnancy may be prevented by sperm antibodies that have developed owing to impairment of the blood-testis barrier. When the problem remains, some men resort to ART to avoid repeated refertilization procedures.

Chronic diseases, such as diabetes mellitus, which may lead to retrograde ejaculation, and renal failure, are often accompanied by infertility. In affected men who desire to become fathers, the best treatment is improvement of the disease. If improvement is not obtained, symptomatic treatment becomes the only choice. Many drugs interfere with fertility, however, and these should be avoided.

4.2. Preventive treatment

Sperm quality and DNA integrity in the adult male can be affected by environmental, occupational, and lifestyle factors. However, in addition to intoxication of industrial or accidental origin, smoking is the only well-documented intoxicating factor with a detrimental effect on human fertility [26,27].

Testicular maldescent, the failure of one or both testes to descend into the scrotal sac, is the most frequent congenital birth defect in male children. Maldescent is the best-characterized risk factor for both infertility and testicular cancer in adulthood. As the effects of human chorionic gonadotropin and gonadotropin-releasing hormone treatments are controversial, orchidopexy became the preferred treatment. The recommended timing for orchidopexy is between the ages of 6 and 12 months, to increase the chances of preserving spermatogonia for spermatogenesis later in life. Fertility is impaired in 33% of the men who underwent unilateral and 66% of the men who underwent bilateral orchidopexy as infants, and the lifetime cancer risk is 5 to 10 times greater in these men than in the general male population. The UK National Screening Committee policy on screening newborn boys for cryptorchidism recommends the following: screening for undescended and maldescended testes both within 72 hours of birth and at the checkup between the 6th and 8th week [28]. Boys with a history of undescended testis should be rescreened during and after puberty because of the risk of testicular malignancy [29].

Sperm cryopreservation preserves fertility, especially in men with cancer. Performed for several decades, it has proved successful in maintaining the fertilizing capacity of sperm for an acceptable pregnancy rate.

4.3. No therapeutic options

It appears self-evident that men with bilateral anorchia, i.e., with no testis on either side, are absolutely infertile. Men who may have testes without spermatogenic tissue, i.e., who have complete Sertoli-cell-only syndrome or gonadal dysgenesis, are also absolutely infertile. Until the arrival of testicular sperm extraction and ICSI, specialists were of the opinion that men with Klinefelter syndrome were also irreversibly infertile. Since then, a single sperm cell found in semen or in testicular tissue can be used to fertilize an egg and to induce a pregnancy. In a review published in 2004, Lanfranco et al. [30] reported that paternity had been achieved via testicular sperm extraction and ICSI for approximately 10% of the men with the 47,XXY karyotype who wished to become fathers. Moreover, studies with mice indicate that pluripotent stem cells may bring fertility even to anorchic men [31].

4.4. Empirical treatment

Since hormones are necessary for normal spermatogenesis, and GnRH and gonadotropin treatments are effective in men with hypogonadotropic hypogonadism, hormones and antihormones have been extensively used in men with idiopathic infertility. However, pregnancy rates following these treatments could not be shown to be better than placebo. Androgens have been prescribed for many years, especially mesterolone. A meta-analysis has revealed, however, that 359 men needed to be treated to achieve 1 more pregnancy than in untreated controls [32]. Finally, antiestrogens are prescribed under the assumption that the resulting increase in endogenous gonadotropins will improve semen quality and enhance the chances for pregnancy. However, a meta-analysis of all published controlled studies demonstrates that this is actually not the case. [32]. In addition, tamoxifen, if taken over long periods, may have toxic effects. Kinins (kallikrein and, more recently, angiotensin-converting enzyme inhibitors for their actions on kinins) as well as antioxidants, such as vitamin C, vitamin E, carnitine, and glutathione, have been ineffective [32] or are still under evaluation [33]. For more than 5 decades, surgical or radiologic occlusion of the spermatic veins has been the treatment of choice for varicocele. However, controlled trials revealed that intensive counseling of the couples and optimization of the female reproductive function result in the same pregnancy rates as interventional treatment for varicocele [34,35].

4.5. Symptomatic treatment

Since, in many cases, the causes of male infertility are unknown or rational treatment is unavailable, therapeutic strategies using ART have been developed to deal with childlessness exclusively as a symptom, without removing the cause of the infertility itself (Table 1). Although ART provides a powerful tool to treat male infertility, the description of ART goes beyond the scope of the present paper, and the reader is referred to reviews of the topic [36].

5. Conclusion

Despite significant recent progress in the pathophysiology of male infertility, the number of conditions whose cause can be treated rationally remains small. However, the prevailing situation should be considered temporary, as andrologic research may succeed in developing treatments that will make ART no longer useful to infertile men. Meanwhile, considering the interdependence of male and female reproductive functions, optimization of female reproductive functions remains of paramount importance to compensate for any male failures.

Conflict of interest

The authors have no conflicts of interest.

References

[1] Nieschlag E, Behre HM, Nieschlag S, editors. Andrology: Male Reproductive Health and Dysfunction. 3rd ed. Heidelberg, Germany: Springer; 2010.
[2] Giwercman A, Giwercman YL. Environmental factors and testicular function. Best Pract Res Clin Endocrinol Metab 2011;25:391–402.
[3] Chia VM, Li Y, Quraishi SM, Graubard BI, Figueroa JD, Weber JP, et al. Effect modification of endocrine disruptors and testicular germ cell tumour risk by hormone-metabolizing genes. Int J Androl 2010;33:588–96.
[4] Toppari J, Virtanen HE, Main KM, Skakkebaek NE. Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. Birth Defects Res A Clin Mol Teratol 2010;88:910–9.

[5] Oatley MJ, Racicot KE, Oatley JM. Sertoli cells dictate spermatogonial stem cell niches in the mouse testis. Biol Reprod 2011;84:639–45.
[6] Figà-Talamanca I, Dondero F, Gandini L, Lenzi A, Lombardo F, Osborn J. Male infertility and occupational exposures: a case-control study. J Occup Med Toxicol 1992;1:255–64.
[7] Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ 1992;305:609–13.
[8] Forti G, Serio M. Male infertility: is its rising incidence due to better methods of detection or an increasing frequency? Hum Reprod 1993;8:1153–4.
[9] Lerchl A, Nieschlag E. Decreasing sperm counts? a critical (re)view. Exp Clin Endocrinol Diabetes 1996;104:301–7.
[10] Fisch H. Declining worldwide sperm counts: disproving a myth. Urol Clin North Am 2008;35:137–46.
[11] Merzenich H, Zeeb H, Blettner M. Decreasing sperm quality: a global problem? BMC Public Health 2010;10:24.
[12] Nieschlag E, Lerchl A. Sperm crisis: what crisis? Asian J Androl 2013;15:184–6.
[13] te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update 2002;8:141–54.
[14] Nieschlag E, Lammers U, Freischem CW, Langer K, Wickings EJ. Reproductive functions in young fathers and grandfathers. J Clin Endocrinol Metab 1982;55:676–81.
[15] Luetjens CM, Rolf C, Gassner P, Werny JE, Nieschlag E. Sperm aneuploidy rates in younger and older men. Hum Reprod 2002;17:1826–32.
[16] Hellstrom WJ, Overstreet JW, Sikka SC, Denne J, Ahuja S, Hoover AM, et al. Semen and sperm reference ranges for men 45 years of age and older. J Androl 2006;27:421–8.
[17] Rolf C, Zitzmann M, Nieschlag E. The aging male and late-onset hypogonadism. In: Nieschlag E, Behre HM, Nieschlag S, editors. Andrology: Male Reproductive Health and Dysfunction. 3rd ed. Heidelberg, Germany: Springer; 2010. p. 239–61.
[18] Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. Fertil Steril 2003;79(Suppl. 3):S1520–7.
[19] Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. Am J Epidemiol 2005;161:816–23.
[20] Frattarelli JL, Miller KA, Miller BT, Elkind-Hirsch K, Scott Jr RT. Male age negatively impacts embryo development and reproductive outcome in donor oocyte assisted reproductive technology cycles. Fertil Steril 2008;90:97–103.
[21] Sartorius GA, Nieschlag E. Paternal age and reproduction. Hum Reprod Update 2010;16:65–79.
[22] Nieschlag E, te Velde E. Why have birth rates dropped? for medical reasons? J Reproduktionsmed Endokrinol 2010;7:403–6.
[23] van der Steeg JW, Steures P, Eijkemans MJ, F Habbema JD, Hompes PG, Kremer JA, et al. Role of semen analysis in subfertile couples. Fertil Steril 2011;95:1013–9.
[24] World Health Organization, Department of Reproductive Health and Research. WHO Laboratory Manual for the Examination and Processing of Human Semen Analysis. 5th ed. Geneva, Switzerland: World Health Organization; 2010.
[25] Simoni M, Tüttelmann F, Gromoll J, Nieschlag E. Clinical consequences of microdeletions of the Y chromosome: the extended Münster experience. Reprod Biomed Online 2008;16:289–303.
[26] Zitzmann M, Rolf C, Nordhoff V, Schräder G, Rickert-Föhring M, Gassner P, et al. Male smokers have a decreased success rate for in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril 2003;79(Suppl. 3):S1550–4.
[27] Gandini L, Lombardo F, Lenzi A, Culasso F, Pacifici R, Zuccaro P, et al. The in-vitro effects of nicotine and cotinine on sperm motility. Hum Reprod 1997;12:727–33.
[28] Main KM, Jensen R, Askland C, Hoi-Hansen C, Skakkebaek N, UK National Screening Committee. Low birth weight and male reproductive function. Horm Res 2006;65 (Suppl. 3):116–22.
[29] Cryptorchidism. In: Tekgül S, Riedmiller H, Gerharz E, Hoebeke P, Kocvara R, Nijman R, et al, editors. Guidelines on paediatric urology. Arnhem, The Netherlands: European Association of Urology and European Society for Paediatric Urology; 2009. p. 8–11 http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf. Accessed April 24, 2013.
[30] Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet 2004;364:273–83.
[31] Hayashi K, Ohta H, Kurimoto K, Aramaki S, Saitou M. Reconstitution of the mouse germ cell specification pathway in culture by pluripotent stem cells. Cell 2011;146:519–32.
[32] Kamischke A, Nieschlag E. Analysis of medical treatment of male infertility. Hum Reprod 1999;14(Suppl. 1):1–23.
[33] Lombardo F, Sansone A, Romanelli F, Paoli D, Gandini L, Lenzi A. The role of antioxidant therapy in the treatment of male infertility: an overview. Asian J Androl 2011;13:690–7.
[34] Nieschlag E, Hertle L, Fischedick A, Abshagen K, Behre HM. Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Hum Reprod 1998;13:2147–50.
[35] Evers JL, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. Lancet 2003;361:1849–52.
[36] De Geyter C, De Geyter M, Behre HM. Assisted reproduction. In: Nieschlag E, Behre HM, Nieschlag S, editors. Andrology: Male Reproductive Health and Dysfunction. 3rd ed. Heidelberg: Springer; 2010. p. 470–504.