J MEDICINE 2012; 13 : 190-199

Male Infertility – A Review

KFM AYAZ[1], MD TITU MIAH[1], HAM NAZMUL AHASAN[2], MD. RAIQ RAIHAN,[3] MD. AMINUL ISLAM,[4] ASHFAQUE AHMED SIDDIQUE[4]

A population size of about 150 million is considered by many to be one of the major problems for Bangladesh. Issues relating to the huge volume of demands and necessities for this huge number of people, the absolute and relative lacking in resources and the hardship that arises as a result of this discrepancy often dominates the discussions. And, so, birth control, contraception and family planning are talked about very frequently as important health issues. On the other end of the spectrum, there are couples who desires child but remain without one after years of marriage. Infertility is a recognized reproductive health problem worldwide with a profound impact on the psychology of the affected couples.

Following regular and frequent unprotected sexual intercourse, about 84% of couples in general population are expected to conceive within one year and about 92% should conceive within two years.[1,2] When a couple fails to conceive even after two years of regular frequent coitus and there is no known reproductive pathology, the couple may be considered infertile.[3-27] The exact prevalence of infertility in Bangladesh is not known. In European countries, about one in seven couples (about 14%) are affected with fertility problems. [3, 4, 7, 10, 11, 15-19, 22, 24, 26, 28-29] In the US, 7.4% of married women aged 15-44 years suffered from infertility problems. [30]

Contrary to the widespread belief that infertility is a female problem, infertility in the male partner contributes to approximately half of all cases. Even, in many studies infertility due to male factors is found to be the commonest single diagnostic category.[31-36]

Causes of Infertility in Male

Male infertility may result from various causes. In most cases, infertility is related to abnormal semen parameters in male. Once upon a time, sperm abnormalities were largely considered as idiopathic, but with advancing of knowledge and technology, explanation is being provided by changes at the genetic level. Apart from seminal causes, varicocele and male accessory gland infections were considered common causes. Systemic causes, medications and endocrinopathies were found responsible in a very low percent of cases.[37] Many environmental and genetic factors have been associated with male infertility or abnormal semen production in male.

Childhood illnesses or conditions may contribute to infertility in the later life. Bilateral cryptorchidism causes significant reduction in spermatogenesis and unilateral cases usually have effects to a lesser degree. Improved fertility rate as a result of orchiopexy at early age is not established. If not corrected by puberty, undescended testis do not function and repair at a later age does not improve fertility rate[38-39]. Testicular trauma and Torsion of testis both may result in atrophic testis. About 30-40% men, who had at least an episode of testicular torsion, have abnormal semen parameters[40-47]. Up to 11% men with a history of testicular torsion have anti sperm antibodies present during or after the event[48-49]. Early childhood mumps usually does not affect testis. But, 30% of male patients of mumps aged above 11-12 years develop unilateral orchitis and, in peripubertal and adult males, bilateral orchitis occurs in about 10% of mumps cases[50]. Severe testicular damage can result from both unilateral and bilateral orchitis from mumps.

Excessive alcohol consumption can be harmful to sperm quality but alcohol consumption of up to three to four units in a day has no proven adverse effect on male fertility[51-55]. Smoking is associated with reduced semen parameters in male.[52, 56-61] But relationship between male smoking pattern and male fertility is not certain. Men with BMI of more than 29 may have reduced fertility. Total number of normal-motile sperm cells may decrease with increased BMI.[62] Sperm DNA fragmentation is higher in male with BMI greater than 25.[63] Obesity may have a negative effect on erectile function in males with coexisting heart disease, diabetes and other existing vascular risk factors.[64]

Increased scrotal temperature has a close association with reduced sperm quality in healthy population.[65-67]

1. Assistant Professor, Department of Medicine, Dhaka Medical College.
2. Professor and Head, Department of Medicine, Dhaka Medical College.
3. Intern Doctor, Department of Medicine, Dhaka Medical College.
4. Indoor Medical Officer, Department of Medicine, Dhaka Medical College.

Correspondence : Dr. KFM Ayaz, Assistant Professor, Department of Medicine Dhaka Medical College.

Occupational heat exposure, sedentary work position, which may lead to inceased scrotal tempertature, have both been associated with abnormal semen quality[67-68] The effect of wearing tight-fitting and loose-fitting underwear on male infertility is uncertain, though there are suggestions that wearing tight-fitting ones may affect fertility adversely.[69-70]

At workplaces, the number of identified chemical and physical agents is about 104,000. Due to the fast pace of their introduction, the effects on reproduction of about 95% of them on reproductive health is not known.[71] Exposure to heat in welders, bakers and drivers lead to abnormal semen parameter.[68] X-ray exposure causes azoospermia and reduced sperm count in radiotherapists but the effects may be reversible.[72-73] Engine drivers, diggers may suffer from oligozoospermia, asthenozoospermia due to effects of vibration.[74] Exposure to Dibromochloropropane in petsicides causes oligozoospermia and azoospermia, which is reversible in most cases, in agricultural workers. [75-78] and is also associated with reduced fertilization rate.[79] Exposure to lead, cadmium, manganese in male metal workers, smelters, battery factory workers may cause reduced fertility through mainly affecting female partners. [80-85] But no association with reproductive problems has also been demonstrated in different study. [86] Glycol ether (solvents) has been associated with reduced fecandibility and oligospermia in painters.[87-88] Ethylene dibromide (pesticide), Polychlorinated biphenyl (in agricultural workers), acetone, carbon disulphide (in chemists and laboratory workers) may cause abnormal semen parameters.[89-93] No association with reproductive problem was reported with the use of carbaryl (pesticides), Mercury (dental amalgam), Toluene, styrene (solvents in plastic and printing industry) and anaesthetic gases (in dentists and anaesthetiss.[94-99] This list is not exhaustive. There are many agents, for which the association is only suspected and need further evaluation.

Prescibed medications including cimetidine, sulfasalazine, long term use of some antibiotics and andogen injection can alter semen quality and cause oligozoospermia.[100-102] After 3 months from withdrawal of the responsible drugs, the effect on semen quality and sperm count may be reversed. Use of â-blockers and psychotropic drugs may lead to impotence.[103] Chemotherapy treamnet may lead to azoospermia, which, in most cases, is permanent.[104] Among recreational drugs, anabolic steroids and cocaine can have adverse effect on the semen quality.[105-107]

Genetic and chromosomal alteration, after all, has its role to play in human azoospermia. Microdeletions on the long arm of the Y chromosome was detected in patients with azoospermia and this region on the Y chromosome was named azospermia factor (AZF) region.[108] Later, close relationship was found between this region and human azoospermia.[109-110]. Microdeletions were found to be concentrated in three regions according to testicular tissue type and AZF region was divided into three subregions AZFa, AZFb and AZFc.[111] The first azopsermia culprit gene to be identified was deleted-in-azospermia (DAZ) gene, isolated in 1995 and is localized to AZFc region.[110] Two years later, a second culprit gene, the RNA-binding motif gene (RBMY, Y chromosome), located in the AZFb region, was reported.[112] In 1999, a new human spermatogenesis gene, USP9Y (DFFRY) was identified in the AZFa region.[113] These three genes are typical spermatogenetic genes located in Y chromosome. Culprit genes were also identified in autosomes following research based on findings in knockout mice. Heterozygous mutation in the human SYCP3 gene, located on chromosome 12 may cause early meiotic arrest. The loss of germ cells leads to clear decrease in the diameter of the seminiferous tubules and vacuole formation in the testes. [114-115] Homozygous mutation of the Human aurora kinase C (AURKC) gene yields large headed polyploidy spermatozoa and causes male infertility in human. [116] Homozygous mutation of SPATA16 (Spermatogenesis-associated 16, also known as NYD-SP12) was found in three brothers of an Ashkenazi Jewish family having Globozoospermia, a rare (incidence <0.1% in male infertile patients) but severe teratozoospermia, characterized by ejaculates consisting completely of round headed spermatozoa that lacks acrosomes.[117-119] Susceptibility to some forms of male infertility may be increased by genetic polymorphism. Polymorphism of several genes have been associated with the human azoospermic population. Polymorphism of MEI1, PRDM9(MEISETZ), SPATA17, PARP-2 and URB-2 genes are considered genetic risk factors as they may contribute to meitotic arrest leading to azoospermia [120-124]. On the other hand, association has been demonstrated between polymorphisms of SEPTIN12 gene and patients with sertoli cell-only syndrome.[125] MTHFR, SHBG, FASLG, BCL2, TSSK6, TSSK2, ESR1, ESR2, eNOS, MDR1, MSH5, TNP1, Piwi, CYP19A1, SOHLH1, MLH3, H2BFWT, EPPIN, NER, GSTM1, GSTT1, PACRG – all these genes have been associated with male infertility. [126]

History Taking in Male Infertility:

A thorough history is the first step in the assessment of suspected male infertility that should carefully include the patients' reproductive and sexual history, developmental history, past medical and surgical history, occupational history, medication and drug history and any history of exposure to toxins or chemicals.

Any prior conceptions with the present of past partners,

previous use of conceptions, frequency and timing of coitus with current partner, frequency of masturbation and timing of first intercourse and masturbation should be included in reproductive and sexual history, Besides, any prior difficulty in achieving conception and previous evaluation and treatments received should be noted. Information about erectile and ejaculatory function should also be recorded.

Presence of unilateral or bilateral undescended testis in the childhood, the age of surgical correction, previous history of testicular trauma and testicular torsion, mumps at any age should be included in the developmental history. The timing of pubertal development, including development of secondary sexual characteristics should be recorded. Any significant delay or incompleteness in pubertal development should be noted and may be an important clue for underlying endocrinopathy.

Any co-existing systemic disease should be noted, including diabetes, liver or renal disease. History of urinary tract infection and sexually transmitted infections should also be obtained.

History of any pelvic or retroperitoneal surgery is important and should be obtained in detail. Testicular cancer and chemotherapy for it and chemotherapy for any malignancy, especially leukemia, lymphoma and sarcomas can cause alteration in male fertility and should be included in the history.

A detailed history of medications and drugs should be obtained including any use of exogenous androgens. History of alcohol consumption and dependency and smoking history may be relevant. Current and past occupations, exposure to excessive heat, radiation, electromagnetic wave or any toxin or chemicals on course of occupational undertakings, involvement of long shift works in work, level of psychological stress related to occupation should be explored during the history taking process.

Physical Examination in Male Infertility:

Physical examination might start with assessing penile curvature, angulation and the location of urethral opening. Careful palpation of the scrotum with the patient in standing position in a warm room should follow. The size and consistency of the testicles may be important and should be noted. An orchidometer can be used for measuring the size of testis. Examination of epididymis should include careful palpation for the caput, corpus and cauda. Full or indurated feeling of the epididymis should also be noted as fullness may indicate obstruction. Presence or absence of vas deferens can be confirmed by palpating the spermatic cord. Any vasal atrophy or nodularity, presence of varicocele within the spermatic cord and surrounding the testicles can be found. If present, varicocele can be graded by palpation and asking the patient to perform valsalva maneuver.

Secondary sexual characters can be assessed and presence or absence of gynaecomastia should be observed. Abnormal andogenization may result from underlying endocrinopathies. Excessive oestrogen, an improper oestrogen-to-androgen ratio or elevated prolactin levels can cause gynaecomastia.

Vital signs recording, BMI estimation, Thyroid gland examination, Abdominal examination for mass, organomegaly, undescended testis or ascitis are parts of routine physical examination. A per-rectal examination can be done to assess perineal sensation, rectal sphincter tone and the size of the prostate gland.[127-128]

Investigations in Male Infertility:

The investigation of a male partner in an infertile or subfertile couple starts with semen analysis. The result of semen analysis indicates fertility status of the male. Semen is collected following 2-7 days' sexual abstinence in a clean container and the container should be transported to laboratory at room temperature. WHO has its own guideline regarding semen parameters based on semen characteristics of "recent fathers". 5th centile is considered the lower range of reference limit. Semen parameters below this reference limit is not enough to consider a man infertile or subfertile and parameters above this level doesnot necessarily confirms fertility of a man, as fertility of a couple may depend on many other factors. For the diagnosis of below par semen quality, two samples should be tested three months apart at the same laboratory.[128]

Table-I

Lower reference limits for semen parameters[129]

Parameters	Lower Reference Limit
Semen Volume (mL)	1.5
Total sperm number ($\times 10^6$ per ejaculate)	39
Sperm concentration ($\times 10^6$ / mL)	15
Total motility(%)	40
Progressive motility(%)	32
Sperm vitality (%)	58
Sperm morphology (Normal forms, %)	4
P^H	>7.2
Peroxidase-positive leucocytes	< 1
Seminal Zinc (µmol/ejaculate)	>2.4
Seminal Fructose (µmol/ejaculate)	>13
Seminal neutral glucosidase (mU/ejaculate)	>20
MAR test (motile spermatozoa with bound particles, %)	<50
Immunobead test (motile spermatozoa with bound beads, %)	<50

Endocrine studies in male infertility should include serum levels of prolactin, LH, FSH, testosterone and E2 (oestradiol). Antisperm antibodies can be found

Reaching a diagnosis:

Azospermia can be classified as obstructive or nonobstructive. In obstructive azoospermia, there is adequate production of sperm but there is failure of delivery of the sperms into the ejaculate due to ductal obstruction. In the nononbstructive azospermia, there is no obstruction, rather a lack of sperm production is responsible.

Small testis with low FSH and testosterone levels suggests hypogonadotrophic hypogonadism and the patient's LH and prolactin level should be measured. Low gonadotrophin associated with elevated prolactin level is found in pituitary prolactinoma and if this is the case, MRI of Brain is necessary.

On the other hand, small atrophic testis with elevated FSH levels suggests germ cell failure. FSH level more than the typical low normal level is suspicious of defective spermatogenesis. FSH level can be raised in unilateral testicular disease. Instead of testicular biopsy, agenetic testing including a karyotype and a Y-chromosome microdeletion analysis should be offered to those with a primary testicular defect without any hormonal deficiency.

Normal-sized testis with a normal FSH level and azospermia raises the possibility of obstruction. A testicular biopsy helps to differentiate between obstruction and maturation arrest.

Low-volume azospermic semen can be found in Hypogonadism (low testosterone level), ejaculatory duct obstruction and absence or hypofunction of seminal vesicles. In Congenital Bilateral Absence of Vas Deferens (CBAVD) and complete bilateral ejaculatory duct obstruction, low-volume azospermic acidic semen is produced.

Oligoasthenoazoospermia (OAT) is the term for defects in number, motility and morphology of sperm in semen. Varicocele is the most common cause followed by environmental toxins, drugs or medications and cryptorchidism. Varicocele can be diagnosed from physical examination and sonographic study.

Defect in sperm morphology is termed teratozoospermia. Mostly idiopathic, varicoceles and effects of temperature in spermatogenesis are potential causes.

Asthenospermia refers to defect in sperm movement with only a low percentage of sperm having any motility. Antisperm antibody and varicocele may be responsible for this defect.

Sperm concentration less than 10×10^6 sperm/mL should warrant estimation of serum FSH and testosterone level. Karyotype and Y chromosome microdeletion analysis should be added to the investigation lists if the concentration is less than 5×10^6 sperm/mL. Varicocele is a common cause of low sperm density but other defects in other sperm parameters usually coexists.

No fluid production in male orgasm is termed complete ejaculatory failure (aspermia). It occurs due to retrograde ejaculation and causes include neurologic abnormalities such as spinal cord injury, diabetes mellitus, multiple sclerosis and the use of á-blockers. Impaired ejaculation can also result from retroperitoneal surgeries, including pelvic surgery and retroperitoneal lymph node dissection. Psychological disturbances and/or serotonin reuptake inhibitors may cause complete inability to obtain orgasm. Differentiation has to be made whether the case is one of true ejaculatory failure or inability to achieve orgasm.[127]

Male infertility can be the consequence of many causes. Structural defect, environmental factors, genetic constitution, chromosomal abnormalities, psychological factors – any one or more of them can act alone or in combination to render a man incapable to procreate.

Abnormal anatomy of male reproductive tract can lead to the failure of delivery of sperm into the ejaculate despite adequate and normal semen production.

Management of male infertility:

As part of management of infertility, couple should be seen together as decisions regarding investigations and treatment affects both partners. The couple should be provided with evidence-based information regarding their care and treatment for making informed decisions. Their choice should be included strongly in the decision-making process. Written information or information through audio-visual media should supplement verbal information.

The couple should be informed about the adverse effect of stress on their relationship which might cause decreased libido and frequency of intercourse and lead to fertility problems. They might be advised to contact a fertility support group and counseling from a person not involved with the management of the fertility issues. Irrespective of outcome, Counselling may be done before, during and after every step in investigation and treatment. Fertility problems should be managed in a specialist settings with access to wider skills rather than a general hospital.

Gonadotrophin drugs should be offered to men with hypogonadotrophic hypogonadism as it may improve infertility. Anti-oestrogens, gonadotrophins, bromocriptins, androgens, kinin-enhancing drugs have not been shown to

be effective in men with idiopathic semen abnormalities. Unless there is an identified infection, men with increased leucocyte count in semen should not be prescribed antibiotics as it doesnot improve outcome. The significance of antisperm antibody is unclear and corticosteroid has an uncertain beneficial effect.

Surgical correction of epididymal blockage may be offered in obstructive azoospermia. Patency of the duct is likely to be restored and fertility may be improved. This may be used as an alternative to in-vitro fertilization or sperm extraction. Surgical correction of Varicocele doesnot improve fertility rates.

Anejaculation can be managed with alpha-agonists or parasympathomimetics and neostigmineand for retrograde ejaculation alpha-agonosts or anticholinergic drugs and antihistamins are used to increase sympathetic tone of the bladder or to reduce parasympathetic activity. In anejaculation, Ejaculation can be stimulated through penile electrovibration or trasnrectal electroejaculation by initiating spinal cord reflex activity and stimulating nerves responsible for ejaculation respectively. In case of retrograde ejaculation, sperms can be retrieved from urine. Obtained sperms can be used for fertilization through Intrauterine Insemination (IUI), In Vitro Fertilization (IVF), Intracytoplasmic Sperm Injection (ICSI) or Gamete Intrafallopian Transfer (GIFT) in the female partner. If ejaculation failure is due to anxiety or psychological problems, anxiolytics may be useful.

If the male partner has obstructive or nonobstructive azoospermia, spermatozoa can be retrieved from both the testis and epididymis using various techniques. This procedure is also useful in case of ejaculatory failure or if only non-motile spermatozoa are present in the ejaculate. Sperm is retrieved from testis or epiddidymis by percutaneous epididymal sperm aspiration (PESA), Testicular Sperm Aspiration (TESA) / Testicular Fine Needle Aspiration (TEFA), Testicular Sperm Extraction (TESE) from a testicular biopsy or Microsurgical Epididymal Sperm Aspiration (MESA).

In obstructive azospermia sperm can be obtained from epididymis by PESA or MESA or from testis by TESA or TESE. Sperm can also be obtained by percutaneous puncture from naturally occurring spermatocele. In nonobstructive azospermia sperm has to obtained from testis by TESA or TESE and chance of sperm extraction is reduced. As the extracted sperm are immature, they have low fertilizing capacity with standard IVF and ICSI has to be used. With ICSI, it is possible to achieve fertilization with a single sperm. ICSI is also useful in men with very low semen quality. But before going for ICSI in patients with nonobstructive azoospermia or very low quality semen, consideration should be given to any underlying genetic abnormality. If a specific genetic condition is known or suspected, the couple should be subjected to appropriate counseling and treatment. Karyotype of the man should be established. Testing for Y chromosome microdeletion may be avoided as a routine procedure but the possible association of this gene with infertility should be informed to the couple.

Prior to the availability of ICSI, donor insemination was the option to solve the male infertility problem in obstructive and nonobstructive azoospermia. Donor insemination is also an option when the male partner is likely to pass on some inherited genetic disorder or infections like HIV to the fetus or when severe Rhesus incompatibility can be a problem.

Often couple may decide to avoid ICSI due to its invasive nature or due to the genetic risks involved. Many couple might find the cost of ICSI-IVF too high to afford. For them, donor insemination is the method of choice. Again, some couple may choose donor insemination as an alternative method following failure with ICSI. On the other hand, often ICSI is preferred over donor insemination on the ground that if successful, the offspring is genetically related to both parents. So a couple should be informed of the relative merits of both options and counseling should be done about the physical and psychological issues of the couple and their offspring, should they consider donor insemination.

Conclusion:

Infertility poses a multidimensional problem for any couple. Though predominantly it is a physical issue, the effect on psychology of both partners is enormous. From detection and in every step of evaluation and management, both partners are subjected to tremendous anxiety. Psychological stress leads to decreased morale, maladjustment between couples and may also cause decrease work performance. Social stigmata are also big issues in developing country like ours. Traditionally, women are inappropriately blamed for infertility problems, where actually men are responsible almost equally. More research is needed regarding male partners' fertility problems, especially regarding the associations with different occupations and occupational and accidental exposure to toxins, chemicals and environmental agents. As newer techniques have been developed, the opportunity for the infertile couples is more to achieve conception. Yet, many of these techniques are costly and remain beyond the affordability of a major portion of the population.

Conflict of Interest: None

References:

1. te Velde ER, Eijkemans R, Habbema HDF. Variation in couple fecundity and time to pregnancy, an essential concept in human reproduction. Lancet 2000;355:1928–9
2. Bongaarts J. A method for the estimation of fecundability. Demography 1975;12:645–60
3. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, et al. Population study of causes, treatment, and outcome of infertility. BMJ 1985;291:1693–7
4. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, et a*l.* Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod 1991;6:811–6
5. The epidemiology of infertility. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1975;582:1–37
6. Rachootin P, Olsen J. Social selection in seeking medical care for reduced fecundity among women in Denmark. J Epidemiol Community Health 1981;35:262–4
7. Rachootin P, Olsen J. Prevalence and socioeconomic correlates of subfecundity and spontaneous abortion in Denmark. Int J Epidemiol 1982;11:245–9
8. Mosher WD. Reproductive impairments in the United States. 1965–1982. Demography 1985;22:415–30
9. Hirsch MB, Mosher WD. Characteristics of infertile women in the United States and their use of infertility services. Fertil Steril 1987;47:618–25
10. Johnson G, Roberts D, Brown R, Cox E, Evershed Z, Goutam P, et al. Infertile or childless by choice? A multipractice survey of women aged 35 and 50. BMJ 1987;294:804–6
11. Marchbanks PA, Peterson HB, Rubin GL, Wingo PA. Research on infertility: definition makes a difference. The Cancer and Steroid Hormone Study Group. Am J Epidemiol 1989;130:259–67
12. Martin TE. Infertility in a large Royal Air Force General Practice. J R Army Med Corps 1989;135:68–75
13. Weinberg CR. Infertility and the use of illicit drugs. Epidemiology 1990;1:189–92
14. Sundby J, Lund E. [Subfertility and infertility. A sample of Norwegian women]. [Norwegian]. Tidsskr Nor Laegeforen 1989;19–21:1996–8
15. Greenhall E, Vessey M. The prevalence of subfertility: a review of the current confusion and a report of two new studies. Fertil Steril 1990;54:978–83
16. Templeton A, Fraser C, Thompson B. The epidemiology of infertility in Aberdeen. BMJ 1990;301:148–52
17. Templeton A, Fraser C, Thompson B. Infertility-epidemiology and referral practice. Hum Reprod 1991;6:1391–4
18. Ghazi HA, Spielberger C, Kallen B. Delivery outcome after infertility – a registry study. Fertil Steril 1991;55:726–32
19. Hogberg U, Sandstrom A, Nilsson NG. Reproductive patterns among Swedish women born 1936–1960. Acta Obstet Gynecol Scand 1992;71:207–14
20. Webb S, Holman D. A survey of infertility, surgical sterility and associated reproductive disability in Perth, Western Australia. Aust J Public Health 1992;16:376–81
21. Rowe PJ, Comhaire FH, Hargreave TB, Mellows HJ. WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple. Cambridge: Cambridge University Press; 1997
22. Gunnell DJ, Ewings P. Infertility prevalence, needs assessment and purchasing. J Public Health Med 1994;16: 29–35
23. Schmidt L, Munster K, Helm, P. Infertility and the seeking of infertility treatment in a representative population. Br J Obstet Gynaecol 1995;102:978–84
24. Schmidt L, Munster K. Infertility, involuntary infecundity, and the seeking of medical advice in industrialised countries 1970–1992: A review of concepts, measurements and results. Hum Reprod 1995;10:1407–18
25. The ESHRE Capri Workshop. Guidelines to the prevalence, diagnosis, treatment and management of infertility, 1996. Hum Reprod 1996;11:1775–807
26. Buckett W, Bentick B. The epidemiology of infertility in a rural population. Acta Obstet Gynecol Scand 1997; 76: 233–7
27. Stephen EH, Chandra A. Use of infertility services in the United States: 1995. Fam Plann Perspect 2000;32:132–7
28. Page H. Estimation of the prevalence and incidence of infertility in a population: a pilot study. Fertil Steril 1989;51:571–7
29. Rantala M-L, Koskimies AI. Infertility in women participating in a screening program for cervical cancer in Helsinki. Acta Obstet Gynecol Scand 1986;65:823–5
30. Chandra A, Martinez GM, Mosher WD, Abma JC, Jones J. Fertility, family planning, and reproductive health of U.S. women: Data from the 2002 National Survey of Family Growth. National Center for Health Statistics. Vital Health Stat 2005;23(25):22,108
31. Collins JA, Wrixon W, Janes LB. and Wilson EH. Treatment-independent pregnancy among infertile couples. N. Engl. J. Med. 1983*;*309:1201-1206
32. Cates W, Farley TMM and Rowe PJ. Worldwide patterns of infertility: is Africa different? Lancet. 1985 Sep 14;2(8455):596-8

33. Haxton MJ and Black WP. The aetiology of infertility in 1162 investigated couples. Clin Exp Obstet Gynecol. 1987;14(2):75-9

34. Randall JM and Templeton AA. Infertility: the experience of a tertiary referral centre. Health Bull. 1991;49:48-53

35. Thonneau P, Marchand S, Tallec A. et al. Incidence and main causes of infertility in a resident population (1 850 000) of three French regions (1988- 1989). Hum. Reprod. 1991;6:811-816

36. Schmidt L, Minister K and Helm P. Infertility and the seeking of infertility treatment in a representative population. Br. J. Obstet. Gynaecol. 1995;102:978-984

37. Irvine DS. Epidemiology and aetiology of male infertility. Hum Reprod 1998;13(1):33-44

38. Grasso M, Buonaguidi A, Lania C, Bergamaschi F, Castelli M and Rigatti P. Postpubertal cryptorchidism: review and evaluation of the fertility. European Urology 1991;20(2): 126-128

39. A. Okuyama A, Nonomura N, Nakamura N, et al. Surgical management of undescenced testis: retrospective study of potential fertility in 274 cases. Journal of Urology 1989;142(3):749–751

40. Anderson JB and Williamson RCN. The fate of the human testes following unilateral torsion of the spermatic cord. British Journal of Urology 1986; 58(6):698–704

41. Anderson JB and R. C. N. Williamson RCN. Fertility after torsion of the spermatic cord. British Journal of Urology 1990;65(3):225-230

42. Bartsch G, Frank S, Marberger H, and Mikuz G. Testicular torsion: late results with special regard to fertility and endocrine function. Journal of Urology 1980;124(3): 375–378

43. Dondero F, Lenzi A, Picardo M, Pastore R, Valesini G. Cell-mediated antisperm immunity in selected forms of male infertility. Andrologia 1980;12(1): 25–29

44. I. Fraser I, N. Slater N, C. Tate C, and J. G. Smart JG. Testicular torsion does not cause autoimmunization in man. British Journal of Surgery 1985;72(3):237–238

45. Mastrogiacomo I, Zanchetta R, Graziotti P, Betterle C, Scrufari P and Lembo A. Immunological and clinical study in patients after spermatic cord torsion. Andrologia 1982;14(1):25–30

46. Puri P, Barton D, and O'Donnell B. Prepubertal testicular torsion: subsequent fertility. Journal of Pediatric Surgery 1985;20(6):598–601

47. Thomas WEG, Cooper MJ and Crane GA. Testicular exocrine malfunction after torsion. Lancet 1984 Dec 15;2(8416):1357-60

48. Hagen P, Buchholz MM, Eigenmann J and Bandhauer K.Testicular dysplasia causing disturbance of spermiogenesis in patients with unilateral torsion of the testis. Urologia Internationalis 1992;49(3):154-157

49. Anderson MJ, Dunn JK, Lipshultz LI and Coburn M. Semen quality and endocrine parameters after acute testicular torsion. Journal of Urology 1992;147(6):1545-1550

50. Werner CA. Mumps orchitis and testicular atrophy; a factor in male sterility. Annals of Internal Medicine 1950;32(6):1075–1086

51. Brzek A. Alcohol and male fertility (preliminary report). Andrologia 1987;19:32–6

52. Marshburn PB, Sloan CS, Hammond MG. Semen quality and association with coffee drinking, cigarette smoking, and ethanol consumption. Fertil Steril 1989;52:162–5

53. Dunphy BC, Barratt CL, Cooke ID. Male alcohol consumption and fecundity in couples attending an infertility clinic. Andrologia 1991;23:219–21

54. Oldereid NB, Rui H, Purvis K. Life styles of men in barren couples and their relationship to sperm quality. Int J Fertil 1992;37:343–9

55. Department of Health. Alcohol and Health. Drinking Sensibly. 2002. [www.doh.gov.uk/alcohol/alcoholandhealth.htm] Accessed 7 January 2004

56. Vine MF, Margolin BH, Morrison HI, Hulka BS. Cigarette smoking and sperm density: a meta-analysis. Fertil Steril 1994;61:35–43

57. Merino G, Lira SC, Martinez-Chequer JC. Effects of cigarette smoking on semen characteristics of a population in Mexico. Arch Androl 1998;41:11–5

58. Zhang JP, Meng QY, Wang Q, Zhang LJ, Mao YL, Sun ZX. Effect of smoking on semen quality of infertile men in Shandong, China. Asian J Androl 2000;2:143–6

59. Trummer H, Habermann H, Haas J, Pummer K. The impact of cigarette smoking on human semen parameters and hormones. Hum Reprod 2002;17:1554–9

60. Dunphy BC, Barratt CLR, von Tongelen BP, Cooke ID. Male cigarette smoking and fecundity in couples attending an infertility clinic. Andrologia 1991;23:223–5

61. Kunzle R, Mueller MD, Hanggi W, Birkhauser MH, Drescher H, Bersinger NA. Semen quality of male smokers and nonsmokers in infertile couples. Fertil Steril 2003;79:287–91

62. Kort HI, Massey JB, Elsner CW, Toledo AA, Mitchell-Leef D, Roudebush WE. Men with high body mass index values present with lower numbers of normal-motile sperm cells. Abstract no. P-355. Fertil Steril 2003;80 Suppl 3;S238

63. Kort HI, Massey JB, Witt MA, Mitchell-Leef D, Durrance MH, Roudebush WE. Sperm chromatin integrity is related

to body mass index: men presenting with high BMI scores have higher incidence of sperm DNA fragmentation. Abstract no. P-333. Fertil Steril 2003;80 Suppl 3;S232

64. Chung WS, Sohn JH, Park YY. Is obesity an underlying factor in erectile dysfunction? Eur Urol 1999;36:68–70

65. Mieusset R, Bujan L. Testicular heating and its possible contributions to male infertility: a review. Int J Androl 1995;18:169–84

66. Hjollund NH, Storgaard L, Ernst E, Bonde JP, Olsen J. Impact of diurnal scrotal temperature on semen quality. Reprod Toxicol 2002;16:215–21

67. Hjollund NH, Bonde JP, Jensen TK, Olsen J. Diurnal scrotal skin temperature and semen quality. Int J Androl 2000;23:309–18

68. Thonneau P, Bujan L, Multigner L, Mieusset R. Occupational heat exposure and male fertility: a review. Hum Reprod 1998;13:2122–5

69. Tiemessen CH, Evers JL, Bots RS. Tight-fitting underwear and sperm quality. Lancet 1996;347:1844–5

70. Munkelwitz R, Gilbert BR. Are boxer shorts really better? A critical analysis of the role of underwear type in male subfertility. J Urol 1998;160:1329–33

71. Gold EB, Lasley BL, Schenker MB. Introduction: rationale for an update. Reproductive hazards. Occup Med 1994;9:363–72

72. Clifton DK, Bremner WJ. The effect of testicular X-irradiation on spermatogenesis in man. A comparison with the mouse. J Androl 1983;4:387–92

73. Brent R, Meistrich M, Paul M. Ionizing and nonionizing radiations. In: Paul M, editor. Occupational and Environmental Reproductive Hazards: A Guide for Clinicians. Baltimore: Williams & Wilkins; 1993. p. 165–200

74. Penkov A, Tzvetkov D. Effect of vibrations on male reproductive system and function. Cent Eur J Public Health 1999;7:149–54

75. Egnatz DG, Ott MG, Townsend JC, Olson RD, Johns DB. DBCP and testicular effects in chemical workers: an epidemiological survey in Midland, Michigan. J Occup Med 1980;22:727–32

76. Slutsky M, Levin JL, Levy BS. Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. Int J Occup Environ Health 1999;5:116–22

77. Potashnik G, Ben Aderet N, Israeli R, Yanai-Inbar I, Sober I. Suppressive effect of 1,2-dibromo-3-chloropropane on human spermatogenesis. Fertil Steril 1978;30:444–7

78. Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. J Occup Environ Med 1995;37:1287–92

79. Tielemans E, van Kooij R, te Velde ER, Burdorf A, Heederik D. Pesticide exposure and decreased fertilisation rates in vitro. Lancet 1999;354:484–5

80. Gennart JP, Buchet JP, Roels H, Ghyselen P, Ceulemans E, Lauwerys R. Fertility of male workers exposed to cadmium, lead, or manganese. Am J Epidemiol 1992;135:1208–19

81. Alexander BH, Checkoway H, van Netten C, Muller CH, Ewers TG, Kaufman JD, et al. Semen quality of men employed at a lead smelter. Occup Environ Med 1996;53:411–6

82. Robins TG, Bornman MS, Ehrlich RI, Cantrell AC, Pienaar E, Vallabh J, et al. Semen quality and fertility of men employed in a South African lead acid battery plant. Am J Ind Med 1997;32:369–76

83. Telisman S, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocic B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect 2000;108:45–53

84. Lancranjan I, Popescu HI, GAvanescu O, Klepsch I, Serbanescu M. Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 1975;30:396–401

85. Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M, et al. Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. Occup Environ Med 2002;59:234–42

86. Coste J, Mandereau L, Pessione F, Bregu M, Faye C, Hemon D, et al. Lead-exposed workmen and fertility: a cohort study on 354 subjects. Eur J Epidemiol 1991;7:154–8

87. Wennborg H, Bodin L, Vainio H, Axelsson G. Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden. Occup Environ Med 2001;58: 225–31

88. Welch LS, Schrader SM, Turner TW, Cullen MR. Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. Am J Ind Med 1988;14:509–26. Erratum in Am J Ind Med 1989;15:239

89. Baranski B. Effects of the workplace on fertility and related reproductive outcomes. Environ Health Perspect 1993;101 Suppl 2:81–90

90. Rozati R, Reddy PP, Reddanna P, Mujtaba R. Xenoesterogens and male infertility: myth or reality? Asian J Androl 2000;2:263–9

91. Hauser R, Altshul L, Chen Z, Ryan L, Overstreet J, Schiff I, et al. Environmental organochlorines and semen quality: results of a pilot study. Environ Health Perspect 2002;110:229–33

92. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H, et al. Occupationally related exposures

and reduced semen quality: a case–control study. Fertil Steril 1999;71:690–6

93. Lindbohm ML. Effects of occupational solvent exposure on fertility. Scand J Work Environ Health 1999;25 Suppl 1:44–6

94. Whorton MD, Milby TH, Stubbs HA, Avashia BH, Hull EQ. Testicular function among carbaryl-exposed exployees. J Toxicol Environ Health 1979;5:929–41

95. Hanf V, Forstmann A, Costea JE, Schieferstein G, Fischer I, Schweinsberg F. Mercury in urine and ejaculate in husbands of barren couples. Toxicol Lett 1996;88:227–-331

96. Kolstad HA, Bisanti L, Roeleveld N, Baldi R, Bonde JP, Joffe M. Time to pregnancy among male workers of the reinforced plastics industry in Denmark, Italy and the Netherlands. Scand J Work Environ Health 2000;26:353–8

97. Plenge-Bonig A, Karmaus W. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. Occup Environ Med 1999;56:443–8

98. Dahl JE, Sundby J, Hensten-Pettersen A, Jacobsen N. Dental workplace exposure and effect on fertility. Scand J Work Environ Health 1999;25:285–90

99. Knill-Jones RP, Newman BJ, Spence AA. Anaesthetic practice and pregnancy. Controlled survey of male anaesthetists in the United Kingdom. Lancet 1975;2:807–9

100. Van Thiel DH, Gavaler JS, Smith WI Jr, Paul G. Hypothalamic-pituitary-gonadal dysfunction in men using cimetidine. N Engl J Med 1979;300:1012–5

101. Marmor D. The effects of sulphasalazine on male fertility. Reprod Toxicol 1995;9:219–23

102. Fody EP, Walker EM. Effects of drugs on the male and female reproductive systems. Ann Clin Lab Sci 1985;15: 451–8

103. Beeley L. Drug-induced sexual dysfunction and infertility. Adverse Drug React Acute Poisoning Rev 1984;3:23–42

104. Shalet SM. Cytotoxic endocrinopathy: a legacy of insults. J R Soc Med 1997;90:192–9

105. Bracken MB, Eskenazi B, Sachse K, McSharry JE, Hellenbrand K, Leo-Summers L. Association of cocaine use with sperm concentration, motility, and morphology. Fertil Steril 1990;53:315–22

106. Knuth UA, Maniera H, Nieschlag E. Anabolic steroids and semen parameters in bodybuilders. Fertil Steril 1989;52:1041–7

107. Torres-Calleja J, Gonzalez-Unzaga M, DeCelis-Carrillo R, Calzada-Sanchez L, Pedron N. Effect of androgenic anabolic steroids on sperm quality and serum hormone levels in adult male bodybuilders. Life Sci 2001;68:1769–74

108. Tiepolo L and Zuffardi O. Localization of factors controlling spermatogenesis in the nonfluorescent portion of the human Y chromosome long arm. Hum Genet. 1976 Oct 28;34(2):119-24

109. Vogt P, Chandley AC, Hargreave TB, Keil R, Ma K, and Sharkey A. Microdeletions in interval 6 of the Y chromosome of males with idiopathic sterility point to disruption of AZF, a human spermatogenesis gene. Hum Genet 1992 Jul;89(5):491-6

110. Reijo R, Lee TY, Salo P, et al. Diverse spermatogenic defects in humans caused by Y chromosome deletions encompassing a novel RNA-binding protein gene. Nat Genet 1995 Aug;10(4):383-93

111. Vogt PH, Edelmann A, Kirsch S, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. Hum. Mol. Genet. 1996;5(7):933-943

112. Elliott DJ, Millar MR, Oghene K, et al. Expression of RBM in the nuclei of human germ cells is dependent on a critical region of the Y chromosome long arm. Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):3848-53

113. Sun C, Skaletsky H, Birren B, et al. An azoospermic man with a de novo point mutation in the Y-chromosomal gene USP9Y. Nat Genet. 1999 Dec;23(4):429-32

114. Yuan L, Liu JG, Zhao J, Brundell E, Daneholt B and Höög C. The murine SCP3 gene is required for synaptonemal complex assembly, chromosome synapsis, and male fertility. Mol Cell. 2000 Jan;5(1):73-83

115. Miyamoto T, Hasuike S, Yogev L, et al. Azoospermia in patients heterozygous for a mutation in SYCP3. Lancet. 2003 Nov 22;362(9397):1714-9

116. Dieterich K, Rifo RS, Faure AK, et al. Homozygous mutation of AURKC yields large-headed polyploid spermatozoa and causes male infertility. Nat Genet. 2007 May;39(5):661-5

117. Dam AH, Feenstra I, Westphal JR, Ramos L, van Golde RJ, and Kremer JA. Globozoospermia revisited. Hum. Reprod. Update (January/February 2007) 13(1): 63-75

118. Dam AHDM, Koscinski I, Kremer JAM, et al. Homozygous mutation in SPATA16 is associated with male infertility in human globozoospermia. Am J Hum Genet. 2007 Oct;81(4):813-20

119. Xu M, Xiao J,Chen J, et al. Identification and characterization of a novel human testis-specific Golgi protein, NYD-SP12. Mol Hum Reprod. 2003 Jan; 9(1): 9-17

120. Sato H, Miyamoto T, Yogev L, et al. Polymorphic alleles of the human MEI1 gene are associated with human azoospermia by meiotic arrest. J Hum Genet. 2006; 51(6):533-40

121. Miyamoto T, Koh E, Sakugawa N, et al. Two single nucleotide polymorphisms in PRDM9 (MEISETZ) gene may be a genetic risk factor for Japanese patients with azoospermia by meiotic arrest. J Assist Reprod Genet. 2008 Nov-Dec;25(11-12):553-7

122. Miyamoto T, Tsujimura A, Miyagawa Y, et al. A single nucleotide polymorphism in SPATA17 may be a genetic risk factor for Japanese patients with meiotic arrest. Asian J Androl. 2009 Sep;11(5):623-8

123. Sakugawa N, Miyamoto T, Tsujimura A, et al. LMTK2 and PARP-2 gene polymorphism and azoospermia secondary to meiotic arrest. J Assist Reprod Genet. 2009 October; 26(9-10): 545–552.

124. Miyamoto T, Tsujimura A, Miyagawa Y, et al. Single nucleotide 4 polymorphism in the UBR2 gene may be a genetic risk factor for Japanese patients with azoospermia by meiotic arrest. J Assist Reprod Genet. 2011 Aug;28(8):743-6

125. Miyakawa H, Miyamoto T, Koh E, et al. Single-nucleotide polymorphisms in the SEPTIN12 gene may be a genetic risk factor for Japanese patients with sertoli cell-only syndrome. J Androl. 2012 May-Jun;33(3):483-7

126. Miyamoto T, Tsujimura A, Miyagawa Y, Koh E, Namiki M and Sengoku K. Male Infertility and its causes is Human. Adv Urol. 2012; 2012: 384520

127. Kobayashi H, Nagao K and Nakajima K. Focus Issue on Male Infertility. Adv Urol. 2012; 2012: 823582

128. Kamel RM. Management of the infertile couple: an evidence based protocol. Reprod Biol Endocrinol. 2010 Mar 6;8:21

129. WHO. WHO laboratory manual for the examination and processing of human semen . 5th ed. Switzerland: WHO press;2010. p. 223-224

130. National Collaborating Centre for Women's and Children's Health (UK). Fertility: Assessment and Treatment for People with Fertility Problems. NICE Clinical Guidelines, No. 11. London (UK): RCOG Press; 2004 Feb. p. 52-120