

Etiology, investigation and treatment of Human men's infertility

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Abstract:

Infertility is a worldwide reproductive health and emotionally charged problem that affects approximately 15% of married couples. In recent years, male infertility has increased in the industrialized countries due to a decline in sperm counts and a rise in testicular and sperm pathologies. There seems to be a direct relationship between modern lifestyles and declining male fertility and the statistics are alarming. In this review, etiological factors of human male infertility known up to date and the techniques employed in fertility research are evaluated.

Key words: Infertility, subfertile, etiology Regards, J.Poongothai

Introduction:

Generally, worldwide it is estimated that one in seven couples have problems in conceiving (1) with the incidence similar in most countries independent of the level of the country's development. Infertility is the failure of a couple to become pregnant after one year of regular, unprotected intercourse. For some couples attempting pregnancy, something goes wrong in the complex reproduction process, resulting in infertility. An estimated 15% of couples are considered infertile, with approximately 35% due to female factors alone, 30% due to male factors alone, 20% due to a combination of female and male factors, and 15% unexplained. Infertility is conceptualized as a major crisis in life. Conditions of the male that affect fertility are still generally underdiagnosed and undertreated. The man should be evaluated concurrently with the woman, since a male factor is the primary or contributing cause in 40% to 60% of cases (2), and about 60%–75% of male infertility cases are idiopathic, since the molecular mechanisms underlying the defects remain unknown (3). One-half of 1% of men

were functionally sterile (Sperm counts below 20 million per milliliter of semen) in 1938. Today it has reached between 8-12% (Cecil Jacobson, Reproductive Genetics Center Vienna, Virginia).

This review will present a comprehensive outline of the etiologies of human male infertility known up to date and to appraise the techniques being employed to produce new insights in fertility research. Review was been done on PubMed by quering the words like “male infertility”, “etiologies” and “treatment-IUI, IVF, ICSI”. The results were limited to the studies on humans written within last 10 years. This review was dedicated to clinicians, scientists, and infertile couples considering Assisted Reproductive Technologies (ART) to realize the complexity of the disorder and to increase the chances of having a healthy infant through proper counseling and treatment.

Milieu of male infertility

Infertility in couples can be classified as primary or secondary. Even some couples are subfertile and unexplained infertility also predominates. The incidence and the causes of male infertility and male reproductive ill-health are important issues that remain poorly characterized. It has been associated with several genetic, non-genetic and epigenetic conditions.

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Genetic causes

Genetic causes account for 10-15% of severe male infertility, including chromosomal aberrations and single gene mutations. Genetic factors involved in male infertility manifest as chromosomal disorders (Klinefelter syndrome (XXY) and specific translocations, point mutations in the androgen receptor and the cystic fibrosis transmembrane conductance regulator (CFTR) gene), mitochondrial DNA (mtDNA) mutations, monogenic disorders, multifactorial disorders and endocrine disorders of genetic origin. The Y chromosome microdeletions in the AZF region have been identified as a relatively common cause of male infertility (4,5). mtDNA play a significant role in the impaired fertility of oligoasthenospermic men (6). Numerous studies have implicated the role of gross genomic rearrangements in male infertility, e.g., constitutional aneuploidy, translocations, inversions, elevated sperm disomy, and DNA damage (7). It is currently unclear to what extent these risk factors influence male infertility. Consequently the identification of genetic factors has become good practice for appropriate management of the infertile couple.

Non genetic causes

Non-genetic causes include hypogonadotropic hypogonadism, testicular maldescence, structural abnormalities of the male genital tract (obstruction of spermatic ducts, agglutination of sperm), genital infections, hormonal causes, impotency, previous scrotal or inguinal surgery, varicoceles, chronic illness, medication, exposure to chemicals, and immunological causes (8,9,10,11,12). It also has been associated with an ever-increasing number of putative risk factors, including current exposures or parental exposures to occupational, lifestyle or environmental factors (13).

Epigenetic cause of male infertility

The accurate transmission of epigenetic information also has considerable influence on fertility in males and on the fertility of their offspring (14). Hypermethylation of the promoter of MTHFR (Methylene Tetra HydroFolate Reductase) gene in sperms is associated with idiopathic male infertility (15,16).

Diagnosis of male infertility

Sperm dysfunction is the single most common cause of infertility, yet what is remarkable is that, there is no drug a man can take or add to his

spermatozoa *in vitro* to improve fertility. In addition to detecting treatable abnormalities, evaluation of the infertile man is critical to uncover life-threatening problems associated with the symptom of infertility, as well as genetic conditions associated with male infertility that could be transmitted to offspring with assisted reproduction (17). The WHO manual has always been the bedrock of andrology and the fifth version is likely to assist the development of the field still further. Technological development is likely to bring the reality of sperm function testing closer to implementation into the clinical pathways (18).

Evaluation of Male infertility

The initial evaluation of the male patient should be rapid, noninvasive, and cost-effective, as nearly 70% of conditions that cause infertility in men can be diagnosed with history, physical examination, hormonal and semen analysis alone. More detailed, expensive, and invasive studies can then be structured if necessary. It is sometimes hard to know whether the sperm problem is the only cause, or just a contributing cause to the infertility. This is a biochemical issue at the molecular level where in semen analysis should be always coupled with sperm testing.

Treatment of Infertility

Andrology or the male counterpart of gynaecology has gradually emerged as a speciality in its own right (19). The histories of progress in the fields of genetics and andrology are rich and include many breakthroughs. Many different causes underlie male factor infertility and its treatment is difficult at best. The clinician first needs a thorough understanding of male reproductive anatomy and physiology. Most hormonal imbalances can be readily identified and successfully treated nonsurgically. Additionally, a large number of patients require surgery to improve sperm production or to improve sperm delivery. However, the treatment of men with unexplained idiopathic infertility remains a challenge. There are three kinds of infertility treatment: Medical treatment, Surgical treatment and Assisted Reproductive Technology (ART).

Medical management of male infertility

Medical management of male infertility occurs when a specific contributing factor that is potentially amenable to attempt at medical treatment (reversible causes of infertility) is identified. Specific medical treatment is applicable for: Hypogonadotropic hypogonadism, Hyperprolactinemia, Luteinizing hormone deficiency, Follicle-stimulating hormone

deficiency, Testosterone deficiency, Hypothyroidism, Congenital adrenal hyperplasia, Anabolic steroid abuse, Immunologic infertility, Genital tract infection, Ejaculation disorders, Reactive oxygen species and antioxidants.

Nonspecific medical treatment:

Despite the advancements in diagnostic methodology, no identifiable cause can be found in relatively less number of infertile men. These patients are treated with nonspecific medications in an attempt to improve semen parameters and subsequent fertility potential through intercourse. Additionally, empiric therapies may be tried for patients with identifiable and potentially treatable causes of subfertility who have failed to adequately respond to specific treatments. These include Gonadotropin releasing hormone therapy, Gonadotropins, Androgens, Testosterone rebound therapy, Anti-estrogens, Aromatase inhibitors, Growth hormone, Carnitine, Kallikrein, Pentoxifylline.

Surgical treatment of male infertility

In the past, surgical procedures for the infertile male were considered by many urologists to fall into two categories: diagnostic and therapeutic. With the advent of testicular sperm extraction (TESE) and ICSI, little remains in the diagnostic category except vasography, which is incorporated into treatment as a part of the surgical correction for obstruction. A testis biopsy still may be defined as diagnostic, although it is probably best used as a prognostic tool to determine the chance of successful reconstruction for men with obstruction or to define for a couple the probability of being able to perform surgical sperm retrieval in cases of non-obstructive azoospermia. Specific surgical treatments are Varicocelectomy, Vasovasostomy, Vasoepididymostomy, Transurethral resection of the ejaculatory ducts (20). In the absence of a correctable etiology, patients can be managed with either empirical medical therapy or assisted reproduction techniques.

Assisted Reproductive Technologies (ART)

Science, thanks to the commitment of huge amount of human capitals and supportive fundings, reaching new position and spreading out the borders on human chances in a sphere so delicate like birth. In recent years there has been increasing concern about a possible decline in reproductive health, and this trend is paralleled by an increasing demand for infertility treatments. As many as 8% of children in some Western countries are born as a result of assisted reproductive techniques (21). As the field of assisted

reproduction has advanced, many previously untreatable men are now biological fathers. The development of assisted reproductive technology (ART), enabling the use of epididymal or testicular sperm for fertilization of the partner's oocytes, has made biological fatherhood possible for men with obstructive azoospermia (22). Quality control is essential for maintenance and improvement of a successful ART technique. ART includes intra uterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). ART technologies made a lot of progress last years and their field of applications extended.

IntraUterine Insemination (IUI) - low-cost subfertility treatment

The first step in the treatment of infertile couples in most cases is the method of intrauterine insemination (IUI), as it is less invasive than the extracorporeal procedures of ART (23). A combination of controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI) remains an important option and is a widely used treatment modality for a mild to moderate male factor and unexplained infertility. An ejaculatory abstinence period of ≤ 2 days before IUI produced the highest pregnancy rates per cycle compared with longer intervals of ejaculatory abstinence despite a lower total number of motile spermatozoa inseminated (24). The reported pregnancy rates per cycle range from 8 to 22%. The pregnancy rates per IUI cycle are quite variable in the literature due to differences in cause and duration of infertility, concomitant usage or lapse of ovarian stimulation, sperm preparation techniques, treatment cycles and number of times IUI is performed during a cycle (single or double) (25). Low pregnancy rates were associated with poor semen parameters, indicating that COH/IUI is not an effective option in these clinical situations. Even though IUI is a less expensive and simpler form of treatment compared with ART-IVF, it still requires frequent monitoring and supervision under specialist care. Prolonged duration of infertility is also associated with decreased success, and should be considered when planning treatment (26).

In Vitro Fertilization (IVF)

With consistently higher success rates, shorter times to pregnancy and a trend to less higher order multiple pregnancies, IVF is now potentially safer and more clinically effective than IUI/COH as a first-line therapy for subfertility (27). The step up to ART procedures should follow after four cycles of unsuccessful IUI at the latest. In terms of cost-

effectiveness, efficacy and benefit of detailed information on germ cell material and embryo development, it must rather be recommended to switch to IVF/ICSI as soon as possible (23). Many couples would opt for one attempt of IVF rather than undergo three to four cycles of COH/IUI. This is especially true for couples travelling long distances seeking treatment in other cities/centers. One IVF treatment programme was more effective, but costlier than an intended course of two cycles of IUI/COH. Approximately 30–40% of couples undergoing IVF treatment will remain childless after treatment (28,29).

Intra Cytoplasmic Sperm Injection (ICSI)

New methods of assisted fertilization such as intracytoplasmic sperm injection (ICSI) is potential beneficial for severe male factor infertility treatment in comparison to classical IVF and IUI (30). PESA (Percutaneous Epididymal Sperm Aspiration) or TESE (Testicular Sperm Aspiration) combined with ICSI is an effective approach to the treatment of male infertility induced by obstructive azoospermia, which may achieve a higher rate of pregnancy in patients with CBAVD (Congenital Bilateral Absence of Vas Deferens) (31).

In short.....

IUI is recommended for unexplained infertility and discussed for male or cervical infertility. IVF is recommended for tubal and unexplained infertility. A limit between IVF and ICSI in case of male infertility remains unclear. In non male infertility ICSI is not recommended (32).

Cultural and ethical challenges of assisted reproductive technologies

Legitimacy of children born through ART, religious obligation, patriarchy, polygamy and value of children are cultural issues surrounding ARTs while decision making about it, discrimination against children born through ART, psychological problems and loss of self esteem, side effects of the technologies and the cost of accessing them are the ethical challenges (33). IVF-seeking patients generally desire privacy, even total secrecy, when pursuing these treatments, due to cultural issues of stigmatization, particularly regarding male infertility. Thus, ethical issues surrounding the informed consent process are of prime importance (34). The greatest ethical problem with all the developments of refined ART technologies seems to be delivery of these complex treatments when health-care resources are increasingly limited (35). Individuals and couples seeking ART may be both vulnerable and fragile,

thus ART providers must gently balance smart business practices with ethical care delivery.

Pitfalls of ART techniques

As a result of advancements in ART, understanding the potential implications of genetic disorders for infertile couples is critical. Even though ART method allows infertile male to father their own child without knowing the cause of their infertility, it also carries the potential risk of transmission of genetic or epigenetic aberrations to the offspring (36). Whether advanced ART techniques are associated with increased birth defects is still debated, and search for alternative options should go on (37). There is no evidence to advise one particular treatment option over another. The choice should be based on hospital facilities, convenience for the patient, medical staff, costs and drop-out levels.

Conclusion

Genomics has brought many revolutionized tools beneficial for better understanding the genetics of male infertility. Analysis of these genetic factors will provide valuable insights into the creation of targeted treatments for patients and the determination of the causes of idiopathic infertility. Knowledge of men's experiences of their own infertility is important as a supporting measure to increase the quality of care of infertile couples.

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