Molecular insights into the causes of male infertility

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Infertility is a reproductive health problem that affects many couples in the human population. About 13–18% of couple suffers from it and approximately one-half of all cases can be traced to either partner. Regardless of whether it is primary or secondary infertility, affected couples suffer from enormous emotional and psychological trauma and it can constitute a major life crisis in the social context. Many cases of idiopathic infertility have a genetic or molecular basis. The knowledge of the molecular genetics of male infertility is developing rapidly, new “spermatogenic genes” are being discovered and molecular diagnostic approaches (DNA chips) established. This will immensely help diagnostic and therapeutic approaches to alleviate human infertility. The present review provides an overview of the causes of human infertility, particularly the molecular basis of male infertility and its implications for clinical practice.

1. Introduction

The recent growth of the Indian population has been unprecedented. It stands currently at over one billion and is expected to touch 2 billion by 2035 (assuming an average growth rate of 2%). Even though curtailing population growth is a major national concern, a substantial number of infertile couples in the Indian population have an equally great concern, that of having a child. This is an equally important national problem concerning reproductive health and the infertile couples have to be treated by medically assisted reproductive technology (MART) for procreation. Globally, the incidence of infertility is estimated to be about 13–18% (Hull et al 1985; Thonneau et al 1991; Jones and Toner 1993; Irvine 1998; Mueller and Daling 1989) in the human population, regardless of race, ethnic group, etc.

Infertility is defined as the state in which a couple wanting a child cannot conceive after 12 months of unprotected intercourse (Mueller and Daling 1989; Thonneau et al 1991). It is a problem faced by couples rather than individuals. Among the causes of infertility, about half of them could be traced to the male partner. When efforts to have children are unsuccessful, feelings of helplessness, frustration and despair are common, it can be a major life crisis for many couples. They go through enormous emotional crisis and psychological distress, as their friends and peers begin to have children. In this review article, causes of infertility in the human female and male, the molecular basis of male factor infertility and the implications of the rapidly developing molecular knowledge on infertility in the context of alleviating human infertility using MART approaches will be described.

2. Causes of infertility

Infertility is either primary, when no pregnancy has ever occurred, or secondary, where there has been a pregnancy, regardless of the outcome. About 67–71% and 29–33% of patients have primary and secondary infertility, respectively (Mueller and Daling 1989; Thonneau et al 1991;
Female and male factors can both contribute to infertility. Idiopathic infertility is a condition of couples unable to conceive for more than two years, with no abnormalities seen on repeated investigations of tubes or as regards ovulation, luteal phase, cervical mucus, semen, sperm–oocyte interaction or intercourse. Among the major causes of infertility, chromosomal abnormalities, microdeletions, cystic fibrosis transmembrane conductance regulator (CFTR) mutations and other genetic factors [follicle stimulation hormone (FSH) receptor mutation] are important (Irvine 1998; Diemer and Desjardins 1999; Egozcue et al 2000; Hargreave 2000; Phillip et al 1998). Because immunological factors operate at almost every step in the human reproductive process, antibodies-induced damage to gametes and developing embryos is a major cause of immunological infertility. Besides, life style, environmental factors (Benoff 1998) are important (Irvine 1998; Diemer and Desjardins 1999; Egozcue et al 2000; Hargreave 2000; Phillip et al 1998). Because immunological factors operate at almost every step in the human reproductive process, antibodies-induced damage to gametes and developing embryos is a major cause of immunological infertility. Besides, life style, environmental factors (Benoff et al 2000; Sharpe 2000), including smoking (Zenzes 2000), can affect gamete and embryo development, leading to sub(in)fertility. A combined cause of infertility is found in about 10–30% of couples (Hill et al 1985; Jones and Toner 1993; Thonneau et al 1991). It is, therefore, important to investigate both partners and inappropriate to assume that infertility is exclusively a female or a male problem.

3. Female infertility

In women, the major causes of infertility, accounting for 50% of cases, are ovulation disorder and tubal damage. Other causes include endometriosis, hyperprolactinemia and reproductive tract disease (Spira 1986; Mueller and Daling 1989). Risk factors include pelvic inflammatory diseases and sexually transmitted diseases (STD). Damaged fallopian tubes are mainly responsible for infertility and Neisseria gonorrhoeae and Chlamydia trachomatis are infertility-inducing organisms. Pelvic surgery is associated with increased risk of infertility (Spira 1986; Mueller and Daling 1989). Also, ectopic pregnancy can lead to tubal infertility. A substantial number of unsafe abortions carried out in the country also contributes to infertility due to genital tract infection. It is reported that cigarette smoking can lead to tubal diseases and abnormal cervical mucus, resulting in an increased risk of infertility and childhood cancer (Zenzes 2000). In India, being a developing country, these are believed to be more prevalent, compared to developed countries.

Even though endometriosis causes infertility, the causative factors are not clearly understood. A multitude of factors are believed to be involved such as ovulatory dysfunction and alterations in gamete/embryo transport. Besides, peritoneally-derived components and macrophages are believed to affect gamete/embryo function and, immunological reactions occurring in uterine lumen affect early development. A common disorder of ovulation is polycystic ovarian syndrome, which also results in oligo-ovulation or anovulation and unexplained infertility (idiopathic infertility).

4. Male infertility

In men, the main causes of infertility are oligospermia, asthenospermia, teratozoospermia and azoospermia, which account for 20–25% of cases (Egozcue et al 2000; Hargreave 2000). There are a number of risk factors such as STD involving N. gonorrhoeae and C. trachomatis. These cause changes in semen quality and chronic infection may lead to a block of the vas deferens or seminal vesicles (Megory et al 1987). Mumps, though rare in adults, can result in azoospermia. Anatomical abnormalities such as varicocele, vesicular damage due to torsion and obstruction of testicular sperm passage can all lead to male infertility. It is however, believed that non-obstructive azoospermia has a strong genetic basis (Hargreave 2000). Male infertility can occur either as an isolated disorder or within the framework of a known complex disorder or syndrome. There is an excess of autosomal abnormalities in men with non-obstructive azoospermia or severe oligospermia. Besides, congenital bilateral absence of the vas deferens (CBAVD) associated with the phenotype of CFTR gene mutations cause obstructive azoospermia (Donat et al 1997).

There appears to be a world-wide concern over decreasing human sperm concentration but this has been highly controversial. Decreasing sperm counts are attributed to the deleterious effects of environmental contamination by heavy metals and estrogenic chemicals (Benoff et al 2000; Mehta and Anandkumar 1997; Sharpe 2000). To what extent there is a genetic contribution is unclear. It has been reported that in a certain ethnic group, men with a particular haplotype (II) have a lower sperm concentration compared with men with haplotypes (III) and (IV) and, the frequency of haplotype (II) is more common in azoospermic men compared with normal men (Kuroki et al 1999). Based on this, it appears that the genetic contribution towards male fertility on account of a decreased sperm concentration might be significant in some ethnic groups.

5. Molecular causes of male infertility

Spermatogenesis is a complex process and it is subject to the influence of many genes; the molecular mechanisms involved are beginning to be understood (Diemer and Desjardins 1999; Egozcue et al 2000; Hargreave 2000). It is estimated that about 2,000 genes regulate spermato-