Male Factor Infertility – Basics Revisited

Nadeem Alam

Despite increasing population of the world, the desire for reproduction remains a basic human desire. Infertility is a complex phenomenon and the suffering couples need emotional and psychological support along with investigations and treatment. A couple is said to be infertile if pregnancy does not result after one year of normal sexual activity without contraceptives. About 25% couples experience infertility at some point in their reproductive lives, the incidence increasing with age. The male partner factor contributes to about 40% of cases of infertility. Clinical evaluation of male partner is warranted after 6 months of unprotected coitus. Endocrine profile and detailed semen analysis are the cornerstones of laboratory investigations after history and physical examination. Oligospermia is the presence of less than 20 million sperms/ml in the ejaculate; azoospermia is the absence of sperm; oligoasthenoteratozoospermia means that the sperms have motility and morphological defects in addition to being less than 20 million/ml. As spermatogenesis takes approximately 74 days, it is thus important to review history from the past 3 months.1

Spermatogenesis is a unique process of continuing differentiation because, unlike thoroughly mitotic processes, such as hematopoiesis, the DNA content of the product is half that of the progenitor cells. In the initial stages, spermatogonia undergo mitotic divisions, giving rise to primary and secondary spermatocytes, the cell type in which the first and second meiotic divisions occur. The haploid products of meiosis are the round spermatids, which elongate during the process called spermiogenesis and compact their chromatin into the sperm head and produce the other sperm components. Despite the research interest in the process involved, little is known about the pathway. An important early observation was that some azoospermic men had deletions of the distal long arm of the Y-chromosome, suggesting that an underlying genetic defect may be responsible in some cases.2 This led to the postulation of a locus encoding the azoospermia factor (or AZF) in this region of the Y-chromosome, a gene essential for normal sperm production. Recent results aimed at mapping this locus in azoospermic men with much smaller Y-chromosome deletions (microdeletions) have complicated this picture substantially and suggest that rather than a single locus, three non-overlapping regions of the Y-chromosome long arm are important for male fertility. These regions are now called AZFa-c.3 Candidate genes have been isolated from AZFb and AZFc, and, surprisingly, both encode distinct RNA-binding proteins.2

Fertilization is a complex process. One of the crucial steps is the recognition and interaction between complementary molecules present on the sperm and zona pellucida of the ovum.3 Mammalian sperms are known to be highly sensitive to injuries caused by high oxygen concentration. Because polyunsaturated fatty acids in the phospholipids of human sperms are highly susceptible to peroxidation, free radicals generated by sperms can be involved in the production of spermicidal cytotoxic end products. The production of abnormal levels of reactive oxygen species is now thought to be engaged in many aspects of human male infertility, in which sperms are rendered dysfunctional by lipid peroxidation and altered membrane function, together with impaired metabolism, morphology and motility. Andrologists still contemplate to know whether the source of reactive oxygen species in semen of subfertile men originate in sperms themselves, the germ cells or the infiltrating leukocytes. Intracellular and extracellular scavenger systems serve to counter the potential effects of superoxide anion and other reactive oxygen species. The superoxide dismutase, glutathione peroxidase – reductase system and catalase have been reported in the sperms of several mammalian species. Vitamin E is an effective, chain breaking lipid soluble antioxidant, which helps maintain membrane stability. Malondialdehyde is a stable peroxidation product of polyunsaturated fatty acids, usually cross linked to proteins, thus malondialdehyde may be viewed as a measure of cumulative lipid per oxidation that has occurred within short life-time of spermatozoa. The mechanism of improved fertilization capacity by vitamin-E involves reducing lipid peroxidation potential. This, biochemical marker might be more useful than sperm analysis in the prediction of sperm fertilization potential.4

Data on Pakistani men are scare and discordant. There have been many years of debate over the causes and therapy of male infertility. Many treatments have been

---

Department of Biochemistry, Civil Hospital/Dow University of Health Sciences, Karachi.

Correspondence: Dr. Nadeem Alam, Associate Professor,
Department of Biochemistry, Civil Hospital/Dow University of Health Sciences, Karachi.
E-mail: drdanishhaseen@hotmail.com

Received March 13, 2009; accepted March 30, 2009.
strongly advocated such as clomiphene citrate, testosterone, human menopausal gonadotropin, corticosteroids for sperm antibodies, cold wet athletic supporters, vitamins and a lot of popularly marketed drugs without any documented evidence of effectiveness. Even varicocelectomy, long proclaimed as the treatment for male infertility, has now come under serious questioning. Reduced sperm count does not rule out natural conception, and a normal sperm count does not necessarily guarantee fertilization. Men with low sperm count often have no difficulty in parenting an offspring and in a small percentage of IVF-ICSI cycles in which semen analysis is completely normal, there is no fertilization, even when there are no female causes.

Hypofunction of seminal vesicles has been suggested as an important factor associated with male infertility. A sub-optimal function of seminal vesicles leading to low seminal fructose can be due to obstruction of excretory ducts or due to low androgen activity at the reproductive tract level. Subjects with low levels of seminal fructose have low ejaculate volume, low sperm motility and low sperm normal morphology. The effect of function of seminal vesicles on sperm chromatin stability seems to be due to the secretion of high-molecular weight zinc ligands that reduce zinc content in sperm chromatin. A high content of zinc available for the sperm chromatin increases the sperm stability as observed in sperms pretreated with EDTA and then exposed to prostatic fluid that markedly increased their chromatin stability. Chromatin decondensation and mud ear swelling, when spermatozoa penetrate the ovum cytoplasm, is important for fertilization. Therefore, a high sperm stability may produce infertility. Further work is necessary to test for chromatin stability by treating washed sperms from normal controls with seminal fluids of samples with low and normal fructose levels. It is, therefore, suggested that quantitative measurement of seminal fructose should be introduced routinely in all infertile males as directed by WHO guidelines, so that males with seminal vesicle pathology can be screened effectively.

REFERENCES