Reclassification of azoospermia: the time has come?

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Azoospermia (the absence of spermatozoa from the ejaculate) is not uncommon, and is present in ~5% of all investigated infertile couples (Irvine, 1998), and in 10–20% of infertile men with abnormal seminal fluid analysis (Stanwell-Smith and Hendry, 1984). Over the past few years there has been much renewed interest in the condition because of increased understanding of its genetic basis and aetiology (Mak and Jarvi, 1996) as well as the availability of surgical sperm retrieval methods and intracytoplasmic sperm injection (ICSI) for the treatment of the resulting infertility (Palermo et al., 1999). As more advances are being made and publicised, clinicians of different disciplines will be dealing with more azoospermic patients than any other time in the past. It is, therefore, both desirable and timely that there is a clear, logical and clinically-orientated classification of azoospermia. This classification should place the different causes of azoospermia into distinct categories which (as much as possible) should be comprehensive and have common aetiology, presentation, prognosis and treatment. This would lend itself to a clearer clinical thought process, and consequently a more correct diagnosis and proper management. It is the opinion of this author that the currently used traditional classification of azoospermia falls short of these goals, and a different classification which better serves these purposes is suggested.

Traditionally azoospermia is classified into 'obstructive' and 'non-obstructive' (Prins et al., 1999). In obstructive cases spermatogenesis is normal but there is obstruction in the seminal ducts, while in non-obstructive cases there is deficient (or absent) spermatogenesis. At the face of it this classification looks descriptive and clear and, indeed, has been used for a long time. But where do cases of azoospermia due to retrograde ejaculation fit? Definitely there is normal spermatogenesis but no real obstruction. Also, cases of azoospermia due to hypogonadotrophic hypogonadism and those due to Sertoli cell-only syndrome are placed in the ‘non-obstructive category’ although they have totally different aetiologies, treatments and prognoses. And what about the patient who has had a vasectomy but also later developed testicular dysfunction following chemotherapy? Can we say that he has both obstructive and non-obstructive azoospermia? Surely, that will confuse rather than clarify the issue. The traditional classification is perhaps simplistic (rather than simple), and forces divergent causes to sit together, rather uncomfortably, in the same category, and is a recipe for potential misdiagnosis and mismanagement.

It is a truism that one needs to appreciate the normal in order to understand the abnormal. Normally, the hormones of the hypothalamic–pituitary axis stimulate the testis, the testis produces spermatozoa which travel to the exterior through patent and properly functioning seminal ducts. Logically, therefore, azoospermia could be divided into causes due to deficient hormonal stimulation of the testis, testicular dysfunction, and seminal ducts obstruction or dysfunction; pre-testicular, testicular, and post-testicular causes respectively. Indeed, a similar classification of male factor infertility in general has been previously described in some textbooks and papers (Berkow and Fletcher, 1992; Mak and Jarvi, 1996). However, almost all current clinical and research papers on azoospermia use the 'obstructive/non-obstructive' classification with its aforementioned drawbacks. The following classification should provide a more logical framework.

**Pre-testicular azoospermia**

This includes all cases of hypogonadotrophic hypogonadism, whether congenital (Kallmann’s syndrome), acquired (trauma, tumour), or idiopathic. These require pituitary assessment (both endocrinological and radiological) and respond very well to hormone replacement therapy (Finkel et al., 1985). After successful spermatogenesis has been established, pregnancy occurs without the aid of assisted conception.

**Testicular azoospermia**

This includes testicular disorders and may be congenital (Klinefelter’s syndrome, Y-deletion), acquired (radiotherapy, chemotherapy, torsion, mumps orchitis), or developmental (testicular maldescent). Treatment of testicular causes require attempt at surgical sperm retrieval, after appropriate genetic screening. Spermatozoa are retrieved in only ~50% of these cases (Gil-Salom et al., 1998). Prognosis, therefore, should be guarded.

**Post-testicular azoospermia**

These cases are due to either ductal obstruction or dysfunction (retrograde ejaculation). Obstruction could be congenital (congenital bilateral absence of the vas deferens or CBAVD) or acquired (post-surgery or infection). Acquired obstructive
cases could be amenable to surgical correction. Those which are unsuccessful, or unsuitable, as well as cases of CBAVD will require surgical sperm retrieval for ICSI. Screening for cystic fibrosis mutations should be undertaken in men with CBAVD (Donat et al., 1997). Cases of retrograde ejaculation may respond to sympathomimetics. Failing that, spermatozoa could be retrieved from alkalinated post-ejaculation urine and used for insemination or in-vitro fertilization/ICSI depending on the available number and quality. Spermatozoa could be obtained in almost all cases of post-testicular origin (Safran et al., 1998).

Concern has been raised about the unchecked speed of development and widespread application of treatments for azoospermia (Steele et al., 1999). Also, infertile male patients have sued clinicians for failing to diagnose lesions where an initial accurate diagnosis and simpler proper treatment could perhaps have avoided the use of expensive and invasive assisted reproductive techniques, albeit successfully (Jequier, 1997). There is a timely need for a clear and logical classification of azoospermia that is simple, clinically-orientated, inclusive of all causes, and lends itself to therapeutic strategies. The ‘pre-testicular, testicular, and post-testicular’ classification seems to fulfil all these aims.

References