COMMENTARY

Infertility in Men: Recent Advances and Continuing Controversies*

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Background

Between 1 in 6 and 1 in 10 couples seek medical help for the problem of subfertility. It is important to recognize that, while in 20–25% of cases the problem was due to the male partner and in 30–40% the problem was predominantly female, in approximately 30% of cases, abnormalities were found in both partners, and in 15% no specific factor could be identified (1). It is also important, when dealing with infertile couples, to recognize that the duration of infertility is a critical prognostic factor, and in couples with a history of primary infertility of longer than 3 yr, the possibility of achieving an unassisted pregnancy is low.

General clinical approach

As is general practice in any branch of medicine, it is essential that the logical clinical approach to diagnosis should be applied in this condition. A detailed history, careful clinical examination, and selected investigations can be used to determine etiological factors that can be classified into pretesticular, testicular and post-testicular (see Table 1). The major frustration for the clinician managing infertile men is the fact that in 40–50% of cases, while the sperm defect can be defined, no specific cause can be found, designating these to the category of idiopathic spermatogenic defects. It is not possible to exhaustively evaluate the approach to each of the specific factors listed in Table 1. Consequently this commentary concentrates on major recent advances and areas of continuing controversy.

Varicocele

Varicocele treatment for infertility remains enigmatic and controversial. Moderate to large varicoceles are found in about 12–25% of men being examined for infertility, and another 15% have small or subclinical varicoceles (2, 3). Varicoceles are more frequent and larger in taller men and usually first appear at the time of puberty. Most men are unaware of a varicocele. Testes associated with large varicoceles are smaller and may be soft with more severe disturbances of spermatogenesis being commoner on the left side. Men with varicoceles have poorer semen quality than those without varicoceles (3, 4) indicating adverse effects of varicoceles on the testis. Despite this, the association of varicocele with infertility is not clear-cut as varicoceles are frequently found in fertile men, and their size may be a positive prognostic factor for fertility in untreated subfertile couples (2, 4). However the semen patterns are significantly impaired in those men with varicoceles (5, 6). Further varicoceles are more common in men with secondary infertility, but this claim may be due to patient selection bias (7). Unfortunately experimental varicoceles in animals have not revealed the pathophysiology of the condition in man. As varicocele might not be the absolute cause of a couple’s infertility, full evaluation of both male and female partner for other factors is necessary.

Treatment of the varicocele involves the venographic obstruction of the incompetent veins or surgery to prevent venous back flow from the abdomen to the pampiniform plexus. Radiographic techniques involve placement of a sclerosant, glue, or coil that promotes clotting in the vein, and they carry a lower morbidity than surgery under general anesthesia, but there are relatively high failure and recurrence rates. A variety of operations can be performed for varicocele, including retroperitoneal ligation and division of the testicular veins with or without preservation of the testicular artery, as well as the more recent new inguinal and scrotal microsurgical approaches with lower failure, recurrence, and hydrocele rates.

Successful venous occlusion will relieve pain if present and will reduce the size of large varicoceles (8), but whether semen quality and fertility are improved is not certain. Several large series were published with claims of high success rates for improving semen and fertility (9). Floating numerator pregnancy rates (proportion of men treated who produce a pregnancy without regard to time of follow-up) averaging 35% (range 20–60%) were commonly reported. Regression toward the mean in semen variables, the nature of subfertility, and the need to include time in the denominator of pregnancy rates were ignored (10). While there are reports of successful treat-
ment of azoospermic men by varicocelectomy (11), transient azoospermia may follow a minor illness or occur for unknown reasons, and so such examples do not prove the value of treatment. Most exponents of varicocele treatment regard azoospermia as a bad prognostic sign especially if the FSH level is elevated.

Follow-up studies of groups of treated and untreated patients with varicoceles suggest that pregnancies are as frequent without treatment as they are with treatment of the varicocele (2, 12). For example, a follow-up study of 651 subfertile men with grade I-III varicoceles showed no significant difference in pregnancy rate after testicular vein ligations in 283 men, compared with that before ligation or without treatment. None of the factors believed to be important for response to varicocelectomy, including size of varicocele, effectiveness of the prevention of reflux, or degree of reduction in varicocele size were related to the outcome (2).

Attempts to conduct randomized controlled clinical trials of varicocele treatment have been difficult because the ideal design incorporating sham operations and blinding, so important in controlling for outcomes affected by psychological factors, have not been possible. Large trials are needed—for example, about 250 pregnancies are required to have a high chance of finding a 25% increase in pregnancy rate after treatment significant at the 5% level (10). So far the trials have produced conflicting results. A small (n = 67) prospective controlled study of percutaneous embolization of the left testicular vein in 17-20-yr-olds showed an increase in testicular volume and sperm concentration in the treated group (13). Others have reported similar beneficial effects of treatment of varicoceles in adolescents in less well controlled studies.

A prospective randomized controlled trial comparing spermatic vein occlusion by surgical or angiographic techniques to follow-up counseling alone for 1 yr in couples without other causes of infertility showed no difference in pregnancy rate: 29% and 25% respectively at 12 months (14).

In a multicenter controlled trial, sponsored by the World Health Organization (WHO), of Palomo ligation in men with infertility of greater than 1 yr duration, abnormal semen analyses, a moderate to large left varicocele, and potentially fertile female partner, volunteers were randomized to immediate operation or operation delayed for 12 months to provide an untreated control group. One of the participating centers reported their results separately and showed a significant improvement in couples after operation compared to controls (15). Semen analysis results also improved after the operation. In the other centers there was a less marked but significant improvement, with life table pregnancy rates at 1 yr being 35% for the operated group and 17% for the unoperated group (relative pregnancy rate 2.7; 95% confidence limits 1.6–4.4). Semen analysis results also improved over the first year in the operated group. In the control patients having the delayed operation, the life table pregnancy rate at 1 yr after the operation was 21% (16). However, there were problems with the WHO trial, particularly with irregular randomization and drop-out rates, and the results have not yet been published in detail. Surprisingly, the pregnancy rates in the control groups were lower than expected for untreated subfertile men with varicoceles, wherein approximately 30% produced a pregnancy in 12 months (2, 15).

After a recent meta-analysis by Evers (17), the Royal College of Obstetricians and Gynaecologists concluded that there was insufficient evidence to recommend occlusion of the left internal spermatic vein in subfertile or oligozoospermic men with a varicocele.

It is difficult to resolve the differing results emerging from a variety of trials, some of which have been carefully designed and executed. Patient populations may differ based on the thoroughness of the exclusion of other causes of male infertility, as varicoceles may co-exist with other abnormalities, for example Y chromosome deletions. Further, with the use of pregnancy as an outcome of varicocele treatment, the fertility of the female partner enters into the analysis. The degree to which the female partner is investigated before confirming normality can vary, and adjustments are not made for the age of the female partner. These issues are raised to provide the reader with some insight into the difficulties of performing such trials.

The possibility that there may be some manner of identifying responders has been raised. Hudson (18) showed that

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**TABLE 1. Aetiological factors in male infertility**

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<tr>
<th>Pretesticular</th>
<th>Post-testicular</th>
<th>Testicular</th>
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<tr>
<td>Endocrine</td>
<td>Obstructive</td>
<td>Genetic</td>
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<tr>
<td>Hypogonadotropic</td>
<td>Epididymal</td>
<td>Klinefelter’s syndrome</td>
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<tr>
<td>Hypogonadism</td>
<td>Congenital</td>
<td>Y chromosome deletions</td>
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<tr>
<td>Coital disorders</td>
<td>Infective</td>
<td>Immotile cilia syndrome</td>
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<tr>
<td>Erectile dysfunction</td>
<td>Vasal</td>
<td>Congenital</td>
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<tr>
<td>Psychosocial</td>
<td>Genetic: cystic fibrosis</td>
<td>Cryptorchidism</td>
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<tr>
<td>Endocrine/neral/vascular</td>
<td>Acquired: vasectomy</td>
<td>Infective (orchitis)</td>
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<tr>
<td>Ejaculatory failure</td>
<td>Epididymal hostility</td>
<td>Antispermagenic agents</td>
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<tr>
<td>Psychosocial</td>
<td>Epididymal asthenozoospermia</td>
<td>Heat</td>
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<td>Post genitourinary surgery</td>
<td>Accessory gland infection</td>
<td>Chemotherapy</td>
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<td>Neural</td>
<td>Immunolgical</td>
<td>Drugs</td>
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<td>Drug related</td>
<td>Idiopathic</td>
<td>Irradiation</td>
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<td></td>
<td>Post-vasectomy</td>
<td>Vascular</td>
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patients who respond to treatment of varicocele had significantly greater GnRH-stimulated rises in FSH than did non-responders, an observation confirmed by others (19). The mechanism of this intriguing observation remains obscure. Androgen deficiency with increased estradiol and SHBG levels may also be attributes of responders (20). The possibilities that responders can be predicted from hormone profiles or age and that the beneficial effect may be greater in younger men deserve study with objective methods of semen analysis and varicocele detection and simpler methods of treatment such as antegrade sclerotherapy (16). Certainly further trials are necessary to meet the demands of evidence based medicine.

Thus while some people remain convinced of the value of treating varicoceles for infertility, it is not easy to demonstrate this unequivocally. The apparent improvements in semen quality and fertility may result from random fluctuations and regression toward the mean (10). It is clear that normal fertility is not achieved in a high proportion of patients treated for varicocele. Assisted reproductive technology is a realistic alternative for most couples who have not conceived after a reasonable time. Our current clinical approach to patients with varicocele and infertility is to advise the patient of the uncertainty of the effectiveness of treatment of the varicocele, and most patients choose alternative management for the infertility. A few may have the varicocele treated because they do not want to use assisted reproductive technologies (ART) or, as a last resort, after ART has been unsuccessful.

**Sperm-oocyte interaction**

Using oocytes that have failed to fertilize in vitro to test sperm function has improved understanding of abnormalities of the human fertilization process (21). Studies with computer image analysis show that particular defects of sperm shape impair sperm-zona pellucida binding (22). The shape of the acrosome area of the sperm head appears to be particularly important. Although some workers have reported patients that appear to have isolated defects of the sperm zona receptors, these appear to be very rare, as poor sperm-zona binding is very uncommon in the absence of an obvious defect of sperm morphology (21, 23). A group of patients with unexpected failure of standard in vitro fertilization has been discovered that have disordered zona pellucida-induced acrosome reactions, which prevent sperm-zona penetration (24). The patients have morphologically normal sperm that bind to the surface of the zona pellucida, but very few undergo the acrosome reaction. They can be successfully treated by intracytoplasmic injection (ICSI), a process in which a single sperm is introduced into the cytoplasm of the oocyte. This condition may be present in 15–30% of couples with idiopathic infertility.

Defective sperm-oolemma binding appears to be uncommon. Abnormalities of intravitelline sperm processing also rarely result from a sperm defect. Only globozoospermic and immotile sperm have been found to produce low fertilization rates with ICSI (25). These sperm may not decondense after intracytoplasmic sperm injection. Other than these cases, failure of the sperm head to decondense in the oocyte cytoplasm appears to be an infrequent cause of infertility.

**Sperm function tests and reactive oxygen species (ROS)**

The mechanisms involved in the causation of the common forms of male infertility associated with oligozoospermia, asthenozoospermia, and teratozoospermia are not understood. It would appear that defects of spermatogenesis, particularly abnormalities in spermiogenesis and spermiation, are the main cause (26). The sperm have a multitude of abnormalities in addition to those tested with standard semen analysis. There is a correlation between the production of abnormal sperm and abnormal sperm DNA as measured by a variety of techniques including acridine orange fluorescence, sperm chromatin structure assay and other techniques for DNA breaks including chromatycin staining, tunnel, and rocket assays (27, 28). Sperm with redundant cytoplasm are common and can be detected by a variety of methods including measurement of cytoplasmic enzymes such as creatine kinase (29). These sperm produce reactive oxygen species that can be assayed, and it is possible that new assays of sperm function will be developed for clinical use (30).

The work of Aitken and colleagues (30, 31) has expanded our knowledge of the role of reactive oxygen species in the sperm physiology and pathology. It is postulated that abnormal reactive oxygen species production could damage not only the sperm plasma membrane but also sperm DNA. Aitken has shown that at low concentrations the ROS may enhance sperm function, in particular the ability to fuse with the oocyte membrane, and yet the sperm may carry the damaged chromatin that could manifest later, after fertilization, as defects of implantation, pregnancy loss, or even impaired health such as increased cancer risk in the offspring (30, 31). Despite this frightening scenario, the results of ICSI do not reveal problems that might be expected. The fertilization, implantation, pregnancy wastage, and congenital malformations rates appear no greater with ICSI than with standard IVF (32). It is possible that abnormal sperm with redundant cytoplasm are excluded in natural or assisted fertilization by sperm aggregation caused by heavy coating with clusterin (33).

**Current clinical approach to semen evaluation.** WHO recently revised its laboratory manual for semen analysis (34). Standard analysis continues to include full microscopic assessment of sperm characteristics and a test for sperm antibodies. The main changes in the new edition include an increase in the numbers of sperm to be counted to increase the precision of the measurements of sperm concentration, motility and morphology, and improved quality control in the laboratory. Computer aided semen analysis and zona free hamster oocyte penetration tests are regarded as optional. ROS measurements and human sperm oocyte interaction are classified as research tests as their place in a routine andrology laboratory is not yet considered established. In clinical practice we follow the WHO manual but believe there will be considerable advances in automated semen analysis in the near future. Tests of sperm-oocyte interaction will continue to be
confined to research laboratories associated with large IVF programs because of the limited availability of oocytes for the tests. We perform these tests when no cause for the infertility can be found in either partner and when there is unexpected failure of standard IVF.

**Genetic basis for male infertility.** Several genetic causes of male infertility, such as Kallmann syndrome and myotonic dystrophy, have been known for some time (35, 36). However, the possibility that genetic disorders could account for a substantial proportion of men hitherto classified as idiopathic, emerge from the studies of Lilford and colleagues (37). Several disordered genes have now been shown to contribute to male infertility and these are discussed below.

**Y chromosome deletions.** The observation that some men with azoospermia had small Y chromosomes has led, following the expansion of our knowledge concerning the Y chromosome, to the identification that deletions of genetic material occur on the long arm (Yq) (38, 39). These deletions map to subintervals 5 and 6, and the reported prevalence varies from 3–37%. This prevalence may reflect the selection bias of the patients evaluated, or it may reflect false positives as the majority of studies have based the diagnosis of a deletion on the absence of a PCR product. Denatured DNA and poor technique could contribute to a falsely elevated detection rate of deletions, and it is strongly recommended that an independent technique such as genomic Southern blotting should always be used to confirm the diagnoses. Three regions within these sub-intervals have been identified and termed AZFa, AZFb, and AZFc (40). To date two candidate genes have been implicated one termed “deleted in azoospermia” (DAZ) in AZFc (38) and the other, now known as RNA binding motif (RBM), which is found in AZFb (40). Both DAZ and RBM appear to encode for proteins with RNA binding capacity, but the their function in spermatogenesis remains unknown. Furthermore, these genes are present as multiple copies on the Y chromosome and deletions of all copies appear to be involved in the patients with these disorders. Phenotypically, patients with Yq deletions have severe oligospermia and azoospermia, with deletions being very rare in men with sperm counts greater than 5 million/mL.

Recently, further new testis-specific genes within these areas have been identified and may represent further candidates for mutations or deletions (41). Some studies have suggested that deletions in each of the AZF regions have specific histopathological features e.g. Sertoli cell only (AZFa), germ cell arrest (AZFb), and severe hypospermatogenesis (AZFc) (40).

Recent data indicate that the use of intracytoplasmic sperm injection (ICSI) can transmit these deletions from father to son (42). Nevertheless these deletions appear de novo for reasons that are unclear. In view of the fact that before the use of assisted reproductive technologies, these men would be infertile and therefore would not propagate their mutation, the frequency with which Yq deletions are found suggests that this region of the Y chromosome is subjected to a high constitutive deletion rate.

**Androgen receptor defects.** It is well recognized that mutations in the ligand binding domain and DNA binding domain can cause androgen insensitivity syndrome (48). However recent studies have identified only a small number of men with single base pair mutations in the androgen receptor as a cause of male infertility (49). However, one of the more dramatic observations has linked expansions of the CAG repeat sequence in the amino-terminal domain of the androgen receptor with spermatogenic defects (50). It has been recognized that Kennedy’s disease, spinal and bulbar muscular atrophy, occurs with CAG repeat lengths greater than 40 resulting in a phenotype of muscular atrophy and infertility. When the size of the CAG repeat was evaluated in groups of men with spermatogenic disorders and normal fertile controls, approximately 30% of the men with severe oligospermia orazoospermia showed an expansion of the CAG repeat structure of the androgen receptor (50, 51). Furthermore, the presence of an expanded CAG repeat size was linked to impaired transactivation. In general, from the studies to date, the chances of a man with a CAG repeat length beyond 25 having a normal sperm...

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Congenital bilateral absence of the vas (CBAVD). Another major advance has explained the etiology of many patients with CBAVD. This disorder occurs in 1–2% of fertile males. It has been suspected that, as most males with cystic fibrosis have CBAVD, a common genetic mechanism may underlie these disorders (43). Over 400 mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), which encodes a cyclic AMP-regulated chloride channel, have been found in cystic fibrosis.

When Caucasian patients without cystic fibrosis but presenting with infertility due to CBAVD were tested, the majority demonstrated one of the common mutations in one or both copies of CFTR (44–46). However there usually appeared to be no respiratory component of cystic fibrosis in the majority of such patients. Further, Chillon and colleagues (47) showed that a variant (5T allele) in the noncoding region (intron) of the CFTR gene, which causes splicing out of exon 9, may cause the production of lower levels of CFTR protein. They noted that the presence of a mutation in CFTR in one copy, when combined with the presence of the 5T allele resulted in CBAVD. This appeared to be unlikely to occur if the mutated gene was found in the presence of the 7T or 9T allele. The presence of the 5T allele decreases the mRNA for the normal CFTR gene resulting in a dysfunctional chloride channel causing disease.

Because it is impractical to screen for all of the mutations in the CFTR gene, a more cost effective approach is to test the female partner for the common mutations in the CFTR gene. If the female partner does not carry a common CFTR mutation then the risk of a child, having been conceived by the extraction of sperm from the testis and the use of ICSI, having cystic fibrosis or CBAVD is considerably reduced.

CBAVD is also common in Asians, but cystic fibrosis is not a common disease, suggesting that there may be other causes of agenesis or prenatal degeneration of the Wolffian duct structures. CBAVD may be associated with malformations of the renal tract with ipsilateral renal agenesis often accompanying unilateral CAVD.
count is small. Because signaling through a defective androgen receptor can impair androgen action, it is possible that these men may represent the larger frequency of androgen receptor binding defects in infertile men identified by Aiman and colleagues (52).

**Gonadotropin and gonadotropin receptor defects.** Mutations in these genes are being discovered in men (53–57). Although normal testicular function is dependent on the production of FSH and LH, the specific role of FSH is the subject of debate as, on one hand, studies of targeted disruption of the FSH-β subunit gene in mice results in complete spermatogenesis albeit with smaller testes (58), while in other studies, infertility is described in men with mutations in the FSH-β-subunit gene (56–57). Further, men homozygous for an inactivating mutation of the FSH receptor gene results in variable suppression of spermatogenesis and fertility.

A recent large study of the FSH receptor gene in infertile and normal men revealed that, while two isoforms were identified, signaling through these receptor polymorphisms were normal (59). These investigators concluded that FSH receptor defects did not appear to constitute a common cause of male infertility. Further they speculate that the FSH receptor polymorphisms may respond in different ways to the known secretion of FSH as a series of isoforms some of which are present in recombinant FSH preparations. However, it should be noted that, to date, there is no evidence to support the use of FSH in infertile men with normal FSH secretion.

**Emerging genetic targets.** The use of homologous recombination to target gene disruption in mice is progressively increasing the number of genes that may have a bearing on human fertility. A number of mice in which specific genes have been disrupted often show infertility as a major phenotype. One of these, the gene encoding for the cell survival molecule Bclw, when disrupted, caused profound testicular damage resulting in tubules without germ cells and subsequently even loosing their Sertoli cells (60). Detailed consideration of all of these genes is not possible within the size of this commentary, but readers are referred to Bhasin et al. (61).

Some traditionally bred animal models may also provide avenues for understanding the causes of defective spermiogenesis that cause the mixed abnormalities of sperm motility and morphology so commonly seen in the infertility clinic (62). The nature of the genes responsible for these disorders are still largely unknown. However there are an increasing number of genes encoding for components of the sperm tail that have now been identified, and future studies will determine if mutations in these will be responsible for motility defects. Human examples of familial motility defects are the patients with immotile cilia syndrome (63). Recently, Chemes and colleagues (64) have identified a sperm phenotype, consisting of flagellar abnormalities, that is likely to result from a genetic defect.

**Epididymal asthenozoospermia**

Over recent years there has been an increased recognition that infertile men with a semen pattern demonstrating a severe reduction in sperm motility (usually less than 20%), a high percentage of dead sperm (70–80%), and evidence of a high percentage of abnormally shaped sperm represent a diagnostic category that has been termed epididymal asthenozoospermia (65). Electron microscopic studies have shown that the microtubular structure of the sperm tail axonemes are disrupted in ejaculated spermatozoa. Instead of linear arrays of microtubules seen in longitudinal sections of the sperm tail that represent the central and outer doublet microtubules, these structures are replaced by a more disordered material. Studies of testicular biopsies in such patients showed that the axonemal structure and microtubular integrity were preserved in testicular spermatozoa, strongly suggesting that the degeneration of the sperm tail occurs at a post-testicular site. Data in support that this degradation occurs within the epididymis emerged from the results of a program of frequent ejaculation in men with this disorder where improvements in sperm motility, an increase in sperm viability, and an improvement in the percentage of sperm showing normal structural features occurred. This included an increase in the percentage of sperm where the axonemal structure was preserved (65). The cause of the hostile “epididymal environment” in patients with epididymal asthenozoospermia remains unknown, but it is important to identify this group of patients as a clinical entity.

**Advances in the treatment of infertile men**

As discussed earlier, the management of the infertile male remains difficult as, in a significant proportion of men, the cause of the infertility remains unclear. The identifiable causes of infertility outlined in Table 1 enabled a logical approach to their correction. However in some of these, no treatment is available to restore the germ cell precursors, which may have been destroyed by a variety of causes e.g., radiation, chemotherapy. In such patients, it is appropriate to raise and discuss the issues of adoption and donor insemination.

Some of the more recently identified causes, such as the presence of Y chromosome deletions, remain untreatable due either to the loss of all sperm precursors or because of the absence of therapeutic modalities that could reverse the spermatogenic disruption induced by the genetic disorder. These patients, and those previously identified as having low sperm counts due to unknown factors, can now benefit from the use of ICSI, which has revolutionized the treatment of male infertility. The capacity to introduce a sperm directly into the oocyte cytoplasm was first described in 1993, where fertilization rates of 68%, embryo transfers in 90% of cycles, and a clinical pregnancy rate of 28.4% were reported (66). In the subsequent 6 yr, these results have been verified by many groups around the world who had the necessary equipment and training to run successful ICSI programs. Further, despite the significant distortion of the cytoplasm of the oocyte during the sperm injection procedure, congenital abnormalities in children born after ICSI have remained no different than those of a control population. The major congenital malformation rate of 3.9% is not significantly altered from that
occurring from natural pregnancies of 3.7% (67). However, although 98.6% of prenatal karyotypes (371 pregnancies) were normal, in 1.4%, sex chromosomal abnormalities were identified consisting of sex chromosomal aneuploidy (68). Also, in some databases there is a change in the sex ratio towards the birth of more girls (31).

These intriguing findings are unexplained but may be related to increased rates of chromosomal nondisjunction, as a general association with abnormal spermatogenesis (69–71). The treatment of rare patients with Klinefelter’s syndrome who produce some sperm has been enlightening as the dogma has been that an extra X chromosome in male germ cells result in their death. Spermatogenesis in such testes results from nondisjunction with loss of one X chromosome, so that a clone of XY spermatogonia results (71). Natural fertility, confirmed by genetic testing, has been reported in Klinefelter’s syndrome. Early experience with ICSI with sperm obtained from the testes or semen of men with Klinefelter’s syndrome produced embryos and babies with normal karyotypes (72, 73). However chromosome analysis of sperm from men with typical or mosaic Klinefelter’s syndrome has revealed an increased frequency of sex chromosome aneuploidy and, in one instance, an unusual ratio of euploid sex chromosomes (2:1, X:Y) (69, 70). This seems contrary to the dogma and may indicate that XXY germ cells may produce sperm. However it is more likely that the occurrence of sex chromosomal aneuploidy in sperm from Klinefelter men and animals results from defects during cell division from stem spermatogonia with normal chromosomes (71).

Further, a recent study suggested that, when children born subsequent to ICSI were assessed using the Bayley’s score at 1 yr of age, their performance was inferior to a control group (74). These results raised significant concerns about the developmental potential of children born after ICSI. However, several points should be noted. First, there are concerns regarding the suitability of the control subjects, who were of a different socioeconomic status from the subjects having ICSI. Secondly, as no karyotypes were performed, children with sex chromosomal abnormalities known to be increased in children conceived using ICSI have been missed. Because some of these children may have a decrease in intelligence, the failure to detect them may have contributed to the lowered Bayley’s Score. Furthermore, it is important to recognize that the Bayley’s scores were within the normal range, even though they appeared to be inferior to the control group. Further studies are clearly required to clarify these issues further.

The use of ICSI has also expanded the capability of achieving fertilization from sperm recovered either from the epididymis or directly from the testis. In patients with congenital absence of the vas or other obstructive disorders, epididymal sperm aspiration can harvest adequate numbers of sperm for ICSI (75, 76). Further, in patients with nonobstructive azoospermia, formerly thought to have irreversible destruction of the seminiferous tubules, multiple biopsies of the testis have identified the presence of small numbers of spermatozoa in scattered areas (77). This has led to the successful achievement of pregnancy from such patients. The precise frequency with which sperm extraction from the testis could be expected to yield sperm in patients with nonobstructive azoospermia is difficult to obtain. Patient selection and the number of testicular biopsies performed may all affect success rates. Nevertheless, the use of such sperm has opened possible treatment methods that were unavailable previously. Although this success is dramatic, there is some need for caution and discussion to fully understand certain implications. The identification that significant numbers of men have deletions in the Y chromosome raises the possibility that male offspring, achieved through ICSI, maybe affected by the Y chromosome deletions transmitted from their father. Indeed preliminary reports have indicated transmission from father to son by ICSI. This finding raises the need for the use of pre-ICSI screening of the Y chromosome in infertile men with sperm counts of less than 5 million/mL. If a deletion is identified, genetic counseling should be provided to the couple.

Future Directions

Apoptosis

It has been recognized for many years that, during spermatogenesis, a significant number of germ cell precursors do not progress to mature spermatozoa. It was recognized that these cells were removed from the seminiferous epithelium without invoking an inflammatory response, and recent data strongly suggest that the mechanism involved is that of apoptosis or “programmed cell death”. (See review by Sinha Hikim and Swerloff (78). Further, there are several pathological processes that can accelerate the loss of germ cells from the seminiferous epithelium and these, together with the normal attrition of germ cells from the normal testis, all occur through the process of apoptosis.

There has been a vast increase in our knowledge of the mechanisms controlling the process of apoptosis, and consideration of such an extensive topic is not possible in this article. Readers are referred to major reviews of this field (78). Evidence that a number of these systems are operative within the mammalian testis has emerged from studies of targeted disruption of genes in the mouse. For instance, targeted disruption of the Bclw gene results in infertility, with damage to the seminiferous epithelium commencing after the onset of puberty (37). The withdrawal of hormones, exposure to heat, and chemotherapeutic agents all induce apoptosis, but as yet the specific proteins controlling these processes in the testis remain unclear. The acquisition of this data is crucial in understanding whether common processes are employed by specific factors inducing disruption of spermatogenesis. Nevertheless this understanding is crucial if we are to explore intervention measures. Such developments may result in diagnostic approaches to determine whether mutations in the genes encoding these proteins may be the cause of infertility.

References

INFERTILITY IN MEN: RECENT ADVANCES, CONTINUING CONTROVERSIES


