Male Infertility

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11.1 Introduction

The male accounts for nearly half of known instances of infertility. Determining the prevalence of male infertility is hampered by lack of thresholds for normal and infertile measures in the semen analysis and other tests of sperm quality and function. Thorough evaluation of the male factor should be a part of the infertility and is essential for defining the course and content of a couple's care. This chapter identifies diagnoses as found in the history, by examination, and in the laboratory; each contributes valuable information. Pathophysiology and management for principal diagnoses are also presented. For many infertile men, attribution of cause for semen abnormalities is not possible. For them, and for men whose conditions are not amenable to specific therapy, intrauterine insemination (IUI) and assisted reproductive technology (ART) with intracytoplasmic spermatozoa injection (ICSI) offer pathways to fertility.

Clinical Case

A couple was referred for management of male infertility. They have been trying to conceive for the last 18th month unsuccessfully. The female partner is 28 years old with normal ovulation and patent fallopian tubes. The male partner is 32 years old without erectile dysfunction. Two semen analyses showed low sperm count and morphology. He had a negative medical history, normal physical exam and hormonal evaluation. Artificial insemination and/or artificial reproductive technologies (ART) were recommended.

11.2 History

11.2.1 Coital Function

Adequate frequency of intercourse and erectile function with ejaculation are essential. Semen quality may decline with daily ejaculation, leading to prescription for alternate day intercourse. However, many studies show better semen quality with daily or more frequent ejaculation [1–5]. Prescribed timing for intercourse can create dysfunction and marital stress related to on-demand performance [6]. Because of this, and because ovulation prediction may have up to a day of error, advice to have intercourse "every day or two" during the fertile portion of the cycle without reference to ovulation prediction may be helpful. It allows some spontaneity without compromise of the chance for optimal timing. Sexual dysfunction frequently accompanies infertility [7]. Men unable to achieve appropriate coital frequency and function should be evaluated for hypogonadism (▶ see Sect. 11.5.4) [8]. Findings will usually be normal and provision for marital/sexual counseling is then appropriate [9].

Ejaculatory dysfunction may be psychogenic, occurs after retroperitoneal node dissection, results from use of some medications, is common in men with diabetes, and is not possible for most men with spinal injury [10, 11]. Induction of ejaculation is often successful using high-amplitude vibratory stimulation, which is less stressful than electroejaculation, and allows for home use and home insemination for some men [12–16]. Induced ejaculation can be complicated by autonomic dysreflexia, so initial attempts should include monitoring for this complication, which can be blunted with the use of nifedipine [17]. Semen quality is often poor in men with spinal cord injury, so the principal benefit of induced ejaculation may be avoidance of testicular spermatozoa extraction (TESE) for ICSI. When azoospermia is found on an initial induced ejaculation, second attempts or use of other methods may yield semen with sperm sufficient for ART with ICSI [18–20].

11.2.2 Surgery, Injury, and Infection

Childhood surgery involving the reproductive tract and/or inguinal region can imply abnormalities resulting from defective androgen synthesis or action that may explain later impaired spermatogenesis. Alternatively, surgery may injure the ductal system. The assemblage of abnormal androgen-dependent development, genital malignancy, and impaired spermatogenesis is suggested to comprise "testicular dysgenesis syndrome" [21–24]. A history of injury, torsion, or vasectomy reversal may explain subsequent infertility. Genital tract infection may compromise semen quality, but does not cause infertility except in cases of post-infective

obstruction [11, 25–27]. Retroperitoneal node dissection compromises ejaculatory function, adding to the damage to germinal epithelium from chemotherapy [12].

11.2.3 Cytotoxic Medications

Chemotherapy for malignant or rheumatologic disease frequently causes azoospermia. This effect depends on the agents used, their doses, whether there was also radiation used [28–31]. Effects may be transient [29]. There is no evidence that these exposures affect health of offspring [30]. Resources for fertility preservation should be provided for men anticipating cytotoxic therapy [32, 33].

11.2.4 Lifestyle

Evidence for adverse effects of tobacco and alcohol on fertility is mixed [34–40]. Studies have not linked recreational drugs to infertility [39]. Obesity is associated with poor semen and reduced fertility in some, but not all studies [39, 41–45]. Genetic variation in hormone metabolism may explain a portion of the variability in obesity's effect on semen quality [46]. Effects of obesity may be mediated by coexisting disturbances in insulin resistance, leptin, systemic inflammation, sleep apnea, and testicular thermoregulation and expressed through altered epigenetic controls [43, 47, 48].

Reversibility of obesity's effect has not been shown, and rapid weight loss may harm semen quality [48]. High intensity endurance training alters hormone levels and some semen measures but has not been shown to cause infertility [49–51]. Most medications have not been investigated for effects on human male fertility. Agents of concern for semen quality or ejaculation include serotonin reuptake inhibitors, anti alpha-adrenergic antihypertensives, and sulfasalazine [11, 44, 52]. Anabolic steroid abuse and testosterone replacement reversibly cause fertility impairment [53, 54]. Nutrition is important for spermatogenesis; dietary elements of interest include selenium, dietary antioxidants, zinc, folate, and folate indirectly via its metabolism [55–61]. Clear linkage between adequacy of these in the diet and infertility has not been shown and limited studies of supplementation have not shown benefit [60, 62].

11.2.5 Environmental Exposures

Air pollutants and heavy metal exposure may impair semen quality but evidence for causation of infertility is weak [63–65]. Recent interest has focused on organochlorines, dioxins, phthalates, phytoestrogens, and chemical mixtures as found in pesticides and tobacco smoke because of mechanistic hypotheses for endocrine disruption and some demonstrated effects on semen quality [66, 67]. Effects are found for PCBs inconsistently, and DDT exposure appears to have minimal effect on semen parameters [68–70]. Pesticide exposure may affect semen quality and fecundability [71]. Overall, however, the literature is not consistent regarding effects of man-made xenobiotics [72–74].

11.3 Physical Examination

11.3.1 Clinical Signs of Hypogonadism

Clinical hypogonadism may be suspected with findings of decreased muscle mass, decreased sexual hair, and increased subcutaneous tissue but there is wide normal variation in expression of sexually dimorphic characteristics.

11.3.2 Examination of Scrotal Contents

Testis size reflects aggregate seminiferous apparatus, not endocrine tissue, and is normal at 30 cc, or a length of 4 cm. Testes smaller than this may reflect decreased sperm production, especially when they exhibit less-than-normal turgor. The vas deferens should be palpable. Absence is usually bilateral, with normal testis findings and azoospermia, and is usually a result of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) complex. Before undertaking ART, partners should be screened to exclude abnormal CFTR genes that would place offspring at risk for cystic fibrosis. Unilateral absence of the vas deferens may indicate CFTR mutations or renal abnormalities and calls for genetic evaluation and urinary tract imaging [75].

11.3.3 Varicocele

Varicocele is posturally expressed and more often left sided. Clinically inevident varicocele is of questionable significance, though can be identified with ultrasound, which may be useful when findings are equivocal. Implications of varicocele for fertility (and response to corrective treatment) are proportional to size of the lesion, but a standard classification is lacking [76]. It is common—the prevalence generally given is 15%—and though more prevalent among infertile men is also commonly innocent. Men with varicocele may have normal semen and fertility or may have infertility, reduced testicular volume, and severely abnormal semen [77, 78]. Proposed mechanisms for infertility include altered testicular thermoregulation, increased seminal plasma reactive oxygen species, and compromised testosterone production [79]. Varicocele effects on semen may be progressive, which argues for surgical treatment for men with normal semen except that this effect is neither consistent nor predictable [80, 81]. Treatment of varicocele is discussed below, under treatment of oligoasthenoteratospermia (OAT).

The Role of Ultrasound in Male Infertility

A role of ultrasound in the diagnosis of male infertility is slowly emerging. Both gray-scale and color Doppler ultrasonography are becoming useful tools in the assessment of male genital tract disorders. Ultrasound can extend the physical exam and explore in more detail the genital area through both the scrotal and trans-rectal approaches.

Scrotal ultrasound is typically performed with patient lying in dorsal supine position, using a high frequency transducer (7–12 MHz) of adequate length to encompass the longitudinal axis of the testicle. Normal ultrasonographic testicular volume is thought to be 12–15 mL. [82] The ultrasound of the scrotal region can also look at parameters such as testicular texture, lesions, and vascularization, the presence of varicocele, epididymal diameter, texture, and vascularization, and the presence of vas deferens. [83] Trans-rectal ultrasound can help in evaluating prostate volume, and texture, and presence of median prostate cysts, ejaculatory ducts cysts, and seminal vesicle volumes. [83]

Clinically, scrotal ultrasound can assist in the diagnosis of absence of vas deferens. It also has a role in confirming the diagnosis of a clinically palpable varicocele. Only patients with palpable varicoceles are thought to benefit from surgical intervention (see below). The role of surgical correction of varicocele diagnosed on ultrasound but not clinically palpable is more controversial. Trans-rectal ultrasound can establish the diagnosis of ejaculatory duct obstruction or CBAVD. Male genital tract color Doppler ultrasound either scrotally and trans-rectally can play an important role in diagnosis of obstructive azoospermia. However, both approaches have more specificity than sensitivity for this diagnosis, indicating that ultrasound is more suitable for exclusion rather diagnosis of obstructive azoospermia. Its current role for other diagnoses of male infertility is limited. [84]

11.4 The Laboratory

11.4.1 Semen Analysis

Pioneering work by Macleod established norms for semen measures based on time required to achieve pregnancy in subjects with currently pregnant partners [82, 83]. Standards for semen analysis were promulgated by the World Health Organization (WHO) in 1987, 1992, 1999, and most recently in 2010 [84]. Yet, excepting the most severely abnormal specimens, semen analysis does not clearly distinguish men with normal fertility from men with infertility [85, 86]. Moreover, because infertility often is multifactorial, and semen exhibits large intra-individual variation, assigning a precise contribution of semen findings to a couple's infertility is usually not feasible [87, 88]. The WHO guidelines published in 2010 are aggregated from findings among fertile men in five studies in eight countries (Table 11.1) [84, 85]. Cutoffs stipulated that 95% of the values were normal, with a one-sided distribution that assumed upper end values do not represent disease. Values below the fifth percentile for these fertile subjects were designated abnormal. The new guidelines simplify quantification of motility from designation of grades to "progressive" or "nonprogressive." Morphology is described by "strict" (or "Tygerberg") criteria and poses some difficulties, as this important measure is subjectively

Table 11.1 Lower reference limits (fifth percentile) and their 95% confidence intervals for semen parameters and 50th percentile values from fertile men whose partners had a time-to-pregnancy of 12 months or less

	N	5th percentile (95% CI)	50th percentile
Semen volume (mL)	1941	1.5 (1.4–1.7)	3.7
Sperm concentration (106/mL)	1859	15 (12–16)	73
Total number (106/ejaculate)	1859	39 (33–46)	255
Total motility (PR, NP, %)[a]	1781	40 (38–42)	61
Progressive motility (PR, %)[a]	1780	32 (31–34)	55
Normal forms (%)	1851	4 (3.0–4.0)	15
Vitality (%)	428	58 (55–63)	79

Adapted from [85]
[a]PR, progressive motility (WHO, 1999 grades a, b); NP, nonprogressive motility (WHO, 1999 grade c)

determined and difficult to standardize across laboratories [82, 89–92]. The new, often lower, cutoffs for normal do not solve the problem of finding values denoting infertility, and have raised concerns regarding clinical application [93–96]. Nonetheless, semen analysis can be used effectively when its limitations are understood [97]. Fertility is a continuously varying characteristic such that reference values cannot segregate absolute fertility from absolute infertility and instead lie within a zone of ill-defined subfertility [86, 92]. Very importantly, decisions to treat with the assumption of infertility on the part of the male (e.g., varicocelectomy, decision for ART/ICSI) should not be made on the basis of results of a single semen analysis, owing to large variations in an individual's semen measures over time [87, 88].

11.4.2 Morphology: A Key Measure of Fertility

Efforts to correlate semen findings with fertility consistently highlight the importance of sperm morphology [83, 86]. Refined standards for morphology, in part based on mucus penetrating capability, led to elaboration of the strict criteria [98]. Morphology by strict criteria varies independently of sperm density and motility and independently predicts success with IUI and ART [90, 99–103]. Strict morphology assessment correlates only roughly with tests of function (e.g., hamster egg penetration test) and has replaced these as predictors of fertilization success in vitro or requirement for ICSI in most ART programs.

11.4.3 Other Measures for Sperm

The advent of ART and ICSI gave impetus to the quest for measures predicting ability to fertilize oocytes and to produce successful embryos. Efforts to this end centered on two principal arenas: first, functional tests of the binding of sperm to the oocyte with execution of the acrosome reaction and second, the integrity of sperm DNA. Examples of functional tests include the hamster egg penetration test, hemizona binding assay, and the zona-induced acrosome reaction (ZIAR) [90, 101, 104–106]. Results of such tests show correlation with morphology, particularly of the acrosome, but are not inconsistently aligned with measures of strict morphology [98, 107, 108]. Sperm function tests remain poorly validated and standardized, their clinical relevance is uncertain, and they are not part of the routine fertility assessment [97, 109].

Fragmentation of DNA is present to varying degrees in sperm, and its extent can be assessed by techniques such as the flow cytometry-based sperm chromatin structure assays (SCSA), terminal deoxynucleotidyl transferase-mediated fluorescein-dUTP nick-end labeling (TUNEL), the single-cell gel electrophoresis assay (also

known as COMET), among several [110–112]. The correlation of findings from these tests with semen measures is often poor, and their ability to predict natural fertility, IUI success, and ART outcomes is variable [110, 112–115]. DNA damage is increased in the presence of varicocele and improves after repair [116]. Measures for DNA damage may be markers for toxicant exposure and oxidative injury to sperm, inflammation, or exposure to certain medications [67, 117–120]. Because of differing results among different tests, lack of standardization, and conflicted data as to utility routine use of DNA fragmentation testing is not justified by current evidence [94, 112, 121, 122]. Emerging work suggests that epigenetic alterations and defects in DNA packaging (protamines, histones) may reflect abnormal spermatogenesis or constitute primary disorders of fertility [123–127].

Special Findings in the Evaluation of Semen

Agglutination of sperm is detected and graded on wet-mount examination. If extensive and associated with a history testicular trauma or vasectomy reversal, it suggests the presence of antisperm antibodies. Evidence suggesting antibodies should be substantiated with specific testing, most commonly with the immunobead test [127–129]. Antibodies may be directed at a variety of antigens on different regions of spermatozoa, with differing consequences for fertility [130, 131]. Pregnancy can occur spontaneously in the presence of antisperm antibodies, but IUI has been used successfully when it does not [132]. Rapid dilution of semen upon collection for IUI may be beneficial [133]. ART has also been used as treatment for antisperm antibodies [132]. The addition of ICSI addresses concern for interference of antibodies with fertilization, but is currently without evidence for clinical benefit [134, 135].

Absent motility occurring with normal measures of vitality indicates one of several ultrastructural defects affecting ciliary function in primary ciliary dyskinesia syndrome. With chronic respiratory infection and situs inversus, the diagnosis of Kartagener's syndrome can be made [136–138]. These disorders are autosomal recessive gene defects affecting the several proteins critical for normal ciliary ultrastructure and movement. Chronic/recurrent respiratory function in these men is due to impaired mucociliary function. Evaluation of sperm tail ultrastructure by electron microscopy can confirm diagnosis, but the classic findings on semen analysis with a typical history of respiratory disease and clinical findings for situs inversus are sufficient for clinical diagnosis. Pregnancy is achieved with ART and ICSI [139, 140].

Absent or minimal ejaculate after orgasmic masturbation suggests retrograde ejaculation or ejaculatory duct obstruction. Distinction between the two depends upon post-ejaculation urine analysis, which will show abnormally elevated sperm numbers after retrograde ejaculation. Causes include anatomic disruptions from prostate surgery, and neurologic dysfunction related to diabetes, demyelinating disorders, or sequelae of retroperitoneal node dissection. Pharmacologic disruption of the ejaculatory signaling pathway may occur with alpha-adrenergic blockers used for urine flow with prostatic hyperplasia. Medical treatments using alpha sympathomimetic agents (ephedrine, phenylephrine) or tricyclic antidepressants may help in some instances [141, 142]. More often, harvesting of sperm from post-ejaculatory urine that has been alkalinized by bicarbonate ingestion is done so that IUI or ART may be undertaken [143–145].

11.5 Clinical Categories of Severe Semen Abnormalities

11.5.1 Oligoasthenoteratospermia

Abnormalities of semen among infertile males are rarely limited to a single parameter and commonly present as subnormal values for sperm density, motility, and normal morphology. This constellation is often termed OAT, or OAT syndrome. OAT, when severe, should be evaluated for genetic, chromosomal, and endocrine origins as described below for the evaluation of azoospermia. OAT is often idiopathic [146]. Two groups of OAT have been described, one affected primarily in density and motility and the other in sperm morphology, with the latter showing higher correlation with the presence of sperm aneuploidy [147, 148]. OAT is associated with sperm aneuploidy in many studies, with the rate of aneuploidy found in normal and abnormally formed sperm from men with OAT being similar to that

in abnormally formed sperm from normal semen specimens [149–152]. Elevated frequencies of aneuploidy in sperm from men with OAT likely explain the increased aneuploidy in embryos created from their sperm using ICSI [153]. Other sperm abnormalities in OAT include increased DNA fragmentation, mitochondrial abnormalities, epigenetic alterations, and disordered chromatin organization [154–156]. Management of infertility due to OAT includes consideration of donor insemination, ART with ICSI, and attempts at medical therapy (discussed below). Surgical or embolic treatment for varicocele for men with OAT may be appropriate.

11.5.2 Treatment of Varicocele

Treatment of varicocele with surgery or embolization is performed for discomfort and for infertility. Additionally, when low serum testosterone levels are present, they may be corrected with surgical treatment [78, 157]. Improvement in semen varies widely after varicocelectomy, and may be more likely in younger individuals. [158] Even azoospermic individuals may show return of sperm to the ejaculate after surgery [158]. Surgical techniques have advanced in recent decades to reduce unintended vascular or lymphatic injury [159, 160].

Despite beneficial effects of varicocelectomy on semen quality, endocrine function, and pain, its role as a fertility treatment is controversial; analyses of literature using live birth as the outcome of interest yields conflicting conclusions [159, 161–163]. The advent of ART and ICSI for male factor infertility adds complexity to knowing varicocelectomy's role [163, 164]. Pregnancy as a result of varicocelectomy may occur over an extended window of time (as is true for pregnancy among normally fertile couples) and, therefore, youth of a couple, and lack of urgency would favor an attempt at correcting infertility with varicocelectomy, prior to advancement of care to ART. The presence of pain or hypoandrogenism would favor surgery, as would religious or other barriers to ART. Alternatively, progression to ART, without varicocele correction, may be preferred for couples not comfortable accepting its uncertain benefit and for couples for whom time to pregnancy is a concern, especially where female age is a factor.

11.5.3 Azoospermia

Azoospermia requires examination of centrifuged semen for confirmation. It may be due to obstruction, inadequate gonadotropins, or defective germinal epithelium. The latter two comprise the two causes for nonobstructive azoospermia (NOA), and the laboratory plays an important role in differentiating between them. The nature of the semen is helpful in distinguishing the causes of azoospermia [165]. Smaller semen volumes and greater acidity without fructose suggest absent seminal vesicles (CBAVD), which can be confirmed on scrotal examination. Smaller semen volumes will also be seen in severe hypogonadism. Normal semen volumes with normal pH suggest primary testicular (germinal) defects or ductal obstruction at the level of the vas or epididymis. Surgery for cryptorchidism in childhood is a risk factor for NOA and these occurring together may implicate the putative "testicular dysgenesis syndrome," warranting careful testicular examination for mass [21, 24, 166]. Surgery for cryptorchidism or for torsion that harms the contralateral ducts or history of prior epididymitis may account for proximal ductal obstruction. Exogenous androgen use may profoundly suppress spermatogenesis [53, 54]. Examination of the scrotal contents helps differentiation of ductal disorders (the presence of normal testicular volume and turgor, palpable ductal abnormalities) from primary testicular and endocrine control disorders (small testes of reduced turgor). Congenital bilateral absence of the vas is evident from palpation and has implications for CFTR mutation screening in the event of ART.

11.5.4 Endocrine Evaluation

The principal value of endocrine testing in evaluation of azoospermia lies in distinguishing testicular from central causes of NOA. It is rarely helpful in the evaluation of OAT or sexual dysfunction. Some degree of elevation of follicle-stimulating hormone (FSH) levels is expected with primary testicular disorders, and though cutoff values for this are elusive, such findings usefully contrast with the very low FSH, luteinizing hormone (LH), and testosterone levels seen in hypogonadotropic disorders [167].

Principal hypogonadotropic disorders are either congenital (frequently as classic Kallman's syndrome, which includes anosmia), in which impaired pubertal development may have led to androgen replacement, or acquired disorders, in which the principal concern is pituitary or juxtapituitary neoplasm [168–170]. Therefore, when adult-onset hypogonadotropic hypogonadism is diagnosed, the serum prolactin levels should be determined; CNS and pituitary imaging should be performed if it is elevated, or if there is evidence for global pituitary insufficiency (central hypothyroidism, hypoadrenalism, or diabetes insipidus) or symptoms of intracranial mass. Treatment of endocrine disorders for fertility restoration is discussed below.

11.5.5 Chromosomal and Genetic Evaluation

NOA of testicular origin and severe OAT warrant genetic and chromosomal evaluation, especially prior to ART. Identifiable chromosomal and genetic abnormalities are common among men requiring ICSI [171–174]. Five percent of ICSI patients exhibit chromosome errors, and these involve the sex chromosomes in approximately two-thirds of instances. Frequency of chromosomal errors increases with the severity of semen impairment, reaching 10% or greater among men with the most profound deficits in sperm density [171, 175]. Y-chromosomal microdeletion is roughly as common as chromosomal error in this population and also most prevalent among men with the greatest depression of spermatogenesis [171, 172].

Sex chromosome aberrations are the most frequent of the few chromosome abnormalities compatible with adult life in men. Klinefelter syndrome (XXY and mosaics) and XYY syndrome both include infertility and each occurs in one to two per 1000 births [173, 174, 176]. Nonmosaic Klinefelter's syndrome is common among azoospermic individuals, and men mosaic for the disorder frequently present with abnormal semen [175]. Klinefelter's patients have harvestable sperm with TESE, more often than not. Testicular volume and hormone levels are of limited utility in predicting TESE success [167, 177, 178]. Because spermatogenesis may be focal, microdissection may provide the best TESE success rate [177, 179]. Fluorescence in situ hybridization (FISH) to exclude embryonic aneuploidy should be considered if ART/ICSI is undertaken for Klinefelter's syndrome [180]. Autosomal-balanced translocations (and the Robertsonian translocation form of these) are associated with infertility, recurrent abortion, and rarely, offspring with deficits owed to unbalanced chromosomes [173–175]. Effects of autosomal translocations and inversions arise through disruption of normal meiotic bivalents such that azoospermia, due to meiotic arrest, or oligospermia occurs. Interchromosomal effects, whereby other, normal chromosomes are collaterally damaged during meiotic errors, add to the reproductive morbidity of autosomal chromosomal rearrangements [181]. Frequencies of sperm aneuploidy, likelihood of embryonic aneuploidy, and successful reproduction vary widely according to the defect present [173, 182].

High percentages of embryos from men with structural rearrangements have aneuploidy, and preimplantation genetic diagnosis (PGD) can increase the likelihood of transferring normal embryos [183]. It is most clearly of use in cases of recurrent abortion, in which ART/PGD may shorten the time to implantation of a normal embryo, or in the uncommon cases in which abnormal offspring with unbalanced chromosomal complement have been born [184]. PGD technologies will be transformed by the advent of emerging array technologies [173].

It is likely that genetic lesions often explain severe male infertility, but only a few are described [185, 186]. Microdeletions in the AZF region of the Y-chromosome long arm have been extensively studied. A prevalence of 7.4% among infertile men is estimated, and their likelihood is proportional to the severity of spermatogenic abnormality. Deletions in the various AZF subregions ("a," "b," or "c") or combinations of them occur with differing frequencies and with differing implications for the degree of impairment of spermatogenesis, and the likelihood of retrievable sperm if there is NOA. Large areas of deletion and deletions involving the a and b subregions are associated with failure to retrieve sperm on TESE [180, 185, 187]. Because of this, testing for AZF deletion is advisable before attempting TESE for NOA. Mutations with severe functional consequence for the androgen receptor lead to infertility and intersex conditions and lesser lesions to infertility alone [188–190]. Such mutations were

found in 1% of a large series of men with severe oligospermia undergoing ICSI [172].

Identification of chromosomal or genetic causes for male infertility thus has implications for health of embryos and offspring, and can predict TESE success for NOA. Using results of genetic and chromosomal evaluation of the male to provide counseling about pregnancy likelihood and outcomes is an important element of care for couples treated for severe male factor infertility [171–173, 187, 191].

11.5.6 Treatment of Azoospermia and OAT

Treatments available for azoospermic disorders include donor insemination in all cases, surgical repair for some ductal obstructions, and ART with TESE and ICSI in selected instances [192–194]. Genetic and chromosome evaluation should be encouraged prior to ART for non-ductal azoospermia (see above). CBAVD signals a high likelihood of CFTR mutation, and ART care should always include screening for these in the female partner prior to ART. When azoospermia is associated with varicocele, treatment may restore sperm to the ejaculate of some patients [158, 195, 196]. Administration of gonadotropins can be effective as sole therapy for hypogonadotropic disorders or to provide ejaculated sperm for ICSI. Fertility can be restored with dopamine agonists for most men with pituitary tumors; when treated surgically, gonadotropins are usually required (see below).

11.5.7 Medical Regimens

Medical therapy for male infertility falls into three categories: replacement of deficient gonadotropins for men with hypogonadism of central origin, empiric direct or indirect augmentation of gonadotropins for men with unexplained infertility, and use of nutritionals and supplements.

11.5.8 Hypogonadal Males with Central Deficiencies of Gonadotropins

Induction of spermatogenesis in constitutional hypogonadotropic hypogonadism, including patients with anosmia (Kallman's syndrome), can be accomplished with administration of pulsatile gonadotropin-releasing hormone (GnRH), which precisely targets the pathophysiology, but is cumbersome [197]. Fertility in Kallman's syndrome and idiopathic or postsurgical hypogonadotropic states is often achievable with administration of human chorionic gonadotropin (hCG) alone, typically in doses of 1500–2000 IU twice weekly, but many patients will require co-administration of FSH [198, 199]. When required, FSH doses as low as 150–225 IU weekly may be sufficient [200]. Pregnancies often occur once there are sperm densities that are usually considered oligospermic [199].

Surgical management of prolactinomas in men is complicated by a high rate of persistent hypogonadotropic hypogonadism and recurrent hyperprolactinemia such that replacement gonadotropins are still necessary for fertility [201]. Medical therapy has emerged as a preferable course for most cases. Treatment with the dopamine agonist Cabergoline allows for regression of lesion size, normalization of the hypothalamic–pituitary–testicular axis, normalization of androgens, and restoration of spermatogenesis in a majority of instances, including cases of large prolactinomas [169, 170, 202].

11.5.9 Empiric Therapies for Idiopathic OAT

There is a limited literature supporting a variety of empiric therapies for unexplained male infertility [203]. These treatments presume etiologies such as minimally defective gonadotropin secretion, oxidative insult, or nutritional deficiency. Administration of gonadotropins for men with apparently intact hypothalamic–pituitary–gonadal axes and poor semen quality is supported by limited trial data [204, 205]. Indirect enhancement of gonadotropin secretion with antiestrogens (tamoxifen citrate and clomiphene citrate) is less cumbersome and costlier than gonadotropin administration and is also supported by limited evidence [204, 206–209]. Use of aromatase inhibitors has also shown some promise, especially for men with low ratios of circulating testosterone to estradiol [210, 211]. Among supplements, zinc and folate may improve semen parameters [212]. Studies of carnitines and of antioxidants suggest possible benefits [209, 213–215]. Evidence for these several putative therapies for unexplained

male infertility is hampered by high intra-individual variation in semen values, limited expression of results in terms of pregnancies, and the likely heterogeneous nature of underlying causes. None of these is adequately supported by high-quality evidence [216]. Large and carefully conducted clinical trials for the treatment of idiopathic OAT that utilize pregnancy as the outcome are needed [146].

11.5.10 Intrauterine Insemination

IUI is widely employed for infertility due to mild or moderate male factor or unknown cause. Often the latter, may have undiagnosed mild male factor. The rationale for IUI is based on several conjectures, including the bypass a hostile vaginal and or cervical environment, reducing the distance for sperm transport, selection of the most fertile sperm, concentrating fertile sperm at the site competition for fertilization, reducing the concentration of spermatotoxic molecules in the seminal fluid (capacitation inhibitors, free radical, etc.), and improved timing of the ovum–sperm exposure. IUI require that the female has spontaneous or inducible ovulation, and has normal anatomy, including normal uterine cavity and patent fallopian tubes. Timing IUI is determined by home kits for detection of the LH surge, or by a triggering injection of hCG given when follicle diameters reach at least 18–20 mm. If hCG is used, artificial insemination is timed 32–36 h after the injection. Success rates are not affected by whether the endogenous LH surge or hCG administration is used for timing [217]. Frequent intercourse through midcycle appears preferable to prescribed abstinence prior to collection of the specimen for IUI [1, 2, 4]. Semen is prepared for insemination using one of several aimed at selecting the most fertile pool of sperm and, importantly, to separate sperm from seminal prostaglandins which can cause painful contractions. Density gradient preparation is commonly used, although there is no evidence of the superiority of any of the sperm preparation techniques [218].

The prepared sperm is typically concentrated to a volume of ½ to 1 cc and injected into the uterine cavity gently, using a sterile catheter passed through the cervical canal after wiping the cervix free of secretions or excess mucus. Triggering of upper reproductive tract infection with IUI is a rare complication. IUI shows a higher pregnancy rate when compared to intracervical insemination in couples with unexplained infertility but may not be superior to timed intercourse when done without superovulation [219, 220]. Although superovulation adds efficacy to IUI, and pregnancy rates show some proportionality to numbers of maturing follicles, this must be balanced against significant risks for high-order multiple pregnancy [219, 221–223]. Double inseminations have been proposed to increase success. However, most studies show little evidence of the benefit of this maneuver, which increases the cost and complexity of IUI considerably [224–227]. IUI success depends on female age and quality of semen. Older women fare poorly, and pregnancies are uncommon if they are older than 40 [228]. Pregnancy success is a function of total motile sperm in the insemination; a preparation that contains 5 million motile sperm appears to be the threshold for benefit of IUI, although preparations with fewer sperm may rarely yield pregnancy [223, 229, 230]. Artificial insemination is typically attempted for 3–4 cycles; series do not show a significant increase in cumulative pregnancies beyond that [223]. A recent critical review found a limited number of adequately conducted trials, few subjects overall for evaluation, and thus limited evidence for a benefit for IUI vs. timed intercourse [220]. It is likely that couples vary in the degree to which IUI might benefit them, and that substantial benefit for some couples, and little benefit for others, underlies the generally low statistics for IUI outcomes. A trial of IUI is often selected in hopes that success will obviate the need to progress to the more invasive and costly undertaking of ART.

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