

APPROACH TO THE PATIENT

Approach to the Infertile Man

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Introduction: Infertility is one of the most common disorders to afflict young men and women. The evaluation of infertility is initiated typically after 1 yr of failure to conceive.

Diagnostic Evaluation: The couple should be evaluated together to determine whether the problem resides in the male partner, the female partner, or both. The objectives of evaluation are to exclude treatable conditions—gonadotropin deficiency, obstruction, and coital disorders—and identify those who are candidates for assisted reproductive technologies, those who are sterile and should consider adoption or artificial insemination using donor sperm, and those who should undergo genetic screening. All infertile men should undergo several semen analyses according to the World Health Organization manual, as well as measurements of testosterone, LH, and FSH levels. Hormone measurements can help determine whether the patient has gonadotropin deficiency (low testosterone and low or inappropriately normal LH and FSH), primary testicular failure (low testosterone, elevated LH and FSH), spermatogenic failure (normal testosterone and LH, elevated FSH), or androgen resistance (high testosterone, elevated LH). A majority of infertile men have normal

testosterone, LH, and FSH levels. Obstruction should be ruled out in azoospermic men with normal testosterone, LH, and FSH levels.

Genetics: Yq microdeletions are the most prevalent cause of spermatogenic failure in men with azoospermia or severe oligozoospermia. Infertile men with azoospermia or severe oligozoospermia should undergo karyotyping and testing for Yq microdeletions. Men with congenital absence of vas should be tested for cystic fibrosis transmembrane conductance regulator mutations.

Therapy: Gonadotropin therapy is highly effective in gonadotropin-deficient men. Intracytoplasmic sperm injection (ICSI) has emerged as the treatment of choice for idiopathic male factor infertility. However, ICSI is expensive and associated with a higher risk of multiple gestation, low birth weight, preterm delivery, perinatal complications, and chromosome aneuploidy than naturally conceived pregnancies. Men considering ICSI should be offered karyotyping, Yq microdeletion testing, and genetic counseling by counselors experienced in reproductive disorders. (*J Clin Endocrinol Metab* 92: 1995–2004, 2007)

I. The Patient

A 32-YR-OLD MAN requests evaluation for infertility. He was a full-term healthy baby who underwent normal pubertal development. Married for 3 yr, his 28-yr-old wife has not conceived despite unprotected intercourse. His wife has normal menstrual cycles, and her gynecological evaluation reveals no abnormality. Physical examination reveals a well-developed man with normal facial, chest, and pubic hair. Testicular volume is 18 ml bilaterally. The rest of his examination is normal.

Blood counts and chemistries are normal. Testosterone level is 450 ng/dl, LH is 6 U/liter, and FSH is 12 U/liter. Semen analyses reveal no sperm in two semen samples and sperm density of 1 million/ml in the third sample. Karyotype is 46, XY in all 100 cells.

Abbreviations: AR, Androgen receptor; ART, assisted reproductive technology; AZF, azoospermia factor; CFTR, cystic fibrosis transmembrane conductance regulator; CREM, cAMP response element modulator; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IHH, idiopathic hypogonadotropic hypogonadism; IVF, *in vitro* fertilization; MSY, male-specific region of Y chromosome; Yq, long arm of Y chromosome.

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II. Case Discussion

This patient with azoospermia/severe oligozoospermia, normal testosterone and LH levels, but an elevated FSH level has primary spermatogenic failure. Although in a majority of men with idiopathic oligozoospermia or azoospermia, the cause cannot be identified, microdeletions of the long arm of Y chromosome (Yq) are the most frequent recognizable cause of spermatogenic failure in 46, XY men with nonobstructive azoospermia or severe oligozoospermia. Our patient likely does not have Klinefelter's syndrome because his testosterone level, testicular volume, and karyotype are normal. Mutations of the androgen receptor (AR) gene may be associated with a variable phenotype that can range from complete feminization to undervirilization and infertility. However, patients with AR mutations typically have high testosterone and elevated LH levels. Obstruction should always be considered in men with azoospermia; however, FSH levels are typically normal in obstructive azoospermia. This patient with severe spermatogenic failure would be an excellent candidate for analysis of Yq microdeletions and consideration of intracytoplasmic sperm injection (ICSI). If some live sperm can be found in the semen, then ICSI can be performed using sperm in the ejaculate. Men in whom no live sperm can be retrieved from the ejaculate may be candidates for ICSI using intratesticular sperm or elongated spermatids obtained from testicular biopsy.

III. Introduction

Reproduction and fertility are central to survival of the species; not surprisingly, the biblical and Vedic lore reflects human preoccupation with both conception and infertility. For instance, Sarah, Abraham's wife, had passed the child-bearing age without producing offspring; she encouraged Abraham to take her Egyptian slave girl, Hagar, as a second wife, who bore him Ishmael. Later, Sarah would produce a son of her own, Isaac. In the Hindu Epic *Ramayana*, King Dashratha, the Father of Lord Rama, married thrice, but he was unable to bear children with any of his queens. King Dashratha's high priest, Balamiki, held a prayer ceremony, invoked the gods, and offered a concoction to the three queens, following which each of them became pregnant—arguably the first report of successful assisted reproductive technology (ART) treatment.

Infertility continues to be a highly prevalent condition; the proportion of couples seeking medical treatment for infertility is estimated at 4–17% (1, 2). From 3–4% of all couples remain involuntarily childless at the end of their reproductive periods (3). The primary problem resides exclusively in the male partner in 20% of infertile couples; in an additional 26%, problems reside in both the male and the female partner (4).

Given the high prevalence of infertility among men and its impact on an individual's well-being and health care expenditures, the neglect that this topic has received in endocrine literature is regrettable. The endocrinologists and the professional societies that represent them have abdicated their natural leadership of this field to others, much to the detriment of patients and the field of endocrinology. The reluctance of the endocrinologists stems in part from their unfamiliarity with simple office procedures such as ultrasound and testicular biopsy/aspiration for ICSI and from the sub-optimal rendition of this topic in endocrinology curricula.

The endocrinologist should play an important role in coordinating the care of the infertile couple and providing counsel on prognosis and treatment options, including ART programs. The endocrinologist should identify those who have a treatable cause of infertility, such as gonadotropin deficiency or obstruction. The evaluation should determine which couples can benefit from ART and whether the patient has untreatable sterility, in which case the couple should be counseled about adoption or artificial insemination with donor sperm. The endocrinologist should present to the couple a realistic prognosis and the pros and cons of treatment options and should guide the couple away from ineffective interventions.

IV. Diagnostic Evaluation

Duration of failure to conceive before diagnostic work-up is initiated

Determination of when diagnostic evaluation should be initiated is important because a majority of couples failing to conceive for 12 months will conceive spontaneously (5, 6)! The World Health Organization (WHO) defined infertility as the inability of a sexually active couple to achieve pregnancy despite unprotected intercourse for a period of greater than 12 months (7). The WHO definition was based on studies that

used time-to-pregnancy estimations and found the probability of conception to be 20% per cycle or approximately 85–90% per year (7–10). The European Society for Human Reproduction and Embryology (ESHRE) defines infertility as failure of pregnancy to occur within 2 yr of regular coital exposure (11).

These recommendations have important implications. First, the probability of conception in any menstrual cycle is only approximately 30%, even among couples who do not have any medical problem. Second, although some couples who fail to conceive within 12 months will never conceive spontaneously, over 50% will have a live birth within the next 36 months (6). As the duration of nonconception increases, the likelihood of spontaneous conception decreases; among couples reporting infertility for 4 yr, conception rates per month are 1.5% (12, 13). Thus, the pressures to initiate evaluation and treatment should be resisted if the period of nonconception is less than 1 yr. However, in couples with known reproductive disorders, an earlier intervention is justified.

The spontaneous conception rates may be even higher than those estimated previously (14, 15). Among Chinese women 20–34 yr of age (14), monthly fecundity rates were approximately 30–35%; 90% became pregnant in their first six cycles. Among German couples (15), cumulative probabilities of conception were estimated to be 38, 81, and 92% at one, six, and 12 cycles. These data have led to suggestions to reduce the time for initiating evaluation to 6 months. However, reducing the time of unwanted nonconception before initiating evaluation will impact the predictive value of diagnostic tests and cost effectiveness of therapeutic procedures.

Causes and pathophysiology. The frequency of etiological factors varies among different surveys (7, 16, 17). In general, 15–20% of infertile men are azoospermic (3, 17), and 10% have sperm density below 1 million/ml. A specific cause of infertility is not determinable in 40–60% men (7, 16, 17). Most infertile men have idiopathic oligozoospermia (7, 16, 17).

Correctable or treatable causes of infertility, such as gonadotropin deficiency, obstruction, and coital disorders, are present in only a small fraction, but it is important to recognize them because effective therapies are available (17). Varicoceles are present in 10–30% of infertile men; their role in pathophysiology of infertility remains unclear (18, 19). A number of genetic disorders have been implicated in spermatogenic failure; of these, Klinefelter syndrome and Y chromosome microdeletions are the most prevalent, accounting for 10–20% of patients (17, 20). Although the prevalence of antisperm antibodies in infertile men is higher than in fertile men (21), the mechanisms by which antisperm antibodies cause infertility are unclear.

Diagnostic evaluation of the infertile man. The objectives of evaluation are to exclude treatable conditions—gonadotropin deficiency, obstruction, and coital disorders—and to identify those who are candidates for ART, those who are sterile and should be counseled to consider adoption or artificial insemination using donor sperm, and those who should undergo genetic screening. The key elements of evaluation are the following (Table 1 and Fig. 1):

1. Evaluate the couple together and determine whether the

TABLE 1. Key considerations in the diagnostic evaluation of an infertile man

	Consideration	Diagnostic approach	Interpretation/management
Step 1	Determine whether the period of failure to conceive exceeds 1 yr.	If the period of involuntary nonconception is less than 1 yr, defer detailed evaluation.	Reassure the couple and reevaluate after sufficient length of time unless an obvious cause of infertility exists.
Step 2	Determine whether the problem resides in the male partner or the female partner.	Evaluate the couple together; obtain health and menstrual history; FSH, TSH, and prolactin in the female partner; and semen analysis and testosterone, LH, and FSH in the male partner.	If the female partner has normal ovulatory menstrual cycles, tubal patency, good general health, and normal FSH, TSH, and prolactin, the problem likely resides in the male partner.
Step 3	Determine whether a systemic health problem explains infertility.	General health evaluation, blood counts and chemistries and other appropriate tests	Rule out systemic illness.
Step 4	Determine whether the patient has a treatable cause of infertility. Exclude gonadotropin deficiency.	Testosterone, LH, and FSH levels	If testosterone levels are consistently low and LH and FSH levels are low or low normal, the man has hypogonadotropic hypogonadism.
Step 5	Determine whether the patient has a treatable cause of infertility. Exclude an obstructive lesion.	Testosterone and FSH levels, testicular volume	If semen analyses reveal azoospermia and the man is well virilized, has normal testicular volumes, normal testosterone and FSH levels, obtain urological evaluation to rule out obstruction.
Step 6	Determine whether the patient has a treatable cause of infertility. Exclude coital disorders: erectile dysfunction, retrograde ejaculation, or anejaculation.	Inquire about sexual function, sexual practices, ejaculation, and time of intercourse. In diabetics, test postejaculatory urine for sperm.	Treat erectile dysfunction; in those with retrograde ejaculation, sperm can be collected from urine or by bladder catheterization after ejaculation. In men with anejaculation, ejaculation may be induced by electrostimulation.
Step 7	Determine whether patient has antisperm antibodies	Test for antisperm antibodies in oligozoospermic men with normal hormone levels, prior history of torsion or testicular injury, or if semen analysis reveals aggregates of sperm.	In men with unexplained infertility and severe autoimmunity (>70–80% IBD binding), consider treatment with ICSI. There is limited evidence of effectiveness of glucocorticoids.
Step 8	Should genetic testing be performed?	Testicular volume, semen analyses	Obtain a karyotype in men with azoospermia, severe oligozoospermia, primary testicular failure, or very small testicular volume. Screen for Yq microdeletions in infertile men with azoospermia or severe oligozoospermia. Test for CFTR mutations in men with absence of vas.

The main objectives of diagnostic work-up are to evaluate general health, determine whether the problem resides in the male or the female partner, rule out treatable conditions such as gonadotropin deficiency and obstruction, and test appropriately selected patients for genetic conditions such as chromosomal aneuploidy and Yq microdeletions. The diagnostic work-up of infertile men is relatively simple and inexpensive because most infertile men only need semen analyses and measurements of testosterone, LH, and FSH levels in their initial evaluation. IBD, Immunobead.

problem resides in the male partner, the female partner, or both. If the female partner has ovulatory menstrual cycles, tubal patency, and normal FSH, TSH, and prolactin, the problem likely resides in the male partner.

2. Initiate the work-up by evaluating general health and excluding systemic diseases.

3. History should focus on duration of infertility, previous fertility in the man or the woman, contraceptive use, sexual function, frequency and timing of intercourse, and sexual practices. Ascertain the timing of pubertal development, shaving frequency, and hair loss. Inquire about scrotal trauma, genitourinary infection, sexually transmitted disease, and scrotal or inguinal surgery including hernioplasty and vasectomy. Ask for history of cancer, especially previous treatment with cancer chemotherapy and radiation to the inguinal or scrotal area. Evaluate hair distribution and es-

cutcheon, body proportions, and voice. Measure testicular volume by Prader orchidometer and palpate epididymis for cysts and vas deferens for total or segmental absence.

4. Analyze three or more semen samples obtained by masturbation after at least 48-h abstinence; determine sperm density, motility, and morphology, using rigorous quality control in accordance with WHO manual (22, 23).

5. Measure testosterone, LH, and FSH in early morning to determine whether patient has gonadotropin deficiency (low testosterone and low or inappropriately normal LH and FSH), primary testicular failure (low testosterone, elevated LH and FSH), selective spermatogenic failure (normal testosterone and LH, elevated FSH), or androgen resistance (high testosterone, elevated LH). A majority of infertile men have normal testosterone, LH, and FSH levels (3, 16, 17).

6. In men with azoospermia and normal testosterone, LH,

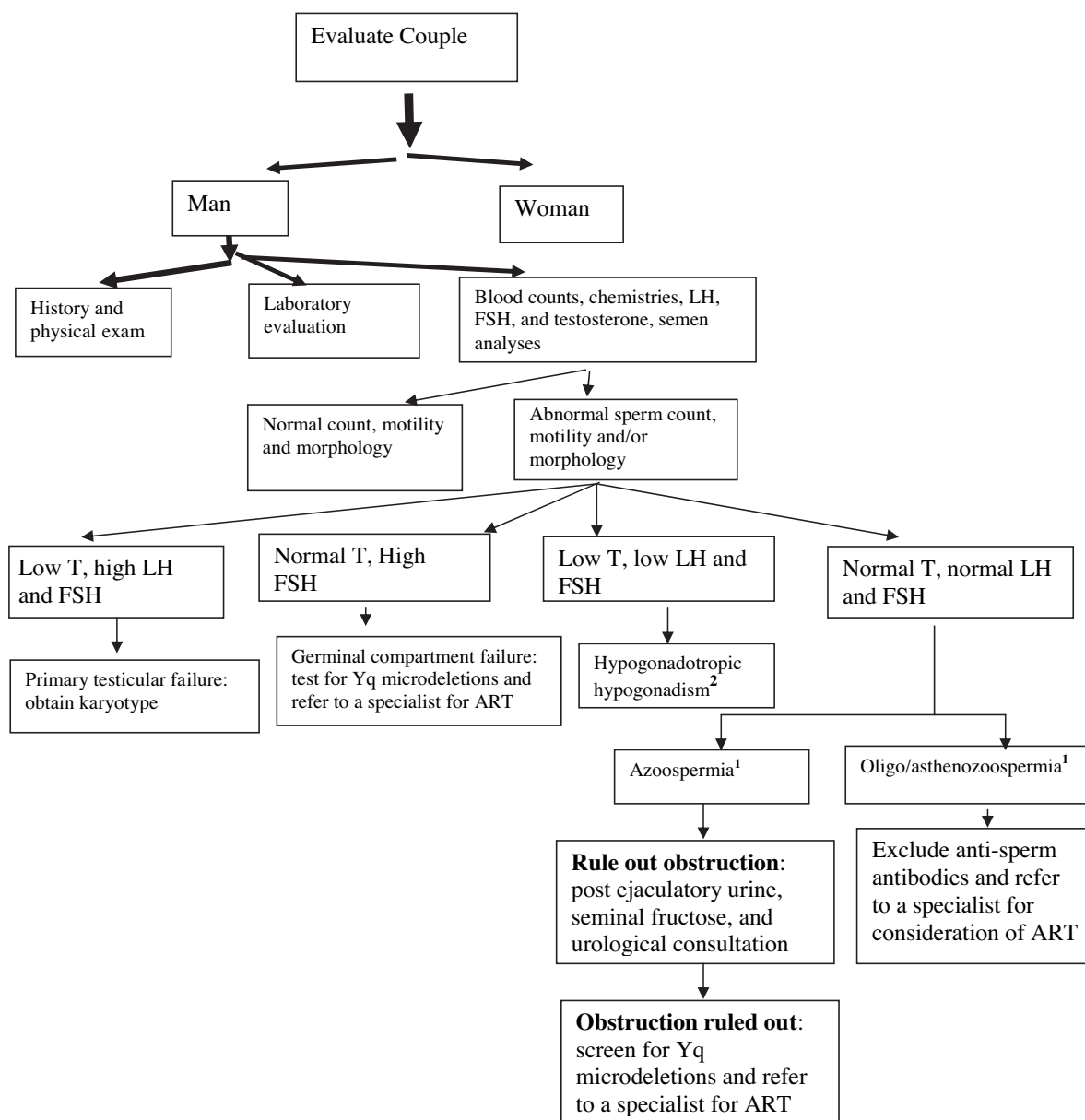


FIG. 1. An algorithmic approach to the evaluation of an infertile man. ¹, Infertile men with nonobstructive azoospermia and severe oligozoospermia with normal or elevated FSH should undergo a karyotype and screening for Yq microdeletions before being referred for ICSI. ², Men deemed to have hypogonadotropic hypogonadism should be evaluated further by an magnetic resonance imaging scan, prolactin, and measurement of other pituitary hormones to exclude space occupying neoplastic or infiltrative lesions of the hypothalamic pituitary region. T, Testosterone.

and FSH levels, exclude obstruction by measuring seminal fructose and obtaining urological evaluation; perform cystic fibrosis transmembrane conductance regulator (CFTR) mutation analysis in those with absence of vas.

7. Check antisperm antibodies in oligozoospermic men with normal hormone levels, history of torsion or testicular injury, or sperm aggregates in semen (21).

8. Normal testosterone, normal LH, and elevated FSH levels in an azoospermic or severely oligozoospermic man are suggestive of primary spermatogenic failure. These men should undergo measurement of testicular volume, karyotyping, and screening for Yq microdeletions.

9. Specialized sperm function tests such as the acrosome

reaction, zona-free hamster egg penetration test, and human zona binding test, have limited clinical utility; they should be performed only in research studies (22, 23).

Genetic causes

Chromosomal disorders. One of 20 infertile men bears a chromosomal abnormality; of these, 80% of cases involve sex chromosomes and 20% involve autosomes (20, 24). The sex chromosomal and autosomal abnormalities occur with 15 and six times greater frequency, respectively, in infertile men than in the general population (20, 24). Klinefelter's syndrome is the most frequent chromosomal disorder associated with infertility (20, 24).

Y chromosome microdeletion syndrome. The Y chromosome contains an important collection of testis-specific genes necessary for spermatogenesis (25, 26). The human Y chromosome consists of a pseudoautosomal region that recombines with homologous regions of X chromosome; the remaining 95% of Y chromosome that does not recombine with X chromosome is referred to as the male-specific region of Y (MSY) (Fig. 2) (25). The MSY contains three classes of sequences: X-transposed, X-degenerate, and ampliconic (25). The ampliconic region contains sequence pairs showing nearly similar nucleotide sequences organized into large palindromes that contain multicopy Y-specific genes that are expressed in the testis (25). Intra-Y gene conversions occur frequently, account for the high degree of sequence similarity between the arms of the palindromes (25, 26), and predispose Y chromosome to high frequency of deletions and rearrangements. The X-transposed sequences have a high degree of homology to X chromosome, whereas X-degenerate sequences represent what is left of ancient autosomes that were transposed to form X and Y chromosomes (25).

Tiepolo and Zuffardi (27) discovered that men with large deletions of Yq were infertile and proposed that loci for “azoospermia factor (AZF)” reside in these Yq regions. Large deletions of Yq that are visible under the light microscope are uncommon in infertile men. However, small deletions of Yq that are not visible under the microscope and are referred to as microdeletions are observed in 10–15% of infertile men with azoospermia or severe oligozoospermia (28–42). In a survey of 3,073 infertile men, the prevalence of Yq microdeletions was 3.2% in infertile men, 8.3% in men with nonobstructive azoospermia, and 5.5% in men with severe oligozoospermia (Fig. 3) (40). Y microdeletions are rare in fertile men and in men with sperm densities greater than 5 million/ml.

There is poor correlation between testicular histology and the location and size of the microdeletion. Most infertile men with Y deletions have either azoospermia or severe oligozoospermia (40) (sperm densities < 5 million/ml) and elevated FSH levels (40–43). Vogt (42) classified Yq microde-

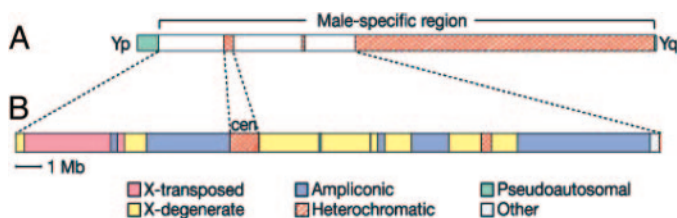


FIG. 2. A schematic representation of the human Y chromosome. The pseudoautosomal region refers to that portion of the Y chromosome that recombines with homologous regions of the X chromosome. The remaining 95% of Y chromosome that does not recombine with the X chromosome is referred to as the MSY. Page and colleagues (25) discovered that the MSY contains many transcription units that are grouped in three classes: X-transposed, X-degenerate, and ampliconic (35). The ampliconic region contains several multicopy Y-specific genes that are expressed in the testis (35). The X-transposed sequences have a high degree of homology to X chromosome, whereas X-degenerate sequences represent remnants of ancient autosomal regions that were transposed to form X and Y chromosomes. Yp, Short arm of Y chromosome; Yq, long arm of Y chromosome. [Reproduced with permission from H. Skaletsky *et al.*: *Nature* 423:825–837, 2003 (25).]

letions into three groups depending on the location of microdeletion: AZFa, AZFb, and AZFc. Subsequently, three additional types of microdeletions were recognized: gr/gr deletion, AZFbc, and AZFabc. These six types of microdeletions account for nearly all the Yq microdeletions that have been associated with infertility (Fig. 3) (40, 41). AZFc deletions account for two thirds of all Yq deletions (40).

With the recognition that most of the Y microdeletions are caused by intra-Y homologous recombination between repeated sequence blocks that are organized into palindromes, the classification of Yq microdeletions has undergone revision. The new classification is based on the mechanism of deletion: AZFa, P5/proximal-P1, P5/distal-P1, P4/distal P1, and b2/b4-AZFc (40).

Y-specific gene families. Several Y-specific gene families, cloned by deletion mapping of Yq deletions, have been associated with spermatogenesis; the RBM (RNA binding motif containing), the DAZ (deleted in azoospermia), USP9Y, and BPY2 (44–55). DAZ and RBM are multiple-copy gene families that contain RNA binding motifs (45–47). The precise role of these proteins in germ cell development remains unclear.

Who should be tested for Yq microdeletions? Infertile men with nonobstructive azoospermia or severe oligozoospermia (sperm density < 5 million/ml) in whom the cause of spermatogenic failure is not apparent should be tested for Yq microdeletions.

How is the testing for Yq microdeletions performed? Yq microdeletions are detected by PCR-based mapping of several conserved molecular markers or genes located within and outside the AZF region (43); these tests are available from commercial laboratories. With the availability of precise Y chromosome maps, more specific molecular markers have been developed, and guidelines for standardized testing of Yq microdeletions have been published by the European Molecular Genetics Network (43). High resolution microarrays for chromosome testing are being developed for detection of Y deletions, but are not yet available for clinical use.

Father-to-son transmission of Yq microdeletions. Although most Yq microdeletions occur *de novo*, transmission of Yq microdeletions from father to son through ICSI has been reported (54, 55). The couples undergoing ICSI should be counseled that their male offspring may be infertile.

Other genetic syndromes associated with infertility in men (Table 2). Approximately three fourths of men with congenital absence of the vas deferens harbor mutations of the CFTR gene (56); many do not have the pulmonary manifestations of cystic fibrosis. Mutations of the cAMP response element modulator (CREM) have been associated with infertility and postmeiotic maturation arrest (57–59). Testicular dysfunction and infertility may be manifestations of other genetic disorders, such as hemochromatosis, sickle cell disease, thalassemia major, and myotonic dystrophy (60–63). Mutations in AR gene have been associated with infertility and undervirilization in phenotypic males, but the overall prevalence of AR mutations among infertile men is low (64, 65). The length of the CAG trinucleotide repeat in exon 1 of AR

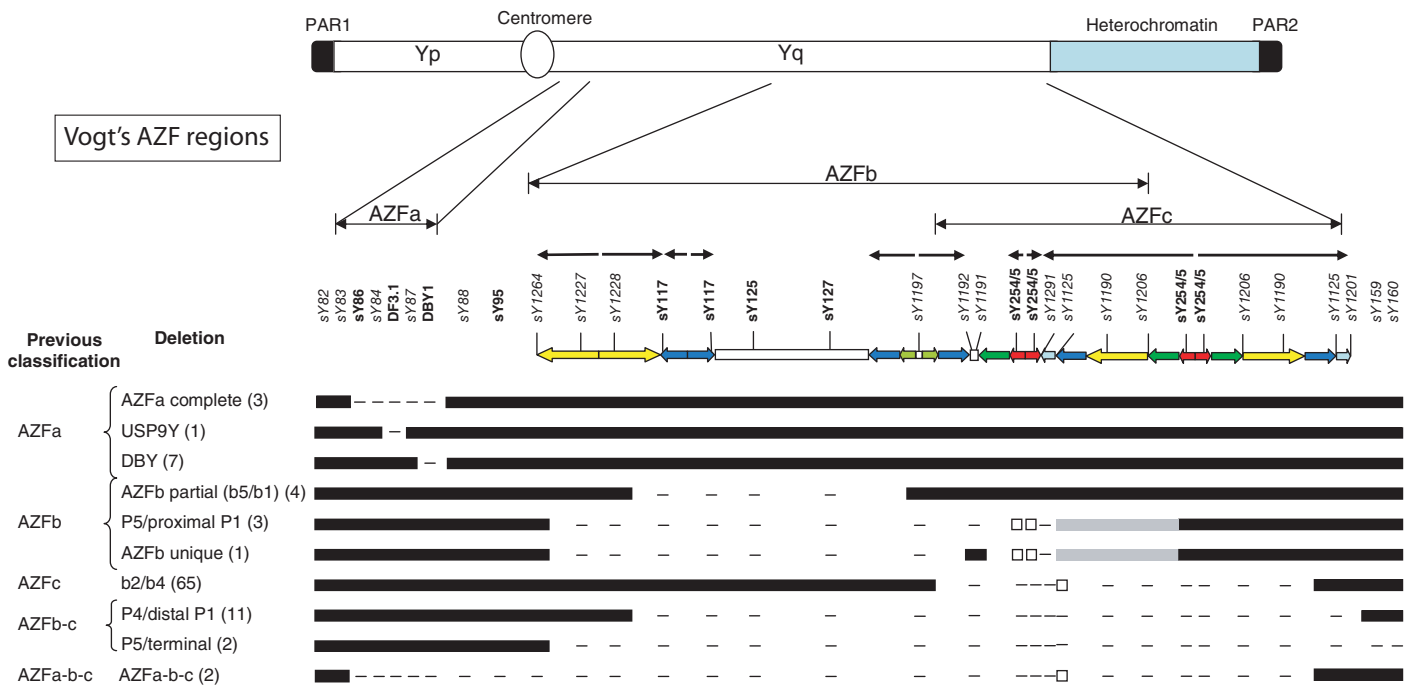


FIG. 3. A deletion map of 99 Yq microdeletions, adapted from that published by Ferlin *et al.* (40) and based on an analysis of 3073 consecutive infertile men. The top shows a schematic of the Y chromosome regions: short arm (Yp), long arm (Yq), pseudoautosomal regions 1 (PAR1) and 2 (PAR2). Below this map are depicted the three AZF regions, AZFa, AZFb, AZFc, described by Vogt *et al.* (34). The sequence tagged sites (STSs) that were used to map these deletions are listed. The palindromic structure of AZFbc region with its amplicons arranged in five palindromes are shown with heavy, colored arrows. The location of the five classes of microdeletions in AZFa, AZFb, AZFc, AZFbc, and AZFabc are shown; the numbers in parentheses represent the number of patients with that type of microdeletion. AZFc microdeletions were the most frequent microdeletions accounting for nearly two thirds of all microdeletions. Solid black bars, STSs present; solid gray bars, STSs that normally amplify by PCR, but their presence or absence cannot be determined; white boxes, STSs that normally amplify by PCR but are assumed to be absent in the context of the deletion pattern; dotted lines, STSs absent. A novel Yq microdeletion, gr/gr, characterized by deletion of two of the four DAZ copies and by failure of STS sY1291 to amplify, has recently been described. [Reproduced with permission from A. Ferlin *et al.*: *J Clin Endocrinol Metab* 92:762–770, 2007 (40).]

gene that encodes for the polyglutamine tract is inversely related to its transactivational activity (66–68); however, data on the association of polyglutamine length with infertility among men are conflicting (66–68). Mutations of anosmin, GnRH receptor, GPR54, DAX-1, SF-1, NELF, and FGFR1 genes have been associated with idiopathic hypogonadotropic hypogonadism (IHH) (69, 70). Hemochromatosis is associated with treatable hypogonadotropic hypogonadism; some men with hemochromatosis might also have primary testicular failure (17).

V. Treatment of Infertile Men

1. Testosterone, human chorionic gonadotropin (hCG), clomiphene citrate and other aromatase inhibitors, and bromocriptine have not been shown to be effective in men with idiopathic oligo/azoospermia; direct the couple away from such unproven therapies (17). Testosterone therapy can further suppress spermatogenesis (17).

2. Men with hypogonadotropic hypogonadism in whom pituitary neoplastic lesions and hyperprolactinemia have been excluded are candidates for gonadotropin or pulsatile GnRH therapy.

3. Men with obstructive azoospermia should be referred to a urologist for surgical correction. With microsurgical techniques, restoration of patency can be achieved in 70–90% of patients, although restoration of fertility is achieved only in

50%. In men with failed vasectomy reversal, verification of patency restoration and surgical revision, if indicated, or ICSI using epididymal sperm are reasonable options.

4. Men with idiopathic oligozoospermia should undergo genetic testing and be referred to a specialized fertility center for consideration of ART treatment, which may include *in vitro* fertilization (IVF) or ICSI. IVF should be attempted if

TABLE 2. Genetic testing in infertile men

Genetic test	Clinical indication
Karyotype	Men with azoospermia, severe oligozoospermia, very small testes
Yq microdeletions	Infertile men with azoospermia or severe oligozoospermia (less than 5 million/ml)
CFTR mutations	Azoospermic men with at least one absent vas deferens on physical examination or azoospermic men with evidence of normal spermatogenesis
CREM tau ^a	Postmeiotic germ cell arrest

The genetic disorders contributing to infertility in the parent may be transmitted to the offspring through a successful ICSI procedure. Therefore, infertile men considering ICSI should be offered genetic testing that includes a karyotype and screening for Yq microdeletions based on clinical indications, as outlined in this table.

^a Some infertile men with postmeiotic germ cell maturation arrest should undergo testing for CREM-tau mutations; this testing is not commercially available, and the data on CREM-tau mutations are more limited than those for Yq microdeletions and CFTR mutations.

there are more than 2 million motile sperm. If there are less than 2 million sperm in the ejaculate, less than 5% sperm with normal morphology, or less than 5% sperm with progressive motility, ICSI should be offered.

5. Men with nonobstructive azoospermia should be offered karyotype and screening for Yq microdeletions. Although ICSI using intratesticular sperm has been successful (71–74), the success rates of ICSI for azoospermic men using intratesticular or epididymal sperm are lower than that for ejaculated sperm (71–74). In some men with nonobstructive azoospermia, no sperm or spermatids may be retrievable from testicular biopsy, whereas for some couples the expense of ICSI may be prohibitive; for these couples, artificial insemination by donor sperm and adoption are realistic options.

Other health considerations in treating infertile men

Some causes of infertility (Klinefelter's syndrome, IHH) in men also are associated with androgen deficiency. Also, spermatogenic failure may be associated with impaired Leydig cell function (75). In men with gonadotropin deficiency, hCG and pulsatile GnRH therapy may restore both spermatogenesis and testosterone concentrations. However, exogenous testosterone administration suppresses spermatogenesis; infertility is a common complication of androgen abuse by body builders. Infertile men with cryptorchidism are at increased risk for testicular cancer (76); it is unclear whether infertility, in the absence of cryptorchidism, increases the risk of testicular cancer, as some reports have suggested (77).

Hormonal treatment of men with hypogonadotropic hypogonadism. Gonadotropin therapy and pulsatile GnRH are highly effective in inducing spermatogenesis in men with IHH (78–84). The two therapies do not differ in the time to first appearance of sperm, sperm densities, or pregnancy rates (78, 80, 81); however, because of its cumbersome nature, few centers use pulsatile GnRH therapy. Also, pulsatile GnRH therapy is not an option for patients with panhypopituitarism.

The therapy of IHH is started with hCG 1000 U three times weekly; the dose is adjusted to achieve nadir testosterone level measured 48 h after hCG injection in the mid-normal range. Recombinant human LH also has become available for clinical use. If after 6–9 months of hCG or recombinant human LH therapy no sperm is detected in the semen, recombinant or highly purified human FSH is added at a dose of 75 U three times weekly. The dose may be increased by 75 U three times weekly every 3 months depending upon the clinical response. Men with postpubertal onset of hypogonadotropic hypogonadism are more likely to respond to hCG alone with reinitiation of spermatogenesis than those with prepubertal onset who are likely to require addition of FSH.

Pulsatile GnRH administration is initiated at an initial dose of 25 ng/kg per pulse administered sc every 2 h by a portable infusion pump (79). Adjust the dose of GnRH until serum testosterone level is in the midnormal range. Doses ranging from 25 to 200 ng/kg may be required to induce virilization (79). After successful induction of secondary sex characteristics, GnRH dose can be reduced. The gonadal

function can be maintained in a majority of IHH men by pulsatile GnRH therapy (79).

The best predictors of response to gonadotropin therapy are testicular volume and time of onset of gonadotropin deficiency (pre- or postpubertal) (78, 82, 84). Those with testicular volumes greater than 8 ml reflecting less severe gonadotropin deficiency and postpubertal onset of gonadotropin deficiency are more likely to respond than those with testicular volumes less than 4 ml and prepubertal onset (78, 84). Cryptorchidism is a negative prognostic factor for fertility induction. Prior androgen therapy does not affect outcome.

ICSI for male factor infertility. ICSI has emerged as the treatment of choice for idiopathic male factor infertility (85–92). In a 2002 ESHRE survey, the clinical pregnancy rates for each aspiration and transfer for ICSI were 27 and 29%, respectively (91); these success rates have been steady for several years (85–92). The pregnancy rates per transfer are higher if fresh sperm is used instead of cryopreserved sperm, and higher if fresh embryos are used instead of frozen-thawed embryos (85–92). The fertilization rates are better for ejaculated sperm than for epididymal and testicular spermatozoa (89). The pregnancy rates are similar for obstructive and nonobstructive azoospermia (71–74). The results of ICSI are affected by the age of the female partner and the quality of the oocyte. The success rates of ICSI are lower in men in whom sperm has been retrieved from the testis by biopsy and in men with necro- or globozoospermia. In men with obstructive azoospermia (86–92), there is insufficient evidence to recommend any specific sperm retrieval procedure before ICSI (74).

Complications of ICSI. Multiple gestation, with its associated risks of low birth weight and preterm delivery, is the most frequent complication of ICSI (85, 88, 93, 94); the incidence of multiple gestation is 25–35% (86, 88, 95–99). The risk of obstetric and perinatal complications is higher for pregnancies resulting from ICSI than for naturally conceived pregnancies (85). Chromosomal abnormalities have been reported with higher frequency in offspring of ICSI than controls; there is also a small but significant increase in the frequency of chromosome aneuploidy, especially sex chromosome aneuploidy, among offspring of ICSI (97–99). The frequency of major congenital malformations is not significantly different between ICSI and IVF (98). When multiplicity is taken into account, the incidence of major or minor malformations is not increased. Even among singleton births resulting from ARTs, the risk of low birth weight, preterm delivery, and adverse perinatal outcomes is increased (85, 95, 97). The developmental outcome of children born after ICSI at 2 and 5 yr is not significantly different from those born after IVF (93, 94, 100). Some reports have suggested increased risk of imprinting disorders, hypospadias, and some types of childhood cancers (101, 102); this issue needs further investigation. Long-term data on the mental and physical well-being of children born through ICSI are not available. Spontaneous pregnancies in infertile women are associated with higher risk for obstetrical complications and perinatal mortality than spontaneous pregnancies in fertile women (85). It

is not apparent whether the complications observed in ICSI pregnancies and births are the consequence of the procedure or of parental infertility. Also, pregnancy complications, perinatal outcomes, and congenital malformation rates are not significantly different for IVF and ICSI (17, 86, 103).

Although ICSI is an effective therapy for many couples with male factor infertility, it is expensive and its long-term safety is unclear. ESHRE has established an ICSI Task Force to collect the outcomes data, including the follow-up of children after ICSI.

Treatment options for patients with azoospermia. The prognosis for men with nonobstructive azoospermia and total teratozoospermia has improved with the advent of ICSI (71–74). There are several reports of successful pregnancies in partners of men with Klinefelter syndrome by ICSI using sperm retrieved from testicular biopsy (104, 105). Success rates for ICSI in azoospermic men using testicular sperm are lower than those in oligozoospermic men using ejaculated sperm (71–74, 86). Couples undergoing ICSI using testicular sperm should be counseled about the risk of sex chromosome aneuploidy and other genetic disorders in the offspring (41, 54–55, 106). Also, adoption, artificial insemination using donor sperm, and acceptance of childlessness are realistic options.

VI. Genetic Testing and Counseling

Genetic testing of infertile couples and the offspring is important, especially in couples who are being considered for ICSI.

1. All infertile men with nonobstructive azoospermia, severe oligozoospermia, or very small testes should be offered a karyotype (Table 2) (85, 106).

2. Screen infertile men with azoospermia or severe oligozoospermia for Yq microdeletions (40, 41).

3. Azoospermic men with at least one absent vas deferens or with evidence of normal spermatogenesis should be tested for CFTR mutations (Table 2) (56).

4. Consider CREM mutations in men with postmeiotic maturation arrest (57–59).

5. Genetic testing is indicated in men in whom personal or family history suggests disorders that have a genetic basis such as hemoglobinopathies and myotonic dystrophy (61–63); these patients also need genetic counseling.

6. Prenatal testing, including chorionic villous sampling, may be appropriate in some couples undergoing ICSI and should be offered on an individualized basis.

Infertile couples considering ART should receive genetic counseling from a counselor who has expertise in reproductive disorders. Infertile couples should understand that:

1. The genetic defects responsible for infertility in the parent may be transmitted to the offspring through ICSI. Y deletions will be transmitted to male offspring (54–55, 106).

2. Children born through ICSI have increased risk of sex chromosome aneuploidy (86).

3. Children born through ICSI to infertile couples may have a higher risk of being infertile or subfertile (41). These children, upon reaching adulthood, may need counseling and surveillance of their reproductive function.

VII. Guidelines

Several societies, including the American Urological Association, American Society for Reproductive Medicine, ESHRE, and European Association of Urologists, have published guidelines for the management of infertile men (13, 94, 107–110). Guidelines for standardized testing for Yq microdeletions, semen analyses, genetic counseling, and prenatal diagnosis have also been published (43, 94). This review has incorporated most of these recommendations.

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