Ultrasound and Infertility: Diagnostic and Therapeutic Uses

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Ultrasound has become essential in the diagnosis and management of the infertile male. Scrotal ultrasonography provides a detailed examination of the testes and assesses the presence or absence of varicoceles and can identify other abnormalities of the scrotal contents and the spermatic cord. Transrectal ultrasonography can "visualize" the excurrent ejaculatory ductal system, including the ejaculatory ducts, seminal vesicles, and vas deferens. The expansion of these ultrasonographic techniques has provided the urologist with non- or minimally invasive techniques with which to evaluate the infertile male. These advancements consequently have led to innovative surgical and radiologic treatments.

Introduction

Current estimates indicate that infertility affects approximately 15% of all couples attempting their first pregnancy [1,2]. In infertile relationships, male factor infertility has been found to be responsible for approximately 30% to 40% of all cases of infertility; abnormalities in both partners have been found to be responsible for 20% of infertile couples. Female infertility accounts for 40% to 50% of all infertility cases. Thus, male infertility contributes to failure to conceive a child in at least 50% of all infertile pairings [3].

Evaluation of the infertile male has become increasingly more detailed in recent years because of technologic advancements. Appropriate evaluation is based on an understanding of normal male reproductive physiology and should be conducted in an orderly, logical sequence that is medically efficacious and cost-effective.

Semen analysis is the bedrock of laboratory testing in dealing with male infertility. Although semen analysis is indicative of the functional status of the testes, it is not highly predictive of fertility, which is a couple-related phenomenon and can only be determined by initiation of pregnancy [4]. Infertility has been defined as the inability to achieve pregnancy within a year of unprotected intercourse [5••].

Semen analysis examines the quantity and quality of sperm present in a specimen [6]. A standard semen analysis evaluates ejaculate volume, semen pH, white blood cell level, sperm concentration, total sperm count, motility, morphology, vitality, and fructose content. While fewer than 20 million sperm/mL is considered abnormal by World Health Organization (WHO) standards, men with sperm counts below this number have achieved fertilization [7,8]. Pregnancies have been initiated with sperm counts as low as 1 million sperm/mL [9]. Motility and morphology may be more predictive of male fertility than sperm count. As of 1993, motility of 50% has been considered normal by WHO, correlated with consideration of the quality of the motility, which is usually assessed on a forward progression scale from 0 to 4, with 0 indicating no motility and 4 indicating linear, high-speed motility [10]. Sperm morphology is a highly predictive parameter of the quality of spermatogenesis and fertility potential [11]. Sperm morphology is evaluated by either phase contrast microscopy or with Papanicolaou (Pap) or hematoxylin and eosin staining to calculate the number of normal (oval heads), amorphous (irregular heads), taper-headed, larger- and smaller-headed, and immature sperm [12]. According to the WHO, normal specimens have 30% normal forms. This is currently being re-evaluated by a WHO multicenter study [13].

The semen analysis measurements concerning fructose and pH also deliver significant information concerning male reproductive physiology. The seminal vesicles produce fructose, so the absence of fructose is indicative of obstruction of the ejaculatory ducts or seminal vesicles. Regarding pH, normal seminal fluid has a pH of 7.2 to 7.8, while the pH of seminal vesicle secretions is typically greater than 7, and the pH of prostatic secretions has a pH of less than 7. Thus, semen with a pH of less than 7 may indicate the absence or the obstruction of the seminal vesicles [14].

The patient's history, physical examination, semen analyses, and laboratory studies may indicate the need for further evaluation using ultrasonographic techniques. These techniques are discussed in this article.

Principles of Ultrasonography

Ultrasonography is used both scrotally and transrectally in the evaluation of male infertility in order to identify structural abnormalities. Sound is the result of mechanical energy traveling through matter (Figs. 1 and 2). Sound travels in

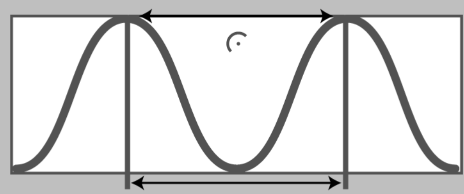

Figure 1. Diagram of the principles of ultrasonography.

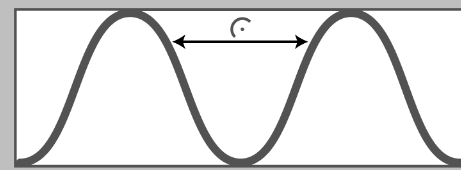

Figure 2. A description of the tenets of ultrasonography.

waves that represent alternating compression and rarefaction. The wavelength of sound (λ) is the distance between corresponding points on a time pressure curve. The ultrasound wave is initiated by a transducer that contains two piezoelectric crystals that transmit equal and opposite electric voltages that are transformed into mechanical oscillations or sound waves [15]. The number of cycles in a unit of time is referred to as the frequency. Hertz is the unit of acoustic frequency. The transmitted sound waves are directed to the area of interest and interact with tissues of various density, reflective, and absorptive characteristics. Some of the transmitted waves are reflected back to the transducer and are received by the piezoelectric crystals. This results in mechanical oscillations, which are then transformed into electric potentials. These potentials are converted into computer-generated images [16]. With the enhanced ultrasound resolution provided by high-frequency transducers, the number of pathologic processes that may be observed within the testes, paratesticular structures, genital ducts, and prostate has markedly increased. Entities that were rarely identified have become readily visible, resulting in more precise and specific treatment for male infertility [17]. One such entity, which only recently has been recognized, is testicular microcalcifications, which are now known to be associated with increased risk of testicular cancer [18••].

Ultrasound imaging techniques include real-time ultrasound, Doppler ultrasound, and color flow Doppler (CFD) imaging. The real-time ultrasound images are produced when high-speed ultrasonic beams create independent images at high rates, providing a dynamic image. This series of dynamic images may then be recorded on videotape or may be "frozen" as individual frames. Transducer frequencies (measured in millihertz) differ between different scanners. Higher-frequency transducers produce greater attenuation and lower tissue penetration, resulting in greater resolution. Thus, for superficial examination of the scrotum and penis, a high-frequency probe (10 millihertz) is optimal, providing greater resolution of the superficial areas of interest. A slightly lower frequency probe (7.5 millihertz), allowing deeper penetration, is used for transrectal ultrasonography (TRUS) [17].

Doppler ultrasonography provides the physician with the ability to measure directional blood flow. Doppler ultrasonography is based on the pulsatile emission of ultrasound waves. Because the reflected tissue interface is moving, a frequency difference is created. This difference is converted into an audible or visual signal. The signal is then recorded electronically as a graph of frequency against time [17]. A pulsed Doppler system measures flow velocity by the transmission at regular intervals of short bursts of ultrasound waves that are reflected from a moving target. Duplex ultrasound combines the pulsed Doppler system with real-time imaging. This technique is extremely valuable in the imaging of small vessels, such as the testicular and cavernosal arteries [16].

Scrotal Sonography

The scrotal contents can be accurately assessed with ultrasonography. The normalcy of the testicles and adnexal and spermatic cord structures may be evaluated. Testicular abnormalities, which may be identified by ultrasonography, include testicular tumors both benign and malignant, testicular cysts, and testicular microlithiasis (Fig. 3). Although ultrasonographic characteristics of tumors may vary, there is little specificity of patterns. Histologic type can be assessed accurately only on the pathologic specimen. Ultrasonography also may be used to calculate testicular volume and texture. A comparison of sonographically calculated testicular volume and texture of infertile and fertile men established that ultrasonic volume and texture are valuable parameters in the evaluation of infertile men. Lenz *et al.* [19••] used a lower frequency 7.5-millihertz transducer to scan participants' testes, measuring each testicle in three dimensions for volume and using the measurements in the formula of an ellipsoid to calculate individual volumes. The mean ultrasonic volume of both the right and left testes was found to be smaller in infertile men as compared with the findings of normal men. A positive correlation between sperm count and ultrasonic volume was seen.

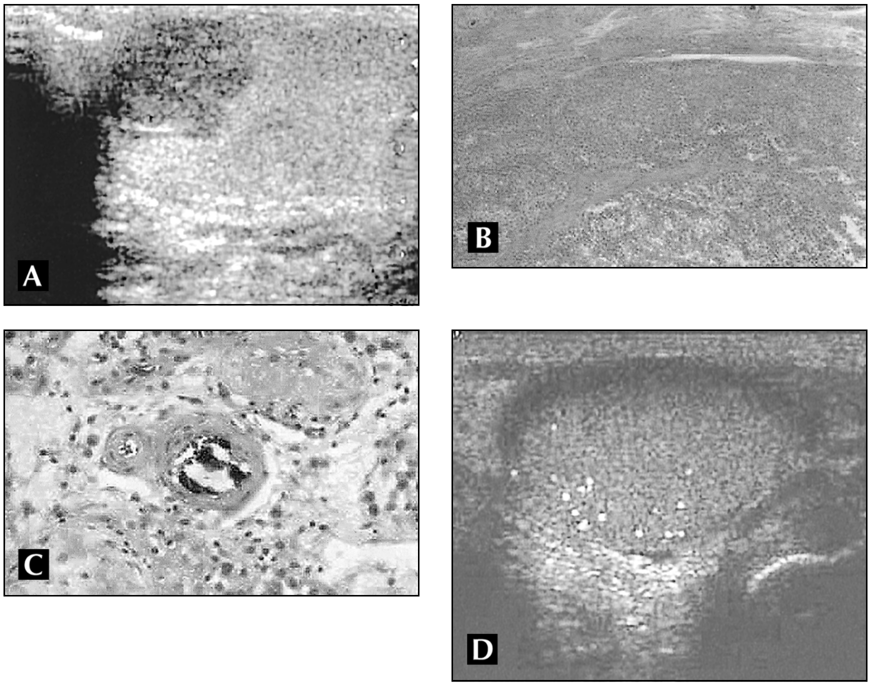

Figure 3. Ultrasound images depicting a patient with microlithiasis who developed testicular cancer; pathologic specimens are included. Clockwise starting from *upper left*: Ultrasound image of testicular mass, pathology specimen of seminoma found at time of radical orchiectomy, pathology specimen of microlith from testicle, and ultrasound of testicular microlithiasis.

Ultrasonic texture also was evaluated and given a score of 1 to 5, indicating increasing degrees of irregularity. The median score for the group of infertile men, 3, was higher than the median score of 2 previously found in normal men. The ultrasonic texture score was lowest in testes with a uniform pattern of 100% spermatogenic tubules, and the rising scale of texture scores correlated with the number of obliterated tubules for both testes [19••]. This study showed that ultrasonic volume and texture scores of testes are additional parameters to aid in the assessment of infertile men [19••].

A higher incidence of testicular tumors has been found in infertile men as compared with the normal population. This finding suggests that male infertility is associated with an increased risk of testicular malignancy and that routine scrotal color Doppler ultrasonography of the high-risk group of infertile men may reveal testicular tumors not detected on physical examination. In a study of infertile men performed by Pierik *et al.* [5••], ultrasonography reports were reviewed to assess the prevalence of scrotal abnormalities, and the results of ultrasonography were compared with their clinical findings. Overall, 60% of sonographic findings of abnormalities were not evident on palpation. Of the testicular tumors detected by sonography, only one of seven had been suspected on examination. Other abnormalities discovered on sonography were varicoceles, testicular cysts, testicular microlithiasis, epididymal cysts, and hydroceles. The rate of testicular tumors found in the infertile group of men was one in 200, which is significantly higher than the one in 20,000 that is reported for the general population. The high prevalence of testicular malignancies evidences the clinical relevance of routine scrotal ultrasonography of infertile men. The scrotal ultrasound provides valuable information in the diagnostic evaluation of infertile men as substantially more pathologic conditions are detected in this group using sonography than with only clinical palpation.

Microlithiasis of the testicle was not diagnosed until the advent of scrotal ultrasonography. In a recent retrospective review, 2215 scrotal scans were taken; 34 cases of testicular microlithiasis were identified (incidence of 1.4%.) Of the 34 cases with testicular microlithiasis, five (15%) had histologically confirmed testicular tumors. The incidence of testicular tumors in the scans showing no microlithiasis was 26 in 2181 (1.1%) [18••].

Testicular torsion can be accurately diagnosed when no blood flow to the testicle is demonstrated by CFD ultrasonography. As indicated in an editorial comment by Jack Elder, "Since this technology is more readily available than nuclear scanning, it has become a mainstay in the evaluation of the acute scrotum. The data indicates that color Doppler ultrasound and testicular scintigraphy are similar in determining whether a boy with testicular pain has torsion. A disadvantage to color Doppler ultrasound is that it is operator dependent, and an inexperienced radiologist may not be able to demonstrate testicular flow in a boy without torsion. The disadvantage of scintigraphy is that at night it may take 2 to 3 hours to obtain the study . . . Nevertheless, neither of these studies should be used to replace a good history and physical examination, which can provide the correct diagnosis in the majority of boys with an acute scrotum" [20••].

Adnexal abnormalities, such as spermatoceles and hydroceles, are well visualized with scrotal ultrasonography, obviating the need for diagnostic exploration.

Although each of these entities may affect male fertility, scrotal ultrasonography plays its major role in the evaluation of the infertile male by the detection or confirmation of varicoceles.

Although the diagnosis of varicocele remains a clinical diagnosis, ultrasonography, nuclear imaging, thermography, and venography all have been used to confirm the clinical suspicion. An inexpensive, readily available Doppler stethoscope also may be used in the diagnosis of varicoceles. Although this technology does not provide an image, it may be attached to a printer and blood-flow patterns may be recorded. With the Doppler stethoscope, a varicocele is confirmed when a "prolonged venous flow augmentation" is heard as a "venous rush" during the Valsalva maneuver [16]. Real-time ultrasonography provides a visual image of the scrotal contents and has also been used to diagnose varicoceles. Using high-frequency ultrasound (7 to 10 millihertz), a varicocele is identified if there is dilation of the venous structures with the Valsalva maneuver. Unfortunately, definitions of varicoceles based on size are inconsistent. McClure *et al.* [21] defined a varicocele ultasonographically as three visible veins, one of which is at least 3 mm in diameter at rest or becomes dilated during the Valsalva maneuver. Others have defined a subclinical varicocele as 2 to 3 mm in diameter [22].

Color flow Doppler ultrasonography combines real-time ultrasonography with pulsed Doppler and uses color identification of blood flow superimposed on the normal ultrasound image. Alteration in the direction of blood flow is represented by color reversal (red to blue or blue to red) (Fig. 4) [17]. This reversal of flow is characteristic of the varicocele. Nevertheless, there continues to be controversy regarding the utilization of ultrasonography in the diagnosis of the varicocele.

Venography typically is considered the "gold standard" for the diagnosis of varicoceles and, if properly performed, nearly always shows reflux if a varicocele is clinically present [23]. To evaluate the efficacy of CFD in detecting varicoceles, Petros *et al.* [24] used venography to establish the presence of a varicocele; CFD was found to have a sensitivity of 93% in this study. The detection of valvular incompetence by venography was diagnostic of a varicocele. Physical examination demonstrated varicoceles in 10 of 14 patients with venographically diagnosed varicoceles (71%), whereas CFD ultrasonographically detected 13 of 14 (93%) of these varicoceles. Thus, CFD ultrasonography is nearly as sensitive and more noninvasive when compared with venography. Therefore, venography is not routinely used as a diagnostic tool, and CFD ultrasonography is used as a sensitive and noninvasive method of detection [24].

Transrectal Ultrasonography

While vasography is the foremost tool in evaluating the male reproductive excurrent system, ultrasonography recently has emerged as a significant diagnostic tool in the evaluation of anatomic abnormalities of the ejaculatory duct apparatus. [16].

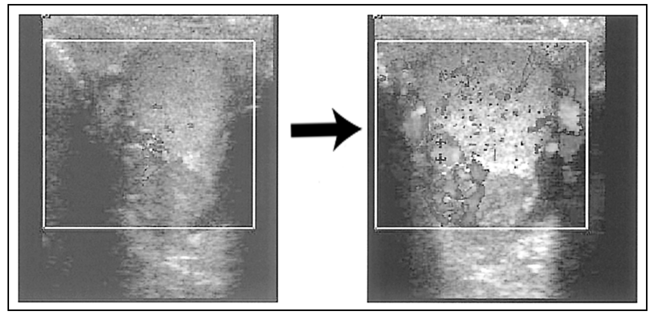

Figure 4. Ultrasound images depicting a varicocele with color flow Doppler sonography used to show an alteration of flow in the dilated vessels (blue → red).

Initially used solely to evaluate the prostate, TRUS recently has gained much attention in the evaluation of male infertility, notably in the diagnosis of distal genital ductal system abnormalities. Prior to the advent of TRUS, the seminal vesicles and ejaculatory ducts were imaged by vasography. However, recent improvements in TRUS with the use of higher frequency multiplanar transducers enabled the ejaculatory ducts to be visualized, and it became possible to image the ejaculatory duct apparatus [25].

Ejaculatory duct obstruction (EDO) currently is recognized more frequently than in the past because of its ability to be diagnosed by transrectal ultrasonography [26,27]. Patients with EDO may present for evaluation of infertility, ejaculatory, and/or testicular pain, perineal discomfort, or hematospermia [28]. Although these patients typically have a low-volume ejaculate, normal semen volumes do not rule out EDO. Presently, infertility patients presenting with a low ejaculate volume, azoospermia, severe oligospermia, or significant motility abnormalities all are appropriate candidates for TRUS. Any patient with a prior history of prostatitis and evidence of diminished seminal volume warrants TRUS. In patients suspected of having EDO, TRUS, being virtually risk-free, has nearly supplanted vasography and its associated risks of vasal scarring and subsequent obstruction [17]. Classically, only patients with fructose-negative azoospermia were considered to have EDO [29,30]. However, as the entities of partial, unilateral, and functional EDO have been recognized, the indications for TRUS in the infertile male have expanded [31]. However, in light of the fact that the treatment of EDO is not without significant risk, treatment alternatives should be discussed prior to proceeding with this evaluation.

Abnormalities of the seminal vesicles and ejaculatory ducts can clearly be imaged [21,32]. TRUS findings that affect infertility consistent with EDO include ejaculatory duct calcifications, ejaculatory duct cysts, and dilated ejaculatory ducts or seminal vesicles (Fig. 5). Prostatic cysts located at or near the ejaculatory ducts may cause complete or partial obstruction of semen efflux. A müllerian duct cyst (prostatic utricle cyst) or wolffian duct cyst may cause extrinsic compression of the ejaculatory ducts or seminal vesicles at the base of the bladder [33,34].

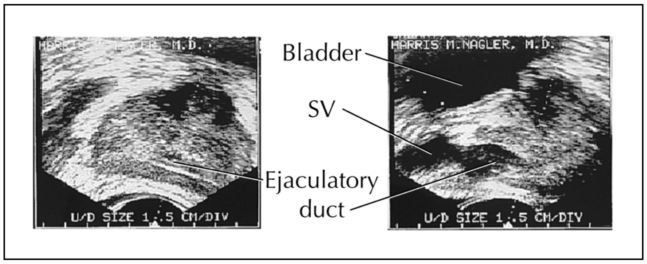

Figure 5. Sagittal *(left)* and longitudinal *(right)* transrectal ultrasonographic images of a patient with ejaculatory duct obstruction. SV—seminal vesicle.

Although vasography is still the gold standard in the diagnosis of complete EDO, there currently is no accepted modality for the diagnosis of partial EDO [34]. Two groups also described the use of TRUS-guided seminal vesiculography in the evaluation of suspected structural abnormalities of the male reproductive tract [34,35]. Originally described transperineally, TRUS-guided seminal vesiculography is an alternative to formal vasography as a contrast evaluation in the male infertility work-up. Under real-time TRUS visualization, a needle is used to puncture abnormally dilated cysts, seminal vesicles, or ejaculatory ducts. If desired, aspiration of cystic structures may be performed and the fluid may be evaluated for the presence of sperm. Next, contrast material is injected into the punctured structure, then plain radiographs are taken. The "vesiculogram" films then are reviewed for the presence of dilated seminal vesicles, EDO, or other correctable anatomic abnormalities that may be causing infertility [36].

Jarow [34] recently demonstrated that sperm are typically absent from nonobstructed seminal vesicles. Patients with vasographically demonstrated EDO were found to have sperm upon TRUS-guided aspiration of the seminal vesicles. Jarow therefore concluded that EDO should be suspected in any patient with sperm in aspirates of the seminal vesicles. Subsequently, he reported that sperm may be retrieved from the seminal vesicles of men even in the absence of obstruction [37].

Kuligowska and Fenlon [38••] conducted a study on a large series of infertile men with low-volume azoospermia to determine the efficacy of higher performance ultrasound equipment. Their study particularly emphasized the critical role of the vas deferens in the pathogenesis of other distal duct anomalies, and they sought to determine if by using transrectal ultrasound these patients may be identified for surgical or radiological intervention.

Transrectal ultrasound was performed with one of three scanners: HDI 3000 (Advanced Technology Laboratories, Best, the Netherlands), Ultramark 9 (Advanced Technology Laboratories), or RT 3600 (GE Medical Systems, Waukesha, WI). Endorectal tranducers of 7.5 to 9.0 millihertz were used. The terminal vas deferens, seminal vesicles, ejaculatory ducts, and prostate were examined in a systematic manner in both the axial and sagittal planes; measurements were recorded in two dimensions. Careful attention was paid to the internal echotexture and architecture of the vas deferens and seminal vesicles. Of the infertile men examined, 25.4% had no anatomic abnormalities. In the remaining patients, abnormalities detected included congenital bilateral absence of the vas deferens (34.1%); unilateral absence of the vas deferens (11.2%); bilateral occlusion of the vas deferens, seminal vesicles, and ejaculatory ducts by calcification or fibrosis (15.6%); obstructing cysts of the seminal vesicles, vas deferens, or prostate (9.4%); and ductal obstruction secondary to calculi (4.4%) [38••].

On the basis of the location and nature of the TRUS findings, patients were selected for either surgical or radiologic intervention. Fourteen patients with EDO had been treated with transurethal resection of the ejaculatory ducts. In the majority of these patients, follow-up seminal analysis demonstrated normal ejaculate volumes and normal spermatozoal counts. Patients with cysts were offered treatment with TRUS-guided cyst aspiration. Cyst aspiration was performed by passing an 18-gauge needle through the rectal mucosa into the cyst under ultrasound guidance. All patients had successful decompression of the cyst, as confirmed by ultrasound appearance. Of the four patients undergoing cyst aspiration, results on follow-up seminal analysis were normal in one, fertility was restored in one, and results were not available in the remaining two. Patients with uncorrectable defects (*eg*, congenital bilateral absence of the vas deferens, unilateral vasal agenesis with contralateral ductal fibrosis or calcification, or diffuse bilateral ductal fibrosis or calcification) were referred for microscopic epididymal sperm aspiration and in vitro fertilization [38••].

Conclusions

Recent developments have resulted in dramatic advancement in the diagnostic evaluation of the infertile male. By developing highly specific imaging modalities, it has enabled more precise targeting of the abnormalities responsible for the previously ill-defined causes of male factor infertility. While the standard semen analysis maintains its position as the initial study, more advanced imaging studies may be used to pinpoint specific abnormalities of physiologic or anatomic significance. Rational diagnostic approaches, using appropriate laboratory and radiologic procedures, permit the selection of therapies designed to treat previously unmanageable problems. The rapid progress in therapeutic options for infertile couples, combined with improvements in the diagnostic arena, will allow physicians to more aggressively, more accurately, and more successfully treat the infertile male.

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This article assesses the range and utility of using new higher performance equipment for transrectal ultrasonography with innovative surgical and radiologic treatments for male infertility. The study particularly emphasized the role of the vas deferens in the pathogenesis of other distal ductal anomalies. Patients with ejaculatory duct obstruction were identified and treated with transurethal resection of the ejaculatory ducts, and the majority of these patients on follow-up seminal analysis demonstrated normal ejaculate volumes and normal spermatozoal counts. Patients with cysts of the vas deferens or seminal vesicles were offered treatment with transrectal ultrasound-guided cyst aspiration. Patients with noncorrectable defects were referred for microscopic epididymal sperm aspiration and in vitro fertilization.