Ultrasound imaging and angiography play a crucial role in the diagnosis and treatment of men with subfertility. The most commonly used imaging modality is ultrasound (US), which can be used for diagnostic purposes or to aid in treatment. Scrotal US can be used to document varicoceles in subfertile men in the context of difficult examination or for confirmation before treatment. Spectral Doppler, sonoelastography, and power Doppler have aided in the evaluation and treatment of azoospermia and oligospermia. They have proven useful in the detection of spermatogenesis and sperm retrieval. In the population with congenital Wolffian duct abnormalities, renal US can evaluate renal anomalies. In subfertile men with low ejaculate volume and oligospermia or azoospermia transrectal US can be used to evaluate and assist in treatment of ejaculatory duct obstruction. Non-US–based modalities are also commonly used in evaluating and treating men with subfertility. Magnetic resonance imaging (MRI) can be used for evaluation of pituitary adenomas in hypogonadism. More invasive imaging modalities used during treatment of subfertile men include vasography for vasal obstruction, venography and angioembolization for varicocele, and US-guided needle placement for testis-sparing surgery. Male subfertility is a complex problem and the use of imaging techniques is often essential in providing accurate diagnosis and appropriate treatment. (Fertil Steril 2016;105:1432–42. ©2016 by American Society for Reproductive Medicine.)

Key Words: Male infertility, ultrasound, imaging in infertility, angiography

Received February 10, 2016; revised April 6, 2016; accepted April 7, 2016; published online April 30, 2016.

M.J. has nothing to disclose. B.R.G. has nothing to disclose.

Reprint requests: Michael Jurewicz, M.D., Department of Urology, University of Miami Leonard M. Miller School of Medicine, Miami, Florida 33136 (E-mail: michael.jurewicz@gmail.com).

Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282/$36.00
Copyright ©2016 American Society for Reproductive Medicine, Published by Elsevier Inc. http://dx.doi.org/10.1016/j.fertnstert.2016.04.009

Ultrasound (US) was first introduced to the field of Urology by Takashi and Ouchi in 1963 as they attempted to perform a transrectal ultrasound (TRUS) of the prostate (1). It was not until Watanabe et al. (2), however, that a discernable image of the prostate was available and able to be used medically to roughly evaluate symmetry and echogenicity and help detect prostate cancer. In 1976 Perri et al. (3) began using Doppler US, their “Doppler stethoscope,” in the scrotum to evaluate testicular blood flow in the acute scrotum. The first case series of ultrasound used in male fertility came in 1977 from Greenberg et al. (4) in their evaluation of men with subfertility and varicocele. They found in this study that men with varicocele, observed using their Doppler stethoscope, either before or after varicocelectomy, had abnormal semen parameters.

Imaging is a useful adjunct to clinical and laboratory examination in the diagnosis and treatment of male factor infertility. One of the most cost effective and minimally invasive imaging techniques used is US. Ultrasound of the scrotum can quantify varicocele size and confirm diagnosis of varicocele, especially when the examination is challenging due to a thickened scrotal wall or contracted scrotum (5). Various US techniques can be used in men with azoospermia to evaluate for obstructive azoospermia versus non-obstructive azoospermia (NOA), to evaluate regions of increased testicular blood flow and potential increased spermatogenesis, and renal abnormalities associated with genetic mutations (6–9). Ultrasound guidance can also be used for intervention, as it may help locate testicular tumors for biopsy or intervention, or seminal vesicle (SV), or utricular cyst aspiration (10, 11). Ultrasound, however, is not the only imaging technique used in male factor infertility. Various other imaging technologies can be used, such as magnetic resonance imaging (MRI), which is more expensive, as well as vasography and venography, with or without embolization, which are more invasive (12, 13). Our intent is to provide an overview of imaging techniques useful in the evaluation and treatment of the subfertile male.

SCROTAL ULTRASOUND
Anatomy and Embryology
The scrotum is divided into two compartments, each of which contains a testicle, an epididymis, and a spermatic cord. The origin of the testicles begins...
in the 3-week-old embryo where the primordial germ cells begin to migrate onto the urogenital ridge. The kidney precursors, gonads, and reproductive tract share a common embryology, also originating from the urogenital ridge. During the eighth week of gestation the Müllerian ducts regress and T from the Leydig cells stimulate mesonephric (Wolfian) development. The mesonephric ducts develop into epididymides, vas deferens, and ejaculatory ducts. The SVs form as an outpouching of these ducts. Vestigial remnants of the mesonephric duct include the appendix epididymis and paradidymis (5).

The spermatic cord contains the ductus deferens, testicular artery, and the pampiniform plexus of testicular veins. The arterial blood supply of the scrotum includes the testicular artery, the cremasteric artery, and the deferential artery. The testicular venous drainage exits the testis as the mediastinum testis (5). The right testicular vein drains into the inferior vena cava, whereas the left testicular vein is normally absent venous valves allowing for retrograde blood flow during valsala. For best visualization of the spermatic cord US should be completed superior and posterolateral to the testes (19, 25, 26). The American Urological Association (AUA) guidelines state that US should be used in any patient with a difficult or inadequate examination. These situations might include obese patients, a thickened scrotal wall, or a contracted scrotum (27) (Fig. 1).

Varicocele is the dilation of the spermatic vein and pampiniform plexus of veins in the spermatic cord. Left-sided varicocele is more common than the right as it is longer and inserts into the left renal vein; however, they have been shown to be bilateral in up to 80% of cases in some series. They are thought to be the result of incompetent or congenitally absent venous valves allowing for retrograde blood flow (19–24). The US findings include multiple anechoic tubular structures >2 mm superior and posterolateral to the testis. Color flow should be used to demonstrate reversal of flow during valsalva. For best visualization of the spermatic cord US should be completed superior and posterolateral to the testis (19, 25, 26). The American Urological Association (AUA) guidelines state that US should be used in any patient with a difficult or inadequate examination. These situations might include obese patients, a thickened scrotal wall, or a contracted scrotum (27) (Fig. 1).

Varicocele is present in >30% of men with primary subfertility and >80% in secondary subfertility, making it one of the most common causes in both cases (28). Clinically significant varicoceles are associated with impaired sperm count, sperm motility, and abnormal sperm morphology. The exact
Amechanism of pathologic change is not known but increased testicular temperature, hypoxia, and reactive oxygen species have all been postulated as causes (29–31). According to the AUA/American Society for Reproductive Medicine (ASRM) guidelines treatment for varicocele should be considered when it is palpable, the couple has known infertility, the woman has normal fertility, or the male partner has abnormalities on semen analysis (32). After their ligation 70% of patients see improved motility, sperm concentration, and morphology (33). Balcı et al. (34) and Tarhan et al. (35) demonstrated a decrease in intratesticular resistive index (RI) after varicocele ligation in patients with improved semen parameters. In addition, Esteves et al. (36) showed that after varicocele ligation for clinical varicoceles, not only were semen parameters improved, but also clinical pregnancy and live birth rates with intracytoplasmic sperm injection (ICSI) were higher than in untreated patients. A Cochrane database review was completed by Kroese et al. (37) who also concluded that patients with a varicocele and otherwise unexplained subfertility were more likely to achieve a pregnancy after surgical or radiological correction of their varicocele. They, however, were not able to provide data on live birth rates.

Venography is another technique that can be used in the diagnosis of varicocele. It is one of the most sensitive and specific imaging techniques, but also one of the most invasive. It is not commonly used as US and physical examination have superseded it and its use is not often necessary for the diagnosis of varicocele. Venography is, however, very useful in providing confirmation of reflux in the veins as well as to define varicocele anatomy in challenging recurrences. Hart et al. (38) advocates for intraoperative use of venography to show collateral drainage in up to 16% of patients, which may have resulted in persistent varicocele.

Although surgical ligation of varicoceles is the preferred method of treatment, venography and percutaneous embolization may be considered in certain patient populations including recurrent varicocele after the surgical approach has failed, patients with history of inguinal surgery, or patient preference. It can also be used as repeat treatment after failed embolization (39). It is typically done with sclerosing agents or endovascular coils under fluoroscopic guidance. Embolization has been shown to have a success rate of 85%–90% in patients with recurrent varicocele (40–42). Embolization, although minimally invasive, does not come without its risks. It has approximately 11% minor complications and a 5% recurrence rate (43). Some of the potential major complications include major vascular injury and endovascular coil migration (44) (Fig. 2).

Azoospermia

Oligoospermia and azoospermia can be signs of underlying pathology including ductal obstruction, testicular tumors, and varicocele. The US provides a noninvasive and real-time assessment when physical examination is inconclusive or intratesticular pathology is suspected. The US can be used to assess testicular size for atrophy, as it commonly relates to spermatogenesis. It can also be helpful in defining an obstructive versus nonobstructive azoospermia (45, 46). According to the American Institute of Ultrasound in Medicine (AIUM) and AUA US is an acceptable tool used in the workup of male infertility (18). Although physical examination is essential to a diagnosis of congenital bilateral absence of the vas deferens or congenital unilateral absence of the vas deferens as it relates to obstructive azoospermia, US is a helpful additional tool for confirmation of the condition. Also, abnormalities in the vas deferens and mesonephric ducts may be related to other congenital malformations such as renal agenesis (47–49).

Spectral Doppler is an US technique that provides increased information about intratesticular blood flow and reproductive function. The RI was shown by Pinggera et al. (6) to be increased in subfertile men with abnormal semen parameters. Unsal et al. (49) found that RI of capsular vessels and branches were indicative of impaired testicular microcirculation. In multiple studies, RI and peak systolic velocity of intratesticular vessels were better predictors of dyspermia than small testicles and elevated FSH. Also, several investigators have found that a RI >0.6 was indicative of abnormal semen quality (5, 9, 50) (Fig. 3).

Sonoelastography is an ultrasound modality that allows the user the ability to evaluate the elasticity of biological tissues, thus providing additional information to the physical examination. It is now being used to aid in diagnosis of NOA. After initial studies found that sonoelastography could be used as an adjunct to examine testicular architecture (51), Li et al. (52) further elucidated a five-point scoring system to

FIGURE 2

Retrograde venography of left gonadal vein. Note embolization coils indicated by small solid arrow in inguinal canal and vascular plug indicated by dashed arrow more cephalad (39).
describe the findings in azoospermic men. They found that on their scale scores of ≥3 were correlated with a diagnosis of NOA, thus aiding in diagnosis and treatment planning for these patients (Fig. 4).

Power Doppler is another modality being studied that can be used in treatment of patients with male factor infertility. Nowroozi et al. (53) conducted a study to assess the ability of power Doppler to improve detection of viable sperm in patients with NOA. They found that areas of increased intratesticular perfusion in patients with NOA represented areas of increased spermatogenesis. As a result, these patients required fewer biopsies as the biopsies obtained were better targeted for sperm retrieval (Fig. 5).

**Testicular Tumors**

Testicular tumors have been found to be the cause of male factor infertility in about 6% of cases (10). The most common and sometimes sole imaging study used to pick up these tumors is US. Leydig cell tumors represent <3% of all testicular tumors. They are commonly benign but can occasionally be malignant. They may cause precocious puberty or gynecomastia in males as a result of androgen production. This may also effect sperm production and maturation causing subfertility. They can be seen on testicular US as a nonspecific mass without any definitive identifying features (19, 20, 26).

Multiple studies have shown utility in testis-preserving surgery in men with solitary testis, bilateral testis lesions, and small incidentally found masses. The preservation of testicular tissue portends for improved spermatogenesis and androgen production in the future (54, 55). Hopp and Goldstein (10) described a technique in which US was used for needle placement into the tumor intraoperatively, which helped in its subsequent excision, thus aiding in preservation of unaffected testicular tissue. De Stefani et al. (54) were able to use US to detect and excise 20 lesions of <2 cm, thus preserving androgen function and spermatogenesis.

Growth of congenital testicular adrenal rests from congenital adrenal hyperplasia may play a role in male subfertility. Testicular adrenal rests are seen in 29% of patients with congenital adrenal hyperplasia. The release of ACTH results in increase size of these rests, which may then present clinically as testicular masses. Sonographically they appear hypoechoic with increased vascularity. There masses typically regress when treated with steroids but if left untreated these lesions may lead to infertility (56–58) (Fig. 6).

Testicular microlithiasis is another US finding associated with male factor infertility in addition to cryptorchism, male pseudohermaphroditism, and Klinefelter syndrome. Testicular microlithiasis is seen as 2- to 3-mm echogenic foci within the testicular tissue. It is defined by more than five foci seen on any particular US image and is typically asymptomatic and incidentally found. Tan and Eng (59) noted that there is evidence of a genetic component to testicular microlithiasis in addition to its role in “testicular dysgenesis syndrome,” which may play a factor in subfertility (60) (Fig. 7).

Papillary cystadenomas of the epididymis are rare benign tumors found in the efferent ductules in the head of the epididymis and may be a presenting cause of infertility. They are commonly bilateral and associated with von Hippel-Lindau syndrome. Patients presenting with von Hippel-Lindau syndrome typically have other manifestations of the disease and warrant close follow-up. Clinically, papillary cystadenomas will present as a solid, nontender mass in the head of the epididymis and sonographically are echogenic when small and can look cystic and vascular when enlarged. There may be some obstructive component related to these lesions causing subfertility, but it is unclear at this time (61–64).

**PROCEDURAL USE OF SCROTAL ULTRASOUND**

Ultrasound has become a very useful tool in many urologic procedures. As discussed previously, in testis-sparing surgery US can be used to localize the lesion, allow needle placement or biopsy of a lesion, and ultimately preserve healthy testicular tissue (10, 54). In addition, power Doppler can help to evaluate spermatogenesis in patients with NOA undergoing testicular sperm extraction (TESE). Increased blood flow was associated with improved sperm retrieval (53). Eytan et al. (65) described using power Doppler to map out areas of increased spermatogenesis and constructing a three-dimensional spatial map of preferential regions where spermatozoa were more likely to exist (Fig. 8).

**RENAIULRUSCOUND**

**Anatomy and Embryology**

Renal US is not commonly used in diagnosis or treatment of male factor infertility. However, the embryologic origin and relation of the metanephric system and the mesonephros is...
one that occasionally is encountered. The metanephric system develops as the mesonephros is regressing. The ureteric bud (metanephric diverticulum) interacts with the metanephric cell mass and eventually forms what will become the adult kidney. The mesonephric system is regulated by the production of T and eventually forms the Wolffian ducts including the SVs, ejaculatory ducts, vas deferens, and epididymis (15–17) (Fig. 9).

Ultrasound Technique
As for all US techniques, a consistent protocol should be followed to ensure consistent results. If possible, the patient should be fasting for 6 hours before the examination to decrease intestinal content. The patient should be in a supine position to image the right kidney followed by a right lateral decubitus position to image the left kidney. In addition, a small width transducer with scanning between 2.5 and

FIGURE 4
Real-time elastography images demonstrates elasticity in men with (A) normal sperm concentration, (B) azoospermia (5).

FIGURE 5
(A) Power Doppler showing vessels in the upper third of testis. (B) Power Doppler showing a vessel in the upper third of testis. (C) Power Doppler with spectral analysis of an artery in lower third of testis. (D) Power Doppler with spectral analysis of an artery in middle third of testis (53).
6 MHz should be selected to adequately visualize important structures and between ribs. Familiarity with renal anatomy is helpful in ensuring an adequate examination. It is not crucial to image surrounding structures but important to be cognizant and recognize them, including the liver, spleen, gallbladder, and aorta. Any abnormalities in these organs should be documented (5, 18).

**INDICATIONS IN MALE FACTOR INFERTILITY**

Although not often used in male infertility workup, the AIUM and AUA recommend the use of renal US to evaluate suspected congenital abnormalities (18). Thus, in male factor infertility it is helpful in evaluating patients with congenital unilateral absence of the vas deferens, congenital bilateral absence of the vas deferens, or absence of any of the Wolffian structures. As mentioned previously, their embryologic origins are intertwined and the absence of Wolffian structures should raise suspicion for renal anomalies. This finding during examination should prompt further workup with renal US to evaluate for renal agenesis (8, 66). Congenital unilateral absence of the vas deferens has been found to be more commonly associated with renal agenesis. Multiple studies have found a much higher incidence of renal agenesis in congenital unilateral absence of the vas deferens with reports between 26% and 75% (67, 68). Congenital bilateral absence of the vas deferens portends a lower risk of renal agenesis, with studies reporting incidence around 10% (69). It is important to counsel patients on the risk of transmission of renal anomalies and cystic fibrosis to patients of reproductive age.

**FIGURE 6**

Ultrasound showing hypoechoic congenital adrenal rests of bilateral testicles (arrows) (5).

**FIGURE 7**

Multiple bilateral microcalcifications of the testis are seen without acoustic shadowing (5).
TRANSRECTAL ULTRASOUND

Anatomy and Embryology

Transrectal ultrasound is most commonly used in general urology for imaging the prostate in the setting of prostate biopsy. It can also be used in male factor infertility for the evaluation and workup of obstructive azoosperma.

Unlike the majority of the male reproductive tract and organs, the embryologic origin of the prostate is from the endoderm. It is derived from the urogenital sinus as the endoderm invaginates into its surrounding mesenchyme around weeks 9–11 of gestation. Also seen on TRUS are the SVs and vas deferens, which are derived from the mesonephric duct around the seventh week of gestation. The
SVs are formed as a diverticulum of the vas deferens at the ampulla of the prostate. The most caudal vestigial remnants of the paramesonephric duct, the prostatic utricle and midline cysts, can be seen on TRUS when dilated (15–17).

The prostate gland is located between the bladder and urogenital diaphragm and abuts the rectum. The prostate is divided into three zones—the transition zone, the central zone, and the peripheral zone. Benign prostatic hypertrophy is typically associated with an enlarged central zone, whereas prostatic carcinoma is most commonly located in the peripheral zone. The volume of the prostate is calculated through measurements of the anteroposterior and transverse dimensions. The SVs are seen posterior to the base of the prostate and normally measure 4.5–5.5 cm in length and 2.2 cm in width. The vas deferens can be seen medial to their respective SVs and are best seen as it is tapering and begins to form the ejaculatory duct. The ejaculatory ducts enter the prostate at the level of the verumontanum, appear as hypoechoic structures on TRUS, and have a normal measurement of <2 mm (5, 18, 70–72).

Ultrasound Technique

As with all US procedures a consistent protocol should be used. Typically patients are placed in the left lateral decubitus or lithotomy position. The knees should be brought toward the chest and the buttocks should be flush with the edge of the table. A digital rectal examination is typically performed to rule out stricture or gross blood that might prevent the study from being performed. A TRUS includes a complete scan in the sagittal and transverse planes to allow for volume calculations. There are several probe options including side fire, end fire, biplane and triplaner. For TRUS frequencies between 6 and 10 MHz are most often used. Moving the probe more cephalad allows imaging of the bladder, bladder neck, SVs, and prostate base, while moving caudal examines the mid-gland and prostatic apex. Rectal wall thickness should also be evaluated for pathology (5, 18, 73).

INDICATIONS IN MALE FACTOR INFERTILITY

The most common use of TRUS in male factor infertility is in patients with low ejaculate volume and oligozoospermia or azoospermia. The AUA guidelines state that TRUS is indicated in “azoospermic patients with palpable vasa and low ejaculate volumes to determine if ejaculatory duct obstruction exists. Some experts recommend transrectal ultrasonography for oligospermic patients with low volume ejaculates, palpable vasa and normal testicular size to determine if partial ejaculatory duct obstruction is present” (27). This is most typical of ejaculatory duct obstruction (EJDO). The SVs are considered to be enlarged when the anteroposterior distance is 1.5–2 cm (33, 74). This may or may not be concurrent with presence of a midline cyst (75). The TRUS may be used to evaluate various causes of EJDO including congenital bilateral absence of the vas deferens or congenital unilateral absence of the vas deferens, congenital or acquired prostatic cysts, dilated ejaculatory ducts, enlarged prostatic utricle, as well as...
enlarged SVs. When compared with complete or infectious EJDO, congenital, noninfectious, or partial EJDO have better improvement in semen parameters after treatment (59, 76–78).

Although TRUS is sensitive in picking up this dilation, it is not specific for EJDO. Other techniques such as SV aspiration for sperm, seminal vesiculography, and chromotubation are decidedly more diagnostic but also more invasive and expensive (11). The TRUS can be used for needle aspiration of the SV or of a midline utricular cyst. If the dilated SV is full of sperm on aspiration a diagnosis of EJDO can be made, the sperm can be stored, and surgical intervention can be planned (45). During transurethral resection of the ejaculatory ducts, cannulation of the vas deferens and/or contrast enhanced seminal vesiculography can be used to ensure adequate flow of fluid from the vas deferens and if indicated, SV into the urethra. Iodinated contrast and/or methylene can be instilled into the SVs through a TRUS-guided needle. During the transurethral resection of the ejaculatory ducts contrast can be seen fluoroscopically or blue dye visually to ensure there is free passage of fluid across the ejaculatory ducts (11, 53, 79) (Fig. 10).

An MRI is also now being used to aid in the diagnosis of EJDO. An MRI with endorectal coil has been used to show similar or improved anatomy; however, it has some additional downfalls. By nature of MRI, patients must have no hardware or devices that would prevent them from undergoing this imaging. In addition, Engin et al. (81) performed a comparison of TRUS and MRI, which had mixed results. The study showed that in some patients MRI picked up increased lesions, whereas in others TRUS showed additional abnormalities. The investigators concluded that TRUS is an adequate and cheaper screening tool and should be used first, allowing for MRI use in ambiguous situations.

OTHER IMAGING MODALITIES

Brain MRI

The use of brain imaging has a specific use in the context of male factor infertility. It is typically used in patients with hypogonadism and hyperprolactinemia (13). Studies have shown brain MRI to be most useful when PRL levels are twice the upper limit of normal. In these men, there is a higher likelihood of a pituitary lesion such as an adenoma (82). An MRI is helpful in imaging the pituitary for microadenomas versus macroadenomas and can aid in the decision for medical or surgical treatment (83) (Fig. 11).

Vasography

Vasography is most commonly used during reconstructive procedures. Typically, it helps to verify the patency of the abdominal portion of the vas deferens from the incision site (13). When a distal obstruction is suspected, often a TRUS or MRI is used to evaluate the prostate, SVs, and distal vas deferens. These imaging methodologies are significantly less invasive than vasography, as it requires an incision in the vas deferens that may result in scar formation and subsequent obstruction at the site. Vasography is performed by instillation of iodinated contrast into the distal vas deferens at the vasotomy and using fluoroscopy to examine for patency. During reconstructive procedures saline can be instilled instead of a contrast agent into the abdominal vas deferens and assessed for ease of instillation and/or backflow instead of injecting contrast into the vas. In addition, a small Proline suture (4–0 or smaller) can be passed toward the abdominal vas deferens to evaluate the distance to any distal obstruction that may be present. It is not advisable to pass saline, contrast, or suture material toward the epididymis as this may cause a chemical or physical irritant that may result in rupture or further obstruction (11, 13).

In conclusion, the diagnosis, decision making, and treatment of patients with male factor infertility is a complex problem and the use of imaging provides essential assistance in the process. Ultrasound examination is a minimally invasive technique that can provide information with regard to male subfertility. It helps to evaluate blood flow, perfusion, and tissue density in the testicles; blood flow and vessel diameter in the spermatic cord; dilation or absence of Wolffian structures. It can be used for intervention, such as in testis tumor location, sperm retrieval, and SV cannulation. The MRI, vasography, and venography are also helpful in evaluating men with subfertility as these scans may provide further details about pathology and aid in more individualized patient care. With the use of these imaging modalities, we are better able to diagnose and treat subfertile men.

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