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NEW IMAGING TECHNIQUES (S RAIS-BAHRAMI AND K PORTER, SECTION EDITORS)

Advanced Imaging in Female Infertility

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Abstract

Purpose of Review This review highlights the role of imaging in the diagnosis and management of reproductive disorders. The additional information that imaging studies can contribute to reproductive medicine is emphasized, including the role of pelvic ultrasonography (US, including sonohysterography and contrast-enhanced hysterosalpingosonography), hysterosalpingography (HSG), and magnetic resonance imaging (MRI) of the female reproductive tract. In addition, the implications of congenital causes of infertility on the urinary tract in females are reviewed.

Recent Findings Summary While the evaluation of infertility in women is initially focused on the assessment of ovulation via serum hormone levels, imaging plays a role in evaluating other causes of infertility. Recent research in this field focuses on the establishment of a comprehensive single imaging study for the assessment of female reproductive disorders. Two proposed methods are MR hysterosalpingography and Fertiliscan, a combination of high-quality 3D ultrasound and assessment of tubal patency with hysterosalpingo-foam-sonography, though more research is needed to determine the risks and benefits of each method, as well as their reliability.

Keywords Reproductive medicine · Sonohysterography · Contrast-enhanced hysterosalpingosonography · Hysterosalpingography (HSG) · Magnetic resonance imaging (MRI)

Introduction

The accepted definition of infertility is the inability to conceive despite 1 year of regular unprotected intercourse or therapeutic donor insemination in women younger than 35 years or within 6 months in women older than 35 years [1, 2••]. Infertility is a multifaceted problem that can cause physical and emotional distress. Approximately 8–15% of reproductive-aged couples are diagnosed with infertility [2••, 3], and the recent trend toward delayed childbearing may increase this number [4]. In both males and females, various congenital and acquired disorders can cause infertility and subfertility and, while diagnostic assessment often focuses on the female partner, about half of infertility cases are due in part to a male factor [3, 5]. Identification of the specific factors underlying a couple's infertility is essential to determine the best possible treatment.

The initial workup of infertility includes a careful history and physical exam, followed by laboratory assessment of ovulatory and thyroid function, semen analysis, and evaluation of tubal patency [2••, 6]. Evaluation of infertility is multimodal in nature, and imaging plays an integral role in assessing anatomic abnormalities, tubal occlusion, and even ovarian reserve [7]. This review focuses on the imaging of the uterus, ovaries, fallopian tubes, and pelvic cavity with regard to the assessment of Müllerian duct anomalies, tubal structural abnormalities, intrauterine adhesions, uterine fibroids, endometriosis, and acquired tubal diseases. The use

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of ultrasonography (US), hysterosalpingography (HSG), contrast-enhanced hysterosalpingosonography, and magnetic resonance imaging (MRI) is emphasized and emerging research regarding the use of a single imaging modality for comprehensive assessment of female reproductive disorders is discussed. Finally, recommendations regarding the possible existence and further imaging of concomitant urinary tract abnormalities are considered.

Ultrasonography

US is preferred as the initial imaging modality for assessing possible causes of female infertility because of its low cost and convenience, providing a basic assessment of ovarian morphology, uterine structure, and detection of such pathology as uterine fibroids and Müllerian anomalies [6, 8] (Fig. 1a). The use of three-dimensional US (3D-US) is particularly important in the evaluation of congenital uterine abnormalities, as the type and degree of the anomaly may increase the risk of obstetric complications including fetal malpresentation and preterm delivery, and some (but not all) of these anomalies may require surgical intervention [9]. 3D-US offers a more comprehensive evaluation of the uterus and uterine cavity, with the advantage of simultaneous visualization of the external uterine contour. One study of patients with infertility and recurrent pregnancy loss showed 100% diagnostic accuracy in the diagnosis of uterine anomalies compared with the gold standard of laparoscopy/hysteroscopy [10]. 3D-US and MRI offer the advantage of flexibility in timing with respect to menstrual phase, whereas other modalities (hysteroscopy/laparoscopy, sonohysterography, and HSG) are restricted to the mid- or late follicular phase. Because the sensitivity of 3D-US and MRI is comparable in the detection of uterine anomalies, factors such as cost, safety, and patient comfort should be considered when deciding between the two imaging methods [11].

Hysterosalpingography

Laparoscopy, considered the gold standard for evaluation of tubal patency, is often not performed due to its invasive nature and the need for general anesthesia. HSG is a less invasive radiographic alternative that uses transcervical injection of iodinated contrast with concurrent fluoroscopy. HSG offers advantages, including the ability to treat proximal obstruction via catheterization, as well as some degree of therapeutic benefit from flushing of the tubes [6, 8]. In addition to tubal occlusion, HSG can reveal abnormal tubal morphology including hydrosalpinges, peritubal adhesions, and the proximal tubal nodularity that is characteristic of salpingitis isthmica nodosa. It is important to note, however, that the absence of filling of one or both fallopian tubes has a relatively low positive predictive value for tubal occlusion. Rather, this finding may represent proximal tubal spasm causing a false-positive HSG result and may require an additional imaging test or laparoscopy with chromopertubation for definitive diagnosis [8].

Disadvantages of HSG include exposure to ionizing radiation, risk of iodine allergy, need for technical facilities, pain, and risk of infection. Further, HSG is less sensitive for the diagnosis of intrauterine pathology compared with sonohysterography [2••]. Another limitation of HSG is its inability to distinguish between septate uterus and other Müllerian anomalies (e.g., unicornuate or bicornuate uteri). Diagnosis of Müllerian anomalies requires 3D-US or MRI for confirmation and cannot be made on the basis of HSG alone [8].

Sonohysterography

Basic sonohysterography (or "saline-infusion sonohysterography") provides information about tubal patency but not laterality: the presence of free fluid post-procedure is sufficient to confirm at least unilateral tubal patency [2••, 12]. Its greater utility, however, is in the evaluation of intrauterine pathology, for which it has high sensitivity (up to 90%) for diagnosing synechiae, polyps and submucosal myomas compared with HSG, which in the case of endometrial polyps has approximately 50% sensitivity [2••].

Contrast-enhanced hysterosalpingosonography permits intracavitary assessment of the uterus as well as tubal patency. Performed during the mid-follicular phase of the cycle, this procedure uses transcervical US contrast injection with visualization of the uterine cavity and fallopian tubes via transvaginal US. The sensitivity of this technique for detecting tubal occlusion is widely variable in the literature, although it may be as high as 96% [6]. Operator technical skill is of great importance with contrast-enhanced hysterosalpingosonography and this technique may be limited in the hands of a less-experienced operator compared with other methods such as HSG [2••]. Studies have also shown that contrast-enhanced hysterosalpingosonography requires an experienced user to interpret the study accurately, with approximately 50 examinations being required to achieve an accurate report [13].

New advances in sonohysterography suggest using three-dimensional contrast-enhanced hysterosalpingosonography with gel foam (HyFoSy) in lieu of traditional microbubbles suspended in liquid as a safe and effective method for assessing tubal patency. The proposed benefit of HyFoSy is

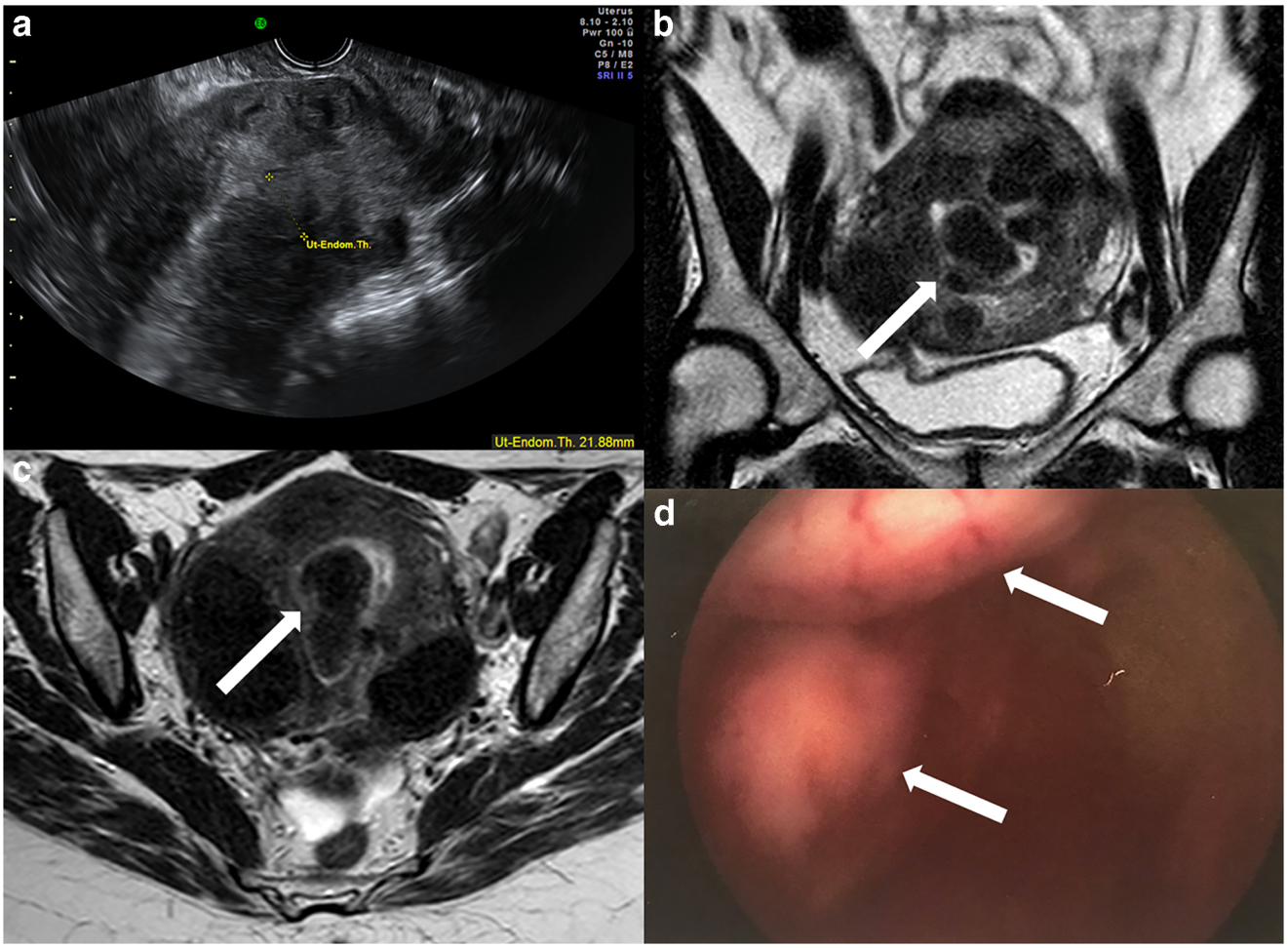

Fig. 1 A 45-year-old female (G2 P1011) with history of fibroids and menorrhagia with iron deficiency anemia. The patient has been trying to conceive for 4 years. Imaging was performed prior to myomectomy with transvaginal US (panel (**a**)) demonstrating an enlarged uterus with multiple fibroids. Coronal T2-weighted MR image (panel (**b**)) and axial T2-weighted MR image (**c**) show multiple T2- hypointense fibroids, including large submucosal fibroids (white arrow). The patient's fibroids were managed with hysteroscopic myomectomy as shown in panel (**d**)

that the foam remains stable for several minutes due to the distribution of air in the suspension, allowing visualization of the entire course of the fallopian tubes. HyFoSy is faster, better tolerated, and has a lower risk of infection than HSG and is less invasive than laparoscopy. Additionally, studies have shown that HyFoSy increases the chances of subsequent spontaneous pregnancy. Currently, HyFoSy is not widely used for various reasons including lack of practitioner training and lack of FDA approval of the foam [14•]. HyFoSy may preclude the need for HSG in 78% of cases, though more research is needed to determine the safety, efficacy, and utility of this modality before it is routinely employed [15•].

Innovatively, Fertiliscan combines HyFoSy with a high-quality 3D-US for comprehensive infertility evaluation [14•]. Fertiliscan consists of a 3D-US and hysterosonography to evaluate the uterine cavity, assess for signs of endometriosis, and gauge ovarian reserve, together with a HyFoSy to assess the patency of the fallopian tubes. Fertiliscan may offer cost advantages and shorter wait-times than the typical diagnostic imaging workup of infertility (pelvic US and HSG) [14•]. As a single examination, Fertiliscan takes on average an hour to complete versus the traditional workup that may require multiple office or hospital visits and many weeks before a diagnosis is made [14•].

With or without the use of contrast, sonohysterographic procedures offer a more detailed evaluation of the uterus and fallopian tubes than transvaginal US alone and can still be performed in an office setting [2••, 8].

MRI and MR Hysterosalpingography

Given its superior soft-tissue contrast, large field of view, and multiplanar capabilities, MRI is the most accurate modality available to assess uterine fibroids, adenomyosis, and congenital anomalies of the reproductive tract, all of which can

contribute to infertility [16, 17•]. MRI is particularly useful in the diagnosis of endometriosis, identified in approximately 30–50% of women diagnosed with infertility. The typical MRI finding of T2-shading within an endometrioma has a specificity of greater than 90% [18]. Further, MRI is less invasive than the gold standard for diagnosis, laparoscopy with biopsy, and has the advantage of a larger field of view than the typical initial imaging modality, transvaginal US [18, 19].

MRI is not traditionally useful for assessing tubal patency. This is notable, as fallopian tube abnormalities account for 25–40% of female infertility cases. As previously discussed, conventional HSG is typically the first-line for detection of fallopian tube abnormalities; however, ionizing radiation is a concern. Contrast-enhanced hysterosalpingosonography is another effective method for studying fallopian tube patency, and though it does not expose the patient to ionizing radiation, it is limited by the need for an experienced operator to accurately perform and interpret the study. MRI, on the other hand, does not expose the patient to ionizing radiation and it may not be as operator-dependent as contrast-enhanced hysterosalpingosonography. More recently, MR hysterosalpingography (MR-HSG) has employed intrauterine injection of gadolinium for evaluation of the fallopian tubes and of tubal patency. MR-HSG is 91.7% sensitive and 92.9% specific for detecting tubal abnormalities when performed on a 1.5-T scanner without completely optimized parameters [17•]. MR-HSG resulted in significantly less patient discomfort than traditional HSG and, when performed with an automated contrast injector, reduced operator dependence. MR-HSG combined with MRI is promising as a comprehensive imaging study for the evaluation of female infertility, given the combination of optimum anatomic detail and tubal patency evaluation [17•].

Müllerian Duct Abnormalities

In females, the urogenital tract formation is a complex process that initially consists of two pairs of genital ducts: mesonephric (Wolffian) and paramesonephric (Müllerian) ducts. In females, the Wolffian (mesonephric) ducts degenerate, but remnants may persist in the broad ligament and in the lateral wall of the uterine cervix and vagina (Gartner's duct cysts). Müllerian duct anomalies in females may contribute to infertility. Approximately 1% of women have a ureterovaginal anomaly [20].

Accurate characterization of the congenital anomaly is essential because pregnancy outcomes and possible interventions vary between the different types of anomalies. The highest reported accuracy for the characterization of Müllerian duct anomalies is with MR imaging, given its superior soft-tissue resolution and multiplanar capabilities [20]. A septate uterus is the most common uterine anomaly and patients with a septate uterus have high spontaneous abortion rates, which can be improved with hysteroscopic resection of a fibrous septum or metroplasty of a muscular septum [20].

When a congenital reproductive tract anomaly is identified, evaluation for possible concomitant urinary tract anomalies must be performed, as there is a high concordance due to their common embryonic origin. Renal anomalies are usually unilateral renal agenesis or ectopia and renal US is usually the first imaging performed, given that is a relatively inexpensive and readily available modality without ionizing radiation. Computed tomography (CT) and MRI are often used to further characterize or confirm the US-detected abnormality and to assess the complexity of the genitourinary anomalies [21].

Conclusion

Currently, there is not one single imaging examination to assess all potential structural/anatomical causes of infertility, as well as intrauterine or tubal pathology. Thus, many different modalities participate in the workup of individuals for infertility, including US, HSG, hysterosalpingo contrast-enhanced US, and MRI. However, emerging research strives to decrease the number of office visits and the amount of time prior to reaching a diagnosis. This is particularly relevant given the increasing age of first-time mothers, as well as the associated risks of advanced maternal age [4]. Any method that decreases the time from the diagnosis of infertility to the establishment of an etiology, treatment, and subsequent pregnancy is a positive for couples struggling with infertility. Recent research promises a "one-stop shop" for infertility imaging evaluation on the horizon; namely, MRI HSG and Fertiliscan appear to show great promise.

Compliance with Ethical Standards

Conflict of Interest Carolyn F. Dishuck, Jordan D. Perchik, and Deidre D. Gunn each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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