Subfertility: What the Radiologist Needs to Know[1]

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The role of imaging in subfertility is well established but is changing. In addition to traditional fertility assessments, there is an emerging role for the radiologist. The role of imaging in fertility-restoring procedures in benign disease and congenital malformations is evolving, and there is a growing need for accurate identification of young candidates suitable for fertility-preserving surgery in the oncologic setting. To facilitate this developing role, knowledge of the key imaging modalities used and potential therapeutic applications is important for accurate diagnosis and interpretation by the radiologist.

Abbreviations: FOV = field of view, HSG = hysterosalpingography

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- List the current imaging techniques used to investigate subfertility.
- Describe the growing role of imaging in optimization of therapeutic options for treatable causes of subfertility.
- Discuss the role of imaging in fertility preservation and restoration.

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Introduction

The term *infertility* is defined as inability to conceive despite regular unprotected intercourse for at least 1 year and is often used synonymously with *sterility*, meaning that there are limited restorative options (1). In comparison, the term *subfertility* describes any form of reduced fertility with a prolonged time of unwanted nonconception and includes many reversible causes (2). Subfertility affects approximately 48.5 million women worldwide, but after treatment, including assisted reproduction, the overall likelihood of successful pregnancy is nearly 50% (3,4). Imaging plays a significant role in diagnosing the cause of subfertility as well as guiding therapeutic options.

Changes in social trends have resulted in women delaying motherhood to later in life; the average maternal age at first birth has risen over the past 4 decades, from 26.4 years in 1973 to 30.0 years in 2013 (5). This pattern of increasing maternal age is an important determinant of female fertility, both natural and with assisted-conception techniques (6).

In addition to these social trends, advances in birth technology and increased use of assisted-reproduction techniques including in vitro fertilization (IVF) allow more women to have children at a later age.

TEACHING POINTS

- At HSG, specific views (early-filling, left and right cornu, true en-face, and spillage views) are required to ensure that a full assessment of the uterine cavity and fallopian tubes has been performed.
- PCOM is traditionally defined as 12 or more follicles of 2–9 mm and/or an ovarian volume of 10 mL or greater, per the Rotterdam diagnostic criteria (2003). The ovaries in PCOS demonstrate increased stroma due to the increased levels of androgens. However, more recently studies have suggested that the threshold of 12 follicles per ovary may no longer be valid and suggested measuring antimüllerian hormone level in its place (a level >35 pmol/L supports a diagnosis of PCOS).
- In endometriosis, MR imaging allows differentiation between single-site and multifocal bowel involvement and provides information about the size of deposits, distance from the anal verge, degree of bowel involvement, and extent of distortion. All of these factors, particularly the depth of bowel wall involvement, provide crucial preoperative information to the surgical team.
- Patients with dilated fallopian tubes (hydro- or hematosalpinges) are advised to undergo tubal ligation/salpingectomy or mechanical tubal occlusion (eg, Essure; Bayer) before starting an in vitro fertilization regimen. The dilated fallopian tubes are well seen at HSG, but caution must be exercised, as inadequate filling of the tube can be mistaken for peritoneal spillage.
- Intrauterine adhesions can form after any insult to the endometrial lining and lead to Asherman syndrome.

Table 1: Congenital and Acquired Causes of Subfertility

Congenital causes
Uterine developmental anomalies, müllerian duct anomalies
Ovarian aplasia or hypoplasia
Tubal structural abnormalities (rare)
Genetic: Klinefelter syndrome, Turner syndrome
Acquired causes
Intrauterine adhesions (infectious or noninfectious)
Fibroids or polyps
Adenomyosis or endometriosis
Tubal disease
Radiation therapy or chemotherapy (systemic or endocrine)

In this article, we outline the current imaging techniques used to investigate female subfertility and explore the growing role of imaging in optimizing therapeutic options for treatable causes as well as the emerging role of imaging in fertility preservation and restoration. The causes can be separated into congenital and acquired (Table 1).

Primary investigations for subfertility include ovulation assessment (serum progesterone, luteinizing hormone, and follicle-stimulating hormone levels), androgen profiling, assessment of thyroid function, and semen analysis. Imaging constitutes the secondary line of subfertility investigations. Radiologists play a crucial role in anatomic assessment, which underpins diagnosis of the congenital causes of subfertility and also many of the acquired causes. While image-based therapeutic options are limited in the congenital setting, imaging is important in quantifying disease burden and can guide treatment of many acquired causes.

Imaging Evaluation of Subfertility

Ultrasonography

Ultrasonography (US) is the first-line imaging-based investigation in subfertility. It is easily accessible, quick, inexpensive, and free of ionizing radiation but is operator dependent.

US can be used to assess basic parameters such as ovarian morphology and diagnose structural anomalies. It is also useful in diagnosing and quantifying acquired diseases that contribute to subfertility, such as fibroids and endometriosis. There are two main approaches to pelvic US: transabdominal and endovaginal.

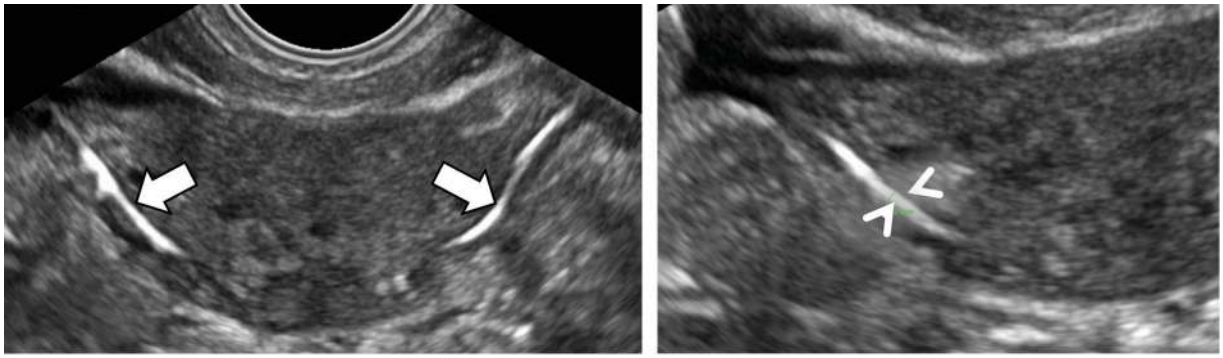
Application of three-dimensional US allows enhanced evaluation of uterine cavity configuration, which is important in congenital uterine anomalies and assessment of fibroid disease. Three-dimensional automated follicle scanning can also be applied to follicle tracking in the fertility setting (7).

Hysterosalpingo Contrast-enhanced US

Hysterosalpingo contrast-enhanced US is a minimally invasive ionizing radiation–free method of assessing the uterine cavity and tubal patency. It is performed during the mid proliferative phase (days 6–10) and uses endovaginal US with simultaneous transcervical injection of a US contrast agent (Echovist, Bayer, Leverkusen, Germany; SonoVue, Bracco, Milan, Italy) or saline. Hysterosalpingo contrast-enhanced US has reported sensitivity of 93.3% and specificity of 89.7% for tubal patency in experienced hands (8).

An initial endovaginal US acquisition is performed to assess the position of pelvic organs, rule out any disease that would limit the procedure, and review the pouch of Douglas for free fluid. This is important, as it is not always possible to demonstrate spillage from the fimbriae. After the procedure, if there is free fluid in the pelvis, this will be evidence of at least one of the fallopian tubes being patent (9).

A speculum is inserted, the cervix is cleaned, and a balloon catheter is passed through the os. The balloon is positioned just within the os and inflated to prevent leakage of contrast material back into the vagina. The speculum is then removed, and the endovaginal probe is re-sited.



a. b.

Figure 1. Hysterosalpingo contrast-enhanced US images after transcervical administration of contrast material. **(a)** Axial image shows contrast material delineating both fallopian tubes (arrows). **(b)** Image shows the right fallopian tube opacified and magnified. The sensitivity of the modality is such that accurate measurements of the lumen can be obtained (arrowheads). (Case courtesy of Fiona Hearn, BSc, MBBS, FRCR, Frimley Park Hospital, Frimley, England.)

The contrast material is then gently instilled. The injected contrast material delineates the uterine cavity and fallopian tubes (Fig 1a).

The spatial resolution is high enough to allow measurement of tubal caliber (Fig 1b). At delayed imaging, contrast material spills around the ovary into the peritoneal cavity and can be visualized to show that the tube is fully patent. Hysterosalpingo contrast-enhanced US is a useful screening test if there is a low index of suspicion for tubal disease but does not offer a therapeutic option. If there is any doubt about tubal patency, the study can be converted to hysterosalpingography (HSG) in a screening room.

Hysterosalpingography

HSG—fluoroscopic uterine and tubal assessment—is performed during the mid proliferative phase of the cycle, ideally between days 7 and 10. Women with amenorrhea are examined after at least 14 days of abstinence. All patients must abstain from intercourse or use contraception from day 1 of their cycle and have a urinary pregnancy test immediately before the examination. Postprocedural infections are an uncommon (1.4%–3.4%) but potentially serious complication, and prophylactic antibiotics are often administered, particularly in high-risk patients such as those with concurrent hydrosalpinx (10).

The success of the study depends on the patient feeling at ease, so the environment must be quiet and calm and preserve dignity. The cervix is cannulated under direct visualization, most commonly using either a 5-F balloon catheter or a Margolin catheter (Cook Medical, Bloomington, Ind), but a wide range of cannulas should be available. Contrast material is instilled while acquiring images of the uterine cavity, until bilateral spillage of contrast material into the peritoneal cavity is demonstrated.

At HSG, specific views (early-filling, left and right cornu, true en-face, and spillage views) are required to ensure that a full assessment of the uterine cavity and fallopian tubes has been performed. Initially, an early-filling image with a small field of view (FOV) (14 × 14 cm) is obtained to ensure that subtle filling defects that may be obscured with continued filling are not overlooked (Fig 2a). The tube is positioned obliquely to visualize each cornu with a small FOV (Fig 2b). The FOV is then enlarged (20 × 20 cm), and the tube is centered to capture distal tubal spillage (Fig 2c).

Finally, a true en-face view of the uterine cavity is obtained (Fig 2d). This final image serves a dual purpose, allowing assessment of the contour of the uterine cavity and also acting as a delayed image demonstrating spreading peritoneal spillage and reducing potential confusion with a hydrosalpinx. If the balloon of the cervical catheter has been inflated within the uterine cavity to ensure a seal, an image must be obtained with the balloon deflated to ensure assessment of the lower uterine segment and complete the study.

Accurate radiologic evaluation of HSG studies is dependent on a full clinical history, including detailed menstrual and gynecologic information. HSG has 92.1% sensitivity and 85.7% specificity for detecting bilateral tubal disease (11). However, it has sensitivity of only 58.2% for detecting intrauterine abnormalities, compared with 81.8% for US (12).

MR Imaging

Magnetic resonance (MR) imaging is a second-line or adjunctive imaging technique that allows multiplanar high-resolution evaluation with a larger FOV than that of endovaginal US. It does not involve ionizing radiation and is not operator dependent but has greater cost and accessibility implications than US. MR imaging is performed

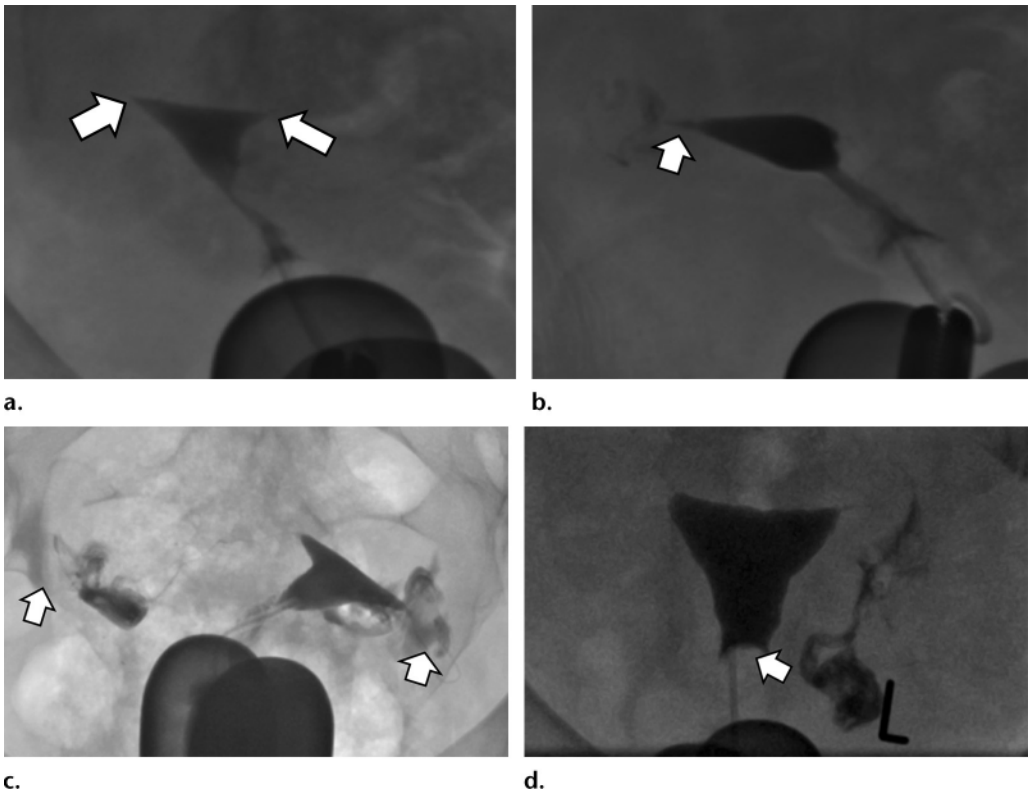


Figure 2. Standard views for HSG. **(a)** Early-filling view. This view shows both cornua (arrows) and has a small FOV (14 × 14 cm). It reduces the chance of obscuration of subtle filling defects by continued filling. **(b)** Cornu view. This oblique view shows an individual cornu (in this case the right) (arrow). It demonstrates any filling defects that may be obstructing passage into or out of the fallopian tube. **(c)** Spillage view. This view has a larger FOV (20 × 20 cm) to provide an overall assessment. It captures spillage out of the tubes (arrows) and possibly around the external contour of the uterus. **(d)** En-face view. This view shows the uterine cavity en face, if this view has not already been captured. It is essential for adequate assessment of the uterine cavity. In this particular image, the balloon lies within the lower uterine segment (arrow). If this occurs, the balloon must be deflated at the end of the study and a final image obtained to show the lower uterine segment and complete the study.

for further clarification of structural abnormalities and also used as a standardized method for quantifying disease burden in many benign conditions, such as fibroids and deep pelvic endometriosis.

Causes of Subfertility

Acquired

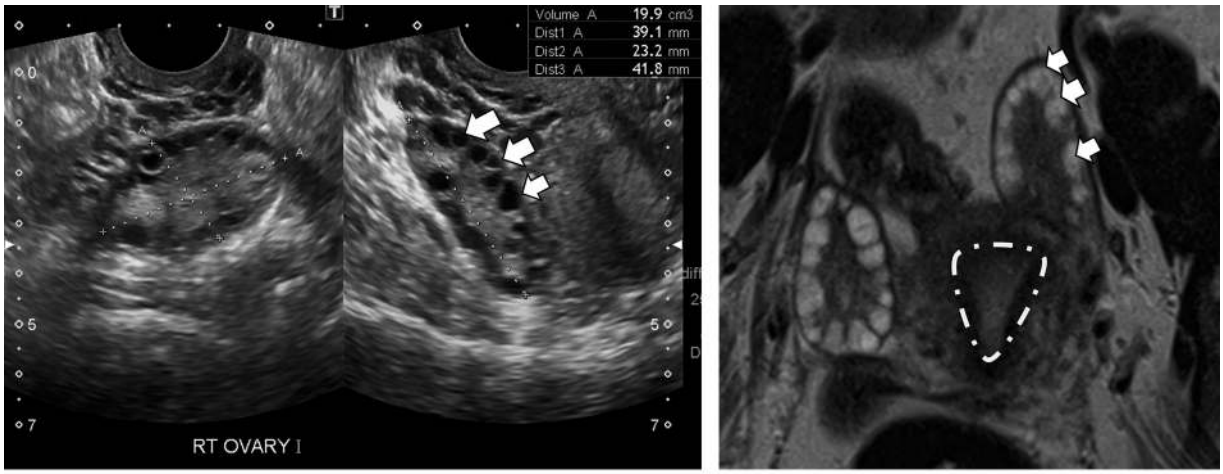
Polycystic Ovary Syndrome.—US is ideal for assessing ovarian morphology and is useful for diagnosing polycystic ovarian morphology (PCOM). If PCOM is present with specific biochemical derangements, it can manifest as polycystic ovary syndrome (PCOS), an endocrine and reproductive disorder that accounts for 80% of anovulatory subfertility cases (13).

PCOM is traditionally defined as 12 or more follicles of 2–9 mm and/or an ovarian volume of 10 mL or greater (Fig 3), per the Rotterdam diagnostic criteria (2003) (Table 2).The ovaries in PCOS demonstrate increased stroma due to the increased levels of androgens (Fig 3). However, more recently studies have suggested that the threshold of 12 follicles per ovary may no longer be valid and suggested measuring antimüllerian hormone level in its place (a level >35 pmol/L supports a diagnosis of PCOS) (14).

It is important to distinguish between PCOM and PCOS, as PCOM in isolation is a variant of normal ovaries and does not affect ability to conceive. PCOS is a biochemical disorder and needs to be managed as such (15).

Fibroids.—Fibroids (leiomyomas) are a common benign gynecologic condition and can pose a hindrance to conception and successful pregnancy, depending on location and size. They affect approximately 35%–77% of reproductive-age women, although this may be underrepresentative of the true prevalence, as many fibroids are asymptomatic (16–18). Fibroids are present in 5%–10% of infertile patients and may be the sole cause of subfertility in 1%–2.4% (19–21).

Submucosal and large intramural fibroids (>6 cm) contribute to subfertility more than small intramural, subserosal, or pedunculated fibroids (19). Submucosal and large intramural fibroids



a. b.

Figure 3. PCOS in a 30-year-old woman. US **(a)** and axial T2-weighted MR **(b)** images show the typical morphology of polycystic ovaries. The large-volume ovaries contain multiple small follicles (arrows) arranged along the periphery with no dominant follicle. The MR image also shows the normal uterine cavity (dashed line).

Table 2: Criteria for Defining PCOS

Rotterdam diagnostic criteria (2003)*
Chemical and/or biochemical hyperandrogenism
Oligomenorrhea or oligo-ovulation
Polycystic ovaries at US: ≥12 cysts with diameters of 2–9 mm or increased ovarian volume (≥10 mL)
Dewailly et al 2011 (14)
Substitute follicles per ovary with antimüllerian hormone level > 35 pmol/L

*Two criteria out of three are needed for diagnosis of PCOS.

may directly cause subfertility by obstructing the fallopian tubes or distorting the endometrial cavity (18). This distortion may cause abnormal endometrial receptivity and hormonal milieu and altered endometrial development (22,23).

At US, fibroids can be seen as structures that disrupt the normal echotexture of the myometrium. The distortion of the cavity caused by the fibroid is better appreciated with HSG (Figs 4, 5a). HSG combined with MR imaging provides a road map for the locations and sizes of the fibroids (Fig 5b). The effect of fibroids on the endometrial cavity can also be appreciated with saline-infused sonohysterography, which could be combined with hysterosalpingo contrast-enhanced US for assessment of tubal patency. This may be an alternative to MR imaging and HSG for some patients (eg, those unable to tolerate MR imaging, those with a small uterus and few fibroids, or those wishing to avoid radiation).

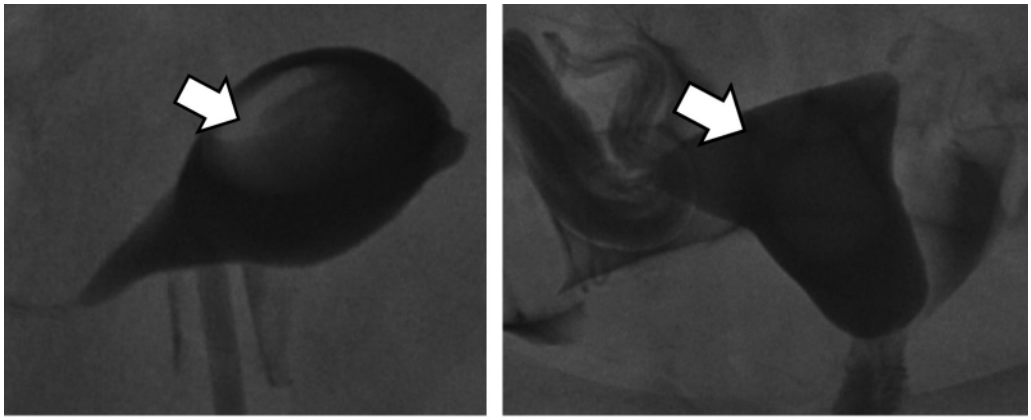
Fibroid treatment options include hysterectomy, myomectomy, uterine fibroid embolization, image-guided ablation (MR imaging–guided focused ultrasound), and medical management. Of the invasive techniques, either myomectomy or image-guided ablation should be performed when fertility is a consideration. Although uterine fibroid embolization is not as invasive as hysterectomy, the risk of damage to the ovaries and uterus makes it unsuitable for patients seeking to optimize their fertility (18).

MR imaging–guided focused ultrasound is a noninvasive outpatient technique that combines MR imaging and high-intensity focused ultrasound to ablate fibroid tissue. There is no general anesthetic involved. The patient lies prone on the MR imaging table, positioned over a high-frequency ultrasound transducer targeted on the fibroid. The transducer releases sonications that heat and destroy small amounts of tissue. The area of treatment is evaluated with MR imaging; multiple sonications may be required, depending on the fibroid volume targeted (Fig 6).

Initial results in terms of symptom management—specifically pain and menorrhagia—are encouraging. Response outcomes may be enhanced by pretreatment with gonadatropin-releasing hormone analogue (8,24). There are only a few retrospective studies to date, which do not provide sufficient evidence to assess the impact of MR imaging–guided focused ultrasound on fertility rates (25).

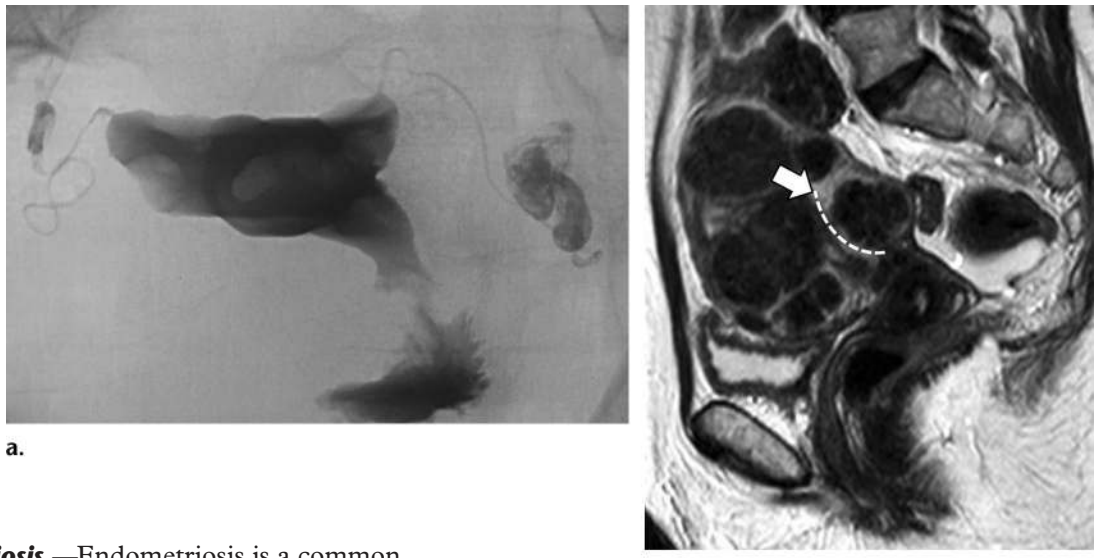
Endometrial Polyps.—Polyps are usually smaller than fibroids and therefore may not affect fertility to the same degree as submucosal or large intramural fibroids. If polyps are large or in a location that impedes gamete passage, such as at the entrance of or in close proximity to the cornu, they too can have a significant effect on fertility.

Figure 4. Fibroids in a 27-year-old woman. The standard HSG views shown in Figure 2 should be used to avoid diagnostic pitfalls. **(a)** Early-filling view shows a filling defect (arrow) caused by a fundal fibroid. **(b)** On a delayed spillage view, the fibroid (arrow) is less visible with continued filling and distention of the cavity. There is too much contrast material in the peritoneum, which can obscure tubal detail. If the early-filling view is omitted, crucial disease contributing to subfertility may be missed.



a. b.

Figure 5. Multimodality imaging of fibroid burden in a 32-year-old woman. A combination of HSG and MR imaging is often used to guide fertility-restoring therapy. **(a)** En-face HSG image with a large FOV shows multiple filling defects of the uterine cavity but preserved distal filling of the tube. **(b)** Sagittal T2-weighted MR image confirms the HSG findings of multiple fibroids distorting the configuration of the uterine cavity (arrow, dashed line). MR imaging better demonstrates the dimensions of the fibroids, their locations, and their suitability for treatment.



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Endometriosis.—Endometriosis is a common gynecologic condition in which endometrial glands and stroma are found outside the uterus. It affects up to 15% of women of reproductive age but is seen in up to 50% of patients with subfertility (26). For women with colorectal endometriosis, surgery can potentially improve fertility outcomes, with pregnancy rates after a laparoscopic procedure to treat rectovaginal endometriosis varying from 44.4% to 72% (27).

Although endovaginal US remains the first-line imaging investigation for endometriosis, MR imaging is increasingly performed in patients with deep pelvic endometriosis to provide further information about disease burden before surgery and to monitor disease after intervention. In endometriosis, MR imaging allows differentiation between single-site and multifocal bowel involvement and provides information about the size of deposits, distance from the anal verge, degree of bowel involvement, and extent of distortion. All of these factors, particularly the depth of bowel wall involvement, provide crucial preoperative information to the surgical team.

Surgical options include shaving, discoid resection, and segmental bowel resection. Adhesions and smaller serosal plaques can be shaved off (Fig 7a); larger plaques (up to 3 cm in diameter) can be treated with discoid bowel wall resection (Fig 7b). However, large deeply infiltrating complexes

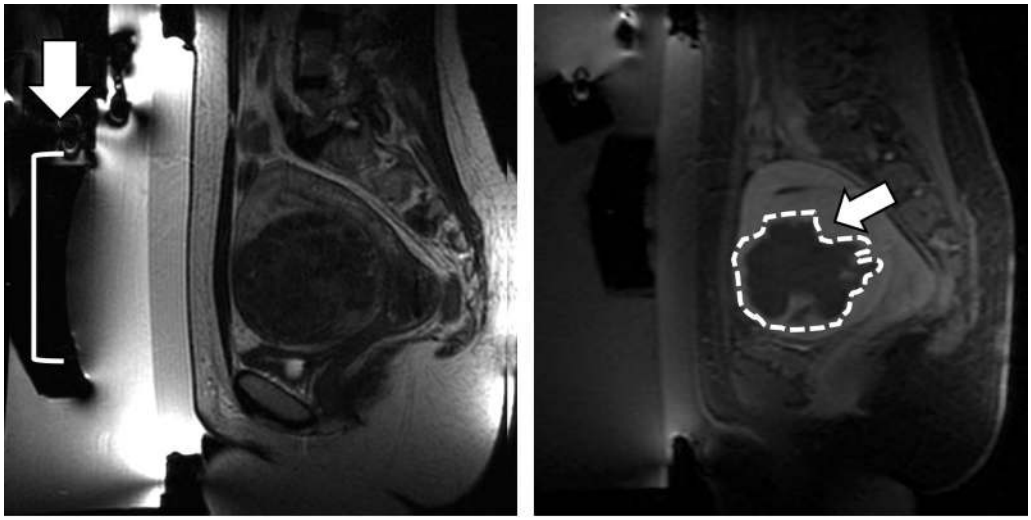

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Figure 6. MR imaging–guided focused ultrasound for treatment of fibroids in a 31-year-old woman. **(a)** Sagittal T2-weighted image before treatment shows the location and size of the target uterine fibroid. The focused ultrasound device can be seen inferior to the patient (arrow, bracket). **(b)** Posttreatment sagittal gadolinium-enhanced T1-weighted fat-saturated image shows that more than 70% of the fibroid was effectively necrosed (dashed line). There is only a small rind of residual vascularized fibroid tissue at the posterior margin (arrow).

require segmental resection, which often requires the presence of a colorectal surgeon (Fig 7c).

Patients with dilated fallopian tubes (hydro- or hematosalpinges) are advised to undergo tubal ligation/salpingectomy or mechanical tubal occlusion (eg, Essure; Bayer) before starting an in vitro fertilization regimen. The dilated fallopian tubes are well seen at HSG, but caution must be exercised, as inadequate filling of the tube can be mistaken for peritoneal spillage (Fig 8). The presence of a hydrosalpinx reduces the probability of conceiving by 50% and doubles the rate of spontaneous abortion (28,29). It is thought that the backwash of tubal fluid is embryotoxic and/or "washes out" the embryo before implantation (30).

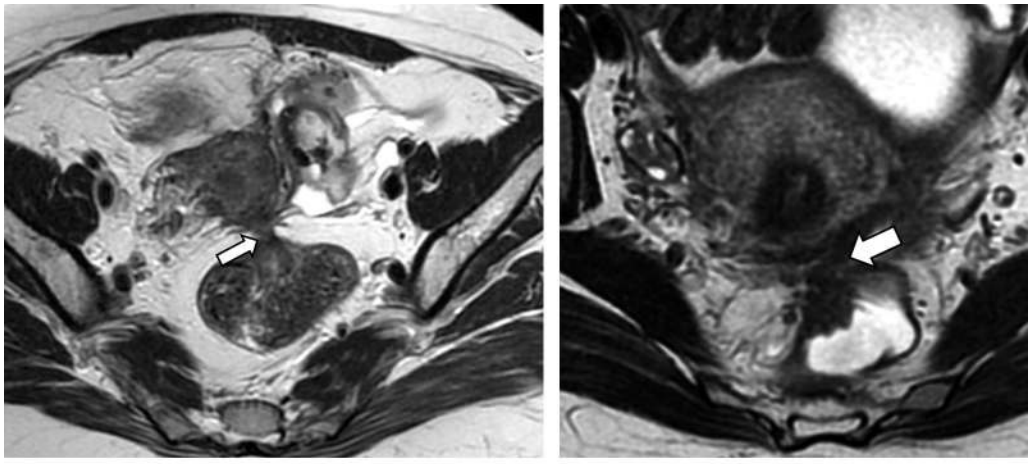
Strandell et al (31) showed that removal of a hydrosalpinx with laparoscopic salpingectomy improved pregnancy outcome, with a significant improvement in implantation rate (27.2% in the postsalpingectomy cohort vs 20.2%). The chance of giving birth doubled (even more so in patients with hydrosalpinges visible at US).

Endometrioma Drainage.—Endometrioma drainage has been controversial within the realm of subfertility, with conflicting ideas about whether drainage should be undertaken (32). The procedure can be easily performed under US guidance (either transabdominal or endovaginal depending on the most appropriate window) with minimal distress for the patient.

In the past, endometriomas were treated surgically regardless of size in the workup for in vitro fertilization, as their presence was thought to adversely affect outcomes in both spontaneous and induced conception. Currently, per the guidelines of the European Society of Human Reproduction and Embryology (ESHRE), drainage of only endometriomas greater than 3 cm is actively pursued (33). However, recent studies suggest that drainage/resection has no direct effect on in vitro fertilization outcomes, regardless of the size of the endometrioma (34). The decision to drain should be made on the basis of symptoms, age of the patient, ovarian reserve, size and laterality of the lesion, and whether there has been prior surgical treatment, assuming there is no suspicion of malignancy (35).

The American Society for Reproductive Medicine (ASRM) suggests that if an endometrioma is large (ie, >4 cm), surgery should be considered to confirm the diagnosis, improve access to follicles during oocyte retrieval, and possibly improve ovarian response (36). This may be especially true for large endometriomas, to help detect occult malignancy (given the association between endometriosis and certain ovarian cancers), avoid possible rupture or contamination of follicular fluid with endometrioma content, and prevent progression of endometriosis (37). However, there are risks, as surgery could compromise the ovary.

Asherman Syndrome.—Intrauterine adhesions can form after any insult to the endometrial lining and lead to Asherman syndrome (Fig 9a). Traditionally, the term *Asherman syndrome* described trauma to the gravid uterus, which triggered an inflammatory response that caused the damaged regions of the endometrium to fuse and form adhesions



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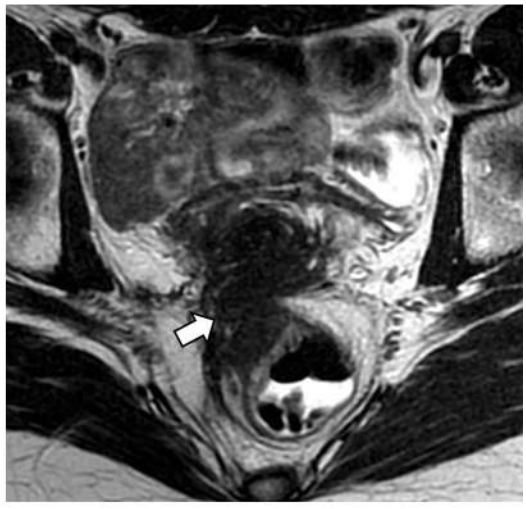


c.

Figure 7. Posterior compartment disease in deep pelvic endometriosis. **(a)** Axial T2-weighted image in a 25-year-old woman shows adhesions/tethering between the torus uterinus and rectal serosa (arrow), which would be amenable to shaving. **(b)** Axial T2-weighted image in a 34-year-old woman shows a larger infiltrative plaque (<3 cm in maximal diameter) (arrow), which would be amenable to discoid resection. **(c)** Axial T2-weighted image in a 30-year-old woman shows a large complex mass involving the posterior myometrial wall and infiltrating into the bowel wall (arrow). This would require segmental resection of the involved bowel and likely involvement of the colorectal team.

(38). Dilation and curettage related to pregnancy accounts for almost 90% of cases of Asherman syndrome; it is diagnosed in 5%–39% of women with recurrent miscarriage (39–42).There are a number of other etiologic factors that can trigger adhesion formation in the gravid and nongravid uterus, including müllerian duct malformation, genital tuberculosis, insertion of an intrauterine device, uterine surgery including cesarean section, diagnostic curettage, myomectomy, hysteroscopic surgery, and uterine artery embolization (43).

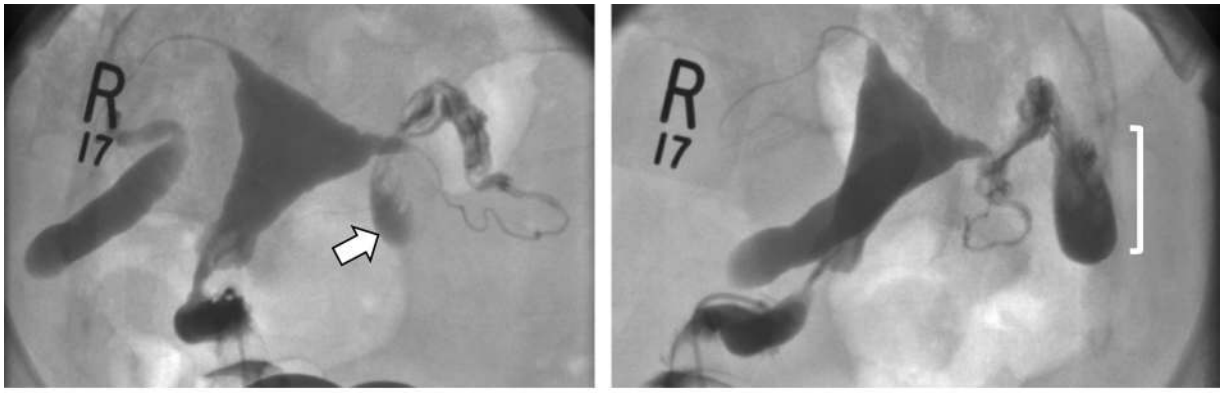
Intrauterine adhesions can cause subfertility, recurrent miscarriage, intrauterine growth retardation (IUGR), and placental adhesive disorders (44). Asherman syndrome/intrauterine adhesions can be identified at hysterosalpingo contrast-enhanced US or combined three-dimensional US and HSG and are a common cause of subfertility. HSG allows identification and quantification of these adhesions and can be used to evaluate treatment response after hysteroscopic adhesiolysis.

HSG provides a road map for the locations and extents of the adhesions before hysteroscopic intervention. At hysteroscopy, adhesions are broken down, and concurrent medications are used to maintain a thin endometrium. Interval HSG studies are performed to track the progression of the adhesions (Fig 9).

Tubal Occlusion.—Tubal disease is the cause of subfertility in 25%–35% of subfertile couples (9). Proximal tubal occlusion can be associated with endometriosis, whereas distal tubal occlusion tends to be secondary to pelvic inflammatory disease (45,46). Tubal patency can be assessed with both hysterosalpingo contrast-enhanced US and HSG. The added benefit of HSG is the additional capacity for therapy via fallopian tube recanalization.

Fallopian tube recanalization is a fluoroscopically guided procedure that targets proximally occluded fallopian tubes (Fig 10) (47). It can be performed with minimal distress for the patient and has good success rates (48). There is a 75% technical success rate for unblocking tubes; in 10%–22% of these cases, pregnancy is achieved without further management (49). Traditionally offered only to patients with bilateral proximal occlusions, there is now a lower threshold for offering fallopian tube recanalization to patients with unilateral occlusion, given the success rates (49).

There are risks associated with this procedure, including tubal perforation (2%), infec-



a. b.

Figure 8. Avoiding diagnostic pitfalls at HSG in a 37-year-old woman with distal tubal occlusion. **(a)** Early-filling view shows tubal opacification with apparent distal peritoneal spillage (arrow). **(b)** Delayed view with continued filling shows opacification of a dilated distal left fallopian tube with no convincing peritoneal spillage (bracket).

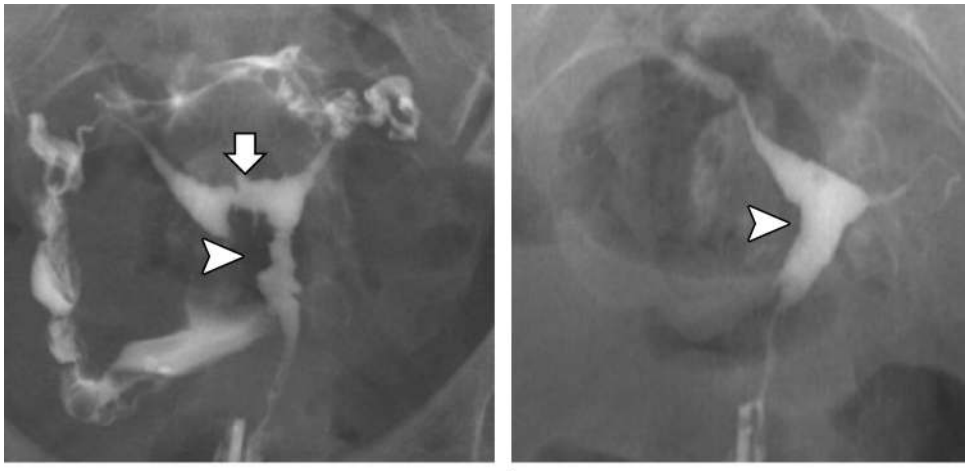


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Figure 9. Asherman syndrome in a 27-year-old woman. **(a)** En-face HSG view with a small FOV shows filling defects related to the right (arrowhead) and fundal (arrow) contours as a consequence of adhesions. **(b)** Frontal HSG view after treatment (3 months after hysteroscopy and adhesiolysis) shows dramatic improvement in the appearance of the cavity, with only a small residual defect at the site of the previous adhesion (arrowhead).

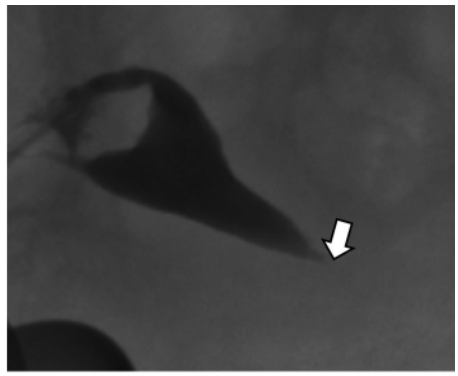
tion (1.4%–3.4%), and tubal pregnancy (3%) (10,50). The procedure may be more painful than HSG and is ideally performed with mild sedation. Careful patient selection is essential to the success of the procedure, and distal tubal disease—especially noncommunicating hydrosalpinx—must be excluded.

Salpingitis Isthmica Nodosa.—Salpingitis isthmica nodosa (SIN) manifests as nodular thickening of the proximal fallopian tube enclosing cystically dilated glands trapped in the muscular layer (51). The isthmic diverticula invade the surrounding muscularis and incite secondary smooth muscle hypertrophy, the exact pathophysiology of which is unclear (52). At HSG, SIN can be seen as a nodular appearance along the tubes, secondary to contrast material filling these diverticula (Fig 11). SIN is typically bilateral and is associated with tubal obstruction and hydrosalpinges.

This condition significantly affects fertility and has a strong association with ectopic pregnancy (51). HSG allows identification of focal or unilateral disease, where there is a role for curative resection of the involved tubal segments, thus reducing the risk for ectopic pregnancy and improving fertility (53). Fallopian tube recanalization can also be used in selected patients. In cases of proximal tubal occlusion secondary to SIN, selective salpingography showed rates of successful recanalization of up to 72%, leading to live births in 32% of cases (54).

Congenital

The full range of congenital anomalies that may affect fertility is vast and beyond the extent of this article (55). The fallopian tubes, uterus, cervix,



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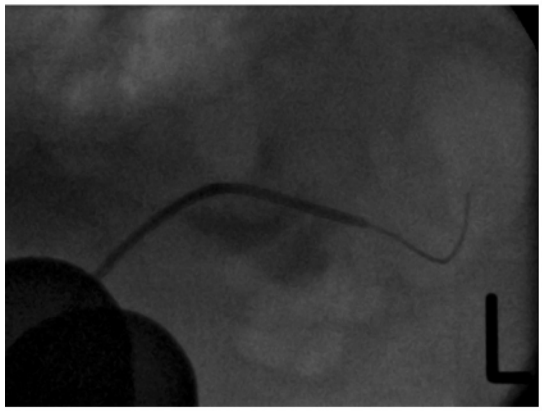

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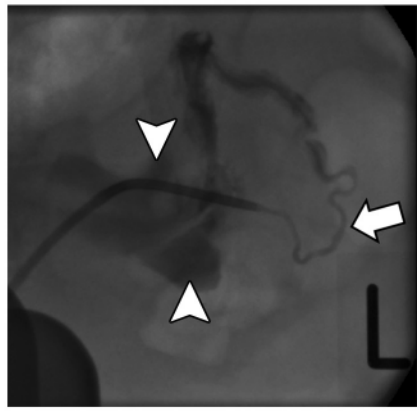


c.

Figure 10. Fallopian tube recanalization for treatment of proximal tubal occlusion in a 42-year-old woman. **(a)** Oblique HSG view shows proximal termination of the left cornu with no tubal opacity (arrow), in keeping with occlusion. **(b)** HSG image shows selective catheterization of the left cornu and passage of a guidewire beyond the point of occlusion. **(c)** Postprocedural HSG image shows a patent tube (arrow) with distal free peritoneal spillage (arrowheads).

and upper two-thirds of the vagina develop from a pair of müllerian ducts (56). Müllerian duct anomalies are a spectrum of conditions with a prevalence of 1%–5% in the general population and involve anomalous development of the uterus, cervix, and upper vagina (57).

The normal development depends on completion of three phases: organogenesis, fusion, and septal resorption (56). Organogenesis is characterized by formation of both müllerian ducts; failure of this results in uterine agenesis/hypoplasia or unicornuate uterus (56). Fusion is the process of ductal fusion to form the uterus; failure of this results in bicornuate uterus or uterus didelphys (56). Finally, septal resorption is resorption of the central septum once the ducts have fused. Defects at this stage result in septate or arcuate uterus (56).

These anomalies are initially assessed with US, which is often supplemented with MR imaging for more detailed evaluation. It is important for the radiologist to know which anomalies contribute to subfertility and which of these are amenable to therapy.

Uterine malformations at the less severe end of the spectrum can manifest as subfertility and are more frequent in patients with recurrent pregnancy loss than in the general population, with a mean prevalence of approximately 12.6%

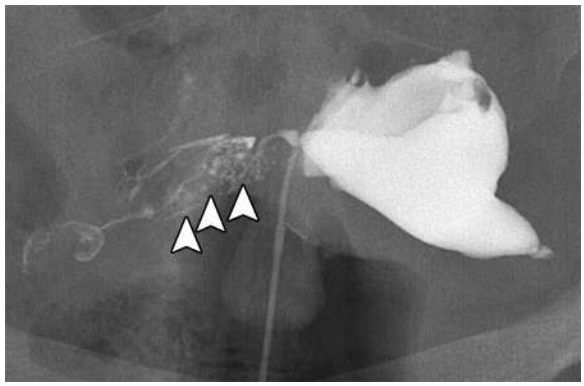
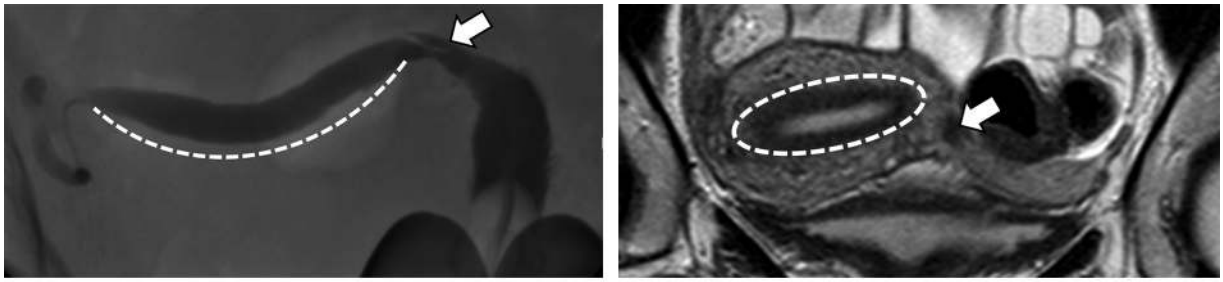


Figure 11. SIN in a 26-year-old woman. HSG image shows nodularity of the right fallopian tube (arrowheads), the typical appearance of SIN.

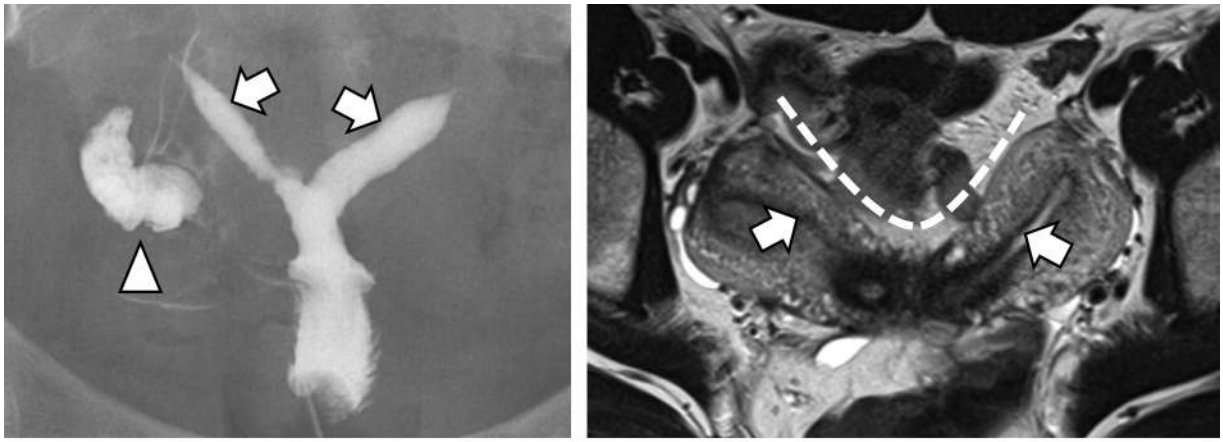
(58). The more severe malformations tend to manifest earlier in life, and natural conception is not possible.

Unicornuate Uterus.—Patients with unicornuate uterus are able to conceive naturally and carry a pregnancy to term, with a live birth rate of 54.2%, prematurity rate of 16.2%, and ectopic pregnancy rate of 4% (58–61). An important consideration in this group is the presence of a rudimentary horn and if there is communication between the rudimentary horn and the unicornuate cavity (Fig 12a). Such a communication increases the risk of



a. b.

Figure 12. Multimodality imaging of unicornuate uterus in a 35-year-old woman. **(a)** HSG image shows a right unicornuate uterine cavity (dashed line). In the lower segment, there is a linear filling defect (arrow), which may represent the origin of a rudimentary left cavity. **(b)** Coronal T2-weighted MR image shows the cavity (dashed line) as well as the general uterine configuration. A rudimentary horn is present, but there is no endometrial tissue or communication (arrow).



a. b.

Figure 13. Bicornuate uterus in a 38-year-old woman. **(a)** HSG image shows a divided endometrial cavity (arrows). It is not possible to differentiate between bicornuate uterus and septate uterus on the basis of HSG images alone, as they do not provide information about the fundal contour. Note the right hydrosalpinx (arrowhead). **(b)** Axial T2-weighted MR image shows the divided nature of the external myometrial contour (dashed line), confirming the diagnosis of bicornuate uterus. Arrows = divided uterine body and cavity.

abnormal implantation into the rudimentary horn, resulting in miscarriage/nonviable pregnancy, with a fetal survival rate of only 6% and with only 46% of these reaching term (62).

MR imaging demonstrates the anatomy of the uterus, allowing assessment of the size of the unicornuate cavity and myometrium as well as the existence of a rudimentary horn. High-resolution images allow identification of the presence of endometrium within the rudimentary horn and can demonstrate a communication (Fig 12b).

Divided Cavity Uteri.—Uterine duplication anomalies occur when there is failure of vertical fusion of the paired müllerian ducts to some degree, resulting in two cavities. These anomalies include uterus didelphys, bicornuate uterus, and septate uterus (56).

Uterus didelphys results from complete failure of fusion, with duplication of the cervix and uterine horns and often a vaginal septum. It is possible for a successful pregnancy to occur within one of the didelphys cavities, and there are options for intervention when the cervix or hymen is imperforate, with a live birth rate of 55.9% and preterm birth rate of 28.3%.

In bicornuate uterus, the inferior portion of the uterus fuses but the superior portions fail to fuse (Fig 13). In comparison, in septate uterus the müllerian ducts have fused, but there is partial or complete failure of resorption of the uterovaginal septum (Fig 14a) (56). Bicornuate uterus has a live birth rate of 55.2% and preterm birth rate of 23% (58,59). Septate uterus has a live birth rate of 50.1% and preterm birth rate of 22.4% (58,59).

The commonest müllerian duct anomalies are septate and bicornuate uterus, with reported prevalences of 55% and 25%, respectively (58,63). In terms of fertility, the distinction is important, as fertility-restoration options differ. Failures of vertical fusion are often incidentally detected when HSG is performed as part of the subfertility workup (Fig 14b) (56). However, it is difficult to differentiate between septate and bicornuate uterus on the basis of HSG alone, as assessment of the fundal contour is central to the diagnosis.

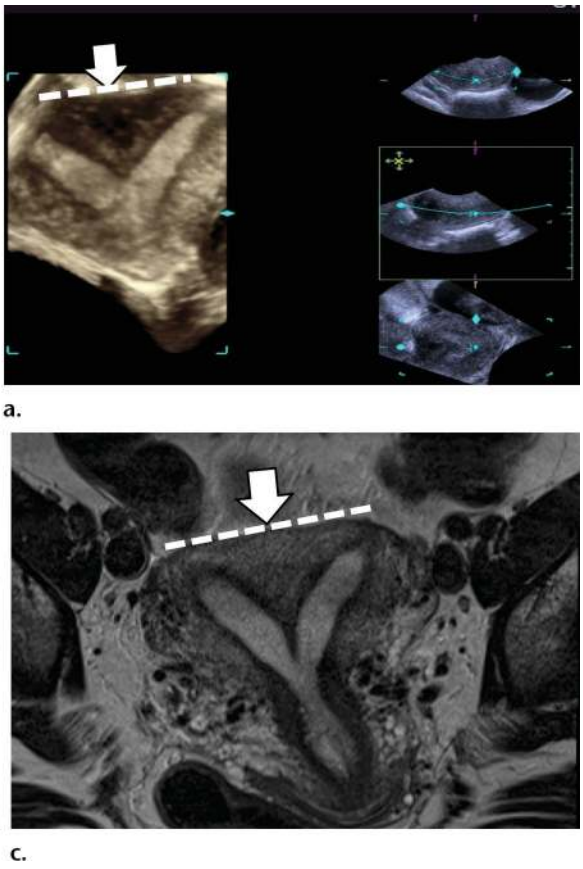


Figure 14. Septate uterus in a 26-year-old woman. Three-dimensional US **(a)**, HSG **(b)**, and axial T2-weighted MR **(c)** images show a septate uterus. The contour of the cavity can be seen in all three images (arrow and dashed line in **a** and **c**). However, the external fundal contour of the uterus can be appreciated only in the three-dimensional US and MR images, confirming the diagnosis of septate rather than bicornuate uterus. The composition of the septum can also be assessed with MR imaging. In this case, the superior aspect of the septum is muscular (intermediate T2 signal intensity in keeping with myometrium) and the inferior portion is fibrous (low T2 signal intensity).

On occasion, contrast material from the tubal peritoneal spillage covers the external contour of the fundus and allows delineation, but the presence of a divided cavity at HSG needs to be further evaluated with US or MR imaging. In most cases, US allows differentiation of a partial septum from a complete one, but MR imaging allows characterization of the nature of the septum, which can be fibrous or muscular (Fig 14c). While previously a transabdominal approach was used for a muscular septum, current best practice advocates use of hysteroscopic metroplasty for the fibrous part of the septum. The muscular component is not resected because of the high risk of bleeding (64).

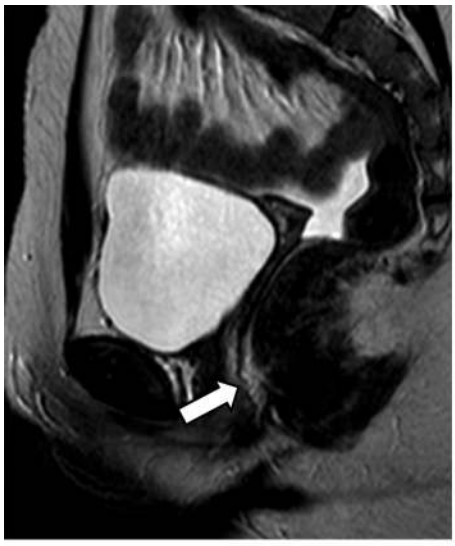
MRKH Syndrome.—The more severe anomalies, such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, often manifest as primary amenorrhea rather than subfertility (65). In this syndrome, there is absence of the normal midline structures (upper vagina, cervix, and uterus), which makes natural conception impossible (Fig 15) (65). However, ovarian development is usually normal (because of a different embryologic pathway), and therefore surrogacy and uterine transplantation are fertility options (Fig 15c) (65).

Candidates for uterine transplantation are restricted to those with absolute uterine factor infertility (UFI) (Table 3). Imaging plays a crucial role in both diagnosing absolute UFI as well as assisting in treatment (66). Approximately one in 500 women have absolute UFI (67).

Worldwide, a total of 11 cases of human uterine transplantation have been reported in three different countries and cultural settings (68–70). There has subsequently been one successful live birth in 2014 (71). As with other subspecialty transplant imaging, it is crucial to select a suitable donor uterus and recipient to optimize outcomes. Imaging continues in the postprocedural stage to monitor successful transplantation.

Fertility Preservation in the Oncologic Setting

A significant number of women with cervical, endometrial, or ovarian cancer will present before the age of 45 years (72). This represents a large group of women, many of whom will not have completed their families. With the development of fertility-sparing surgery/therapy, there is an increasing need for pretreatment stratification of suitable patients. Full discussion of this important topic is beyond the scope of this article and can be found elsewhere (73). Once the patient has completed her pregnancy, completion surgery (standard-of-care hysterectomy and bilateral salpingo-oophorectomy) is recommended (74,75).



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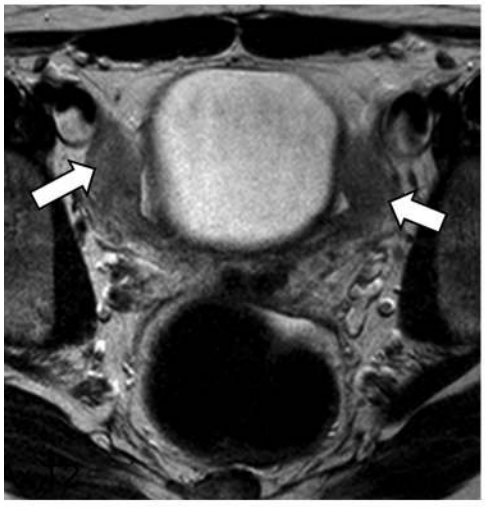

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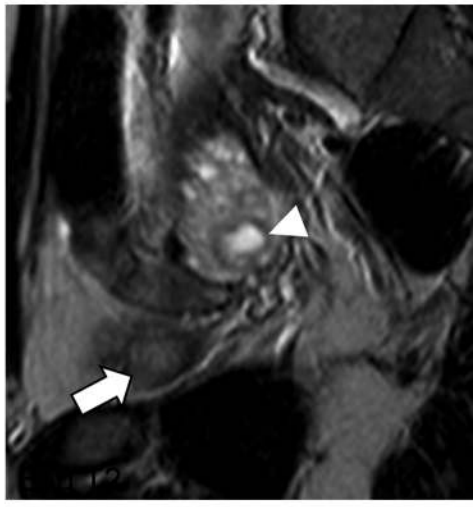


c.

Figure 15. MRKH syndrome in a 27-year-old woman with bilateral nonfunctioning uterine buds/anlages. **(a)** Sagittal T2-weighted image shows a short distal vagina (arrow) but no midline uterus or cervix. **(b)** Axial T2-weighted image shows bilateral uterine buds/anlages with no visible endometrial tissue (arrows). **(c)** Sagittal T2-weighted image shows that the uterine bud (arrow) is typically positioned caudal to a normally positioned ovary. Note the presence of a corpus luteum (arrowhead), in keeping with normal ovarian function.

Table 3: Causes of Absolute UFI

Congenital absence of uterus (MRKH syndrome)
Hysterectomy due to obstetric complications (eg, postpartum hemorrhage)
Hysterectomy for benign disease (eg, PID, fibroids, pelvic tuberculosis)
Early invasive cervical or ovarian malignancy at early age (<30 y)

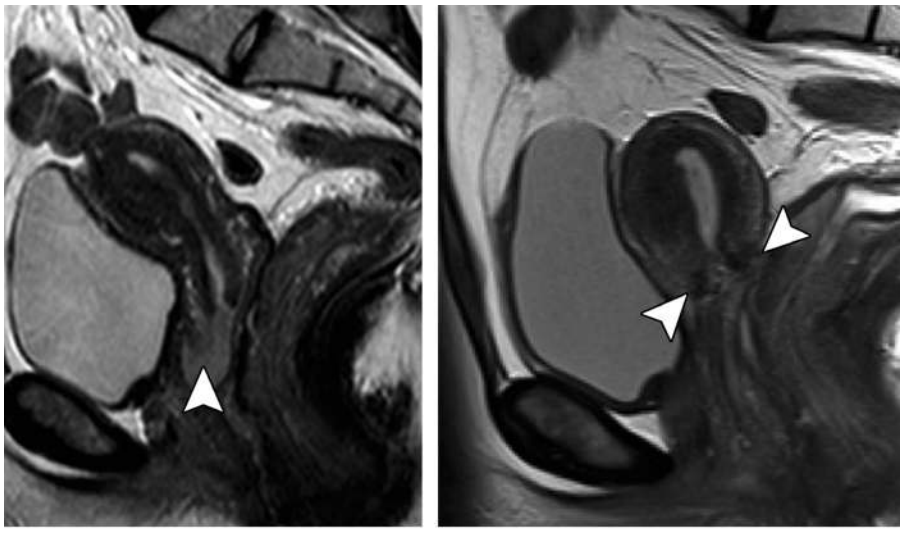
Source.—Reference 66.
Note.—PID = pelvic inflammatory disease.

Cervical Cancer

Owing to the success of screening programs, early cervical cancers are being identified in younger patients who have not yet completed their families. The radiologist plays a pivotal role in identifying suitable patients for fertility-sparing treatment on the basis of staging MR imaging. Small cervical cancers—specifically International Federation of Gynecology and Obstetrics (FIGO) stage IA and IB1, which do not involve the uterus, parametrium, or vagina (note that those with subtle vaginal involvement may be considered)—may be amenable to limited resection (vaginal radical trachelectomy and laparoscopic pelvic lymphadenectomy) (76,77) (Fig 16). There are strict criteria that must be met to safely offer fertility-preserving treatment options.

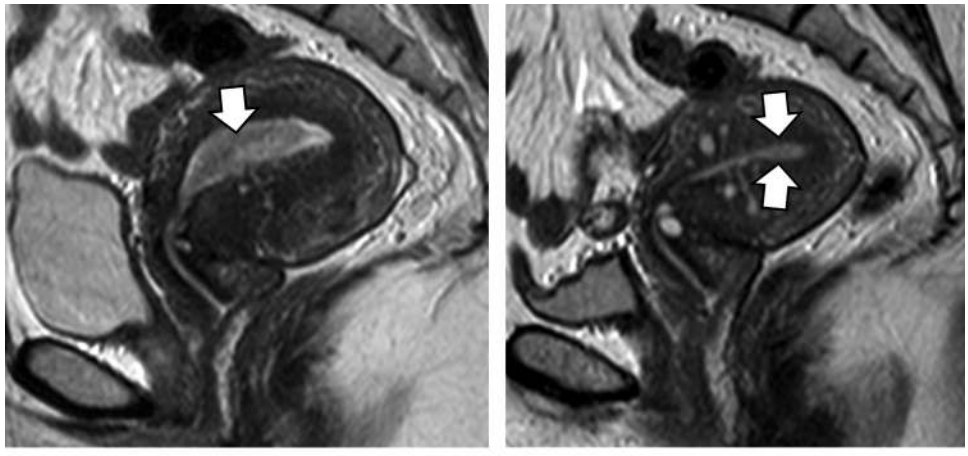
Endometrial Cancer

Endometrial cancer is largely considered a cancer of postmenopausal women. However, there is a cohort of patients, estimated to be between 15% and 25% of patients, who will be diagnosed before menopause (78). In addition, there is a higher prevalence of endometrial cancer in women with subfertility (79). Some of these younger patients may wish to retain fertility, and eligible patients need to be carefully selected and thoroughly counseled.



a. b.

Figure 16. Squamous cell carcinoma in a 29-year-old woman with intermenstrual bleeding and a positive result at cervical cone biopsy. The patient had no children and therefore wished to preserve her fertility. **(a)** Sagittal T2-weighted image shows an exophytic, 2-cm, intermediate-signal-intensity tumor arising from the anterior cervical lip (arrowhead). **(b)** Sagittal T2-weighted image after trachelectomy shows the typical appearance of an end-to-end uterovaginal anastomosis (arrowheads).



a. b.

Figure 17. Histologically confirmed grade 1 endometrioid adenocarcinoma (FIGO stage IA) in a 32-year-old woman. **(a)** Sagittal T2-weighted image obtained for staging shows a widened endometrial cavity (arrow) but no myometrial invasion. The patient fulfilled criteria for fertility-sparing treatment with Provera (medroxyprogesterone acetate; Pharmacia & Upjohn/Pfizer, New York, NY). **(b)** MR image after 3 months of treatment shows that the endometrial cavity has normal signal intensity and diameter (arrows). Histologic analysis showed no evidence of malignancy, and the patient went on to have a successful pregnancy. Note the background adenomyosis (better seen on the posttreatment image).

Only low-grade endometrial cancers confined to the endometrial cavity may be treated with hormonal therapy (high-dose progesterone) (Fig 17). Before therapy, disease burden must be assessed, specifically to rule out myometrial invasion and/or extrauterine spread. The presence of myometrial invasion is a contraindication to progesterone therapy, and this is best assessed with MR imaging (90% accuracy) (78,80).

After progesterone therapy, these patients must be monitored closely because of the risk of disease extending beyond the uterus. Also, there is a higher rate of synchronous ovarian cancer among young women with endometrial cancer, ranging from 5% to 29% (81,82).

Conclusion

There is a wide range of pathologic conditions that contribute to female subfertility, many of which are diagnosed and classified on the basis of imaging. Imaging techniques are also used to directly restore fertility, aid surgical planning, and stratify use of pharmacologic agents versus surgical intervention.

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