Saline Infusion Sonography: Tips and Tricks for Improved Visualization of the Uterine Cavity

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ABSTRACT

Saline infusion sonography (SIS), also known as hysterosonography or sonohysterography, is a minimally invasive ultrasound (US) technique that involves infusion of a small volume of sterile saline into the uterine cavity. It acts as a negative contrast medium that delineates hyperechogenic endometrial lining. Contrast enhanced sonographic studies provide high-resolution images of the uterine cavity enabling detection of focal and diffuse intrauterine abnormalities. In addition to visualizing intrauterine lesions, such as endometrial polyps, fibroids, and adhesions, it can assist in differentiating between different types of congenital uterine anomalies. The objective of our article is to assess the diagnostic value, indications, contraindications, and possible complications of SIS. Various clinical scenarios and typical appearances of intrauterine, endometrial, and subendometrial lesions detected by SIS are illustrated and compared with hysteroscopy images and/or macroscopically similar surgical pathology specimens. The literature on SIS is reviewed and authors discuss case-specific pitfalls and technical challenges that may lead to patient discomfort, poor image acquisition, incomplete assessment, and wrong interpretation of the images.

Keywords: Congenital uterine anomalies, Endometrial polyp, Hysterosonography, Intracavitary fibroid, Intrauterine adhesion, Saline infusion sonography, Sonohysterography, Submucosal fibroid.


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INTRODUCTION

Saline infusion sonography, sonohysterography, or hysterosonography is a minimally invasive US technique that involves infusion of a small volume of sterile saline into the uterine cavity, followed by a pelvic US evaluation. Saline acts as a negative contrast medium which clearly delineates hyperechogenic endometrial lining. This results in improved visualization of the endometrial cavity and uterine lining. The procedure can be performed under the guidance of two- (2D) or three-dimensional (3D) US.

The clinical indications for SIS include abnormal uterine bleeding in pre- and postmenopausal women, uterine cavity abnormalities noted on native transvaginal sonogram (such as abnormal endometrial thickening), suspected congenital uterine anomalies, infertility studies, or recurrent pregnancy loss. This technique can also be useful for better differentiation between different endometrial pathologies in patients using tamoxifen.

Our objective is to describe different clinical scenarios illustrating the most common intrauterine abnormalities associated with abnormal uterine bleeding. The 2D and 3D SIS images are correlated with hysteroscopy findings and/or gross anatomy images. Authors focus on specific pitfalls and technical challenges that may lead to patient discomfort, poor image acquisition, incomplete assessment, and wrong interpretation of the images.

CASE REPORTS

Case 1

A 34-year-old woman (G3P0A3), with a previous history of regular menstrual cycle, presents with secondary infertility. Her obstetrical history is significant for three missed abortions: 6 years ago at 8 weeks gestation, 4 years ago at 9 weeks gestation, and 1 year ago at 10 weeks gestation. Her menstrual cycles have always been regular (28–30/4–6). Sperm analysis of her husband is normal. An order was placed for SIS because her gynecologist noticed an “unusual shape of the uterine cavity” on 2D transvaginal US. The SIS was performed without complications and findings are presented in Figure 1. Patient was also assessed by 3D US (Fig. 2).

Case 2

A 27-year-old woman (G1P0A1) presents for SIS with symptoms of secondary amenorrhea. Her history is
significant for a miscarriage at 8 weeks gestation 2 years ago. Due to retained products of conception, she underwent dilatation and curettage (D&C). Since then, she reports absence of menstrual bleeding (secondary amenorrhea). Before D&C, her menstrual cycles were regular (25–28/5 days). Figures 3 and 4 illustrate her 2D SIS and 3D SIS findings respectively.

**Case 3**

A 44-year-old patient (G2P2A0) presents with irregular menstrual cycles and prolonged menstrual bleeding. She also complains of pelvic discomfort and bloating. Because of clotting disorder, the patient cannot use birth control pills. Her 2D SIS and transvaginal color Doppler US findings of the right ovary are presented in Figures 5 and 6.

**Case 4**

A 46-year-old woman (G3P3A0) presents with symptoms of prolonged uterine bleeding and vaginal spotting. Transvaginal US reveals abnormal endometrial thickening. Her SIS findings are demonstrated in Figures 7 to 9.
A 32-year-old woman (G1P1A0) presents with a history of heavy menstrual flow and chronic pelvic pain, not relieved with nonsteroidal anti-inflammatory drugs (NSAIDs). Her gynecologist performed a transvaginal US and revealed an enlarged uterus with multiple fibroids. The patient is interested in preserving her fertility and “by all means would like to have another baby.” Two-dimensional SIS findings are demonstrated in Figures 10 and 11. Figure 12 illustrates 3D SIS image of the same patient.

Fig. 5: Saline infusion sonography demonstrates diffuse endometrial thickening (the measurement of both single layers at their thickest level is 12 mm)

Fig. 6: The same patient as in Figure 5. Note a well-delineated sonolucent cystic structure on the right ovary (2.7 × 2.5 × 2.8 cm) with moderate vascular impedance (resistance index 0.48). Sonographic and Doppler findings are suggestive of an unruptured follicle

Fig. 7: Saline infusion sonography reveals hyperechogenic focal endometrial thickening. Contrast-enhanced sonography is suggestive of an endometrial polyp. Multiple small intramural fibroids are visualized

Fig. 8: Color Doppler depicts a well-defined vascular pedicle of the endometrial polyp

Fig. 9: The 3D SIS of the same patient confirms the diagnosis of endometrial polyp, protruding into the dilated cervical canal

Fig. 10: Saline infusion sonography reveals a pedunculated intracavitary fibroid
Case 6
A 78-year-old patient (G2P2A0) presents with abnormal uterine bleeding. Her history is significant for breast cancer diagnosed 5 years ago, for which she is using tamoxifen. She has a past medical history significant for hypertension and type II diabetes mellitus. Nonenhanced pelvic US reveals abnormal endometrial thickness with multiple small cystic inclusions. Transvaginal 3D US and color Doppler images are shown in Figures 13 and 14 respectively. Before starting the SIS procedure, the consulting physician explained sonographic and Doppler findings. She indicated that injection of saline may carry a risk of spreading potentially malignant endometrial cells into the peritoneal cavity. After thorough discussion of the advantages and disadvantages of SIS, the patient did not consent with SIS procedure. Endometrial biopsy was performed and endometrial carcinoma cells were detected. The patient underwent total abdominal hysterectomy.

Case 7
A 39-year-old G0P0 presents with oligomenorrhea. Her history is significant for hirsutism, hypertension, and type II diabetes mellitus. Her last menstrual period was 6 months ago. Laboratory findings illustrate elevated testosterone levels, elevation of luteinizing hormone (LH), and normal follicle-stimulating hormone (FSH) levels. Her sonographic findings are presented in Figures 15 and 16.

DISCUSSION
Case 1: Septate Uterus
In order to correctly diagnose uterine anomalies, it is important to understand the embryology events and nomenclature of the congenital uterine defects. The female reproductive tract develops from complex embryologic interactions involving the Müllerian ducts and urogenital sinus. Müllerian duct abnormalities occur due to a variety of different embryologic anomalies,
which may also involve different organ systems (such as the urinary and axial skeletal systems). However, Müllarian duct anomalies are usually associated with normal functioning ovaries and age-appropriate external genitalia, due to their embryological independence from Müllarian duct differentiation. The incidence and prevalence of various Müllarian anomalies vary widely between different studies, but congenital uterine malformations are estimated to involve 3 to 4% of the general population. A recent study using 3D US reported that the rate of congenital uterine anomalies in the subfertile female population is estimated to be 13.3%.

Septate uterus is the most common Müllarian duct abnormality, accounting for approximately 55% of such anomalies. It is defined as the uterus in which the uterine cavity is longitudinally divided by the septum, which fails to regress (class V Müllarian duct anomaly). This fibromuscular septum may be complete, extending from the midline fundal area to the internal os, or it may be partial. This anomaly may significantly impact a pregnancy’s outcome and is associated with recurrent pregnancy losses, preterm labor, abnormal fetal presentations, and infertility. It is estimated that the prevalence of septate uterus is about 1% in both females with normal fertility and infertility. However, the prevalence of septate uterus is significantly higher in women with pregnancy loss. Ghi et al have prospectively assessed the association between septate uterus and pregnancy outcome using 3D US in early pregnancy. Overall, 66.7% of women with septate uterus in this study experienced miscarriage before 22 weeks of gestation (54.2% prior and 12.5% after 12 weeks of gestation). Only 33.3% of patients resulted in the delivery of a live neonate.

Fig. 15: Saline infusion sonography reveals diffusely thickened endometrium

As previously mentioned, normal external genitalia and age-appropriate developmental changes are often masked in prepubertal females with septate uterus, but postpubertal females can often present with menstrual disorders, infertility, and obstetrical complications, which include early trimester miscarriages, premature delivery, abnormal fetal position, and intrauterine growth restriction (IUGR).

Septate uterus has a spectrum of configurations including variations from incomplete or partial septa to complete septate uterus. The size and shape of the septum can vary by width and length. Initially, uterine septa were believed to be avascular, consisting of predominantly fibrous tissue. For many years, poor vascularization of the septum was proposed as a potential cause of miscarriages. Electron microscopy study by Fedele et al indicated a decrease in the sensitivity of the endometrium covering the septa of the malformed uteri to the preovulatory changes, which could play a role in the pathogenesis of primary infertility in patients with a septate uterus. Connective tissue in the septum may explain poor decidu alization and placentation in the area of implantation. Salle et al performed a histological study of the uterine septa from 16 patients undergoing abdominal metroplasty. Statistical analysis confirmed less connective tissue in the septum compared with the amount of muscle tissue, which was contradictory to the classic view of the histopathologic features of the uterine septum. Biopsy specimens suggest that septa are composed primarily of muscle fibers and less connective tissue, which could noninvasively be visualized by 2D and 3D color and power Doppler US. Increased amounts of muscle tissue in the septum may lead to an abortion by higher and uncoordinated contractility of these muscles, as suggested by Kupesic et al. In another study, correlation between the septal height and thickness and occurrence of obstetrical complications was detected (p > 0.05). However, pregnancy loss rates correlated significantly with septal vascularity. Patients with vascularized septa had a significantly higher incidence of early pregnancy failure and late pregnancy complications than those with...
an avascularized septa (p < 0.05). Following septal incision of the vascularized septa, uncoordinated contractility of uterine muscle and pregnancy complications rate were significantly reduced.16,17

A proposed mechanism of septate uterus formation involves decreased levels of a B-cell lymphoma (BCL)-2 protein, which is involved in regulating apoptosis. Decreased levels of BCL-2 have been identified in the uterine septal tissue, which may explain the incomplete resorption of the medial septum from fusion of the paramesonephric ducts.18

The diagnosis of a uterine abnormality is usually first suspected on clinical grounds, which is then followed by imaging studies [2D and 3D transvaginal sonography, SIS, and magnetic resonance imaging (MRI)] and/or hysteroscopy. As in our case, this type of congenital uterine anomaly is clinically asymptomatic until pregnancy occurs, or patient may report episodes of dysmenorrhea. History of missed abortions (secondary infertility) and “abnormal uterine shape” on a native pelvic US strongly support a congenital uterine malformation. Figure 1 illustrates two separate endometrial echoes in transverse views of the uterus following 2D SIS, resembling “cat’s eyes” sign, but the interpretation is operator dependent. Using 3D US, uterine anatomy can be better assessed in multiplanar view even without instillation of any contrast medium (Fig. 2). The coronal plane allows physician to view both horns of the endometrium, and the cervix at the same time, simultaneously assessing the uterine cavity shape, myometrium, and external contour of the uterus. A complete division of the uterine cavity from fundus to cervix and convex external contour are typical for septate uterus. Being noninvasive and more economical than MRI, 3D US became the gold standard for diagnosis of septate uterus and differentiation between different types of congenital uterine anomalies.

Two endometrial cavities separated by a fibromuscular septum were confirmed by hysteroscopy and septal incision was performed (Fig. 17A). Gross anatomy image of complete uterine septum is presented in Figure 17B. Microscopically, the septum often consists of poorly vascularized, fibrous connective tissue with varying amounts of smooth muscle tissue.

Clinical history, presentation, and imaging modalities (X-ray hysterosalpingography, transvaginal 2D and 3D US, MRI, or diagnostic hysteroscopy) are necessary for a definite diagnosis of a septate uterus.19 Septate uterus often has a more adverse reproductive outcome compared with other Müllerian duct abnormalities, but it is most amenable to simple hysteroscopic surgical treatment, involving a hysteroscopic incision of the septum. Complications may include significant hemorrhage, infection, intrauterine adhesions (IUAs), uterine perforation (<5%), or even uterine rupture in subsequent pregnancies. When assessing a patient with congenital uterine anomalies, carefully examine the vagina and cervix to rule out vaginal septa, duplication of the cervix, or other abnormalities. Look for associated anomalies of the urinary tract and do not scare patient with misinformation.

The new European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynecological Endoscopy (ESGE) classification system of female genital anomalies aims to provide a more suitable classification system for the accurate, clear, correlated with clinical management, and simple categorization of female genital anomalies.20 Until now, three systems have been proposed for their categorization, but all of them are associated with serious limitations. The ESHRE/ESGE have established a common working group, under the name CONUTA (CONgenital UTerine Anomalies), with the goal of developing a new updated classification system. A scientific committee has been appointed to run the project, looking also for consensus guidelines.
within the scientists working in the field. The new system is designed and developed based on: (1) scientific research through critical review of current proposals and preparation of an initial proposal for discussion between the experts, (2) consensus measurement among the experts through the use of the DELPHI procedure, and (3) consensus development by the scientific committee, taking into account the results of the DELPHI procedure and the comments of the experts. In the ESHRE/ESGE classification system, based on anatomy, anomalies are classified into the following main classes, expressing uterine anatomical deviations deriving from the same embryological origin: U0, normal uterus; U1, dysmorphic uterus; U2, septate uterus; U3, bicornoreal uterus; U4, hemi-uterus; U5, aplastic uterus; U6, for still unclassified cases.20 Main classes have been divided into subclasses expressing anatomical varieties with clinical significance. Cervical and vaginal anomalies are classified independently into subclasses having clinical significance. The ESHRE/ESGE classification of female genital anomalies seems to fulfill the expectations and the needs of the experts in the field, but its clinical value needs to be proved in everyday practice.

Case 2: Intrauterine Adhesions

Intrauterine adhesions describe bands of fibrotic tissue occurring within the endometrial cavity with varying levels of cavity involvement, size, and density. They are typically secondary to trauma or damage of the basilar layer of the endometrium following curettage after pregnancy loss.21 In fact, 67% of women with IUA have history of curettage secondary to an induced or spontaneous abortion.22 Endometrial trauma in a nonpregnant patient can also result in formation of IUA, but the risk is lower [1.6% after diagnostic curettage, 1.3% after abdominal myomectomy, 0.5% after cervical biopsy or polypectomy, and 0.2% after insertion of an intrauterine device (IUD)].23 Regardless, the true incidence of IUA is unknown since a significant number of patients are asymptomatic.23,24 Terms “Asherman syndrome” and “IUA” are often used interchangeably, but they are not exactly the same entities. While IUA mainly describes intrauterine findings, regardless of clinical presentation, Asherman syndrome requires the presence of signs and symptoms (such as menstrual disturbance and pain) in a patient with confirmed IUA.23

As the severity of this disorder varies, so does its clinical presentation. Thin, fragile adhesions with minimal endometrial involvement are typically asymptomatic, but thicker, denser adhesions may obliterate the entire uterine cavity and obstruct menstrual flow. Menstrual abnormalities, such as amenorrhea, hypomenorrhea, and/or menorrhagia are the most common symptoms in patients with Asherman syndrome.24 Pelvic pain is commonly present as a cyclical association with menstrual dysfunction, as well as infertility and pregnancy loss, which occur due to distortion of the uterine cavity.24 In cases with cervical obstruction and retrograde menstruation, hematometra and hematosalpinx can also be visualized on US.25,26

Typically, IUAs do not have specific physical examination findings, so the diagnosis is usually made by imaging (X-ray hysterosalpingography, 2D and 3D transvaginal US, SIS, and MRI) and/or hysteroscopy. Based on diagnostic techniques and clinical presentation, multiple classification systems have been developed to better characterize IUA, but no classification or grading system has been validated or received universal endorsement at this time, which may reflect deficiencies in all of the proposed systems.21

The histopathology of IUA shows endometrial stroma and glands replaced by hypocellular, fibrotic tissue with inactive cuboidal or columnar endometrial epithelium, which results in a similar microscopic appearance between the functional and basal endometrial layers.27,28 In addition, avascular or slightly vascular bands of fibrotic tissue are present, representing the IUA bands. IUA may attach to different layers of endometrium and myometrium, and often are attached at two or more points as illustrated in Figure 18.

Since IUAs are not life threatening and patients are often asymptomatic or minimally symptomatic, treatment may not be necessary. However, severe symptoms of pain or menstrual dysfunction as well as a patient’s desire to conceive after a history of infertility and recurrent pregnancy loss are indications for treatment.29,30 Hysteroscopic surgery enables lysis of IUAs under direct visualization and is considered the main treatment modality (Fig. 19). Mild IUA may simply be treated with fluid distention, while more severe adhesions require

Fig. 18: Hysterectomy specimen with intrauterine adhesions. Note fibrotic endometrial bands attaching endometrium at multiple points.
hysteroscopic resection. This may be followed by mechanical measures (e.g., placement of an intrauterine balloon and/or postoperative estrogen treatment). Postoperative evaluation of the uterine cavity by office hysteroscopy, SIS, or X-ray hysterosalpingography is recommended to assess whether a normal contour of the uterine cavity has been restored. Patients undergoing hysteroscopic lysis of IUA should be informed about a high recurrence rate: 33% in patients with mild-to-moderate adhesions, and 66% in patients with severe adhesions. If adhesions recur, second or third hysteroscopic procedure may be required. A recent study assessing the reproductive outcomes in 357 patients with IUA following hysteroscopic adhesiolysis revealed 61, 53 and 25% pregnancy rates in mild, moderate, and severe disease respectively. In this study, the mean time to conception was 9.7 ± 3.7 months, the miscarriage rate was 9.4%, and the overall live birth rate was 86%. Pregnancies in women with history of IUA should be considered high risk, and are commonly associated with abnormal placation (e.g., placenta accreta), preterm delivery.

These functional or follicular cysts typically resolve in 6 to 12 weeks and are more frequently asymptomatic. However, larger cysts (>7 cm) may present with pelvic pressure effects, pain, cyst rupture, or ovarian torsion. These patients are typically treated with progestin (cyclic, or levonorgestrel IUD), and low-dose combination hormonal contraceptive therapy (20–35 μg ethinyl estradiol), which is the mainstay of treatment for adolescent patients.

Simple, unilocular follicular cysts that are less than 10 cm in size are highly likely to be benign with a malignancy rate of less than 1%. Recommended management of the follicular cysts differs with respect to menopausal status (pre- vs postmenopausal) and size. In the case of premenopausal females, no clinical follow-up

Case 3: Unruptured Follicle/Diffuse Endometrial Thickening

During normal ovulatory menstrual cycles, a dominant follicle develops and ruptures to release mature oocyte with subsequent development of a corpus luteum. In the case of follicular cysts, there is a failure of the follicle to rupture or regress. Unruptured follicles are typically thin-walled, avascular unilocular sonolucent cystic structures with mean diameter exceeding 25 mm. They are typically found in a wide age range, including adolescent and perimenopausal patients. In normal female physiology, gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile fashion from the hypothalamus, stimulating secretion of FSH and LH. The FSH stimulates ovarian follicular cells to produce estradiol, resulting in a single dominant follicle, and the increasing estradiol levels have a negative feedback on FSH production. On the contrary, LH causes luteinization of ovarian granulosa and theca cells, resulting in increased progesterone. Follicular cysts result from excessive stimulation by FSH or from a lack of the normal preovulatory LH surge. They usually consist of luteinized cells surrounding a unilocular cyst. By sonography, the endometrium of these patients is either triple line (trilaminar) or hyperechogenic. No signs of ovulation are apparent, and progesterone in the second phase of a cycle (on day 21) is low. The continued estrogen secretion results in an excessively thickened endometrium without adequate progesterone levels for coordinated menstrual sloughing. In this particular case, the SIS study excludes certain anatomical uterine abnormalities, and visualization of “thickened endometrium,” supports a diagnosis of dysfunctional uterine bleeding. These patients usually present with amenorrhea (6–10 weeks), which is followed by prolonged dysfunctional uterine bleeding. In contrast to Polycystic Ovarian Syndrome (PCOS), no androgen excess is present.

These functional or follicular cysts typically resolve in 6 to 12 weeks and are more frequently asymptomatic. However, larger cysts (>7 cm) may present with pelvic pressure effects, pain, cyst rupture, or ovarian torsion. These patients are typically treated with progestin (cyclic, or levonorgestrel IUD), and low-dose combination hormonal contraceptive therapy (20–35 μg ethinyl estradiol), which is the mainstay of treatment for adolescent patients.

Simple, unilocular follicular cysts that are less than 10 cm in size are highly likely to be benign with a malignancy rate of less than 1%. However, recommended management of the follicular cysts differs with respect to menopausal status (pre- vs postmenopausal) and size. In the case of premenopausal females, no clinical follow-up
is necessary in cysts that are 3 to 5 cm sizes, but an annual follow-up is needed if the cysts are between 5 and 7 cm in diameter. In postmenopausal females, an annual follow-up is needed if the cysts are from 1 to 7 cm in size. Regardless of age, a persisting cyst that is greater than 7 cm size requires additional imaging and/or surgical evaluation. High-risk patients (obese, hypertensive, diabetic positive history of uterine cancer) should have an endometrial biopsy performed to exclude endometrial abnormalities (such as hyperplasia or endometrial malignancy).

**Case 4: Endometrial Polyp**

Endometrial polyps are common, localized growths of the endometrial tissue, containing endometrial epithelium, stroma and blood vessels. These lesions may be single or multiple, sessile or pedunculated protrusions into the uterine cavity. The size of endometrial polyps can vary from few millimeters to few centimeters, and plays a significant role in the signs and symptoms patients experience. Smaller polyps tend to be minimally symptomatic or asymptomatic, and may spontaneously regress, while larger polyps in both pre- and postmenopausal women are usually associated with abnormal uterine bleeding. The prevalence of endometrial polyps has been reported to be up to 20% in symptomatic premenopausal women, and up to 40% in symptomatic postmenopausal women. However, their prevalence depends on the population studied and the imaging technique utilized. It has been reported that SIS detected endometrial polyps in about 10% of asymptomatic premenopausal women over 30 years of age.

The exact cause of endometrial polyps is unknown, but genetic factors associated with anomalies of chromosomes 6 and 12, which may alter the processes of epithelial proliferation, were reported. Postmenopausal women with endometrial polyps demonstrate an increase of a proliferating-regulating protein p63, known as marker for reserve cells in the endometrial basal layer. Estrogen and progesterone may also play a role in the formation of endometrial polyps, since increased number of estrogen receptors is noticed in patients with endometrial polyps compared with patients with normal endometrium. Similar data are available to support the role of progesterone receptors in their pathogenesis.

Endometrial polyps typically present with abnormal uterine bleeding, menorrhagia, irregular menses, postcoital bleeding, or intermenstrual bleeding. Rarely, reproductive-age patients may present with infertility, even though a clear mechanism is unclear. Smaller endometrial growths tend to be asymptomatic, and regression of incidentally detected endometrial polyp in 1 year has been estimated to be 27%.

On hysteroscopy, endometrial polyps appear as polypoid structures protruding into the uterine cavity (Fig. 21). Figure 22 shows a hysterectomy specimen with a solitary endometrial polyp, protruding into the uterine cavity. Microscopically, it demonstrates dilated, nonproliferative endometrial glands and less dense, surrounding stroma with fibrosis and thick-walled blood vessels (Fig. 23). In reference to their neoplastic potential, most endometrial polyps are benign, but hyperplasia with atypia and epithelial malignancy has been noted to arise from these lesions. A recent meta-analysis reported that the prevalence of premalignant and malignant changes within endometrial polyps varies from 0.2 to 23.8% and from 1 to 12.9% respectively. The highest risk of malignancy is present in symptomatic postmenopausal patients with a four-fold higher risk of presenting with endometrial cancer as compared with similar women in reproductive age.

Management of endometrial polyps depends on patient’s symptoms, risk of malignancy, and consideration...
of fertility. Smaller, asymptomatic endometrial polyps are typically not considered for surgical treatment, but larger, symptomatic polyps with increased risk of malignancy should be removed by hysteroscopy.53 Between 75 and 100% of patients reported a favorable improvement on periodic blood loss following polypectomy.53,56 Also, polypectomy appears to have a positive impact on fertility of the patients in reproductive age.54,56

**Case 5: Submucosal/Intracavitary Fibroid**

Uterine fibroids or leiomyomas are benign smooth muscle tumors arising from different myometrial locations (such as submucosal, subserosal, and intramural). These lesions are rare in women under the age of 20, but their prevalence increases up to 70 to 80% in perimenopausal women.58 In addition, they are more common in women of African ancestry. As a result, the prevalence of uterine fibroids varies based on age, ethnicity, and geographic location. The exact causes of uterine fibroids are not fully understood, but ethnic propensity suggests a hereditary component. In addition, both estrogen and progesterone are known to stimulate their growth by mechanisms that are not fully understood.59,60

The number, size, and location of uterine fibroids play an important role in symptomatology of the patients. In submucosal fibroids, the most common symptom is abnormal uterine bleeding (often manifested as menorrhagia), occurring in approximately 30% of this patient population.61 It is generally perceived to be due to distortion of the uterine cavity and interference with normal uterine contractility. However, the exact mechanism by which uterine fibroids cause abnormal uterine bleeding is unknown.62 Adenomyosis can also present with similar symptoms and commonly coexists with uterine fibroids.

In intramural fibroids, the distortion and added uterine weight often result in an insidious feeling of pelvic discomfort, related to the enlarged uterus impacting adjacent organs or structures. This results in “bulk” symptoms, which include increased urinary frequency, constipation, pelvic cramping, bloating, and dyspareunia. Pelvic pain is also a common symptom, which may be related to torsion of pelvic structures or impingement of the broad ligament. The prevalence of clinically significant uterine fibroids declines following menopause.63

On gray scale US, the uterine fibroids are usually represented by uterine enlargement, distortion of the uterine contour, and varying echogenicity depending on the amount of connective or smooth muscle tissue.64 Transvaginal color Doppler sonography demonstrates increased peripheral vascularity (within the capsule), which often assists in better delineation of the lesion. Simultaneous display of three perpendicular planes by 3D US improves determination of the number, size, and location of the uterine fibroids. Figure 24 illustrates the gross anatomy specimen of the enlarged uterus with multiple uterine fibroids (intramural, subserosal, and submucosal) and endometrial polyp protruding through the cervix.

Infertility and recurrent pregnancy loss are possible symptoms of submucosal and/or intracavitary fibroids (Figs 10 to 12 and 25). The uterine environment of patients with submucosal/intracavitary fibroids may not be conducive to the nidation of a blastocyst due to inadequate blood supply. Microscopic evaluation typically reveals normal appearing smooth muscle forming a nodular growth pattern, which eventually grossly appears as a circular lesion. Endometrium overlying submucosal and/or intracavitary fibroids frequently show glandular atrophy, which may be related to pregnancy loss, since it is perceived to impair implantation and nourishment of the developing embryo.
Classifications of submucosal fibroids are frequently used to help consider the different therapeutic options. The most widely used systems are the FIGO (International Federation of Gynecology and Obstetrics) and the ESGE (European Society of Gynecological Endoscopy) systems which both take into account the extension of the fibroid into the uterine cavity. However, insufficient data exist to suggest which system provides the best combination of clinician acceptance and clinical utility.

Although uterine fibroids are very common, malignancy arising from these lesions in women under the age of 50 is extremely low. The incidence of uterine leiomyosarcoma arising from a presumed uterine fibroid is between 0.23 and 0.49%, but this percentage may rise above 1% for hysterectomy specimens of patients above 60 years of age.

Management of uterine fibroids is not simple, since each patient presents with unique circumstances. The timing and type of intervention depend on the severity of symptoms, size and location of the fibroids, patient age, obstetrical history, and reproductive plans. The expectant management is an option for some with submucosal leiomyomas, since the growth rate is similar to uterine fibroids in other locations. Medical treatment is typically considered the first-line of treatment in asymptomatic women, including perimenopausal patients.

There is evidence that levonorgestrel intrauterine system (LNG-IUS) may be effective for patients with heavy menstrual bleeding.

A number of medical interventions have been shown effective in temporarily reducing the size of leiomyomas including GnRH agonists, selective progesterone receptor modulators, and aromatase inhibitors, each of which reduces uterine and leiomyoma volume a mean of approximately 30% to 45% after three months of administration. However, it is not recommended for any long-term use. Ulipristal acetate is a progesterone receptor modulator which may be administered preoperatively, and is associated with resolution of menorrhagia, increase in hemoglobin level, and significant reduction of the fibroid volume.

Numerous studies suggest that uterine artery embolization is effective for treatment of heavy menstrual bleeding and bulk symptoms; however, its role in the management of submucosal fibroids is controversial. Similarly, submucosal fibroid ablation with radiofrequency electricity, laser energy, cryotherapy, microwaves, and focused ultrasonography is not yet approved. As a result, surgical treatment remains as the mainstream therapy, which explains why uterine fibroids remain as one of the leading indications for hysterectomy in the United States.

As illustrated in Figures 10 to 12, 2D and 3D SIS can precisely determine the size of the fibroid, as well as extent of its protrusion and is helpful for differentiation between intracavitary, submucosal, and intramural fibroids when planning a hysteroscopic resection. When the entire fibroid is visualized arising from the pedicle, the lesion is classified as intracavitary. SIS is superior to hysteroscopy for determining the depth of fibroid penetration to the endometrium and/or myometrium.

**Case 6: Tamoxifen-induced Endometrial Changes**

Tamoxifen is a nonsteroidal estrogenic antagonist that binds to estrogen receptors in mammary epithelium, making it appropriate for both the treatment and prevention of breast cancer. It is used widely in patients with hormone receptor-positive breast carcinoma treated with surgery with the aim to lower the risk of breast cancer recurrence and getting a breast cancer in the opposite breast. The literature suggests that tamoxifen can prevent hormone-positive breast cancers from developing in women at risk for the disease. Subsequently, indications of this medication have been broadened to include long-term adjuvant therapy and preventative therapy for selected high-risk patients. Owing to its molecular structure, tamoxifen has a complex mechanism of action, boasting both estrogenic and anti-estrogenic properties depending on the target tissue. Due to its dual action, it is better described as selective estrogen receptor modulator.

Although tamoxifen has antagonistic estrogen effect on breast tissue, it has a weakly agonistic estrogen activity on the vaginal and endometrial epithelium. As a result, proliferative endometrial abnormalities have been reported to occur in up to 40 to 50% of tamoxifen treated women by imaging studies, and 15 to 61% of endometrial
biopsies respectively. Endometrial polyps represent one of the most common endometrial pathologies associated with tamoxifen exposure, developing in up to 36% of postmenopausal patients on tamoxifen. Malignant transformation of endometrial polyps has been reported to occur in up to 11% of postmenopausal women on tamoxifen. Most studies reported two to three times higher relative risk of developing endometrial malignancy for women taking tamoxifen, compared with an age-matched population. The risk of endometrial carcinoma and sarcoma is dose-dependent; women treated with a higher dosage of tamoxifen (40 mg/day) for a longer duration are more prone to develop more biologically aggressive tumors.

The clinical presentation in tamoxifen-treated patients with polyps is similar to other patients with endometrial lesions. Abnormal uterine bleeding is the most common presenting symptom occurring in 64 to 88% of patients with endometrial polyps. In these patients, transvaginal sonography typically demonstrates thickened endometrium with multiple cystic inclusions (Fig. 13). Microscopic evaluation obtained from D&C or hysteroscopy specimens most frequently demonstrates dilated glands with atrophy of overlying epithelium (termed “glandulo-cystic atrophy and peri-glandular stromal fibrosis”). Figure 26A illustrates a tamoxifen-induced endometrial polyp with typical glandulo-cystic appearance (refer to “Swiss-cheese” appearance on pelvic US imaging). Microscopic findings are demonstrated in Figure 26B.

The increased risk of uterine malignancies in tamoxifen-treated patients has fostered a search for effective methods of their early detection. The diagnostic methods most frequently used in the surveillance of these patients include transvaginal US, outpatient endometrial biopsy, and hysteroscopy. However, no effective method of tamoxifen-user surveillance has yet been developed and current recommendations do not advise any screening for endometrial malignancy. Transvaginal sonography is a poor screening method for detection of endometrial abnormalities in asymptomatic tamoxifen-treated patients, because induced edema of the cystically dilated endometrial glands with periglandular stroma and myometrial condensation often leads to misinterpretation of abnormal endometrial thickening. Although asymptomatic postmenopausal tamoxifen-treated women should not have routine testing to diagnose endometrial pathology, SIS has improved the accuracy of transvaginal US in excluding or detecting anatomic changes, when necessary.

It was demonstrated that postmenopausal patients may benefit from transvaginal sonography before initiation of tamoxifen therapy. The incidence of atypical hyperplasia was 11.7% in the group with initial lesions vs only 0.7% in the group without lesions (p < 0.0001), an 18-fold increase in risk. In addition, polyps developed in 17.6% of the group with initial lesions vs 12.9% in the group without. There is an increased risk of endometrial polyp formation secondary to tamoxifen use for both premenopausal and postmenopausal women.

A systematic review and meta-analysis of 24 observational studies in 1,001 women showed that the LNG-IUS was more effective than oral progestins in inducing regression of endometrial hyperplasia. In women treated with tamoxifen for breast cancer, the use of LNG-IUS reduced the occurrence of de novo endometrial polyps as

well as hyperplasia. Indeed, the LNG-IUS prevents endometrial polyps with continued use in women taking tamoxifen for up to 4.5 years. However, further studies are needed to establish the correlation between these treatment results and a decreased risk of endometrial carcinoma on one side, and an increased risk of breast cancer recurrence on the other, particularly in women with progesterone receptor-positive breast cancer.110

**Case 7: Diffuse Endometrial Thickening/PCOS**

Polycystic ovarian syndrome, first described by Stein and Leventhal,111 is a heterogeneous endocrine disorder associated with irregular menstrual periods, hyperandrogenism, and polycystic appearance of the ovaries. The prevalence of PCOS varies depending on the criteria used to make diagnosis, but it is estimated to affect up to 15 to 20% of women.112,113

An exact etiology is not known, although a genetic component has been described. Clinical manifestations include oligomenorrhea or amenorrhea, hirsutism, and frequently infertility.112,115,116 Insulin resistance affects 50 to 70% of women with PCOS, leading to a number of comorbidities including metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes.117 Studies show that women with PCOS are more likely to have increased coronary artery calcium scores and increased carotid intima–media thickness. Mental health disorders including depression, anxiety, bipolar disorder, and binge eating disorder also occur more frequently in women with PCOS.118

Diagnostic criteria for PCOS have been established by the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD), the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), and the Androgen Excess Society (AES) (Table 1).119-121 Each group considers PCOS a diagnosis of exclusion, implicating that other diagnoses, such as congenital adrenal hyperplasia, nonclassic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders are excluded.113 The NIH/NICHD and the AES require that patients have signs or symptoms of hyperandrogenism, such as hirsutism, or hyperandrogenemia, defined as elevated free testosterone, reduced SHBG (sex hormone-binding globulin), elevated free testosterone index, or elevated dehydroepiandrosterone sulfate. However, the ESHRE/ASRM or Rotterdam criteria allow for the diagnosis of PCOS without the presence of hyperandrogenemia or clinical hyperandrogenism. Women with ovulatory dysfunction and the presence of polycystic ovaries are considered to have PCOS by the Rotterdam criteria. The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group include the presence of 12 or more follicles measuring between 2 and 9 mm in diameter and/or an increased ovarian volume of greater than 10 cm³. This presentation in one ovary sufficiently defines the polycystic ovary.120 However, since that time, significant advancements in US image technology have been made, improving resolution and allowing for the detection of smaller follicles (Fig. 16). Recently, follicle number per ovary threshold of 26 follicles assessed by 3D US achieved the sensitivity of 85% and specificity of 94% in discriminating PCOS and controls.122

In Case Study #7, the patient’s US demonstrates more than 12 follicles and enlarged ovarian volume (Fig. 16). The clinical history of oligomenorrhea, signs of hyperandrogenism, and laboratory and US findings are sufficient to meet the ESHRE/ASRM criteria for PCOS.

The uterine endometrial lining is thickened due to the normal endometrial response to sustained estrogen levels, which are unrelieved by progesterone breakdown (Figs 15 and 27). This is a common finding in PCOS due to anovulation without the postovulatory progesterone production needed for shedding of the endometrial lining, known as menstruation. Along with complaints of menstrual irregularity, chronic anovulation that is associated with PCOS can increase a patient’s risk of endometrial hyperplasia and carcinoma.

**Table 1: Criteria for the diagnosis of PCOS**

<table>
<thead>
<tr>
<th>NIH/NICHD119</th>
<th>ESHRE/ASRM120</th>
<th>AES121</th>
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</thead>
<tbody>
<tr>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
</tr>
<tr>
<td>• Menstrual dysfunction</td>
<td>• Oligo-ovulation or anovulation</td>
<td>• Ovarian dysfunction and/or polycystic ovaries</td>
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<td></td>
<td>• Polycystic ovaries</td>
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Fig. 27: Gross anatomy of diffusely thickened endometrium
Management of PCOS involves a symptom-oriented approach and a preventative strategy for long-term associated morbidity. Weight loss, often including diet and exercise, is the recommended first line of treatment. Women with significant weight loss (at least 5–10% of weight loss) demonstrate improvement in all PCOS symptoms as well as decrease in the risk of long-term associated endocrine and cardiovascular disorders.123 Using either cyclic progestin or a low-dose combined hormonal contraceptives containing estrogen and progestin can help inhibit endometrial proliferation.124 Low-dose combined hormonal contraceptives are the primary recommended treatment option for PCOS-related menstrual disorders and improved menstrual regularity.123,124 Clomiphene citrate remains the first treatment of choice for medical ovulation induction in PCOS.125 Other medications (gonadotropin therapy) or treatment techniques (laparoscopic ovarian diathermy) may also be offered in women who experience resistance or failure to clomiphene. The effectiveness of other medications (metformin and letrozole) at this point has not been proven.125,126

IMPORTANT TIPS AND TRICKS
The SIS is a technique that requires a well-coordinated team, including special nurse assistance. The role of the nurse is to: (1) document the indication(s) for SIS; (2) ask about eventual contraindications; (3) verify that the reproductive-age patients are scheduled in the appropriate phase of the menstrual cycle (early follicular phase). perform a pregnancy test on the day of or one day before the procedure, and document negative pregnancy results; (4) prepare the necessary set of instruments needed for SIS procedure; (5) prepare a written consent for the patient; and (6) take necessary steps in the postprocedural sterilization of the instruments.

On the contrary, physicians performing SIS are obliged to (1) review the patient’s chart before the procedure; (2) document the negative finding of the pregnancy test; (3) obtain clinical history and inform the patient of allergic reactions to iodine and/or contrast media (if other than saline), (4) explain the examination procedure to the patient in a manner appropriate to the patient’s ability to understand, (5) give the patient a written consent, (6) perform the procedure according to the criteria of the national association (e.g., American College of Obstetrics and Gynecology, ACOG); (7) assess and monitor the patient’s physical and mental status during the examination; (8) document and evaluate sonographic findings throughout the course of the procedure, so that sufficient data are provided to the referring physician; (9) comment if the procedure was not completed and document the reasons why the US exam/SIS was not completed, and (10) provide timely, accurate, concise, and complete documentation according to the policy and procedures of the US service department.

To achieve best results, the entire team (sonographer, physician, and nurse) has to be aware of potential pitfalls and strategies how to prevent technical difficulties which may lead to incomplete study and/or unnecessary termination of SIS.

Scheduling for SIS
Reproductive-age patients undergoing SIS should be scheduled in the early postmenstrual phase, preferably after completion of the menstrual bleeding. In patients with menstrual bleeding, the presence of blood or blood clots may obscure a pathologic condition.127 In general, this technique should not be performed in patients with active uterine bleeding, since the reflux of menstrual blood could result in an increased risk of infection. It is not recommended to perform SIS during the peri-ovulatory period to avoid the possibility of flushing out a fertilized ovum during the procedure.128 In patients with an irregular menstrual cycle, a preprocedure pregnancy test may be performed unless the patient has recently had her menses or the use of reliable contraception is confirmed. Patients should be counseled to call for an appointment between day 1 and day 3 of the menstrual cycle, but scheduling of patients should be individualized, depending on the duration of their menstrual period. In early postmenstrual phase, the endometrium is thin, which is the best time to determine if there is any focal or diffuse abnormality.

Postmenopausal women who are not undergoing hormone replacement therapy may undergo SIS at any time, as well as patients undergoing a continuous, combined regimen of hormone replacement therapy.128 Their endometrium is supposed to be thin enough that specific timing is not required. For patients who are undergoing sequential hormone therapy (estrogen followed by progesterone), SIS should be performed at the end of the progesterone phase.128

Contraindications for SIS
The contraindications for SIS include pregnancy and pelvic infections. This is why patients of reproductive age should have a pregnancy test on the day of this sonographic examination. In addition, patients need to be asked about uterine discharge, pain, or any other symptom, which may indicate a pelvic inflammatory disease (PID). Any symptoms suggestive of PID should be conveyed to the referring physician, and if necessary, prophylactic antibiotics should be provided.129,130 Patients with IUD and known tubal occlusion or peritubal adhesions are reported
to have increased stasis of the saline in the pelvis, which may increase the risk of PID.\textsuperscript{127,131}

**Use of NSAID**

Unless contraindicated, administering a NSAID 30 to 60 minutes before the procedure may be helpful particularly in patients with adenomyosis who may experience more pain.\textsuperscript{128}

**Patient Education and Preprocedure Imaging**

Patient education and preprocedure imaging are highly recommended before starting SIS. Familiarize yourself with patient history, ask relevant questions (e.g., history of tubal ligation), and request signed consent form and time out. In patients with bilateral tubal ligation, the amount of saline should be adjusted, since injection of a large volume of the contrast medium may cause patient discomfort and pain. Patients should also be informed that an empty urinary bladder is required and that pelvic discomfort and cramping pain may occur during the procedure.

During preprocedure US imaging, observe the uterine and cervical position and assess the cervical length. Perform detailed measurements and evaluate the adnexal region carefully. Rule out dilated tubes, presence of PID and adnexal masses. Explore cul-de-sac for the presence of free fluid. Document all the findings.

**Equipment Preparation**

Equipment needed for the procedure should be carefully prepared, draped, and kept out of sight of the patient. Multiple specula of variable sizes and shapes should be available to accommodate patient size and parity.\textsuperscript{128} Both specula and saline may be warmed to prevent patient discomfort and cramping.

**Patient Positioning and Cervical Access**

Inappropriate positioning of the patient and inability to visualize the cervix are the most common causes of unsuccessful SIS. Patient should be placed on the gynecological examination table in semi-lithotomy position, with buttocks extended slightly beyond the edge of the table, and the feet in stirrups.\textsuperscript{128} Obese patients may benefit from positioning the knees toward the chest. Improper size and shape of the speculum may impair the access to the cervix, so it is extremely important to be informed about the orientation and position of the cervix at the time of preprocedure imaging supplemented with bimanual palpation.

A mobile cervix may be stabilized by maintaining steady pressure while cannulating the cervix, or using a tenaculum which should be placed at the 12 o’clock and/or 6’oclock position, where vascularity is sparse.\textsuperscript{132} Cervical stenosis may prevent catheter placement, and in this situation, sound and cervical dilators may be used to gently widen the passage.\textsuperscript{133}

**Optimal Distension of the Uterine Cavity**

Placement of the catheter, distension of the balloon, and rapid injection of saline may cause pain in patients with small uterine cavity (nulliparous and postmenopausal patients). Catheter should be flushed and filled with saline before insertion into the uterine cavity to prevent unintentional instillation of air that can cause obscuring artifacts.\textsuperscript{128} To avoid blood clots in reproductive-age patients, SIS should be performed after cessation of the menstrual bleeding (during the early proliferative phase) when the endometrium is relatively thin. In patients presenting with constant bleeding in whom blood clots and/or debris are unavoidable, color Doppler can be used to visualize a lack of flow in a patient with blood clot vs a feeding vessel in an endometrial polyp.

Optimal distension of the uterine cavity is required for accurate visualization of the focal and diffuse endometrial, intracavitary, and/or submucosal lesions. For lesions in the lower uterine segment, the catheter balloon should be deflated, which may lead to fluid leakage. Simultaneously with deflation of the balloon, withdraw the catheter and install more saline to ensure optimal distension of the uterine cavity. Rapid acquisition with volume imaging is useful in obtaining a set of images before fluid reflux/leakage. In patients with IUAs, limited distension of the uterine cavity is expected. In these patients, better visualization may be achieved with lower-frequency transabdominal transducer.\textsuperscript{128}

**Visualization of the Cervical Lesions**

Cervical lesions are best visualized by deflating the catheter balloon and moving it caudally toward the external os, continuously slowly injecting saline to allow appropriate distension of the endocervical canal (Fig. 28).
Self-Assessment Quiz

1. A 3D SIS imaging study of a septate uterus would show a transverse sonographic image demonstrating:
   a. Obliteration of the uterine cavity
   b. A single uterine cavity with a polypoid, hypoechoic mass
   c. An uterine cavity with a thickened endometrial lining
   d. An uterine cavity with distortion from submucosal masses
   e. Two uterine cavities separated by a fibromuscular septum

2. The sensitivity and specificity of SIS in detecting a septated uterus is:
   a. About 20% and 100% respectively
   b. About 98% and 20% respectively
   c. About 20% and 20% respectively
   d. About 98% and 100% respectively
   e. The sensitivity and specificity for SIS in septated uterus have not been characterized

3. The most common cause of intrauterine adhesions are:
   a. Vaginal labor and delivery
   b. Curettage secondary to an induced or spontaneous abortion
   c. Cesarean section delivery
   d. Endometrial cancers
   e. Endometritis

4. On SIS intrauterine adhesions are visualized as:
   a. Hyperechoic bridges of tissues in the intrauterine cavity
   b. Hypoechoic bridges of tissues in the intrauterine cavity
   c. Fibrotic tissue and inactive cuboidal or columnar endometrial epithelium
   d. Hypoechoic myometrial nodules of tissues
   e. Thickened endometrium with ill-defined invasion into myometrium

5. Which of the following would be most likely seen upon histological examination of the patient with intrauterine adhesions:
   a. Avascular fibrous bands joining the uterine walls
   b. A thin and atrophic endometrium
   c. Thickened endometrium with complex glands
   d. Multiple large bundles of smooth muscle cells arranged in a whorled sparse glands
   e. Fibrotic tissue and thick cuboidal or columnar endometrial epithelium

6. What is the treatment of choice for reproductive-age patients with moderate intrauterine adhesions?
   a. Laparoscopic hysterectomy
   b. Dilatation and curettage
   c. Watchful waiting
   d. Saline infusion sonography
   e. Hysteroscopic adhesiolysis

7. On SIS, endometrial polyps are visualized as:
   a. Single or multiple protrusions into the uterine cavity
   b. Sessile or pedunculated protrusions into the uterine cavity
   c. Diffusely thickened endometrium
   d. a and b
   e. Hyperechogenic bridges within the uterine cavity

8. Endometrial polyps with malignancy are most likely to occur in:
   a. Asymptomatic, premenopausal women
   b. Asymptomatic, postmenopausal women
   c. Symptomatic, premenopausal women
   d. Symptomatic, postmenopausal women
   e. None of the above

9. Which of the following is the embryologic cause of a septate uterus?
   a. Persistence of mesonephric duct
   b. Regression of the entire mesonephric duct
   c. In utero exposure to diethylstilbestrol
   d. Failed regression of the septum
   e. None of the above

10. A proposed mechanism of septate uterus formation involves:
    a. Increased levels of CBL-2 protein
    b. Increased levels of a BCL-2 protein
    c. Decreased levels of a BCL-2 protein
    d. Decreased levels of CBL-2 protein
    e. None of the above

Correct answers: 1) e.; 2) d.; 3) b.; 4) a.; 5) b.; 6) e.; 7) d.; 8) d.; 9) c.; 10) c.
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Saline Infusion Sonography


