TITLE: Benign uterine conditions: correlating MRI and US findings – retrospective

analysis of 33 patient**s**

Name: **Dr SK Gounden**

Supervisor: **Dr DP Ramaema**

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DECLARATION OF AUTHORSHIP

I, Dr Sharadini Karen Gounden, declare as follows:

1 .That the work described in this dissertation has not been submitted to UKZN or any other institution for the purposes of an academic qualification, whether by myself or any other party.

2. That my contribution to the project is as follows:

- Formulation of a hypothesis regarding the correlation of benign uterine conditions with Ultrasound (US) compared with Magnetic Resonance Imaging (MRI)
- Performing a literature review that would either support or refute the findings generated from the study
- Collection of data and data analysis
- Collation of results and formulation of a conclusion based on the results
- Selection of most relevant and appropriate pictures pertinent to the study

3. That the contribution of others to the project are as follows:

Dr DP Ramaema (supervisor)

- Assistance and guidance of how to design a hypothesis
- Guidance with choosing an appropriate study population
- Most appropriate and efficient way to collate the data collected for analysis and comparison
- Statistical analysis
- Guidance with analysing, interpretation and communication of the data results

Prof B Sartorius- assistance with provisional statistical analysis

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To my supervisor, Dr DP Ramaema for her assistance with the study.

DEDICATION

To my family, my greatest treasure, for always believing in me and encouraging me to follow my dreams.

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CHAPTER 1

INTRODUCTION

Ultrasound (US) is the primary imaging modality of choice for gynaecological related abnormalities due to its affordability and good diagnostic accuracy particularly with the use of high resolution transvaginal ultrasonography (TVUS). Limitations however do exist, such as field of view restrictions, inherent patient related and operator dependent factors [1].

The use of Magnetic resonance imaging (MRI) in benign pelvic diseases is widely used in the developed countries [2-6]. Nationally, however, there have not been many studies done on the use of MRI in imaging of benign uterine conditions. MRI provides the most comprehensive imaging of the uterus in comparison to other imaging modalities [2]. It allows for good characterization of tissues, high contrast resolution, pre- and post-procedural evaluation as well as allowing for multiplanar reconstruction without the risks of ionizing radiation [1-3]. Furthermore there is less blurring from motion artifact from the chest and upper abdomen, and technological improvements in system hardware have resulted in shorter imaging times [7]. MRI has good delineation of perivascular fat planes and differentiates well between fluid, protein and haemorrhage on T1 weighted imaging. T2 weighted imaging allows for assessment of the uterine zonal anatomy, the cervical canal and vagina [7]. Use of local pelvic phased array coils also result in better resolution and improved signal to noise ratio [3, 8]. The pelvic phase array coils are however more expensive and not generally available at all institutions. MRI itself has much greater cost implications in comparison with ultrasound imaging and is valuable in cases where ultrasound is non-diagnostic or equivocal [1, 3].

The purpose of our study was to identify the spectrum of benign uterine conditions of both MRI and US, and to highlight the accuracy and limitations of the different imaging modalities (US and MRI) as seen at our institution. Further, its purpose was to provide a guide to the clinician of the initial investigation of choice and importantly, when to proceed to further imaging with regard to benign uterine pathology.

Critical literature review

Amongst the benign uterine conditions, fibroid tumours are the most common occurring in approximately 25% of females over the age of 35 years. The evidence has shown that they occur earlier and with a higher incidence in black females compared with white females [9, 10]. This section will review the benign uterine conditions and will further outline the purpose, advantages and disadvantages of MRI and US. The conditions can be categorized into three areas, namely: congenital anomalies of the uterus, benign diseases of the uterine corpus and infections/inflammatory conditions.

Congenital anomalies of the uterus

Congenital anomalies of the uterus can present in a number of ways, with the following being reviewed for the purposes of this study: mullerian agenesis and hypoplasia, unicornuate uterus , uterine didelphys, bicornuate uterus, septate uterus, arcuate uterus, diethylstilbestrol uterus. Each of these will be discussed with respect to their development, appearance, and how they are diagnosed by both MRI and US.

Congenital uterine anomalies arise due to partial or complete failure of fusion of the mullerian ducts [2] which normally occurs between the 6th- 11th gestational week [11]. Mullerian duct anomalies do not affect the external genitalia or the ovaries as these arise from the sinovaginal bud and primitive yolk sac respectively [11]. They are found in approximately 1% of women of reproductive age [4] and approximately 25% of these cases may lead to obstetric related complications [1]. 3% of cases of infertility are thought to be attributed to mullerian duct anomalies [3] while 15% of women with recurrent miscarriages are found to have these mullerian duct anomalies [11]. Hysterosalpingography (HSG) and US evaluation may initially suggest the presence of an anomaly [4], however the use of MRI is almost entirely 100% accurate with the characterization of these anomalies[2], and is now the imaging modality of choice for evaluation of mullerian duct anomalies. Accurately differentiating these anomalies is also important as it serves to guide appropriate management [1].

There is an association with mullerian duct anomalies and renal/urinary tract anomalies. The prevalence of these associated renal anomalies is 30-50% [11].

The mullerian anomalies are divided into 3 categories [3]:

- duct agenesis and hypoplasia

- defects of vertical fusion of the ducts with the ascending urogenital sinus

- defects of lateral duct fusion: may include uterine didelphys, septate uterus, and bicornuate uterus

a. Mullerian duct agenesis and hypoplasia

This is due to early development failure of the mullerian ducts [11] seen as either complete agenesis or hypoplasia of the uterus and upper two thirds of the vagina and account for approximately 10% of all uterine anomalies. In most instances the ovaries appear normal with resultant normal secondary sexual characteristic development, however patients lack the ability to reproduce. In some cases the endometrium remains functional within the hypoplastic uterus and patients may present with cyclical pelvic pain as well as primary amenorrhea due to haematometra [2].

On US a normal uterus may not be seen due to the varying anatomical positions of the uterus thus MRI is of benefit. Normal appearing ovaries are seen [11].

On MRI the following features are seen:

- Uterus- hypoplastic or absent, reduced to absent zonal anatomy in the hypoplastic uterus, diffuse low T2 signal [2, 4]

- Endometrial canal (hypoplastic uterus) - increased T2 signal, depending on the amount of obstruction of the endometrial canal, it may be may be expanded accordingly.

- Vagina- agenesis is noted, seen best in the axial plane with no normal vaginal zonal anatomy between the rectum and urethra[2]

One of the syndromes associated with uterine agenesis or hypoplasia is that of Mayer-Rokitansky- Kuster- Hauser syndrome which is a syndrome of failure of vaginal development. 90% of cases are associated with uterine agenesis and the remaining approximate 10% with uterine hypoplasia. The ovaries appear normal [3].

b. Unicornuate uterus

Unicornuate uterus is due to absence or hypoplasia of one of the two mullerian ducts, and accounts for approximately 20% of all uterine anomalies of which 40% have associated renal abnormalities (renal agenesis or a pelvic kidney), which are always ipsilateral to the rudimentary horn. [2, 4] . The abnormal uterine horn is absent in a third of cases and under-developed in two thirds of cases [3]. Clinically, the presence or absence of a rudimentary horn is of significance for surgical reasons including preventing a possible pregnancy within the rudimentary horn as well as intervention to prevent obstruction in the rudimentary horn by retrograde menses [2].

There are 4 possible subtypes of this anomaly [11]:

- Absent rudimentary horn

- Presence of a rudimentary horn with absent uterine cavity

- Presence of a rudimentary horn with a communicating cavity to the normal side

- Presence of a rudimentary horn with a non-communicating cavity.

US: The uterus appears small and curved off the midline (banana shaped uterine configuration). The rudimentary horn is difficult to visualize and may be mistaken for a pelvic mass or the cervix [11].

MRI: the following features can be seen [2-4]:

- Uterus- also seen as elongated and curved away from the midline with a reduced uterine volume. The endometrium has a low T2 signal if no cavity is present (with loss of zonal anatomy) within the rudimentary horn (endometrium absent). There will be a high T2 signal if the rudimentary horn contains a cavity (endometrium present) with zonal anatomy maintained to a degree [2, 3].

c. Uterine didelphys

Uterine didelphys results from almost complete failure of midline fusion of the 2 mullerian ducts with no communication between the endometrial canals. Each duct develops completely and results in duplication of the uterine horns, cervix and in 75% of patients the proximal vagina. It is essential to identify the fundal cleft on a coronal image to be able to identify the type of anomaly present [11].

Uterine didelphys accounts for approximately 5-7% of the uterine anomalies. In 75% of cases of this anomaly, a vertical vaginal septum is associated. In some cases a horizontal vaginal septum may also be found. Patients may present with ipsilateral haematometrocolpos [2, 11].

On US and MRI, two divergent horns with the presence of two endometrial cavities and two cervices are seen [11].

US: Presence of the vaginal septum is difficult to visualize on ultrasound and differentiating between uterine didelphys and a bicornuate bicollis uterus becomes challenging [11].

MRI: Zonal anatomy of the uterus is preserved [2]. A fundal cleft >1cm is diagnostic of a fusion anomaly (uterine didelphys and bicornuate uterus) versus a reabsorption anomaly (septate and arcuate uterus). In the case of a unilateral vaginal septum and associated haematometrocolpos, high signal intensity from contained blood products will be demonstrated [11].

d. Bicornuate uterus

This is due to incomplete fusion of the uterine horns with an associated fundal cleft that may be partial or complete (extending to the internal os) and may be identified on MRI and US [11]. One or two cervices may be present. The bicornuate uterus is found in approximately 10% of uterine anomalies and in 25% of these cases a vertical vaginal septum may be present. These patients face an increased threat of spontaneous miscarriage and premature labour [2].
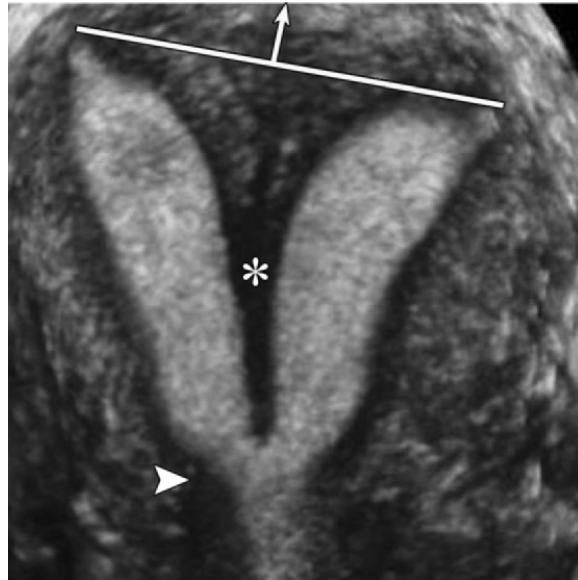
US: Bicornuate uterus is best assessed in the secretory phase of the menstrual cycle as the endometrium demonstrates an increased echogenicity and the divergent uterine horns and separation of the cavity are best seen [11].

MRI: Presents with an incompletely fused divergent uterine horns and an associated fundal cleft of >1cm depth similar to uterine didelphys. A muscular or fibrous septum is seen. When the septum extends to the cervix it is termed bicollis and when it does not reach the external cervical os it is termed unicollis. Zonal anatomy of the uterine horns are preserved. In cases where a longitudinal vaginal septum is present, it is difficult to differentiate between a bicornuate bicollis uterus and that of uterine didelphys. The presence of the duplicated cervix in the bicornuate bicollis uterus demonstrates a feature termed "owl eyes" and is diagnostic in the absence of vaginal duplication [2, 4, 11].

e. Septate uterus

The septate uterus is formed after fusion of the mullerian ducts and is due to incomplete resorption of the medial fibromuscular septum between the mullerian ducts [2, 3]. A complete septum is one which extends to external cervical os and may even extend to the upper vagina [4]. It is the commonest uterine anomaly accounting for approximately 55% of cases and is also strongly associated with infertility [2, 3].

US: Features to suggest a septate uterus include myometrial interruption by the presence of a septum at the uterine fundus. The fibrous septum is of a lower echogenicity compared with the myometrium. US cannot accurately diagnose a septate uterus, however 3D US may be of more benefit than 2D US in suggesting this anomaly. In order to differentiate between a septate and a bicornuate uterus uterus a line is drawn between the uterine ostia and the apex of the external uterine fundal contour is assessed- if the apex is >5mm above the interostial line it represents a septate uterus, however if the apex is <5mm above or below the interostial line it may represent a bicornuate or didelphys uterus [11].

Coronal 3D US image of uterus. The white line represents the interostial line (between the tubal ostia). If the apex of the fundal contour is >5mm above this line it is in keeping with a septate uterus [11].

MRI: The uterus is of normal size [11]. The external contour of the fundus of the uterus may be concave, convex or flat. The associated fundal cleft measures <1cm depth and one or two cervices may be present. The fundal segment of the cleft demonstrates the same intensity as the myometrium, while the inferior segment of the septum is of a low signal intensity [2]. <75 degree angle between the uterine horns is thought to represent a septate uterus versus a bicornuate uterus [11].

f. Arcuate uterus

This anomaly or variant results in a mild, smooth, concave indentation at the uterine fundus and is due to almost complete reabsorption of the uterovaginal septum. The uterus is normal in size with the external uterine contour preserved [11].

US: On US the uterine zonal anatomy is also preserved while there is an inward contour deformity noted resulting in the fundal indentation [2, 4, 11].

On MRI there is a prominence of soft tissue in the region of the fundus which has the same T2 signal intensity to that of the myometrium with no fibrous tissue noted [11].

g. Diethylstilbestrol uterus

This occurs in women exposed to diethylstilbestrol prenatally and results in a hypoplastic T-shaped uterus due to narrowing of the horizontal and vertical segments of the endometrial cavity. The lower uterine segment also appears widened. Indentations on the endometrium are noted which are attributed to the presence of constriction bands [2, 11].

US: 2 Dimensional (2D) ultrasound does not aid in diagnosis as US features are non-specific [11].

MRI: demonstrates the constriction band which is a focal area of thickening of the junctional uterine zones [11].

Benign diseases of the uterine corpus

There are a number of benign diseases of the uterine corpus that require assessment and for the purposes of this study, the following will be reviewed: endometrial polyps, endometrial hyperplasia, endometrial synechiae, uterine peristalsis,

leiomyomas (fibroids), adenomyosis and endometriosis. The anatomical features of each will be described as well as how it is detected radiologically by US and MRI.

a. Endometrial polyps

These are focal outgrowths of endometrial hyperplasia occurring in approximately 10% of women. They are found in 3 different types namely atrophic, hyperplastic and functional polyps and may be sessile or pedunculated. Polyps are commonly found in the uterine fundus or cornua.   Malignant change has been noted in approximately 0.5% of these endometrial polyps [2].

US: used for initially detecting and characterizing endometrial polyps. They appear as either non-specific endometrial thickening or as a focal echogenic mass within the endometrium.

MRI: used in cases when US is non-diagnostic, in equivocal cases or when sampling or biopsy of the lesion is difficult (e.g. due to increased habitus or cervical stenosis). On T2 weighted sequences polyps may be hypo- or iso-intense to endometrium and on T1weighted images appear isointense to endometrium. Polyps demonstrate a non-specific pattern of enhancement post gadolinium and MRI features of endometrial polyps and endometrial carcinoma may demonstrate some overlap. Malignancy may be suggested by the presence of metastases or myometrial invasion. Studies have shown that MRI has a sensitivity of 79%, specificity of 89% and an accuracy of 86% in its ability to differentiate a benign polyp from malignancy[7]. Endometrial polyps also should be distinguished from submucosal fibroids which demonstrate a lower signal intensity on T2 weighted images compared with endometrial polyps [2, 12].

b. *Endometrial hyperplasia*

Endometrial hyperplasia is due to increased focal or diffuse proliferation of the endometrial glands, and is often attributed to unopposed oestrogen stimulation. It is categorized in two ways: with or without cellular atypia. In 25% of cases of cellular atypia, endometrial carcinoma may be found or will develop. This is in comparison to 2 % of patients without cellular atypia who carry a risk of endometrial carcinoma [2, 12]. As with endometrial polyps, malignancy can only be diagnosed based on the presence of metastases or myometrial invasion [2]. It is difficult on imaging to distinguish diffuse polyps from endometrial hyperplasia [2].

TVUS is one of the studies used to characterize endometrial hyperplasia however the findings are non- specific and cannot be differentiated from endometrial carcinoma . Endometrial biopsy is however diagnostic [2, 4, 12].

MRI: used in cases where TVUS is non- diagnostic or when endometrial sampling is unsuccessful in yielding a result. The endometrium appears diffusely widened and the endometrium that is hyperplastic appears iso- or hypo-intense on T2 weighted images relative to normal endometrium. There is an increased gland- to- stroma ratio and cystically dilated glands within the endometrium appear as high T2 signal intensity foci.

Post intravenous contrast the hyperplastic endometrium will demonstrate less enhancement to that of the normal myometrium [2, 4, 12].

c. Endometrial synechiae

These are bridging adhesions across the myometrium of which Ascherman Syndrome is an example, which results in partial or complete obliteration of the uterine cavity. It forms in response to infection/inflammation or trauma [2].

US: US is not reliable in diagnosing endometrial synechiae. Hysterosalpingogram (HSG) and hysteroscopy are primarily used for diagnosis.

MRI: the endometrial synechiae have a low signal intensity on T2 weighted images and appear as bands across the endometrial canal. Post-contrast gadolinium enhanced images show enhancement of the synechiae. MRI also plays a role in determining the underlying aetiology and is also useful in assessing the uterus proximal to the adhesions not visualized on hysteroscopy or seen on HSG [2].

d. Uterine peristalsis

Uterine peristalsis is the transient relaxation and contraction of the uterus which may be seen during pregnancy on TVUS and may be subject to hormonal changes usually seen a week prior to menstruation [2].

MRI: Ultrafast MRI sequences allow uterine contractions to be imaged in a non- gravid patient. It appears as a transient hypointense T2 weigthed signal with distortion of the endometrium and myometrium with no distortion of the external uterine contour. Due to their transient nature they are differentiated from adenomyosis and leiomyoma [2].

e. Leiomyomas (fibroids)

These are benign neoplasms comprised mainly of smooth muscle cells and over time may undergo degeneration as they outgrow their arterial supply. They are intramural, subserosal or submucosal in location and may even occur in the cervix, broad ligament or in areas outside the female genital tract although this is uncommon. They occur in

approximately 25% of females over the age of 35 years and <2% may undergo sarcomatous degeneration[2].

TVUS: can accurately detect leiomyomas. Ultrasound is, however, of reduced diagnostic value to detect these leiomyomas in obese patients where image quality is suboptimal. It is further of limited value in cases of very large fibroids where the anatomy becomes distorted. Calcifications and associated shadowing may also obscure the imaging of adjacent structures.

MRI: can accurately characterize and assess these lesions, particularly when there are a greater number of fibroids present. MRI is of further benefit prior to and following medical or minimally invasive therapy including uterine artery embolization, to compare the changes in the lesions. Pre-embolisation magnetic resonance angiographic imaging is also required to assess vascularity including collateral supply from the gonadal vessels to the fibroids that may also require embolisation. On MRI the uterus appears enlarged and abnormal in contour. Lesions appear hypointense on T2 weighted images in comparison with the myometrium and sharply marginated. With intramural or subserosal fibroids a high intensity rim may be seen. Calcifications may also be noted within the fibroid- on US the associated posterior acoustic shadowing would obscure adjacent tissues, however on MRI the calcifications would appear as signal voids without the obscuration of surrounding tissues. Calcifications are best seen on gradient- echo T1 weighted images. Post contrast images show a variable appearance of the leiomyomas. They show decreased enhancement once they undergo degeneration. The characteristics also may vary depending on the type of degeneration it undergoes, however only haemorrhagic degeneration can be determined on MRI. Leiomyosarcomas have a similar appearance to that of a degenerated fibroid. They occur rarely and are difficult to consider or diagnose without a history of metastatic disease [1-3, 8].

Newer techniques include that of MRI-guided focused US used to treat fibroids that are symptomatic.

US waves are focused on these fibroids resulting in thermal ablation while monitoring on MRI is perfomed. At 6 month follow-up, this technique of MRI- guided focused US has shown to provide improved symptoms [2].

f. Adenomyosis

Adenomyosis is characterized by the presence of heterotopic glandular and stromal tissue within the myometrium and may present in a focal pattern (usually the posterior uterine wall) or diffusely. Secondary overgrowth of the musculature in the region surrounding the endometrial glands is noted resulting in a globular shaped uterus. The presence of adenomyosis is noted in 19-62% of hysterectomy specimens. 70-80 % of cases are those of parous women aged 40-50 years [2, 8].

US: It is not well seen on TVUS.

MRI: is accurate in definitive diagnosis including that of adenomyomas (focal adenomyosis) [1, 2], as well in treatment monitoring. One of the criteria used to diagnose adenomyosis is the width of the junctional zone and T2 weighted imaging sequences are best used to delineate the uterine zonal anatomy.

Adenomyosis is seen as focal or diffuse widening of the junctional zone or as a hypointense myometrial mass. Post- contrast images do not assist in diagnosing adenomyosis [2]. A "swiss cheese" appearance suggesting dilated endometrial glands within the myometrium together with perfusion abnormalities may be seen on early phase images to suggest adenomyosis [12]. Newer conservative uterine artery embolization therapy as well as endometrial ablation may be performed, and MRI may be useful to evaluate response post-intervention [1].

g. Endometriosis

Endometriosis is the presence of functional endometrial glands and stroma, in an ectopic location i.e. outside the uterine cavity [1], with a response to cyclical hormonal stimulation [8]. The most common site for implantation is along the uterine serosal surface and along the ovaries. It may also occur at the scar site post operatively from previous uterine surgeries. The endometrial deposits can, however, occur along any peritoneal surface. Rarely, endometrial deposits may even be found within the lungs or central nervous system.

There are two forms of endometriosis- a diffuse form with scattered implants and a focal form with formation of endometriomas or "chocolate cysts" [8].

MRI: is advantageous in that it is able to identify deposits that are obscured by dense adhesions at laparoscopy, which is the gold standard for diagnosing endometriosis. The appearance of endometriomas on MRI is dependent on the stage of presentation as well as the age of blood products contained within. They are generally T1 hyperintense and of T2 low- intermediate signal intensity. "T2 shading" may be seen, and this is due to repeat haemorrhage at varying time intervals attributed to methaemoglobin, protein and iron [1]. Endometriomas display a fibrous capsule which is seen as a low signal intensity peripheral rim [8].

Infections/inflammatory conditions

Two infections/inflammatory conditions will be reviewed, endometritis and tuberculous pelvic inflammatory disease (PID). Each condition will be described in terms of how it manifests, and its detection using US and MRI will be reviewed.

a. *Endometritis*

This refers to infection or inflammation of the uterus. A majority of cases occur following caesarean section while a few cases occur post normal vaginal delivery. It may also occur associated with PID with endometrial involvement as well as post- instrumentation.

US: Initial scan may appear normal, however as the disease progresses the endometrium may appear thickened and heterogenous with the prescence of air and/or fluid within a thickened endometrial cavity. Uterus appears mildly enlarged with increased hypoechogenicity and poorly defined uterine margins.

MRI: the uterus may also appear bulky or enlarged with increased signal intensity on T2 weighted imaging. On T1 weighted gadolinium enhanced images enhancement of the entire uterus may be seen [13-15].

b. Tuberculous pelvic inflammatory disease

Tuberculosis (TB) of the genital tract occurs in approximately 1-3% of patients with TB. Spread occurs either haematogenously from an extragential location, via lymphatics or from the peritoneal cavity. It primarily affects the fallopian tubes however approximately half of the cases spread to the endometrium. In a majority of cases the uterine cavity appears normal however may contain synechiae and may appear irregular, shrunken or contain an irregular filling defect. Scarring may also result in formation of a T-shaped uterine cavity, complete obliteration of the uterine cavity or in cases with unilateral scarring the impression of a unicornuate uterus termed the "pseudounicornuate" uterus. These features described above are not specific for endometrial TB however it is suggested in cases with no history of previous curettage or surgical termination of pregnancy [16, 17].

Methods

Modalities: magnetic resonance imaging and ultrasound

Both magnetic resonance imaging (MRI) and ultrasound (US) may be used to evaluate benign uterine conditions particularly that of mullerian duct anomalies [11]. Previous methods included hysteroscopy or hysterosalpingogram to assess the uterine cavity and laparoscopy to assess the fundus [18]. The MRI and US technologies will be described as well as the advantages and disadvantages in diagnosing uterine conditions in female patients (Table 1: Advantages of MRI and US).

a. *Magnetic Resonance Imaging*

Magnetic resonance scanners make use of magnetic fields and the magnetic resonance properties of the proton which are abundant in tissues. The patient is placed within the magnetic field and radiowaves are generated by coils placed around the patient. Radiowaves are absorbed by the protons and energy is re-emited depending on the local magnetic properties of the surrounding tissue. These are again detected by coils surrounding the patient. Signal localization requires magnetic field gradients - along the gradient a unique magnetic field strength produces a specific lamor frequency corresponding to each location. The frequency of the returning radiowaves helps determine the position of each signal from the patient. A set of tomographic slices is produced. Different tissues (e.g. gray matter, white matter and fat) demonstrate different local magnetic properties thus contrast between tissues is achieved. [19]

MRI Equipment used:

Siemens 1.5 T strength magnet with use of a phased array surface coil [2].

MRI technique used for obtaining images at time of investigation:

The patient's bladder must be empty prior to the study [2]. Ideally the patient should be nil per os 6 hours prior to the study to reduce motion artifact from peristalsis. If not possible, anti- peristaltic medication may be administered [7].

The best imaging of the female pelvis in MRI particularly that of the three uterine zones including the endometrium, junctional zone and myometrium, is

with the use of T2 weighted sequences with planar reconstruction. The endometrium has a high signal intensity, the junctional zone has a low signal intensity and the myometrium an intermediate signal intensity on T2 weighted images [4]. On T1 weighted images, differentiation between fat and soft tissues is useful [8] however the uterine zones are not clearly distinct [3] and are also less clearly distinguished on gadolinium post- contrast images. The serosa surrounding the myometrium, if seen, may be subject to chemical shift artifact [2].

The MRI sequences employed for pelvic imaging typically use T1 and T2 weighted sequences. Axial T1 weighted images are useful in assessing the uterine contour, bone marrow as well as lymphadenopathy. T2 weighted sequences using multiplanar reconstruction are performed with one plane generally demonstrating the short and long axis orientation of the uterus well. Imaging of suspected congenital uterine anomalies begins with the T2 weighted sagittal images to determine the longitudinal axis following which images are taken parallel to this to adequately assess the uterine contour. Axial T1W images with fat suppression are also employed to evaluate for blood products as well as to differentiate lesions that contain fat or protein. Post- contrast T1 images are useful in evaluating for features of necrosis within the uterine fibroids [3].In the evaluation of benign conditions fast breath- hold sequences can be used even though this may decrease the resolution to a small degree. Further optional images include the Diffusion Weighted Imaging (DWI) and Attenuation Diffusion Coefficient (ADC) measurement which is used to monitor if satisfactory results have been obtained post procedures such as uterine artery embolization [4].

The MRI sequences employed are as follows:
- 3 plane gradient-echo scout views of the pelvis
- T2W single-shot fast spin echo (SSFSE):

    Axial sequence of the pelvis (showing the uterine orientation)
    Coronal sequence (assess for renal abnormalities)

- Fast spin echo (FSE) T2W sequences in the sagittal plane.

- Gadolinium enhanced T1W sequence in the sagittal plane.

- 3D fat saturation T2W* - thin section volumetric acquisition allows for multiplanar reformatting. This includes coronal images in the uterine plane.
- Fat saturated T1W volume interpolated GRE- axial plane allows for assessment and characterisation of the uterus [2, 3, 18]

Two further sequences are employed when mullerian duct anomalies are suspected;

- FSE T2W sequence parallel to the long axis of the uterus which is a true coronal uterine view to demonstrate the external contour of the uterus.
- The second sequence employed is either the gradient echo or SSFSE T2W sequence to assess the retroperitoneum for any commonly associated urinary tract anomalies [2].

Locally, at Inkosi Albert Luthuli Central Hospital (IALCH), the following technique for pelvic MRI of benign uterine conditions is used:

- A body coil is used.
- Pre-contrast, T1 weighted axial plane images, T2 weighted axial, coronal and sagittal plane images are taken.
- Post-contrast T1 weighted fat saturated axial, coronal and sagittal plane images are performed.

b. Ultrasound

US describes the propagation of sound waves (mechanical energy) in a medium. Transducers are used to generate sound pulses as well as detect returning echoes which result in encoding of a gray-scale value to create a tomographic image of tissues. A 2D ultrasound image is formed by sweeping an ultrasound beam over an area of interest and displaying echo signals through a specific echo display mode for 2D gray-scale imaging known as B – mode. With 2D ultrasound the image is progressively formed as the beam sweeps through the area of interest. With 3D ultrasound imaging, sound waves are propagated at different angles and the returning echoes are reconstructed into a 3D

volume from a number of different individual B – mode scans or 2D images of a volume of tissue [19].

US   Equipment   used:
Siemens Accuson S2000

US technique that was used for obtaining images at time of investigation:

A high frequency intracavitatory transducer probe (10-12 MHz) for transvaginal ultrasonography (TVUS) is used as well as the curvilinear transabdominal probe (2-5 MHz)[18].

A standardized technique known for 3 dimensional US known as the Z technique is described by the American institute of ultrasound in medicine (AIUM) in the 2013 Journal of ultrasound in medicine to improve evaluation   of the uterus and thus improve diagnostic ability. The technique is performed as follows [20]:

- Reference/rotational point is placed at the midlevel of the endometrial stripe in the sagittal plane
- Z rotation is used to align the long axis of the endometrial stripe along the horizontal axis in the sagittal plane of the uterus
- The reference/rotational point is then placed at the midlevel of the endometrial stripe in the transverse plane
- Z rotation then aligned to the endometrial stripe with the horizontal axis in the transverse plane of the uterus. Midcoronal plane of the uterus will then be displayed- Z rotation applied to display the midcoronal plane in the traditional orientation [20]

Locally, at IALCH, the transabdominal and endocavitatory transvaginal ultrasound probe are used with similar frequencies as above.

Use of 2D TVUS has shown to be highly sensitive (90-92%) as a screening investigation for uterine anomalies, however the ability to differentiate the various subtypes is user dependent [20]. The advent of 3D ultrasound allows for improved delineation of the external uterine contour including the coronal plane showing the superior

endometrial and serosal region of the uterine fundus [20]. Diagnostic accuracy of 3D ultrasound is therefore comparable to that of MRI or combined hysteroscopy/ HSG and laparoscopy. It is however still not available at all centres [20] and MRI is still regarded as the imaging modality of choice for evaluation of the mullerian duct anomaly subtypes, depicting both external uterine contour as well as the internal uterine cavity [11]. This greatly reduces the need for invasive testing as was previously employed with comparable accuracy [20]. MRI is particularly of benefit in young or adolescent patients with an intact hymen in which transvaginal approach is not ideal, or in cases with distortion of the uterus secondary to large fibroids, particularly those at the fundus [20, 21].

In centres with the availability of 3D ultrasonography, it may provide a valid alternative imaging option to that of MRI due to the low associated cost factors. It also showed good concordance in studies to MRI in the diagnosis of uterine anomalies with a kappa index of 0.880 (95% CI, 0.769–0.993) [18]. Discrepancies obtained were those involving the lower aspect of the uterus involving the cervix where ultrasound is essential. MRI is able to discriminate a septum from the cervical myometrium as well as the vaginal wall from vaginal septae by the differing signal intensities. This discrimination cannot however be made on 2D or 3D ultrasound and it is thus advised that if 3D ultrasound is performed it should be done in conjunction with a pelvic examination (bimanual and speculum examination) for cervical assessment [18].

3D ultrasound provides the following advantages [18]:

- Calculation of septum length and thickness

- Calculation of intra-uterine cavity volume

- Assessment of uterine vascularity

It is proposed that in centres with the availability of 3D ultrasound facilities, 3D ultrasound in conjunction with pelvic examinations be performed, and in cases that are equivocal should proceed with MRI [18]. 3D US provides improved imaging compared with 2D US with improved evaluation of the uterine cavity [11, 12]

(An X indicates where the criteria apply)

	Advantages	MRI	US
1	Wider availability		X [11]
2	Fast imaging modality		X [11]
3	No risk of ionizing radiation	X [11]	X [11]
4	Low expense		X [11]
5	Able to assess renal tract anomalies	X [11]	X [11]
6	Able to assess skeletal tract anomalies	X [11]	
7	Non- invasive	X [20]	
8	Safe in pregnant patients during organogenesis	X [1]	X [1]
9	Non-user dependent	X [22]	
10	Able to outline and assess uterine zonal anatomy	X [2]	

Table 1: Advantages of MRI and US

Research question

1. The purpose of the study was to describe the spectrum of ultrasound and magnetic resonance imaging appearances of benign uterine conditions based on the literature.

2. To compare the diagnostic accuracy of magnetic resonance imaging and ultrasonography, at our institution, in the evaluation of benign uterine conditions.

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CHAPTER 2

**Benign uterine conditions: correlating MRI and US findings -
retrospective analysis of 33 patients**

*Prepared according to the Instructions for Authors of the South African Journal
of Radiology*

Abstract

Aim: The purpose of our study was to compare the diagnostic accuracy of Magnetic Resonance Imaging and ultrasound in evaluating benign uterine conditions.

Method: We analysed records of patients who have had pelvic MRI for benign uterine conditions during the period of January 2011- June 2014. Of the initial 46 patients identified who had both pelvic US and MRI performed, only 33 were analysed following the exclusion of those who did not have surgical or histological results. Patients were categorised into 4 groups: congenital, mass, infection and other. Diagnostic accuracy was assessed against the gold standard of surgery and/or histology.

Results: The age range of patients was 8 - 83 years. Overall 60.6% of the cases were congenital, 21.2% had mass lesions, 6.1% had infective causes and 12.1% were other aetiologies. Of the 33 cases, MRI revealed a sensitivity and specificity of 68.9% and 100% respectively (P< 0.0001), with US yielding a sensitivity of 66% and sensitivity of 55% (P= 0.8048) at a cut-off value of >4.

Conclusion: The MRI demonstrated an overall improved sensitivity and specificity to US when compared to the gold standard, and was particularly beneficial in diagnosing congenital anomalies. The study concludes that US should still be used as the primary means of assessment for benign uterine conditions, especially in resource poor communities, with MRI reserved for cases where it is equivocal or where an intervention is planned.

Keywords: female, magnetic resonance imaging, pelvis, retrospective analysis, uterine diseases, ultrasound

Introduction

Ultrasound (US) is the primary imaging modality of choice for gynaecological related abnormalities, due to its affordability and good diagnostic accuracy, particularly with the use of high resolution transvaginal ultrasonography (TVUS). However, limitations do exist, such as field of view restrictions, inherent patient related and operator dependent factors [1].

The use of Magnetic Resonance Imaging (MRI) in benign pelvic diseases is widely used in developed countries [2-6], and provides the most comprehensive imaging of the uterus in comparison to other imaging modalities [2]. It allows for good characterization of tissues, high contrast resolution, pre- and post-procedural evaluation and multiplanar reconstruction without the risks of ionizing radiation [1-3]. Furthermore, there is less blurring from motion artifact from the chest and upper abdomen, and technological improvements in the system hardware have resulted in shorter imaging times. MRI has good delineation of perivascular fat planes and differentiates well between fluid, protein and haemorrhage on T1 weighted imaging [7]. T2 weighted imaging allows the uterine zonal anatomy, the cervical canal and vagina to be assessed [7]. Use of local pelvic phased array coils also result in better resolution as well as improved signal to noise ratio [3, 8]. The pelvic phase array coils are however more expensive and not generally available at all institutions. MRI has much greater cost implications in comparison with ultrasound imaging, but is valuable in cases where ultrasound is non-diagnostic or unequivocal [1, 3].

Amongst the benign uterine conditions, fibroid tumours are the most common, occurring in approximately 25% of females over the age of 35 years [9, 10]. Further benign uterine conditions include congenital anomalies (mullerian duct agenesis and hypoplasia, unicornuate uterus, uterine didelphys, bicornuate uterus, septate uterus, arcuate uterus, diethylstilbestrol uterus), benign diseases of the uterine corpus (endometrial polyps, endometrial hyperplasia, endometrial synechiae, uterine peristalsis, leiomyomas, adenomyosis) as well as infective and inflammatory conditions, such as endometritis and pelvic inflammatory disease [2, 11]. The purpose of our study was to

idenitfy the spectrum of benign uterine conditions of both MRI and US, and to further compare their diagnostic accuracy.

Material and methods

Patients

All patients that underwent US and pelvic MRI at Inkosi Albert Luthuli Central Hospital (IALCH) during the 3.5year time period from January 2011- July 2014, were retrospectively analysed with a purposive sampling strategy used.

Inclusion criteria included female patients of any age group who had undergone a pelvic MRI for benign uterine pathology. Cases of benign uterine pathology on MRI who had a corresponding US findings were then further selected. This resulted in 33 patients with benign uterine conditions seen on pelvic MRI and US being included in the study. The cases were divided into 4 groups: 'mass lesions', 'congenital', 'infection/inflammatory' and 'other'. The images were reviewed by two radiologists in consensus. A comparison was drawn between each modality, US and MRI, with a gold standard method of diagnosis being histopathology or surgical findings (laparotomy or laparoscopy).

Exclusion criteria included patients with absent or incomplete ultrasound records and those with no histology or surgical findings. Parameters that were recorded include age, diagnosis, surgical and/or histological findings, uterine and endometrial thickness as well as the uterine size. Ethical approval was obtained from the institution review board Biomedical Research Ethics Committee (BREC: reference number BE 288/14).

MR imaging protocol

The MRI scans were performed on a 1.5T (Siemens, Erlangen, Germany) machine with the use of a body coil. The standard protocol used for the pelvic MRI imaging of the benign uterine conditions was as follows: pre-contrast T1 axial plane, T2 weighted axial, coronal and sagittal planes, post-contrast T1 weighted fat saturated axial, coronal and sagittal planes.

US scanning technique

All exams were performed by a single sonographer trained in obstetric and gynaecological scanning, for which the Siemens Accuson S2000 machine was used. The transabdominal 4 megahertz (MHz) US probe was employed in the majority of cases, and where needed, as in cases of suboptimal visualisation, a transvaginal 8 MHz probe was used.

Statistical analysis

Data was entered onto Excel spreadsheet and analysed using MedCalc statistical package. Summary statistics were used to analyse the demographics and the diagnoses. McNemar chi-square test was used to compare the performance of the two modalities. The ROC analysis was used to evaluate the sensitivity and specificity of each modality, with a P value of <0.05 being considered statistically significant. The Mann- Whitney test was employed to compare two sample means arising from the same population and to ascertain whether or not the two sample means are equal. In this study in particular, they were be used to compare MRI and US measurements of endometrial thickness and uterine size.

Results

Patient demographics

The 33 patients' ages range from 8-83 years old. The main finding of the patients imaged was that of congenital abnormalities (20 cases, 60.6%), while 7 cases (21.2%) were found to be mass lesions all of which were fibroid uteri. A further 2 cases (6.1%) were infective causes and 4 cases (12.1%) fell under the category of "other" aetiologies all of which were cases of endometrosis. The final case diagnoses are indicated in Table 1.

All cases of congenital anomalies imaged were age <35 years, the most common anomaly being an absent uterus (5 cases, 15.15%) (Figure 1); hypoplastic uterus (4 cases,12.12%); septate uterus (2 cases, 6.06%), (Figure 2); uterine didelphys (2 cases, 6.06%), (Figure 3); bilateral uterine horns (non-specified) (1 case, 3.03%) ,and haematometra secondary to absent/ hypoplastic vagina (3 cases, 9.09%) ; or a vaginal septum (3 cases, 9.09%), (Figure 4). MRI was accurate in diagnosing 19 of the 20 cases of congenital anomalies in comparison to US, which accurately diagnosed 14 of 22 cases, demonstrating that MRI is superior to US in diagnosing congenital uterine anomalies.

The most common presenting anomaly was that of hypoplastic, or absent uteri, which accounted for 45% of the congenital uterine anomalies. Fibroid uterus accounted for 21% of cases and was the commonest benign uterine condition for patients over the age of 35 years (Figure 5).

The 33 cases allowed a comparison with a gold standard (surgery or histopathology) in order to determine which cases had a correct imaging diagnosis. As per the McNemar test, of these confirmed cases, US yielded a correct diagnosis in 72.7% (24 of 33 cases), as illustrated in Figure 6a. Similarly, as per the McNemar test, of these confirmed cases, MRI yielded a correct diagnosis in 87.9% (29 of the 33 cases) (Figure 6b). Seven of the 29 MRI correct cases were incorrectly diagnosed on US, and two of the 24 correct US cases were incorrectly diagnosed on MRI (P value= 0.1797). Using the Chi-squared test, there was correct agreement between the MRI and US in 22 of the 33 cases.

The commonest indication for performing an MRI was to assess congenital abnormalities, of which 19 of the 20 cases were correctly diagnosed, but this was not statistically significant (p=01128) (Figure 7). Using the Mann-Whitney tests, there was no statistically significant difference in the MRI and US measurements of endometrial thickness (P = 0.6294) (Figure 8).

Similarly, using the Mann-Whitney tests, there was no statistically significant difference in the MRI and US measurements of uterine size (P= 0.5096), this being illustrated in the box plot below (Figure 9). Using the ROC analysis to compare the diagnostic accuracy of MRI and US, a cut-off value of >2 for the MRI yielded a 96.5% sensitivity and 25% specificity. Raising the cut-off value to >4 yielded 68.9% sensitivity and 100% specificity (Figure 10a), these findings being statistically significant (P< 0.0001). Using the same cut-off value of >4 for US, a sensitivity of 66% and specificity of 55% was obtained, but was not statistically significant (P= 0.8048) (Figure 10b).

Discussion

The main restriction to the use of MRI is the availability of equipment, and it is thought that an improvement in resources will result in wider use of pelvic MRI in the future [7]. Our study found that while MRI was superior to US in sensitivity (87.9% versus 72.7%), this was not statistically significant (P= 0.1797). There was agreement between the two modalities in 72% of cases, and the study therefore supports the use of US as a primary imaging modality.

In our study, all cases of congenital anomalies were in the <35 year age group, accounting for the majority of the cases (60.6 %). This correlates with the local clinical practice, in which most of the clinical indications were to further evaluate congenital abnormalities suggested after an ultrasound scan. The most commonly presenting uterine anomaly described by Wolfman and Ascher was the septate uterus, resulting in 55% of uterine anomalies [2]. However, this finding was not represented in our study, where the most common presenting anomaly was that of hypoplastic or absent uteri, which accounted for 45% of the congenital uterine anomalies. Studies have shown that MRI is almost 100% accurate in characterising these anomalies, as supported in the study by Wolfman and Ascher [2].

However, in studies by Baird and Okolo, fibroids were the commonest benign uterine condition [9, 10]. Fibroids accounted for 25% of cases in the over 35 year old adult group as outlined in a study by Wolfman [2]. This was similar to our study, in which fibroids accounted for 21% of cases.

Among the 'infections' group, only two cases were identified, namely TB and schistosomiasis. Both were suggested as positive on US, with only one case suggestive on the MRI of a suspected infective/inflammatory aetiology. As only two cases were included in the study, the accuracy of either modality is not possible to establish. The miscellaneous category included four cases of endometriosis, with an accuracy comparison also being restricted by the limited number of cases in this category, this being a limitation of the study.

There was no statistical difference in the endometrial thickness and uterine size between the two modalities as demonstrated in the box plot figures 9 and 10, demonstrating little

variation between the two modalities from the range, median, 25th and 75th percentile values. Findings with respect to the endometrial thickness are in contrast to the study by Mitchell et al. who showed that the endometrial thickness was significantly greater with US than MRI. The cause for this was unknown and the study advised further histological correlation to determine the cause for the discrepancy [12].

There were limitations to our study, including the MRI technique used in our institution being different from that mentioned in the literature [2, 3, 13]. Studies by Wolfman, Sydow and Bermejo recommend three plane gradient-echo scout views of the pelvis using a T2W single-shot fast spin echo (SSFSE) axial sequence of the pelvis to visualise the uterine orientation. The coronal sequence is recommended for renal abnormalities; fast spin echo (FSE) T2W sequences in the sagittal plane; gadolinium enhanced T1W sequence in the sagittal plane; 3D fat saturation T2W*-thin section volumetric acquisition allowing for multiplanar reformatting including coronal images in the uterine plane; and for fat saturated T1W volume interpolated Gradient Recalled Echo (GRE)- axial plane that allows for assessment and characterisation of the uterus [2, 3, 13]. To evaluate the mullerian duct anomalies, some studies recommend including the FSE T2W sequence parallel to the long axis of the uterus, which is a true coronal uterine view, to demonstrate the external contour of the uterus [2]. The second sequence employed is the gradient echo or SSFSE T2W sequence to assess the retroperitoneum for any commonly associated urinary tract anomalies [2].

Other limitations included performing the US by one competent sonographer, which may introduce operator dependent bias. The retrospective nature of the study contributed to some data missing, resulting in a small sample size.

Our study demonstrates that US findings have a high degree of correlation with those of the MRI, the latter demonstrating improved accuracy. However, US has many advantages, particularly regarding cost, time and ease of availability, and can be the primary imaging modality to assess benign uterine conditions, especially in resource poor communities such as in many South African health facilities. MRI can be

reserved for situations where ultrasound is non-diagnostic or when invasive therapy is to be performed [2]. In our clinical setting, access to MRI is very limited in the public sector, with further challenges including lack of funding to cover these specialized investigations. As such, there are often long waiting times for patients if and when they are able to obtain advanced imaging at a tertiary institute. The recommendation thus in our current environment would be to perform ultrasound as a first line investigation, and thereafter, pending the clinical query and ultrasound findings to proceed to MRI.

Disclosure

All authors declare that there are no conflicts of interest and have received no financial support or have any relationship with any company that has an interest in the subject matter or materials discussed in the manuscript.

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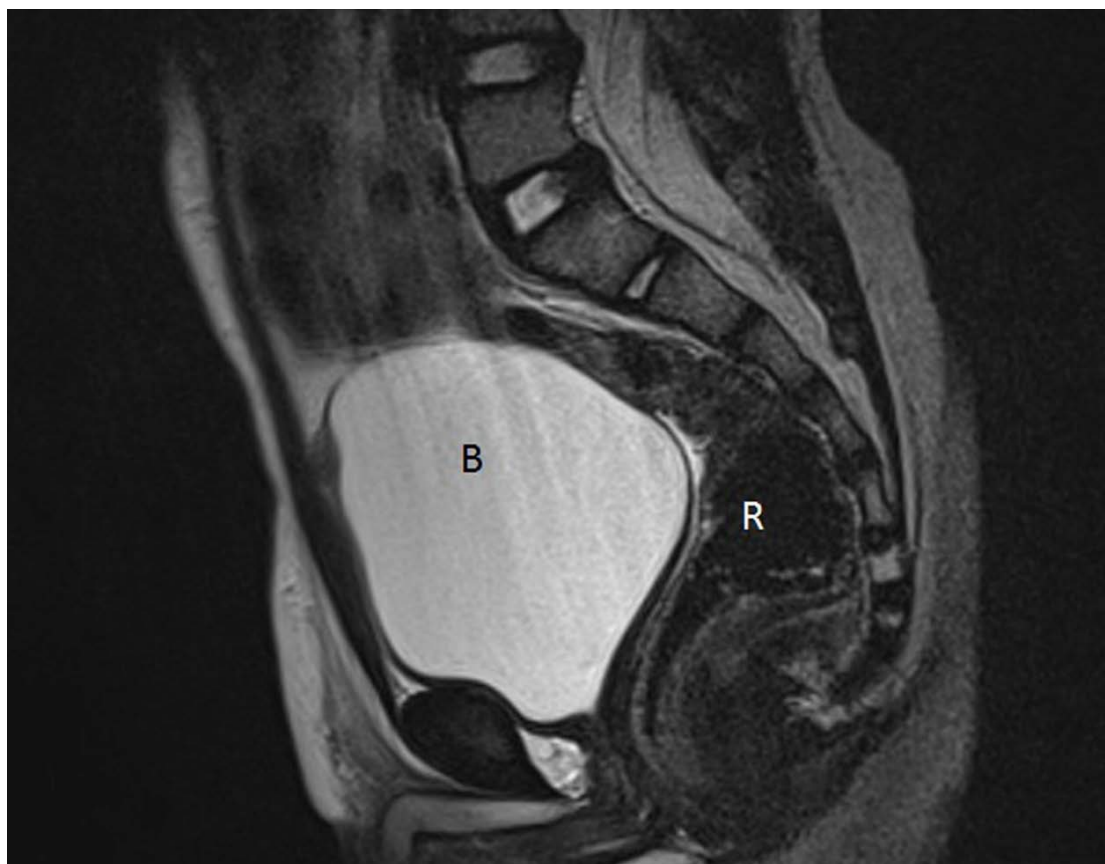
Figure legends

Figure 1: 6 year old female. Sagittal MRI demonstrating an absent uterus on T2 weighted imaging (TE 100, TR 4000) (B- bladder; R- rectum).
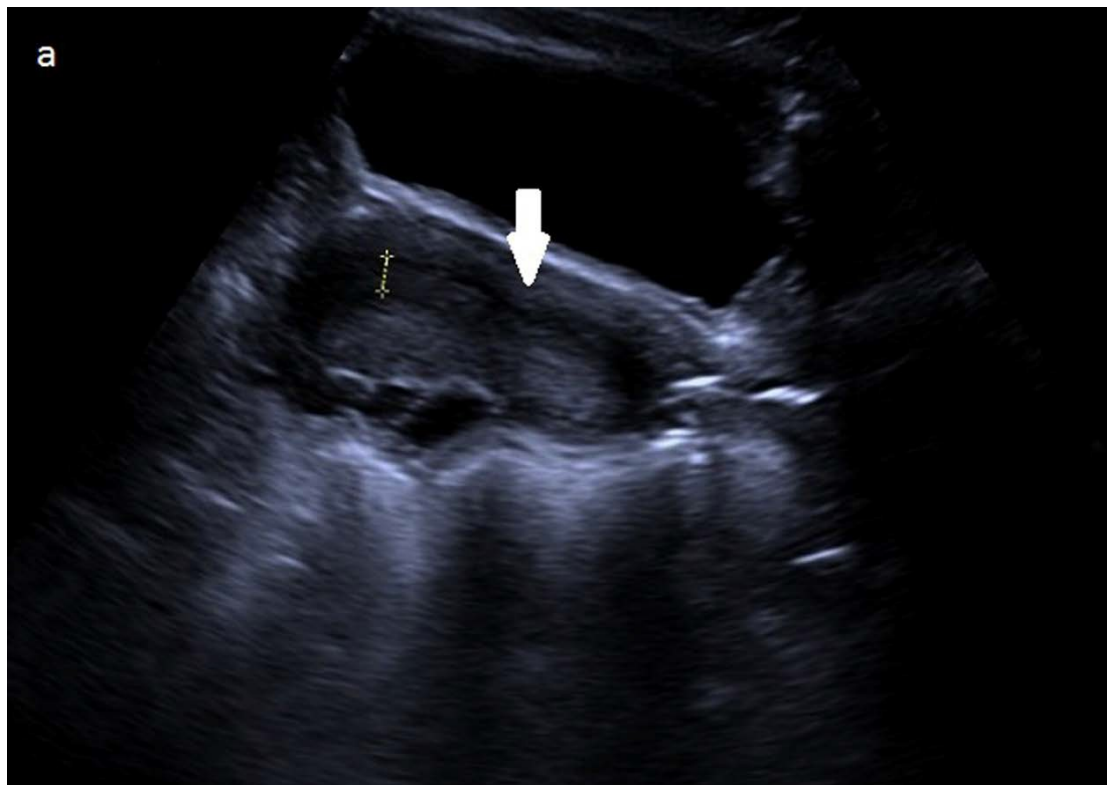
Figure 2: 30 year old female transabdominal ultrasound. (a) Transverse US image demonstrating a muscular septum within the uterine cavity.

Figure 2: 30 year old female. MRI T2 weighted (TE 100, TR 4000) (b) axial and (c) coronal images demonstrating a muscular septum within the uterine cavity (solid white arrow= muscular uterine septum).

Figure 3: (a) 31 year old female, transvaginal US image demonstrating bilateral uterine horns in a patient with uterine didelphys.
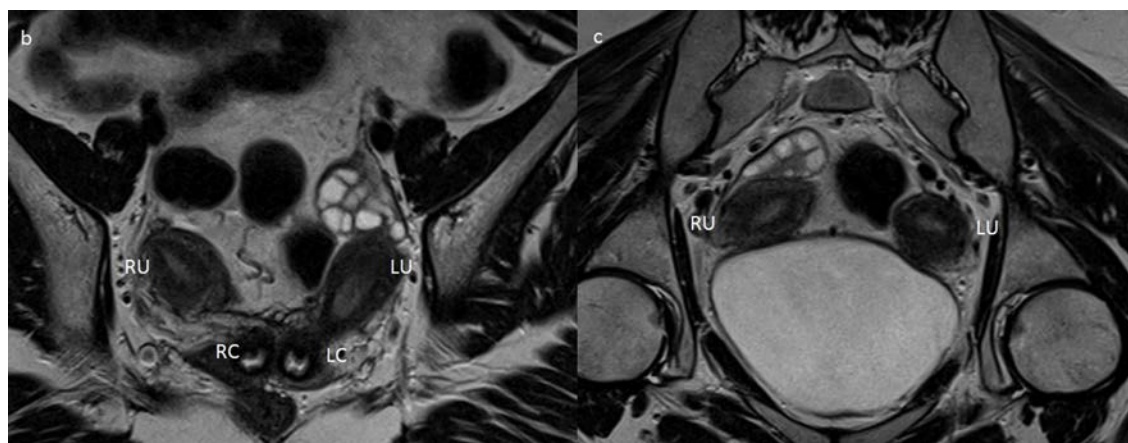
Figure 3: Corresponding MRI image of the same patient as in figure 3a demonstrating (b)

Axial and (c) coronal T2 weighted (TE 100, TR4000) images depicting uterine didelphys

(RU- right uterus, LU- left uterus, RC- right cervix, LC- left cervix).
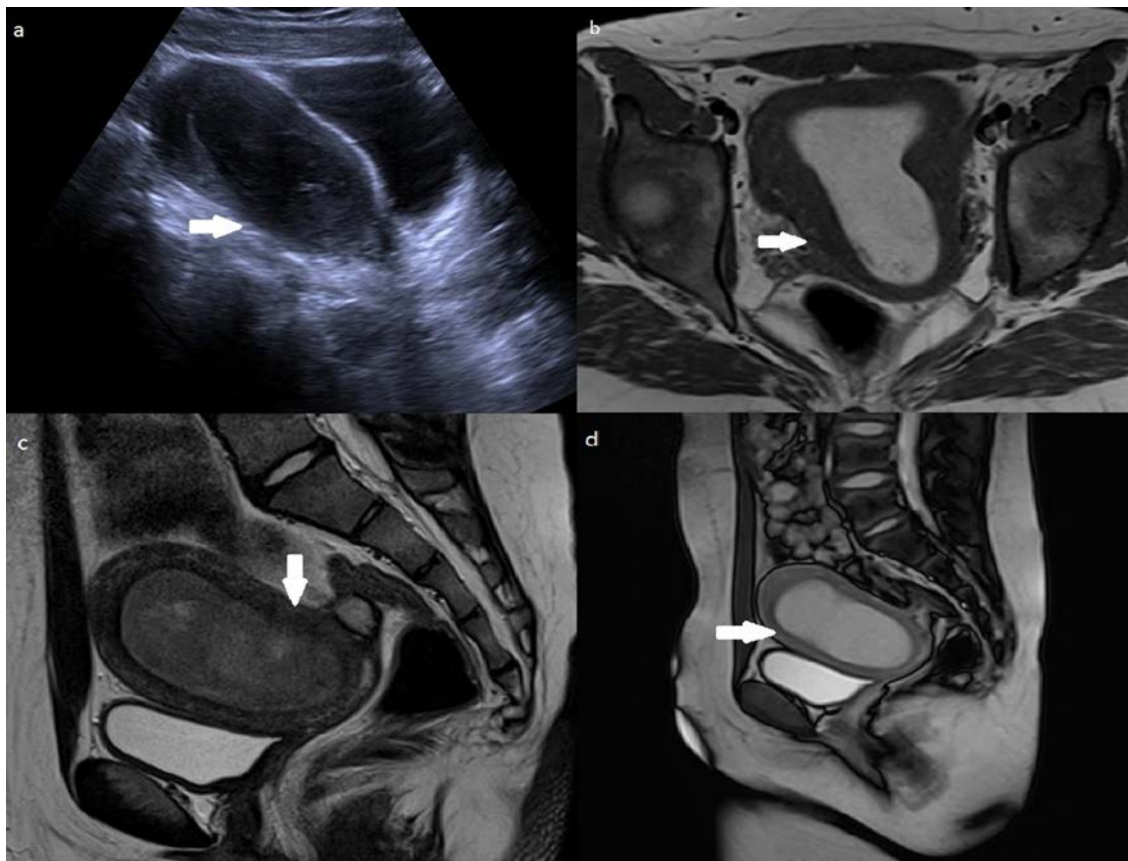
Figure 4: 11 year old female (a) longitudinal transabdominal US demonstrating complicated fluid in uterine cavity. (b) axial T1 (TE11, TR 500). (c) sagittal T2W (TE 100, TR 4000). (d) T2 sagittal TRUFI (TE 1.9, TR 3.79) demonstrating haematometra.
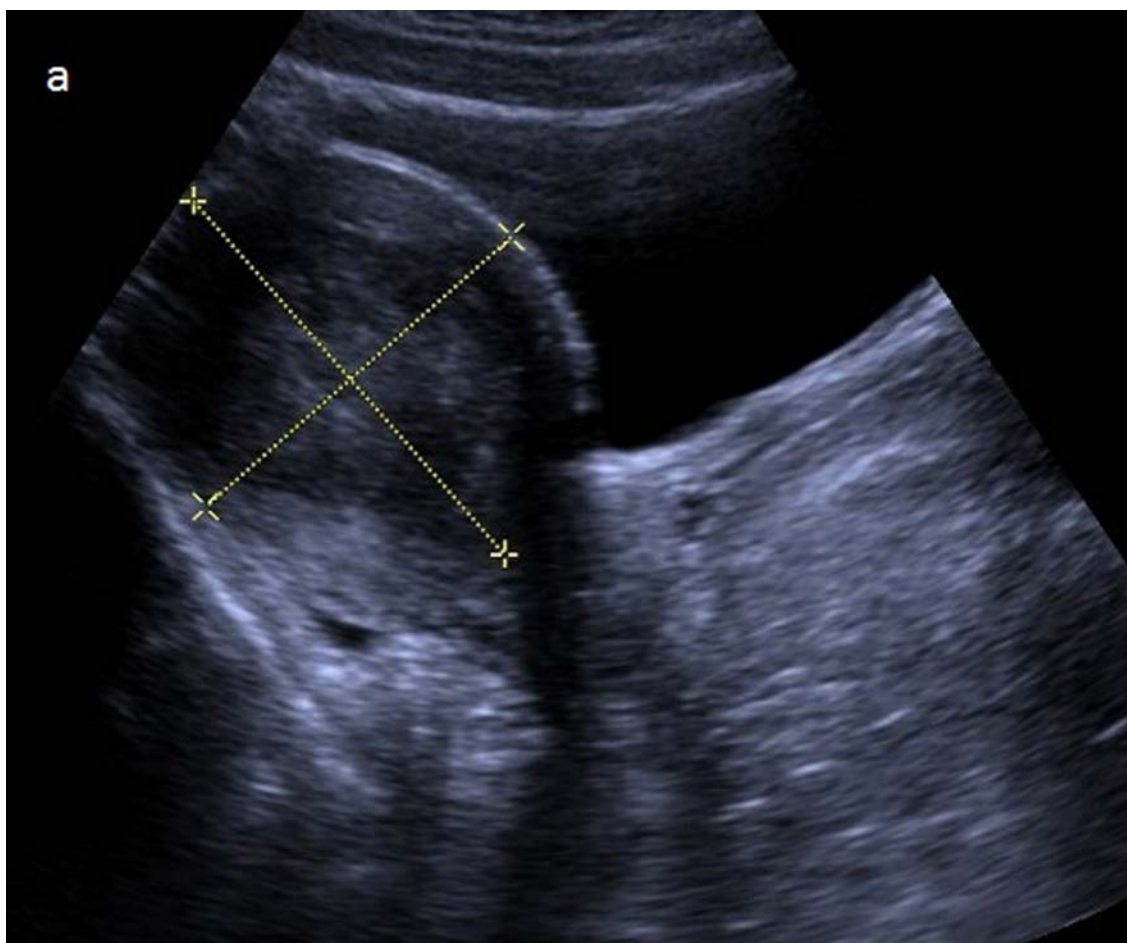
Figure 5: 23 year old female. (a) Transabdominal US demonstrating a mass in uterine cavity in keeping with a uterine fibroid.
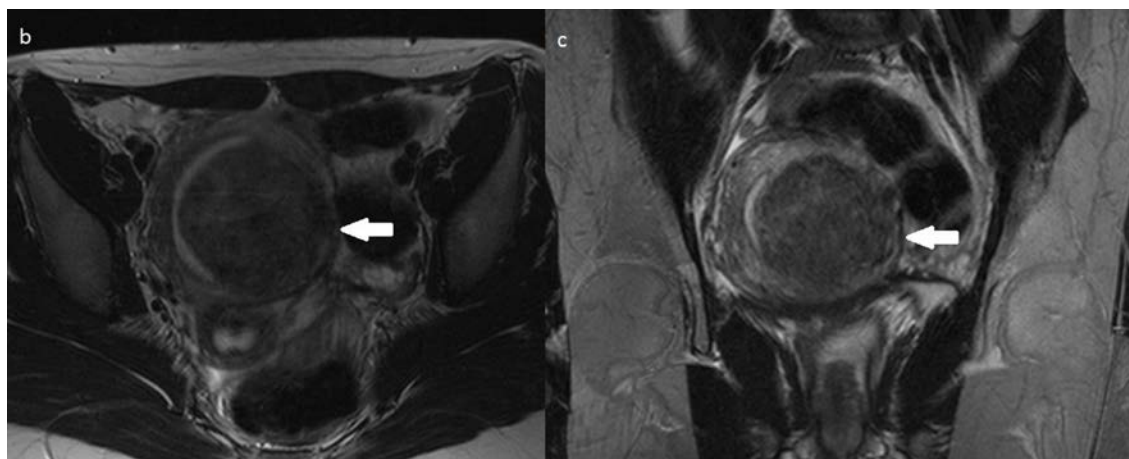
Figure 5: Corresponding MRI images of the same patient in image 5a above. T2 weighted (TE100, TR4000) (b) axial and (c) coronal images demonstrating a uterine fibroid (solid white arrow = uterine fibroid).
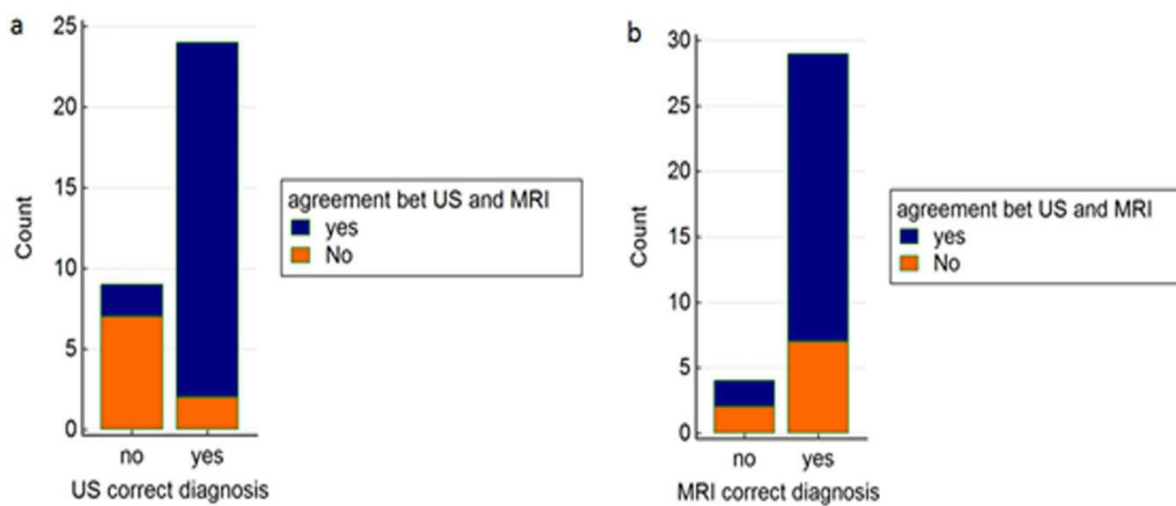

Figure 6: (a) Comparison of US with the gold standard. (b) Comparison of MRI with the gold standard.
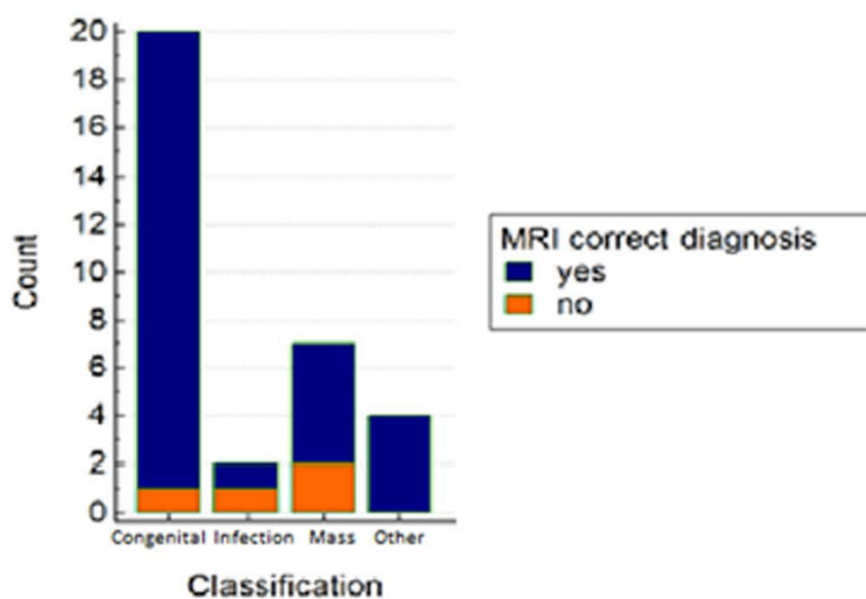
Figure 7: Classification of diagnoses made on MRI of pelvis for benign disease, reflecting the number of correct diagnoses in each category.
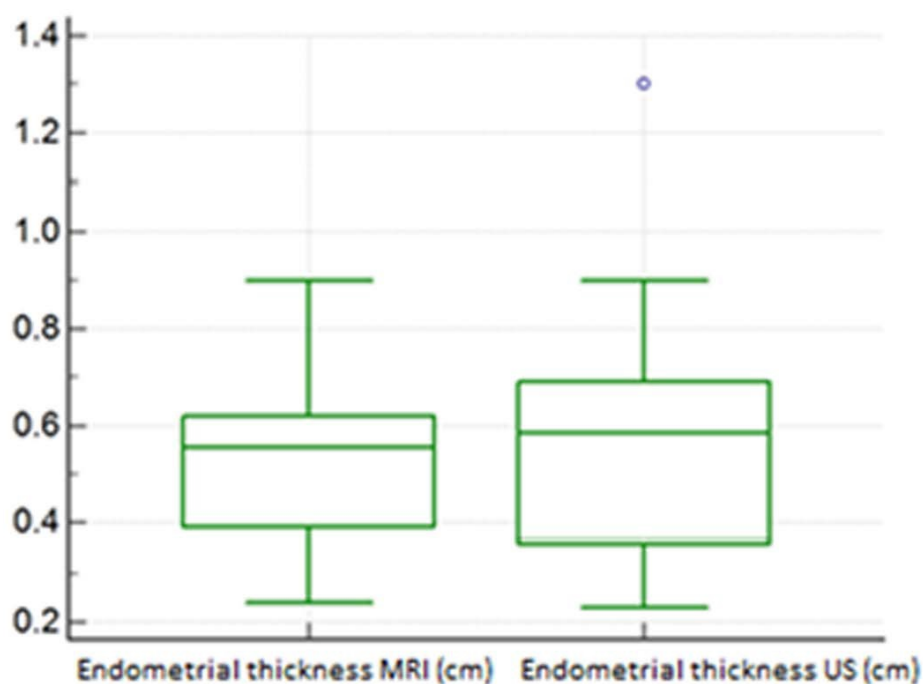

Figure 8: Box plot showing comparison of endometrial thickness between MRI and US.
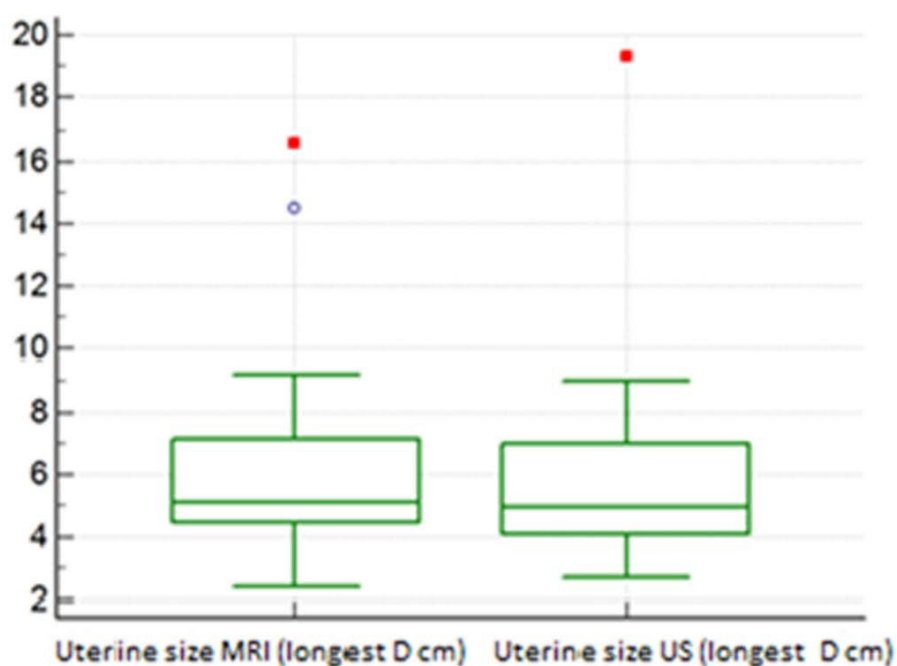
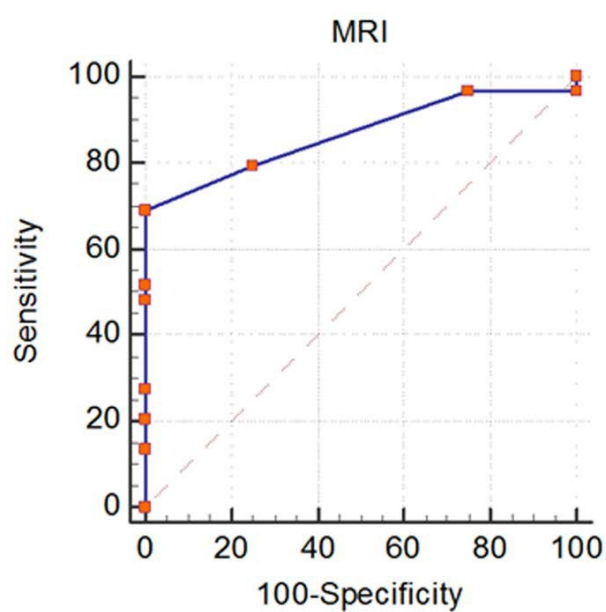Figure 9: Box plot showing comparison of uterine size between MRI and US.

Figure 10: (a) ROC analysis comparing diagnostic accuracy of MRI compared with the gold
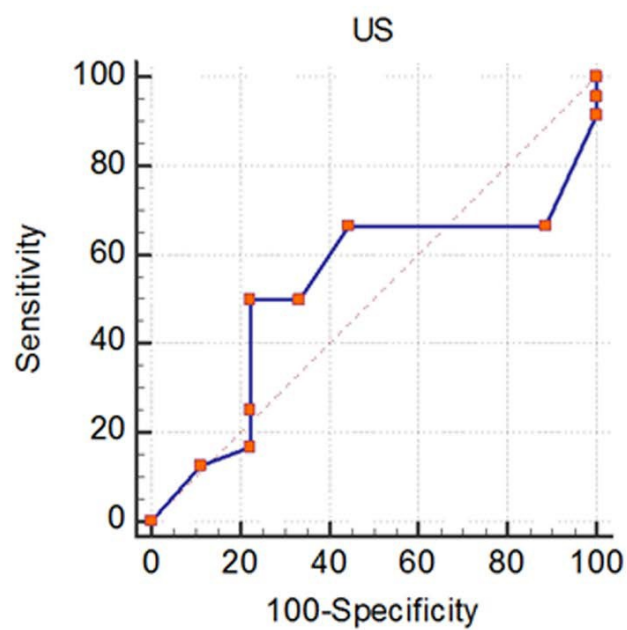
standard (AUC for MRI=0.866).

Figure 10: (b) ROC analysis comparing diagnostic accuracy of US compared with the gold standard (AUC for US= 0.528).

Tables

Table 1

Final diagnosis (n)	n (%)	Total (n=33)
Congenital		**20 (60.6%)**
Absent uterus	5 (15.15%)	
Hypoplastic uterus	4 (12.12%)	
Septate uterus	2 (6.06%)	
Uterine dideplphys	2 (6.06%)	
Bilateral uterine horns (non specified)	1 (3.03%)	
Haematometra		
Absent/ hypoplastic vagina	3 (9.09%)	
Vaginal septum	3 (9.09%)	
Infection		**2 (6.1%)**
Schistomiasis	1 (3.03%)	
Tuberculosis	1 (3.03%)	
Masses		**7 (21.2%)**
Fibroids	7 (21.2%)	
Other		**4 (12.1%)**
Endometriosis	4 (12.12%)	

CHAPTER 3

SYNTHESIS

The purpose of the study was to allow for a comparison of the evaluation of benign uterine conditions using both Magnetic Resonance Imaging (MRI) and ultrasonography (US), drawing on a sample from a central hospital (Inkosi Albert Luthuli Central Hospital). Our findings are summarised in the following conclusions and recommendations.

Conclusion 1:

MRI is the superior modality compared to US for the evaluation of benign uterine conditions, particularly congenital anomalies.

Conclusion 2:

Despite MRI being superior to US in diagnosis, US is still the primary imaging modality of choice in our resource limited setting.

Recommendations:

The recommendation for the practising physician is that the majority of benign uterine conditions can be confidently diagnosed on US, which is of particular benefit especially in the under-resourced areas.

Limitations:

1. The small sample size was taken from one central hospital: this can produce false-positive results or result in over-estimation of the magnitude of an association.

2. There was no blinding between readers therefore inter- observer variability and consistency was not measured.

3. The total population was not known therefore prevalence could not be determined.

Suggestions for future research:

1. A prospective study drawing from a bigger sample cohort may provide more direct comparative analysis between the two modalities.

2. To compare the benign MRI with malignant findings for diagnostic accuracy.

CHAPTER 4

APPENDICES

Appendix 1: Protocol proposal submitted to ethics

Identifying benign uterine conditions in female patients: comparing mri with ultrasonography

MMed: **Department of Radiology**

Supervisor: **Dr DP Ramaema**

Date of protocol: **19/11/2013**

Table of contents

1. Aim

To compare the diagnostic accuracy of magnetic resonance imaging and ultrasonography in evaluating benign uterine conditions.

2. Objectives

1. To describe the spectrum of magnetic resonance imaging appearances of benign uterine conditions

2. To describe the spectrum of ultrasound findings of benign uterine conditions

3. To describe any incidental radiological findings identified using magnetic resonance imaging and ultrasound

4. To determine and compare the prevalence of the benign uterine conditions identified by both techniques

3. Literature review

Ultrasound (US) is the primary imaging modality of choice for gynaecological related abnormalities due to its affordability and good diagnostic accuracy particularly with the use of high resolution transvaginal ultrasonography (TVUS). Limitations however do exist such as field of view restrictions, inherent patient related and operator dependent factors [1].

The use of Magnetic resonance imaging (MRI) in benign pelvic diseases is widely used in the developed countries [2-6]. Nationally, however, there have not been many studies done on the use of MRI in imaging of benign uterine conditions. MRI provides the greatest and most comprehensive imaging of the uterus in comparison to other imaging modalities [2]. It allows for good characterization of tissues, high contrast resolution, pre- and post-procedural evaluation as well as allowing for multiplanar reconstruction without the risks of ionizing radiation [1-3]. Furthermore there is less blurring from motion artifact from the chest and upper abdomen, and technological improvements in system hardware have resulted in shorter imaging times [7]. MRI has good delineation of perivascular fat planes and differentiates well between fluid, protein and haemorrhage on T1 weighted imaging. T2 weighted imaging allows for assessment of the uterine zonal

anatomy, the cervical canal and vagina [7]. Use of local pelvic phased array coils also result in better resolution and improved signal to noise ratio [3, 8]. The pelvic phase array coils are however more expensive and not generally available at all institutions. MRI itself has much greater cost implications in comparison with ultrasound imaging and is valuable in cases where ultrasound is non-diagnostic or equivocal [1, 3].

Amongst the benign uterine conditions, fibroid tumours are the most common occurring in approximately 25% of females over the age of 35 years. The evidence has shown that they occur earlier and with a higher incidence in black females compared with white females [9, 10]. This section will review the benign uterine conditions and will further outline the purpose, advantages and disadvantages of MRI and US. The conditions can be categorized into three areas, namely: congenital anomalies of the uterus, benign diseases of the uterine corpus and infections/inflammatory conditions.

3.1   *Congenital anomalies of the uterus*

Congenital anomalies of the uterus can present in a number of ways, with the following being reviewed for the purposes of this study: mullerian agenesis and hypoplasia, unicornuate uterus , uterine didelphys, bicornuate uterus, septate uterus, arcuate uterus, diethylstilbestrol uterus. Each of these will be discussed with respect to their development, appearance, and how they are diagnosed by both MRI and US.

Congenital uterine anomalies arise due to partial or complete failure of fusion of the mullerian ducts [2] which normally occurs between the 6th- 11th gestational week [11]. mullerian duct anomalies do not affect the external genitalia or the ovaries as these arise from the sinovaginal bud and primitive yolk sac respectively [11]. They   are found in approximately 1% of women of reproductive age [4] and approximately 25% of these cases may lead to obstetric related complications [1]. 3% of cases of infertility are thought to be attributed to mullerian duct anomalies [3] while 15% of women with recurrent miscarriages are found to have these mullerian   duct   anomalies   [11]. Hysterosalpingography (HSG) and US evaluation may initially

suggest the presence of an anomaly [4], however the use of MRI is almost entirely 100% accurate with the characterization of these anomalies,[2] and is now the imaging modality of choice for evaluation of mullerian duct anomalies. Accurately differentiating these anomalies is also important as it serves to guide appropriate management [1]. There is an association with mullerian duct anomalies and renal/ urinary tract anomalies. The prevalence of these associated renal anomalies is 30-50% [11].

The Mullerian anomalies are divided into 3 categories [3]:

- duct agenesis and hypoplasia

- defects of vertical fusion of the ducts with the ascending urogenital sinus

- defects of lateral duct fusion: may include uterine didelphys, septate uterus, and bicornuate uterus

a. Mullerian duct agenesis and hypoplasia

This is due to early development failure of the mullerian ducts [11] seen as either complete agenesis or hypoplasia of the uterus and upper two thirds of the vagina and account for approximately 10% of all uterine anomalies. In most instances the ovaries appear normal with resultant normal secondary sexual characteristic development, however patients lack the ability to reproduce. In some cases the endometrium remains functional within the hypoplastic uterus and patients may present with cyclical pelvic pain as well as primary amenorrhea due to haematometra [2].

On US a normal uterus may not be seen due to the varying anatomical positions of the uterus thus MRI is of benefit. Normal appearing ovaries are seen [11].

On MRI the following features are seen:

- Uterus- hypoplastic or absent, reduced to absent zonal anatomy in the hypoplastic uterus, diffuse low T2 signal [2, 4]

- Endometrial canal (hypoplastic uterus) - increased T2 signal, depending on the amount of obstruction of the endometrial canal, it may be may be expanded accordingly.

- Vagina- agenesis is noted, seen best in the axial plane with no normal vaginal zonal anatomy between the rectum and urethra [2]

One of the syndromes associated with uterine agenesis or hypoplasia is that of Mayer-Rokitansky- Kuster- Hauser syndrome which is a syndrome of failure of vaginal development. 90% of cases are associated with uterine agenesis and the remaining approximate 10% with uterine hypoplasia. The ovaries appear normal [3].

b. Unicornuate uterus

Unicornuate uterus is due to absence or hypoplasia of one of the two mullerian ducts, and accounts for approximately 20% of all uterine anomalies of which 40% have associated renal abnormalities (renal agenesis or a pelvic kidney), which are always ipsilateral to the rudimentary horn. [2, 4] . The abnormal uterine horn is absent in a third of cases and under-developed in two thirds of cases [3]. Clinically, the presence or absence of a rudimentary horn is of significance for surgical reasons including preventing a possible pregnancy within the rudimentary horn as well as intervention to prevent obstruction in the rudimentary horn by retrograde menses [2].

There are 4 possible subtypes of this anomaly [11]:

- Absent rudimentary horn

- Presence of a rudimentary horn with absent uterine cavity

- Presence of a rudimentary horn with a communicating cavity to the normal side

- Presence of a rudimentary horn with a non-communicating cavity.

US: The uterus appears small and curved off the midline (banana shaped uterine configuration). The rudimentary horn is difficult to visualize and may be mistaken for a pelvic mass or the cervix [11].

MRI: the following features can be seen [2-4]:

- Uterus- also seen as elongated and curved away from the midline with a reduced uterine volume. The endometrium has a low T2 signal if no cavity is present (with loss of zonal anatomy) within the rudimentary horn (endometrium absent). There will be a high T2 signal if the rudimentary horn contains a cavity (endometrium present) with zonal anatomy maintained to a degree [2, 3].

c. Uterine didelphys

Uterine didelphys results from almost complete failure of midline fusion of the 2 mullerian ducts with no communication between the endometrial canals. Each duct develops completely and results in duplication of the uterine horns, cervix and in 75% of patients the proximal vagina. It is essential to identify the fundal cleft on a coronal image to be able to identify the type of anomaly present [11].

Uterine didelphys accounts for approximately 5-7% of the uterine anomalies. In 75% of cases of this anomaly, a vertical vaginal septum is associated. In some cases a horizontal vaginal septum may also be found. Patients may present with ipsilateral hematometrocolpos [2, 11].

On US and MRI, two divergent horns with the presence of two endometrial cavities and two cervices are seen (11).

US: Presence of the vaginal septum is difficult to visualize on ultrasound and differentiating between uterine didelphys and a bicornuate bicollis uterus becomes challenging [11].

MRI: Zonal anatomy of the uterus is preserved [2]. A fundal cleft >1cm is diagnostic of a fusion anomaly (uterine didelphys and bicornuate uterus) versus a reabsorption anomaly (septate and arcuate uterus). In the case of a unilateral vaginal septum and associated haematometrocolpos, high signal intensity from contained blood products will be demonstrated [11].

d. Bicornuate uterus

This is due to incomplete fusion of the uterine horns with an associated fundal cleft that may be partial or complete (extending to the internal os) and may be identified on MRI and US [11]. One or two cervices may be present. The bicornuate uterus is found in approximately 10% of uterine anomalies and in 25% of these cases a vertical vaginal septum may be present. These patients face an increased threat of spontaneous miscarriage and premature labour [2].
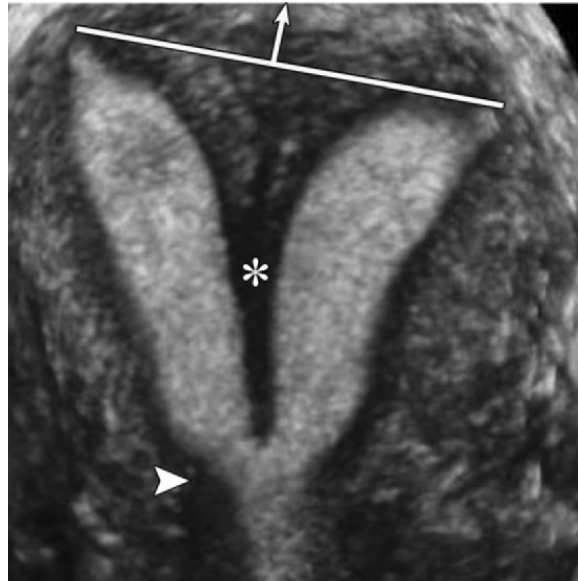
US: Bicornuate uterus is best assessed in the secretory phase of the menstrual cycle as the endometrium demonstrates an increased echogenicity and the divergent uterine horns and separation of the cavity are best seen [11].

MRI: Presents with an incompletely fused divergent uterine horns and an associated fundal cleft of >1cm depth similar to uterine didelphys. A muscular or fibrous septum is seen. When the septum extends to the cervix it is termed bicollis and when it does not reach the external cervical os it is termed unicollis. Zonal anatomy of the uterine horns are preserved. In cases where a longitudinal vaginal septum is present, it is difficult to differentiate between a bicornuate bicollis uterus and that of uterine didelphys. The presence of the duplicated cervix in the bicornuate bicollis uterus demonstrates a feature termed "owl eyes" and is diagnostic in the absence of vaginal duplication [2, 4, 11].

e. Septate uterus

The septate uterus is formed after fusion of the Mullerian ducts and is due to incomplete resorption of the medial fibromuscular septum between the Mullerian ducts [2, 3]. A complete septum is one which extends to external cervical os and may even extend to the upper vagina [4,6]. It is the commonest uterine anomaly accounting for approximately 55% of cases and is also strongly associated with infertility [2, 3].

US: Features to suggest a septate uterus include myometrial interruption by the presence of a septum at the uterine fundus. The fibrous septum is of a lower echogenicity compared with the myometrium. US cannot accurately diagnose a septate uterus, however 3D US may be of more benefit than 2D US in suggesting this anomaly. In order to differentiate between a septate and a bicornuate uterus uterus a line is drawn between the uterine ostia and the apex of the external uterine fundal contour is assessed- if the apex is >5mm above the interostial line it represents a septate uterus, however if the apex is <5mm above or below the interostial line it may represent a bicornuate or didelphys uterus [11].

Coronal 3D US image of uterus. The white line represents the interostial line (between the tubal ostia). If the apex of the fundal contour is >5mm above this line it is in keeping with a septate uterus [11].

MRI: The uterus is of normal size [11]. The external contour of the fundus of uterus may be concave, convex or flat. The associated fundal cleft measures <1cm depth and one or two cervices may be present. The fundal segment of the cleft demonstrates the same intensity as the myometrium, while the inferior segment of the septum is of a low signal intensity [2]. <75 degree angle between the uterine horns is thought to represent a septate uterus versus a bicornuate uterus [11].

f. Arcuate uterus

This anomaly or variant results in a mild, smooth, concave indentation at the uterine fundus and is due to almost complete reabsorption of the uterovaginal septum. The uterus is normal in size with the external uterine contour preserved [11].

US: On US the uterine zonal anatomy is also preserved while there is an inward contour deformity noted resulting in the fundal indentation [2, 4, 11].

On MRI there is a prominence of soft tissue in the region of the fundus which has the same T2 signal intensity to that of the myometrium with no fibrous tissue noted [11].

g. Diethylstilbestrol uterus

This occurs in women exposed to diethylstilbestrol prenatally and results in a hypoplastic T-shaped uterus due to narrowing of the horizontal and vertical segments of the endometrial cavity. The lower uterine segment also appears widened. Indentations on the endometrium are noted which are attributed to the presence of constriction bands [2, 11].

US: Two dimensional (2D) ultrasound does not aid in diagnosis as US features are non-specific [11].

MRI: demonstrates the constriction band which is a focal area of thickening of the junctional uterine zones [11].

Benign diseases of the uterine corpus

There are a number of benign diseases of the uterine corpus that require assessment and for the purposes of this study, the following will be reviewed: endometrial polyps, endometrial hyperplasia, endometrial synechiae, uterine peristalsis, leiomyomas (fibroids), adenomyosis and endometriosis. The anatomical features of each will be described as well as how it is detected radiologically by US and MRI.

a. Endometrial polyps

These are focal outgrowths of endometrial hyperplasia occurring in approximately 10% of women. They are found in 3 different types namely atrophic, hyperplastic and functional polyps and may be sessile or pedunculated. Polyps are commonly found in the uterine fundus or cornua. Malignant change has been noted in approximately 0.5% of these endometrial polyps [2].

US: used for initially detecting and characterizing endometrial polyps. They appear as either non-specific endometrial thickening or as a focal echogenic mass within the endometrium.

MRI: used in cases when US is non-diagnostic or when endometrial is unsuccessful in yielding a result. Sampling or biopsy of the lesion may difficult (e.g. due to increased habitus or cervical stenosis). On T2 weighted sequences polyps may be hypo- or iso-intense to endometrium and on T1weighted images appear isointense to endometrium. Polyps demonstrate a non-specific pattern of enhancement post gadolinium and MRI features of endometrial polyps and endometrial carcinoma may demonstrate some overlap. Malignancy may be suggested by the presence of metastases or myometrial invasion. Studies have shown that MRI has a sensitivity of 79%, specificity of 89% and an accuracy of 86% in its ability to differentiate a benign polyp from malignancy[7]. Endometrial polyps also should be distinguished from submucosal fibroids which demonstrate a lower signal intensity on T2 weighted images compared with endometrial polyps[2, 12].

b. *Endometrial hyperplasia*

Endometrial hyperplasia is due to increased focal or diffuse proliferation of the endometrial glands, and is often attributed to unopposed oestrogen stimulation. It is categorized in two ways: with or without cellular atypia. In 25% of cases of cellular atypia, endometrial carcinoma may be found or will develop. This is in comparison to 2
% of patients without cellular atypia who carry a risk of endometrial carcinoma [2, 12]. As with endometrial polyps, malignancy can only be diagnosed based on the presence of metastases or myometrial invasion [2]. It is difficult on imaging to distinguish diffuse polyps from endometrial hyperplasia [2].

TVUS is one of the studies used to characterize endometrial hyperplasia however the findings are non- specific and cannot be differentiated from endometrial carcinoma. Endometrial biopsy is however diagnostic [2, 4, 12].

MRI: used in cases where TVUS is non- diagnostic or when endometrial sampling is of difficulty. The endometrium appears diffusely widened and the endometrium that is hyperplastic appears iso- or hypo-intense on T2 weighted images relative to normal endometrium. There is an increased gland- to- stroma ratio and cystically

dilated glands within the endometrium appear as high T2 signal intensity foci. Post intravenous contrast the hyperplastic endometrium will demonstrate less enhancement to that of the normal myometrium [2, 4, 12].

c. Endometrial synechiae

These are bridging adhesions across the myometrium for of Ascherman Syndrome is an example, which results in partial or complete obliteration of the uterine cavity. It forms in response to infection/inflammation or trauma [2].

US: US is not reliable in diagnosing endometrial synechiae. Hysterosalpingogram (HSG) and hysteroscopy are primarily used for diagnosis.

MRI: the endometrial synechiae have a low signal intensity on T2 weighted images and appear as bands across the endometrial canal. Post-contrast gadolinium enhanced images show enhancement of the synechiae. MRI also plays a role in determining the underlying aetiology and is also useful in assessing the uterus proximal to the adhesions not visualized on hysteroscopy or seen on HSG [2].

d. Uterine peristalsis

Uterine peristalsis is the transient relaxation and contraction of the uterus which may be seen during pregnancy on TVUS and may be subject to hormonal changes usually seen a week prior to menstruation [2].

MRI: Ultrafast MRI sequences allow uterine contractions to be imaged in a non-gravid patient. It appears as a transient hypointense T2 weigthed signal with distortion of the endometrium and myometrium with no distortion of the external uterine contour. Due to their transient nature they are differentiated from adenomyosis and leiomyoma [2].

e. Leiomyomas (fibroids)

These are benign neoplasms comprised mainly of smooth muscle cells and over time may undergo degeneration as they outgrow their arterial supply. They are intramural, subserosal or submucosal in location and may even occur in the cervix, broad ligament

or in areas outside the female genital tract although this is uncommon. They occur in approximately 25% of females over the age of 35 years and <2% may undergo sarcomatous degeneration[2].

TVUS: can accurately detect leiomyomas. Ultrasound is, however, of reduced diagnostic value to detect leiomyomas in obese patients where image quality is suboptimal. It is further of limited value in cases of very large fibroids where the anatomy becomes distorted. Calcifications and associated shadowing may also obscure imaging of adjacent structures.

MRI: can accurately characterize and assess these lesions, particularly when there are a greater number of fibroids present. MRI is of further benefit prior to and following medical or minimally invasive therapy including uterine artery embolization, to compare the changes in the lesions. Pre-embolisation magnetic resonance angiographic imaging is also required to assess vascularity including collateral supply from the gonadal vessels to the fibroids that may also require embolisation. On MRI the uterus appears enlarged and abnormal in contour. Lesions appear hypointense on T2 weighted images in comparison with the myometrium and sharply marginated. With intramural or subserosal fibroids a high intensity rim may be seen. Calcifications may also be noted within the fibroid- on US the associated posterior acoustic shadowing would obscure adjacent tissues, however on MRI the calcifications would appear as signal voids without the obscuration of surrounding tissues. Calcifications are best seen on gradient- echo T1 weighted images. Post contrast images show a variable appearance of the leiomyomas. They show decreased enhancement once they undergo degeneration. The characteristics also may vary depending on the type of degeneration it undergoes, however only haemorrhagic degeneration can be determined on MRI. Leiomyosarcomas have a similar appearance to that of a degenerated fibroid. They occur rarely and are difficult to consider or diagnose without a history of metastatic disease [1-3, 8].

Newer techniques include that of MRI-guided focused US used to treat fibroids that are symptomatic.

US waves are focused on these fibroids resulting in thermal ablation while monitoring on MRI is perfomed. At 6 month follow-up, this technique of MRI- guided focused US has shown to provide improved symptoms [2].

f. Adenomyosis

Adenomyosis is characterized by the presence of heterotopic glandular and stromal tissue within the myometrium and may present in a focal pattern (usually the posterior uterine wall) or diffusely. Secondary overgrowth of the musculature in the region surrounding the endometrial glands is noted resulting in a globular shaped uterus. The presence of adenomyosis is noted in 19-62% of hysterectomy specimens. 70-80 % of cases are those of parous women aged 40-50 years [2, 8].

US: It is not well seen on TVUS.

MRI: is accurate in definitive diagnosis including that of adenomyomas (focal adenomyosis) [1, 2], as well in treatment monitoring. One of the criteria used to diagnose adenomyosis is the width of the junctional zone and T2 weighted imaging sequences are best used to delineate the uterine zonal anatomy. Adenomyosis is seen as focal or diffuse widening of the junctional zone or as a hypointense myometrial mass. Post- contrast images do not assist in diagnosing adenomyosis [2]. A "swiss cheese" appearance suggesting dilated endometrial glands within the myometrium together with perfusion abnormalities may be seen on early phase images to suggest adenomyosis [12]. Newer conservative uterine artery embolization therapy as well as endometrial ablation may be performed, and MRI may be useful to evaluate response post-intervention [1].

g. Endometriosis

Endometriosis is the presence of functional endometrial glands and stroma, in an ectopic location i.e. outside the uterine cavity [1], with a response to cyclical hormonal stimulation [8]. The most common site for implantation is along the uterine serosal surface and along the ovaries. It may also occur at the scar site post operatively from previous uterine surgeries. The endometrial deposits can, however, occur along any peritoneal surface. Rarely, endometrial deposits may even be found within the lungs or central nervous system. There are two forms of endometriosis- a diffuse form with scattered implants and a focal

form with formation of endometriomas or "chocolate cysts" [8].

MRI: is advantageous in that it is able to identify deposits that are obscured by dense adhesions at laparoscopy, which is the gold standard for diagnosing endometriosis. The appearance of endometriomas on MRI is dependent on the stage of presentation as well as the age of blood products contained within. They are generally T1 hyperintense and of T2 low- intermediate signal intensity. "T2 shading" may be seen, and this is due to repeat haemorrhage at varying time intervals attributed to methaemoglobin, protein and iron [1]. Endometriomas display a fibrous capsule which is seen as a low signal intensity peripheral rim [8].

Infections/inflammatory conditions

Two infections/inflammatory conditions will be reviewed, endometritis and tuberculous pelvic inflammatory disease (PID). Each condition will be described in terms of how it manifests, and its detection using US and MRI will be reviewed.

  a. *Endometritis*

This refers to infection or inflammation of the uterus. A majority of cases occur following caesarean section while a few cases occur post normal vaginal delivery. It may also occur associated with PID with endometrial involvement as well as post- instrumentation.

US: Initial scan may appear normal, however as the disease progresses the endometrium may appear thickened and heterogenous with the prescence of air and/or fluid within   a thickened endometrial cavity. Uterus appears mildly enlarged with increased hypoechogenicity and poorly defined uterine margins.

MRI: the uterus may also appear bulky or enlarged with increased signal intensity on   T2 weighted imaging. On T1 weighted gadolinium enhanced images enhancement of the entire uterus may be seen [13-15].

  b. *Tuberculous pelvic inflammatory disease*

Tuberculosis (TB) of the genital tract occurs in approximately 1-3% of patients with TB. Spread occurs either haematogenously from an extragential location, via lymphatics or

from the peritoneal cavity. It primarily affects the fallopian tubes however approximately half of the cases spread to the endometrium. In a majority of cases the uterine cavity appears normal however may contain synechiae and may appear irregular, shrunken or contain an irregular filling defect. Scarring may also result in formation of a T-shaped uterine cavity, complete obliteration of the uterine cavity or in cases with unilateral scarring the impression of a unicornuate uterus termed the "pseudounicornuate" uterus. These features described above are not specific for endometrial TB however it is suggested in cases with no history of previous curettage or surgical termination of pregnancy [16, 17].

Modalities: magnetic resonance imaging and ultrasound

Both magnetic resonance imaging (MRI) and ultrasound (US) may be used to evaluate benign uterine conditions, particularly that of mullerian duct anomalies [11]. Previous methods included hysteroscopy or hysterosalpingogram to assess the uterine cavity and laparoscopy to assess the fundus [18]. The MRI and US technologies will be described as well as the advantages and disadvantages in diagnosing uterine conditions in female patients.

a. *Magnetic Resonance Imaging*

Magnetic resonance scanners make use of magnetic fields and the magnetic resonance properties of the proton which are abundant in tissues. The patient is placed within the magnetic field and radiowaves are generated by coils placed around the patient. Radiowaves are absorbed by the protons and energy is re-emitted depending on the local magnetic properties of the surrounding tissue. These are again detected by coils surrounding the patient. Signal localization requires magnetic field gradients
– along the gradient a unique magnetic field strength produces a specific lamor frequency corresponding to each location. The frequency of the returning radiowaves helps determine the position of each signal from the patient. A set of tomographic slices is produced. Different tissues (e.g. gray matter, white matter and fat) demonstrate different local magnetic properties thus contrast between tissues is achieved. [19]

MRI Equipment used:

Siemens 1.5 T strength magnet with use of a phased array surface coil [2].

MRI technique used for obtaining images at time of investigation:

The patient's bladder must be empty prior to the study [2]. Ideally the patient should be nil per os 6 hours prior to the study to reduce motion artifact form peristalsis. If not possible, anti- peristaltic medication may be administered [7]. The best imaging of the female pelvis in MRI particularly that of the three uterine zones including the endometrium, junctional zone and myometrium, is

with the use of T2 weighted sequences with planar reconstruction. The endometrium has a high signal intensity, the junctional zone has a low signal intensity and the myometrium an intermediate signal intensity on T2 weighted images [4]. On T1 weighted images, differentiation between fat and soft tissues is useful [8] however the uterine zones are not clearly distinct [3] and are also less clearly distinguished on gadolinium post- contrast images. The serosa surrounding the myometrium, if seen, may be subject to chemical shift artifact [2].

The MRI sequences employed for pelvic imaging typically use T1 and T2 weighted sequences. Axial T1 weighted images are useful in assessing the uterine contour, bone marrow as well as lymphadenopathy. T2 weighted sequences using multiplanar reconstruction are performed with one plane generally demonstrating the short and long axis orientation of the uterus well. Imaging of suspected congenital uterine anomalies begins with the T2 weighted sagittal images to determine the longitudinal axis following which images are taken parallel to this to adequately assess the uterine contour. Axial T1W images with fat suppression are also employed to evaluate for blood products as well as to differentiate lesions that contain fat or protein. Post- contrast T1 images are useful in evaluating for features of necrosis within the uterine fibroids [3].In the evaluation of benign conditions fast breath- hold sequences can be used even though this may decrease the resolution to a small degree. Further optional images include the Diffusion Weighted Imaging (DWI) and Attenuation Diffusion Coefficient (ADC) measurement which is used to monitor if satisfactory results have been obtained post procedures such as uterine artery embolization [4].

The MRI sequences employed are as follows:

- 3 plane gradient-echo scout views of the pelvis

- T2W single-shot fast spin echo (SSFSE):

    Axial sequence of the pelvis (showing the uterine orientation)
    Coronal sequence (assess for renal abnormalities)

- Fast spin echo (FSE) T2W sequences in the sagittal plane.

- Gadolinium enhanced T1W sequence in the sagittal plane.

- 3D fat saturation T2W* - thin section volumetric acquisition allows for multiplanar reformatting. This includes coronal images in the uterine plane.
- Fat saturated T1W volume interpolated GRE- axial plane allows for assessment and characterisation of the uterus [2, 3, 18]

Two further sequences are employed when mullerian duct anomalies are suspected:

- FSE T2W sequence parallel to the long axis of the uterus which is a true coronal uterine view to demonstrate the external contour of the uterus.
- The second sequence employed is either the gradient echo or SSFSE T2W sequence to assess the retroperitoneum for any commonly associated urinary tract anomalies [2].

Locally, at IALCH, the following technique for pelvic MRI of benign uterine conditions is used:

- A body coil is used.
- Pre-contrast, T1 weighted axial plane images, T2 weighted axial, coronal and sagittal plane images are taken.
- Post-contrast T1 weighted fat saturated axial, coronal and sagittal plane images are performed.

b. Ultrasound

US describes the propagation of sound waves (mechanical energy) in a medium. Transducers are used to generate sound pulses as well as detect returning echoes which result in encoding of a gray-scale value to create a tomographic image of tissues. A 2D ultrasound image is formed by sweeping an ultrasound beam over an area of interest and displaying echo signals through a specific echo display mode for 2D gray-scale imaging known as B – mode. With 2D ultrasound the image is progressively formed as the beam sweeps through the area of interest. With 3D ultrasound imaging, sound waves are propagated at different angles and the returning echoes are reconstructed into a 3D

volume from a number of different individual B – mode scans or 2D images of a volume of tissue [19].

US   Equipment   used:
Siemens Accuson S2000

US technique that was used for obtaining images at time of investigation:

A high frequency intracavitatory transducer probe (10-12 MHz) for transvaginal ultrasonography (TVUS) is used as well as the curvilinear transabdominal probe (2-5 MHz)[18].

A standardized technique known for 3 dimensional US known as the Z technique is described by the American institute of ultrasound in medicine (AIUM) in the 2013 Journal of ultrasound in medicine to improve evaluation   of the uterus and thus improve diagnostic ability. The technique is performed as follows [20]:

- Reference/rotational point is placed at the midlevel of the endometrial stripe in the sagittal plane
- Z rotation is used to align the long axis of the endometrial stripe along the horizontal axis in the sagittal plane of the uterus
- The reference/rotational point is then placed at the midlevel of the endometrial stripe in the transverse plane
- Z rotation then aligned to the endometrial stripe with the horizontal axis in the transverse plane of the uterus. Midcoronal plane of the uterus will then be displayed- Z rotation applied to display the midcoronal plane in the traditional orientation [20]

Locally, at IALCH, the transabdominal and endocavitatory transvaginal ultrasound probe are used with similar frequencies as above.

Use of 2D TVUS has shown to be highly sensitive (90-92%) as a screening investigation for uterine anomalies, however the ability to differentiate the various subtypes is user dependent [20]. The advent of 3D ultrasound allows for improved delineation of the external uterine contour including the coronal plane showing the superior

endometrial and serosal region of the uterine fundus [20]. Diagnostic accuracy of 3D ultrasound is therefore comparable to that of MRI or combined hysteroscopy/ HSG and laparoscopy. It is however still not available at all centres [20] and MRI is still regarded as the imaging modality of choice for evaluation of the mullerian duct anomaly subtypes, depicting both external uterine contour as well as the internal uterine cavity [11]. This greatly reduces the need for invasive testing as was previously employed with comparable accuracy [20]. MRI is particularly of benefit in young or adolescent patients with an intact hymen in which transvaginal approach is not ideal, or in cases with distortion of the uterus secondary to large fibroids, particularly those at the fundus [20, 21].

In centres with the availability of 3D ultrasonography, it may provide a valid alternative imaging option to that of MRI due to the low associated cost factors. It also showed good concordance in studies to MRI in the diagnosis of uterine anomalies with a kappa index of 0.880 (95% CI, 0.769–0.993) [18]. Discrepancies obtained were those involving the lower aspect of the uterus involving the cervix where ultrasound is essential. MRI is able to discriminate a septum from the cervical myometrium as well as the vaginal wall from vaginal septae by the differing signal intensities. This discrimination cannot however be made on 2D or 3D ultrasound and it is thus advised that if 3D ultrasound is performed it should be done in conjunction with a pelvic examination (bimanual and speculum examination) for cervical assessment [18].

3D ultrasound provides the following advantages [18]:

- Calculation of septum length and thickness

- Calculation of intra-uterine cavity volume

- Assessment of uterine vascularity

It is proposed that in centres with the availability of 3D ultrasound facilities, 3D ultrasound in conjunction with pelvic examinations be performed, and in cases that are equivocal should proceed with MRI [18]. 3D US provides improved imaging compared with 2D US with improved evaluation of the uterine cavity [11, 12].

(An X indicates where the criteria apply)

	Advantages	MRI	US
1	Wider availability		X [11]
2	Fast imaging modality		X [11]
3	No risk of ionizing radiation	X [11]	X [11]
4	Low expense		X [11]
5	Able to assess renal tract anomalies	X [11]	X [11]
6	Able to assess skeletal tract anomalies	X [11]	
7	Non- invasive	X [20]	
8	Safe in pregnant patients during organogenesis	X [1]	X [1]
9	Non-user dependent	X [22]	
10	Able to outline and assess uterine zonal anatomy	X [2]	

Table 1: Advantages of MRI and US

4.   Key References

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5.   Problem statement

In some centres [23] both locally and nationally, US has been accepted as the primary imaging modality of gynaecological related abnormalities for practical reasons. It is inexpensive and useful in providing good diagnostic accuracy. Limitations however do exist: These include field of view restrictions, inherent patient related and operator dependent factors [1]. In the case of 2D US, studies have found MRI superior to ultrasound in assessing uterine lesions [23]. MRI provides the greatest and most comprehensive imaging of the uterus in comparison to other imaging modalities and is also of benefit in the following ways [2]:

- in cases where ultrasound is non-diagnostic or equivocal [2]

- provides excellent soft tissue contrast [3]

- can be used for monitoring pre- and post- medical therapy or minimally invasive treatments e.g. uterine artery embolization [2]

- able to use multiplanar images for evaluation [2]

- MRI imaging may be an adjunct to diagnostic laproscopy, hysteroscopy, hysterosalpingography, and transvaginal ultrasound when assessing patients with infertility [24]

This study aims to compare the use and diagnostic accuracy of US and pelvic MRI in the assessment of benign uterine conditions. Nationally, however, there have not been many studies done on the use of MRI in imaging of benign uterine conditions and a further aim of this study is to demonstrate the benefit and role of the use of pelvic   MRI in imaging of benign uterine conditions. The main restriction to use of MRI is the availability of equipment and it is thought that an improvement in resources will result in wider use of pelvic MRI in the future [7].

6.   Study design

This is a retrospective descriptive qualitative chart review using non-probability, purposive sampling to identify participants.

6.1   *Study Location*

University of KwaZulu-Natal (UKZN), Neslon R Mandela School of Medicine (NRMSM) and Inkosi Albert Luthuli Central Hospital (IALCH). The electronic records will be obtained from the IALCH data base, selecting specifically pelvic gynaecologically related MRI cases performed, comparing to ultrasound reports also obtained from the electronic records from the IALCH data base.
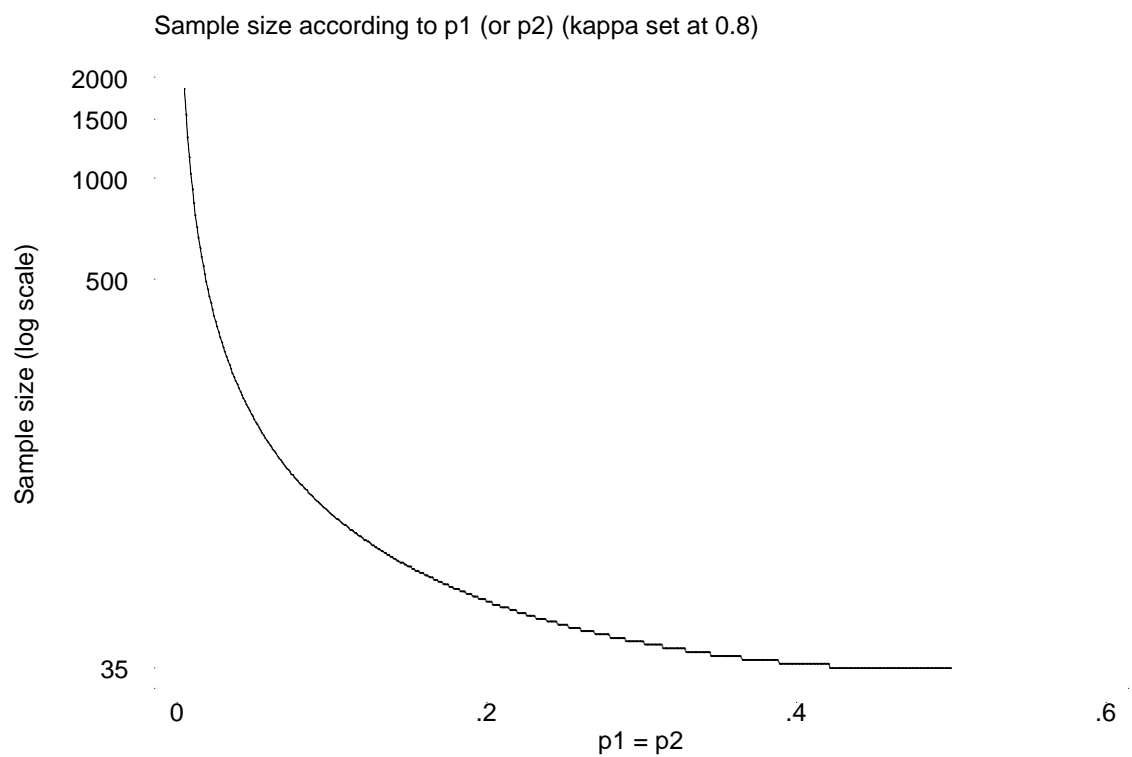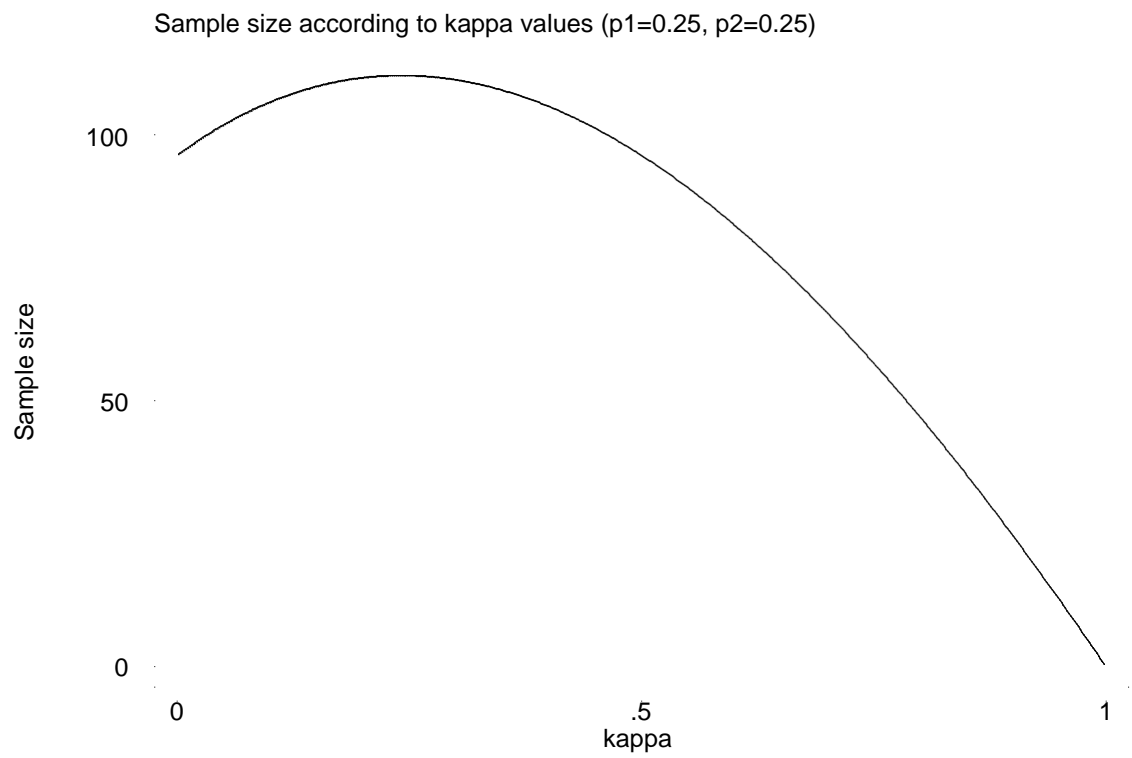
6.2   *Study population*

This includes females from birth to 50 years of age who have undergone a pelvic MRI for benign uterine pathology. The initial routine investigation for these patients is usually ultrasound. MRI is performed as secondary investigation if ultrasound is not conclusive, and for preoperative planning.

6.3   *Sampling strategy*

A purposive sampling strategy will be used, as patients will be selected who meet specific criteria from a designated hospital (IALCH)
Of these patients are identified and selected for the study.

6.4   *Sample size*

All the relevant cases over the three year period will be included. To detect a high level of agreement (kappa coefficient or k=0.8) between the 2 diagnostic tests with 95% confidence and 80% power, assuming a baseline prevalence of fibroid tumours of 25% (diagnosed by both measurements) and with an absolute precision of 20%, a minimum sample size of 47 paired measurements is needed (i.e. 47 women).

Sample size according to kappa values (p1=0.25, p2=0.25)

Sample size according to p1 (or p2) (kappa set at 0.8)

6.5   *Inclusion/ exclusion criteria*

The study will have the following criteria:
Inclusion criteria:

- female patients

- any age

- those who have undergone a pelvic MRI for a benign uterine condition during the last three years (2011- 2014 June)

Exclusion criteria:

- absent or incomplete ultrasound results

- no histology or surgical findings

6.6   **Data collection tools**

A spread sheet of patients having undergone pelvic MRI in a 3 ½ year period has been obtained from the IALCH IT department. Patients who form part of the study must meet the inclusion criteria having undergone   a   pelvic M R I with a corresponding US report. Patient files will be obtained electronically from the IALCH Picture archiving and communication system (PACS) with their hospital identity number.

6.7   **Data collection Process**

Once ethical approval has been granted by UKZN BREC, and permission from the Department of Health and the IALCH hospital managers have been obtained, the statistics of the relevant pelvic MRI studies and corresponding US studies are accessed via the radiology and hospital information systems using patient hospital numbers already provided by IALCH IT technicians. All the electronic data will be collected on site by myself with no removal of files.

6.8   *Data analysis techniques*

Data pertaining to US and MRI findings (both written reports and available imaging) will be entered into MicroSoft Excel spread sheet and comparison made thereafter. The analysis will be done using Statistical Package for Social Sciences (SPPS) software version 2.1. The pertinent findings that will be documented include:

- Clinical diagnosis made in both modalities

- A comparison of the diagnoses will be made i.e. whether they correspond

- The additional information (if any) obtained from the pelvic MRI studies not noted on the available US findings will be documented. These will be open- ended depending on the number of varying findings elicited once comparison has been made.

Continuous variables will be summarized using mean, standard deviation and range (minimum- maximum). If the data are skewed then medians and interquartile ranges will be presented. Box plots will also be employed   to graphically summarise continuous variables. Categorical data will be represented using frequency tables. The Kappa statistic will be used to assess   the pairwise agreement between the two diagnostic tests. The following has been proposed as a general standard for assessing the strength of agreement   for   the   kappa coefficient: $\leq$ 0 poor, .01-.20 slight, .21- .40
fair, .41- .60 moderate, .61-.80 substantial, and .81 -1 almost perfect (Landis and Koch 1977). Significant association in contingency tables (cross tabulations) will be assessed using the standard Pearson's chi-square (x^2) test. If an expected cell count in the cross tabulation is less than 5 then the Fishers exact test will be preferred. A p-value of less than 0.05 will be deemed statistically significant [25].

7. Limitations of the study

A number of limitations are envisaged in the study:

- US is performed by one competent sonographer and may be operator dependent.
- Due to smaller number of available pelvic MRI's performed, a lower absolute precision rate of 20% instead of 10% is used.
- Missing data on incomplete records are likely to effect the final study sample size.

8. Ethical considerations

The following ethical issues will be addressed:

- Ethical clearance from UKZN
- Permission from the Department of Health to work in the hospital
- Permission from the hospital managers at IALCH
- As this is a retrospective chart review, patient permission will not be required. Patients' demographic information will also be anonymized. Names of patients will not be disclosed and confidentiality will be maintained.
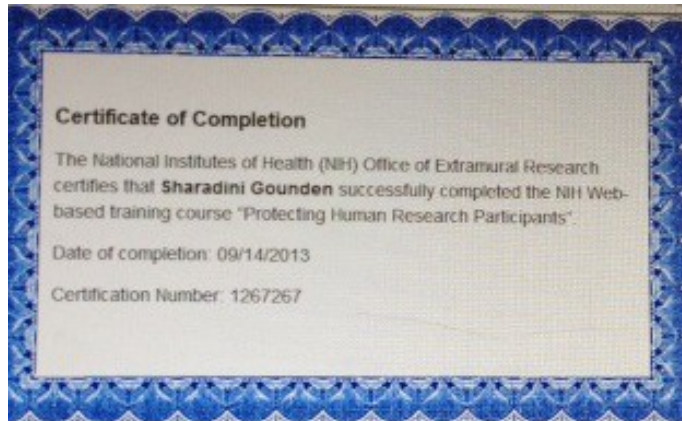
9. Study period

Date	Task
May 2014	BREC application and submission
June 2014	Data collection
July/August/ September 2014	Data analysis
October 2014	Article submission for journal publication

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Appendix 2: Ethics certificate

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research
certifies that **Sharadini Gounden** successfully completed the NIH Web-
based training course "Protecting Human Research Participants".

Date of completion: 09/14/2013

Certification Number: 1267267

Appendix 3 : BREC approval 288/14

22 October 2014

Dr Sharadini Gounden
7 Midsomer Cresent
6 Norfolk
Somerset Park
4139
karen.gounden@gmail.com

Dear Dr �ounden

PROTOCOL:. Identifying benign uterine conditions in female patients: Comparing magnetic resonance imaging **with** ultrasonography: Degree Purposes (MMed). BREC REF: BE288/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 04 June 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 30 September 2014 to queries raised on 13 August 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from 22 October 2014. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be RATIFIED by a full Committee at its meeting taking place on 11 November 2014.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

A Professor D.R Wassen�r

Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Professor DR Wassenaar (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 Facsimile: +27 (0) 31 260 4609 Email; brec@ukzn.ac.za
Website: http:/Jresearch. ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Appendix 4: Department of Health approval

⚰ health

Depa tment:
Health

PROVINCE OF KWAZULU-NATAL

Health Research & **Knowledge Management sub-component**
10 - 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg

3200
Tel.: 033 – 3953189

Fax.: 033 – 394 3782
Em ail.: hrkm@kznhealth.gov.za

Dear Dr SK Gounden

Subject: Approval of a Research Proposal

1. The research proposal titled 'IDENTIFYING BENIGN UTERINE CONDITIONS IN FEMALE PATIENTS: COMPARING MRI WITH ULTRASONOGRAPHY' was

reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby approved for research to be undertaken at lnkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
    a. Make the necessary arrangement with the identified facility before commencing with your research project.
    b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200 and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Dr. E Lutge
Chairperson, KwaZulu-Natal Health Research Committee
Date: *@Mf/t!-*

Reference   : HRKM244/14
Enquiries: Mrs G Khumalo
Telephone: 033 – 395 3189

uMnyango Wezempilo. Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

Appendix 5: Inkosi Albert Luthuli Central Hospital approval

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE 245/14
Enquiries: Medical Management

22 August 2014

Dr S Gounden
Department of Radiology
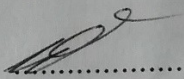IALCH

Dear Dr Gounden

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Identifying benign uterine conditions in female patients: Comparing magnetic resonance imaging with ultrasonography.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

Dr K.E Letebele-Hartell
Medical Manager

uMnyango Wezempilo . Departement van Gesondheid

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