COMPARISON OF TRANSVAGINAL ULTRASOUND, SALINE INFUSION SONOHYSTEROGRAPHY VERSUS DIAGNOSTIC HYSTEROSCOPY IN EVALUATION OF ENDOMETRIAL CAVITY PATHOLOGY AMONGST WOMEN WITH ABNORMALUTERINE BLEEDING IN NAIROBI.

A PROSPECTIVE COHORT STUDY

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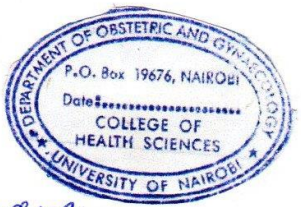

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May God bless you

DEDICATION

To my parents Mr. Chandrakant Dedhia and Mrs. Ila Dedhia,
My in laws Mr. Jagdish Patel and Mrs. Gita Patel
For their everlasting love and support,
For giving me the best education and making me who I am today
To my niece &nephews Kyra, Aavir, Saavir & Rayan,
Who have brought so much love and blessings into my life,
To my siblings Paras& Swetal and Hemal & Rajvi,
For always being there for me and always making it easier for me
To my husband Ashish Patel,
My teacher, my partner, my beloved, my Rock
Who has unconditionally led me to this path and walked me through it,
Without whom this would not have been possible.
And above all to the Almighty,
My source of strength, wisdom, knowledge and understanding

This research is dedicated to you.

DECLARATION

I do declare that this research has been undertaken in part fulfillment of the Master of Medicine in Obstetrics and Gynecology from the University of Nairobiand will be my original work and has not been undertaken and presented for a degree in any other university.

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LIST OF ABBREVIATIONS

AUB	Abnormal Uterine Bleeding
GIS	Gel Instillation Sonohysterography
HS	Hysteroscopy
HSG	Hysterosalpingography
KNH	Kenyatta National Hospital
NPV	Negative Predictive Value
PPI	Present Pain Intensity
PPV	Positive Predictive Value
RCT	Randomized Control Trial
SDG	Sustainable Development Goal
SIS	Saline Infusion Sonohysterography
TVS	Transvaginal Sonography
UON	University Of Nairobi
VAS	Visual Analogue Scale
HMB	Heavy Menstrual Bleeding

DEFINITION OF TERMS

Abnormal Uterine Bleeding (AUB): an episode of bleeding among a woman of reproductive age, who is not pregnant that is sufficient quantity to require immediate intervention to prevent further blood loss.

Transvaginal Ultrasound (TVS): a pelvic ultrasound used by gynecologists to examine female reproductive organs.

Saline Infusion Sonohysterography (SIS): refers to a procedure in which fluid is instilled into the uterine cavity transcervically to provide enhanced endometrial visualization during a transvaginal ultrasound examination.

Hysteroscopy: is a process of using a viewing endoscope to examine the interior of the uterus along with the vaginal and cervical canal.it can be both diagnostic and therapeutic.

Menorrhagia: abnormally prolonged or heavy menstrual bleeding

Oligomenorrhea: irregular menstrual periods among women of childbearing age. This is often described among women who go for more than 35 days without receiving their menstrual periods.

Polymenorrhea: this is a type of abnormal uterine bleeding marked by a menstrual cycle shorter than 21 days

Postmenopausal bleeding: this is described as the occurrence of vaginal bleeding twelve months after menopause.

Amenorrhea: this is the absence of menstrual bleeding in women of childbearing age. This often occurs during lactation and pregnancy.

Consecutive Random Sampling: is a sampling technique in which every subject meeting the criteria of inclusions is selected until the required sample size is achieved.

ABSTRACT

Background: Hysteroscopyiscurrently the gold-standardprotocol for evaluating patients with abnormal uterine bleeding (ABU).Unfortunately, though accurate, its adoptionin low-resource countries such as Kenya is limited due to lack of equipment and qualified personnel.As such, there is a need for an alternative diagnostic procedure that is as accurate as hysterectomy, but is also affordable, easy to administer,and acceptable by women with endometrial pathologies. Transvaginal Sonography (TVS) and Saline Infusion Sonohysterography (SIS) are proposed. However, their diagnostic accuracy versus hysterectomy have not been determined in Kenya.

Objective: Compare the diagnostic efficacy of TVS and SIS versus diagnostic hysteroscopy in evaluation of endometrial pathology among pre-menopausal and post-menopausal women and to determine the etiology of AUB amongst these women.

Methodology: A prospective cohort study was done at the Mediheal Minimal Access Surgery Hospital, Nairobi between May and September 2019.Forty patients referred for diagnostic hysteroscopy due to AUB were recruited using consecutive sampling, hospital files reviewed, and women who met our inclusion criteria consented and recruited until we reached our sample size. All participants underwentTVS, SIS and Diagnostic Hysteroscopy (DH) evaluation in the first half of the menstrual cycle and the findings recorded on a patient's information sheet. The etiology of AUB was recorded. The sociodemographic and bleeding characteristics of patients and the outcomes of TVS, SIS, and DH evaluations were also recorded and data analysed using version 5 of the Software for Statistics and Data Science (STATA). The descriptive and health characteristics of patients were summarized and visualized in a table. Summary statistics on the etiology of AUB were presented in a table and a bar graph and the sensitivity of TVS and SIS versus DH as the gold-standard evaluated using two by two tables and the ROC curve.

Results: The mean age of participants was 38.1±8.8 years, range of 25-71 years. A majority were nulliparous (62.5%), of African descent (75.0%), married (67.5%), and were unemployed (52.5%).Heavy Menstrual Bleeding **(**HMB)was reported in 70.0% of participants, while about 12.0%, 7.5%, and 7.5% had post-menopausal bleeding, amenorrhea, and hypomenorrhea. The incidence of submucosal fibroids and endometrial polypswere 17.5% and 15.0% via TVS, 47.5% and 20.0% via SIS and 52.5% and 20% via DH respectively. The overall sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SIS was 92.1%, 83.3%, 96.9%, 62.5%, and 90.0% while TVS was 38.2%, 100%, 100%, 22.2%, and 47.5%. The sensitivity, specificity, PPV, andNPV of TVS in diagnosis of endometrial polyp was 75.0%, 100%, 100%, and 94.0%. SIS did better with asensitivity, specificity, PPV, and NPV of 100%, 100%, 100%, and 100%.

Conclusion: With hysteroscopy as a reference, the sensitivity, NPV, and accuracy of SIS of 92.1%, 62.5%, and 90.0% was higher than TVS (38.2%, 22.2% and 47.5%). TVS demonstrated a higher specificity (100%) and PPV (100%) than SIS (83.3% and 96.9%) but could not detect synechia and endometrial cysts that were detected via SIS. Overall, SIS had a higher diagnostic accuracy than TVS and showcased a comparable diagnostic accuracy to hysteroscopy. Thus, it makes a suitable alternative technique for investigating AUB in pre/post-menopausal women.

CHAPTER 1: INTRODUCTION

1.1 Background

Non-bleeding symptomatic uterine conditions, abnormal uterine bleeding (AUB), or incidental findings on screening investigations need a comprehensive assessment of the endometrial cavity to make a definitive diagnosis. Abnormal Uterine Bleeding is among the most common indications for gynecological surgical intervention in both premenopausal and postmenopausal women (1), with studies reporting that 70% of gynecologicalconsultations of premenopausal women are for AUB(2). Several tools and approaches have been developed to ensure a proper diagnosis of endometrial cavity anomalies, encompassing hysteroscopy, SIS, and TVS(3–6).

Hysteroscopy is a diagnostic and therapeutic intervention for the detection and treatment of the causal factors for AUB(7). Even though hysteroscopy is regarded as the gold standardfor the defining the causes of AUB because it allows direct visualization of the endometrial cavity and facilitating excision of a small portion of a suspected abnormality, it is an invasive procedure(8). Moreover, it does not offer additional information on adnexa and myometrium(9), and has been associated with severe pain and discomfort during its administration and possibility of complications, which lengthens hospital stay, increases acquisition of nosocomial infections, and increases the cost of management of co-morbidities that are associated pain(10).

Transvaginal Ultrasound is sensitive in the detection of endometrial carcinoma and hyperplasia (11,12), submucosal fibroids(13), and endometrial polyps (8).The procedure also facilitates clear observation of the endometrial cavity, but has a high false positive and false negatives rate(3,14)and does not isolate focal uterine lesions well(15,16).However, even though TVS is associated with tolerable pain, SIS has been cited to be less painful and thus more acceptable than TVS and DH(1,15,16). SIS also offers detailed imagesof endometrial cavities than TVS and hysteroscopy,is cheaper, and can distinguish focal endometrial lesions that need a directed biopsy with a lower risk of complications and or prolonged hospital admissions, which makes it a suitable substitute ofDH as an initial diagnostic procedure for women suffering from AUB.Nevertheless, its efficacy in comparison to DH has not been evaluated sufficiently in Kenya.

CHAPTER 2: LITERATURE REVIEW

2.1 Efficacies of TVS, SIS and Diagnostic Hysteroscopy

Saline infusion sonohysterography is a simple and precise procedure that entails gradual administration of sterile saline into the uterine cavity through a catheter inserted via the cervix (5). The procedure generates better ultrasound scans of the endometrial cavity than traditional approaches like TVS or hysteroscopy with Dekroon et al.(17) reporting a success rate of 93%.

In 2007, Alborzi et al.(18)used SIS and TVS to evaluate endometrial cavity in a cohort of women suffering from AUB. Both diagnostic approaches were matched with hysteroscopy as the gold standard for the diagnosis of intrauterine pathologies. Alborzi found that SIS had a general specificity, sensitivity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)of 95%, 94%, 96%, and 90% respectively, while the figures for TVS were 92%, 72%, 94%, and 65% respectively. Similar findings have been reported in other studies(13,19).

In a prospective study by Nanda et al. in 2010 (20) on the efficacy of TVS versus SIS in the detection of endometrial polyps and submucous fibroids in 50 women with AUB, both interventions were useful, but SIS was more sensitive and specific than TVS in the diagnosis of the target lesions.In 2018, Swaleh et al.(21), in a prospective study on the efficacy of SIS in detection of uterine pathologies, evaluated 87 women presenting with AUB at the Kenyatta Hospital, Kenya. The comparative study of TVS and SIS in evaluation of endometrial cavity pathology in abnormal uterine bleeding found that TVS facilitates clear observation of endometrial cavity but is marked by high false positive and false negative results and has a poor precision in the isolation of focal uterine lesions. The results showed that even though TVS was simple, affordable, and less painful in detecting pathologies in the endometrium, SIS was more sensitive. However, Swaleh did not compare the efficacy of SIS versus hysteroscopy and histopathology due to infrequent and high cost of hysteroscopic guided giopsies in Kenya.

In another retrospective study(22), Vitner and others compared the diagnostic usefulness of TVS versus hysteroscopy in the detection of endometrial anomalies in 2013. The results showed that while TVS was highly sensitive in the identification of the retained products of conception, hysteroscopy posted substantially higher sensitivity in the detection of intra-

uterine fibroids and had superior PPV and NPV values for diagnosis of uterine polyps.Alborzi et al. (18)and Radwan et al. (23)found similar results in 2007 and 2014 respectively. In the study by Radwan assessing the expediency of SIS versus hysterectomy and histological examinations in evaluating endometrial polyps among 241 infertile patients, both SIS and hysteroscopy detected endometrial polyps, but SIS posted 2.7% and 4.2% false-negative and false-positive results respectively. Radwan and colleagues also noted that the specificity, sensitivity, and error of the SIS in diagnosing endometrial polyps were 95.8%, 97.3%, and 3.7% respectively, and the NPV and PPV were 98.7% and 91.1% respectively.However, a 2016 prospective study by Reda et al. (24), reported an extremely low sensitivity of SIS (41.2%), but the NPV (81.1%), the specificity (100%) and the PPV (100%) were all exceptional.

In prospective investigation by Pasrija et al. (9)in 2004 , SIS detected ten uterine anomalies in 56 women, while TVS failed to detect one endometrial hyperplasia and three endometrial polyps, and resulted in the mislabeling of two cases of intramural fibroids as submucosa. A comparison of hysteroscopy findings with those of SIS showed that the latter failed to detect one endocervical polyp and one endometrial polyp. A false positive was reported by SIS but the specificity, sensitivity, NPV, and PPV for SIS werehigh at 88.5%, 94.1%, 92%, and 91.4% respectively. In another study (25), Dueholm found SIS to have a higher accuracy than TVS in the detection of endometrial cavity anomalies, but failed to describe if the cavity was normal or abnormal in 24% of cases. SIS was also unable to differentiate between myoma and polyp, suggesting the necessity for mapping of more lesions to make definitive diagnoses through SIS.

Clark et al.'s systematic review in 2002 (26)reported that the accurateness of hysteroscopy is high for endometrial lesions but moderately accurate in the detection of hyperplastic cells. In the study by Rogerson(27), a similar finding was reported in 2002 in which SIS failed to detect 20 cases, while hysteroscopy failed in a single case. Both procedures failed in six other cases.

2.2 Conceptual Framework

2.2.1 Narrative

Saline infusion sonohystography is a medical procedure that is deemed a suitable alternative to diagnostic hysteroscopy, which is considered the gold standard. Literature portrays it as a non-invasive office procedure that offers a clear view of endometrial pathologies with little discomfort at an affordable cost. Performed after a Transvaginal ultrasound, its sensitivity and specificity have been reported to be high, which makes it an ideal substitute for diagnostichysteroscopy, which is invasive and expensive, but offers an added benefit in that it handles both diagnostic and therapeutic procedure accurately.

2.3 Schematic

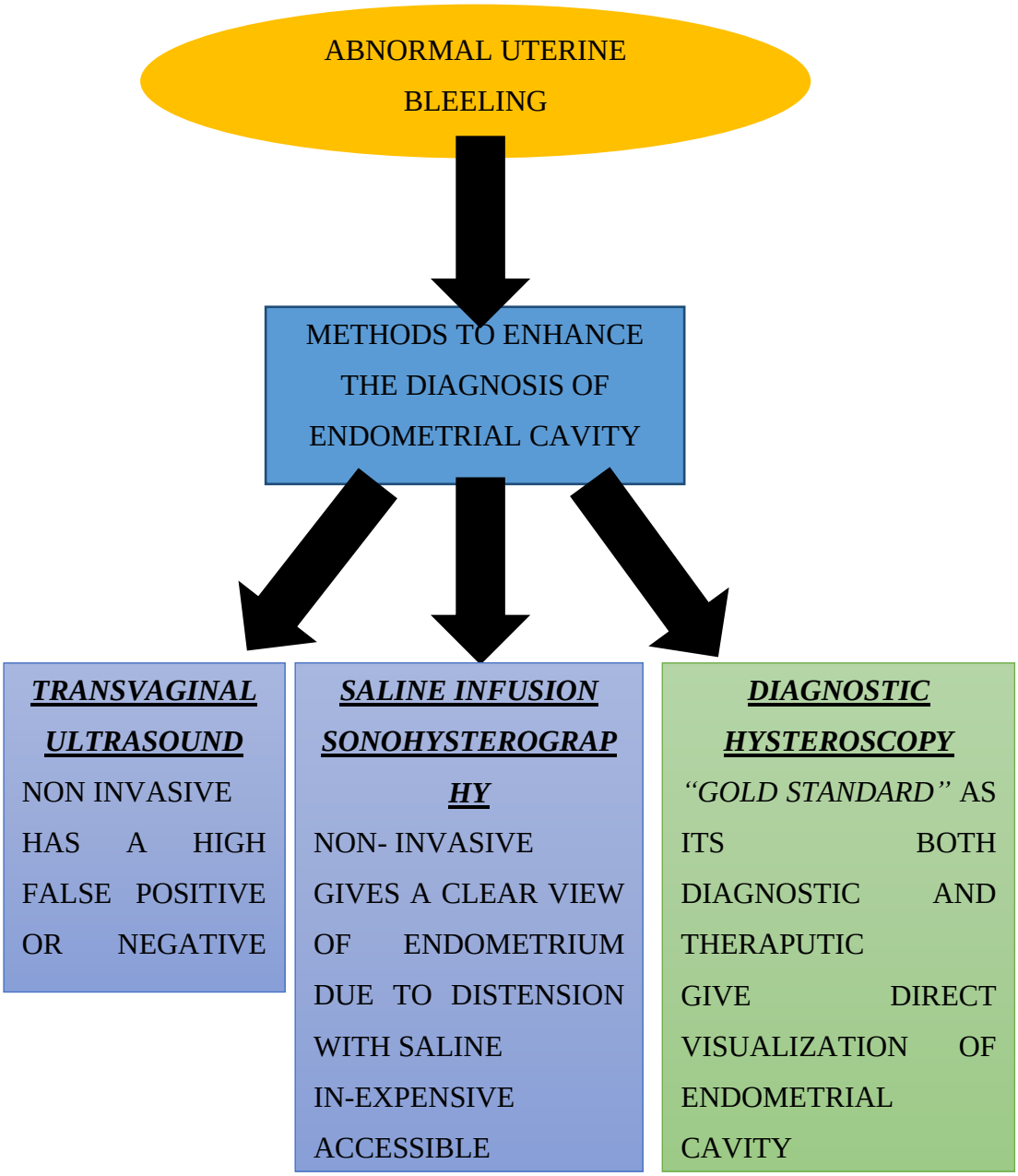

Figure 1. Conceptual framework

2.4 Study Justification

Endometrial pathologies are associated with high hospitalization rates, skyrocketing healthcare cost, high morbidity, and mortality rates. In literature, diagnostic hysteroscopy is considered the gold standard for the analysis of uterine cavity disorders but has a few limitations. During its administration, it can induce a plethora of complications such asthrombosis, infection, bowel or bladder damage, and hemorrhage and is highly and expensive (28).This calls for an alternative diagnostic procedure that is both accurate and acceptable by patients.

TVS is a suitable alternative to hysteroscopy due to its safety and ease of use, but has been found to have a high rate of false negativeswhile used to detect focal intrauterine abnormalities.

Whereas SIS has been touted as the best alternative to hysteroscopy, there are mixed findings regarding its efficacy and acceptability in terms of patient satisfaction. Although, many authors (13,17–19) have reported the diagnostic accuracy or SIS to be slightly higher or comparable with hysteroscopy, its efficacy in diagnosing some pathologies has been questioned(9,23,26)

However, most of these focus on either premenopausal or postmenopausal women only, which introduces bias. Besides, no study has evaluated thediagnostic efficacy of TVS and SIS versus DH for the evaluation of endometrial cavity pathologies in a hospital setting in Kenya. This underscores the necessity for an evaluation of the efficacy of TVS and SIS versus hysteroscopy in the diagnosis of endometrial pathologies among pre- and post-menopausal patients.

2.5 Research Question

How does diagnostic efficacy of TVS and SIS versus diagnostic hysteroscopy compare with regards to their specificity and sensitivity, in the evaluation of endometrial pathology in pre- and post-menopausal women with AUB?

2.6 Study Objectives

2.6.1 Broad Objective

To compare the diagnostic efficacy of TVS and SIS versusdiagnostic hysteroscopy in the evaluation of endometrial pathology among pre-menopausal and post-menopausal women and to determine the etiology of AUB amongst these women.

2.6.2 Specific Objectives

i. To determine the etiology of abnormal uterine bleeding amongst pre- /post-menopausal women undergoing diagnostic hysteroscopy.
ii. To determine the sensitivity and specificity of TVS vs diagnostic hysteroscopy in evaluation of endometrial pathology in pre-/postmenopausal women.
iii. To determine the sensitivity and specificity of sis vs diagnostic hysteroscopy in evaluation of endometrial pathology in pre-/postmenopausal women.

CHAPTER 3: METHODOLOGY

3.1 Study Design

Aprospective, cohort study for assessing the demographic pattern of undiagnosed Abnormal Uterine Bleeding and the efficacies of TVS, SIS in diagnosing abnormalities of uterine cavity as compared to hysteroscopy.

3.2 Study Site and Setting

The study was carried out at Mediheal Minimal Access Surgery and Day Care Centre (MMAS), a well-known hospital for performing minimally invasive operations. The hospital is situated in the Parklands area of Nairobi County, approximately 10 kilometers from the central business district (CBD). MMAS has bed capacity of 250 in patients but attends to an average of 400 patients every year. Under laboratory medicine, a team of microbiologists, pathologists, clinical pathologists, and biochemists oversee a plethora of medical procedures, including DH. Approximately 150-200 patients undergo the procedure for abdominal uterine bleeding, fibroid tumors or polyps, retained products of conception or placenta, and scarring or adhesions.

3.3 Study Population and Study Period

The study targeted all premenopausal and postmenopausal patients aged 19 to 75yrs who presented with suspected AUB and were referred for inpatient diagnostic hysteroscopy from May 1st, 2019 and September 30st, 2019.

3.3.1 Inclusion Criteria

- Pre- menopausal women with abnormal uterine bleeding in the 1st half of menstrual cycle
- Post-menopausal women with Abnormal Uterine Bleeding
- Provision of informed consent

3.3.2 Exclusion Criteria

- Expectant women/positive pregnancy test.
- Women below 18 years/virgin women
- Pelvic Inflammatory Disease/Active vaginal infection.

- Congenital anomalies/structural anomalies such as Rudimentary Uterus, Mullerian, Agenesis, Fraser's Syndrome, McKusick Kaufman Syndrome, Bardet-Biedl

3.4 Sample Size and Sampling Process

The sample size of women included in the study was calculated using Buderer's formula for sample size calculation in diagnostic accuracy studies at the required absolute precision level for sensitivity and specificity. The assumptions in the sample size calculation are derived from a similar study conducted by Bittencourt(29), where 32.7% of the patients had endometrial polyp with sensitivity and specificity of SIS, taking hysteroscopy as gold standard as follows:

Sample size (n) based on sensitivity

$$\frac{Z^2_{1-\alpha/2} \times S_N \times (1 - S_N)}{L^2 \times Prevalence}$$

Where:

n = required sample size

S_N =anticipated sensitivity = 94%, (95% Confidence Interval 89% – 97%)

S_P = anticipated specificity = 81% (95% Confidence Interval 76% - 86%)

α= size of the critical region (1 – α is the confidence level = 0.05)

$Z_{1-\alpha/2}$ = standard normal deviate corresponding to the specified size of the critical region (α) = 1.96

L = absolute precision desired on either side (half – width of the confidence interval) of sensitivity = 96-89/2 = 3.5

Using a prevalence of endometrial polyp to calculate the sample size, N, for the study substituting the figures in the statistical formula at 95% confidence level and a power of 80, the sample size calculation for this study is 37. Allowing for 10% non-response, the recalculated sample size will be 100/90x37= 40.

3.5 Recruitment and Consenting Procedures

3.5.1 Patient Recruitment

The eligibility of patients was evaluated on admission and participants who met or inclusion criteria recruited until sample size was attained (see appendix 3 and 4). The Optimal timing

for SIS depended on the clinical presentation. In a woman who had regular menstrual cycles, SIS was typically done early in the follicular phase of the cycle, after cessation of menstrual flow, but no later than day 10 of the cycle this is because a thin endometrium gave proper visualization of focal lesions. The secretory phase was avoided because folds of the endometrium can mimic small fibroids or polyps or focal areas of endometrial hyperplasia. In cases where there is prolonged or irregular bleeding the procedure was carried out when there is no active bleeding. Recruitment and enrolment were carried out by the research assistants or principal investigator who were all part of the study team.

3.5.2 Consent

Once identified, the principal investigator or research assistant briefed the patients on the purpose and method of the study and attained a verbal consent. After that, written approval was obtained on a pre-designed consent form (see appendix 1) that describes the main goal of the study, the study procedure, and the potential risks and benefits of participating in the research. The consent form was also be translated into Swahili for the ease of understanding (see appendix 2). Any pertinent questions or concerns regarding the procedures were responded to at that point. This process was free from coercion and explicitly voluntary. Those who agreed to take part in the study were asked to sign the consent form and this was then countersigned by the investigator. Records were kept regarding reasons for non-participation of eligible participants, and a copy of the signed consent form was given to the participant.

3.6 Data collection

3.6.1 Sociodemographic Characteristics:

Sociodemographic characteristics was collected from patients presenting with AUB at the time of admission. Data collected included the age, BMI, parity, medical surgical obstetric and gynecological history. This data was collected by the research assistants or principal investigator. All information taken was used to complete the questionnaire. The patient then proceeded for TVS and SIS and findings of each procedure were recorded separately.

3.6.2 TVS

Patient was asked empty the bladder and lie on an examination table in lithotomy position for transviginal ultrasound. A 3D-TVS was conducted with Seimens Acuson NX3 USG machine

using a transvaginal probe of 5.0-8.0MHzwas covered with a plastic or latex sheath and lubricated. The tip of the transducer will be inserted into the posterior fornix. The transducer was gently turned and angled to measure the endometrial cavity allowing clear visualization in longitudinal and transverse planes by TVS the endometrial lining. If the endometrium is found to be normal, >5 mm in postmenopausal women or >12 mm in a premenopausal patient, they were subjected to saline infusion sonohysterography.

3.6.3 SIS

A SIS catheter (Sion-Test sonosalpingography device) was inserted into the uterine cavity following direct visualization, without dilating the cervix or use of local anesthesia. A vaginal probe was re-inserted in the posterior fornix of the vagina behind the catheter. Approximately 20-30 ml of 0.9% saline was injected into the catheter to inflate the endometrial cavity allowing clear visualization in longitudinal and transverse planes by TVS. SIS protocol was documented and followed to limit errors in procedure. Upon completion of both procedures data was collected by the research assistants and filled in on the data collection form.

3.6.4 Diagnostic Hysteroscopy

The consultant gynecologist consultant together with the principal investigator performed the inpatient hysteroscopy using Olympus A4673A 12-degree rigid hysteroscope under aseptic techniques and following all infection prevention and control guidelines. A rigid hysteroscope was introduced into the cervix under direct visualization followed by inflation with isotonic solution. Upon completion of both procedures data was collected by the research assistants and filled in on the data collection form to complete the form.

3.7 Study Procedures

3.7.1 Study Flow Diagram

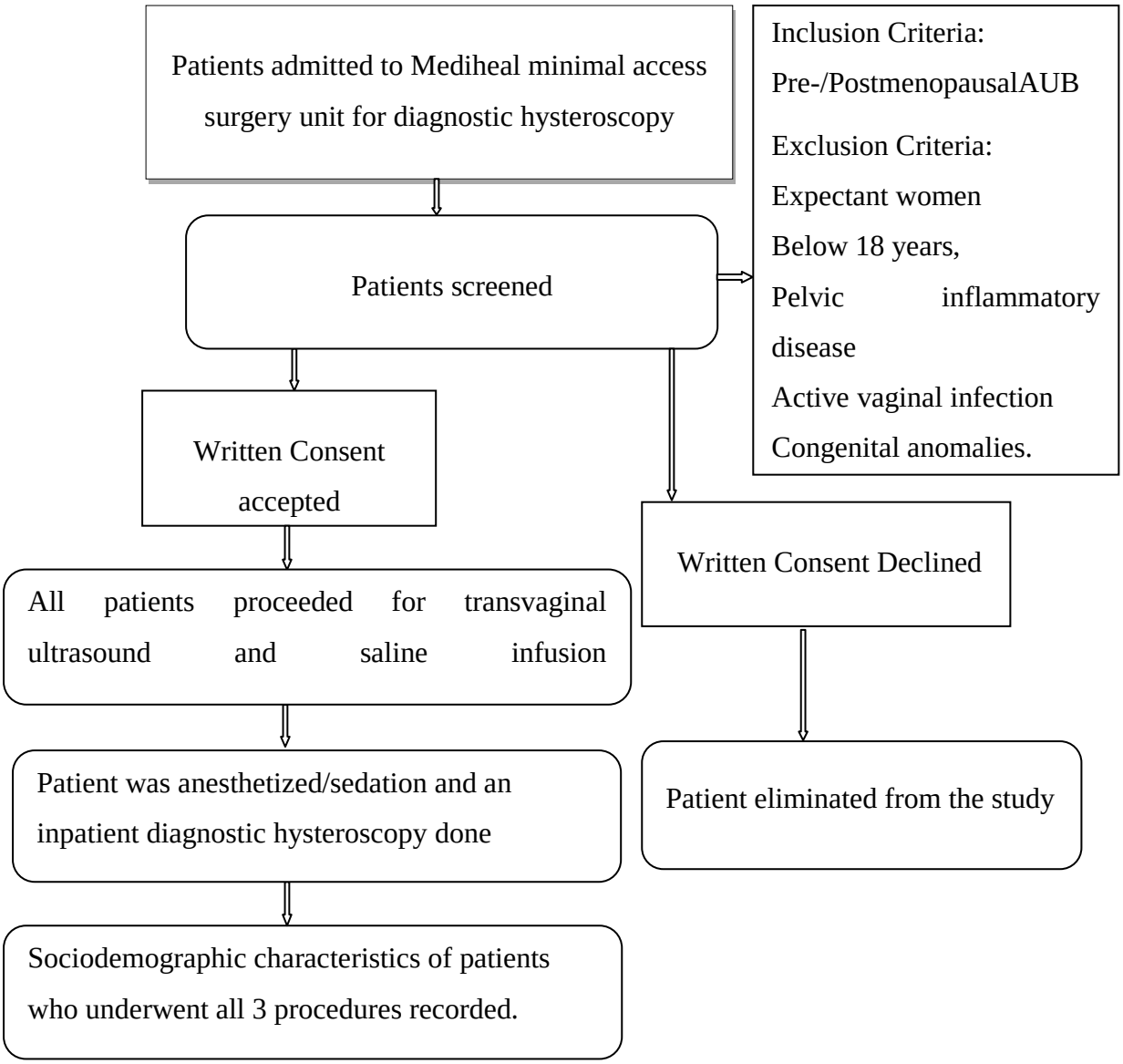

Figure 2. Study flow chart

3.8 Study Procedure and Tools

3.8.1 Saline Infusion Sonohysterography

All the patients who met the selection criteria underwent 3D-Transvaginal ultrasound followed by 3D- SIS as shown in the study protocol (see appendix 7). This was conducted under supervision of Consultant Radiologist. The results of both procedures (TVS, SIS and diagnostic hysteroscopy) were documented separately without the knowledge of each other's observations and findings and was therefore blinded. SIS was done using a transvaginal scan and thereafter followed by inpatient hysteroscopy as described by Rudra et al.(6).

After the bimanual exam of the pelvis, 3D-TVS was conducted with Seimens Acuson NX3 USG machine using a transvaginal probe of 5.0-8.0MHz. Subsequently maintaining asepsis, A 3D-SIScatheter (Sion-Test sonosalpingography device,India) was inserted into the uterine cavity following direct visualization, without dilating the cervix or use of local anesthesia. A vaginal probe was re-inserted in the posterior fornix of the vagina behind the catheter. Approximately 20-30 ml of 0.9% saline was injected into the catheter to inflate the endometrial cavity allowing clear visualization in longitudinal and transverse planes by TVS. Any abnormal outcomes were recorded in the data sheet attached as shown in appendix8 (Table 2).

3.8.2 Inpatient Diagnostic Hysteroscopy

Following TVS and SIS evaluation participants were subjected to diagnostic hysteroscopy.The gynecologist consultant together with the principal investigator performed the inpatient hysteroscopy under General anesthesia using Olympus A4673A12 degree rigid hysteroscope under aseptic techniques following all infection prevention and control guidelines. A rigid hysteroscope was introduced into the cervix under direct visualization followed by inflation with isotonic solution. Any abnormal observations were recorded on a data sheet (Appendix 8)

3.9 Data Collection

3.9.1 Patient Data

A log was available at Mediheal Minimal Access and Day Care Centre for all the principal investigators, research assistants, and enrolled patients. Any data which was collected from the eligible patients were entered and signed in the logbook (see appendix 6). A structured survey questionnaire was used to gather all sociodemographic and medical details from the participants. Consultants and principal investigator reviewed all patients during admission into the center. After that, those who met the inclusion criteria and consented were recruited for the procedures. Those females who had undergone the interventions were interviewed to further complete the questionnaire (see appendix 5).

3.9.2 Data Quality Assurance

Quality assurance was enhanced continuously throughout the study period to maximize on the validity and reliability of the findings. The questionnaires were checked for completeness

at the end of each day by the principal investigator during data collection period to ensure completeness and accuracy of data collected. The questionnaires were availed in English and Kiswahili and pre-testing of study instrument were carried out in a non-study site to correct it for bias, misinterpretation of the questions and ambiguity. The validity of the study was ascertained by ensuring that the data collection instruments reflect the objectives of the study. The research instrument was validated by the University of Nairobi supervisors.

3.9.3 Data Management and Analysis

The collected data was entered and analyzed using the STATA software version 23. The demographic characteristics were summarized and presented as means and standard deviations, medians, and interquartile ranges, as well as frequencies and proportions where applicable for continuous and categorical data. Specificity, sensitivity, positive predictive values (PPVs), negative predictive values (NPVs), and diagnostic accuracy (DA) were computed as shown in Appendix 9 and used to determine the diagnostic precision of TVS, SIS and hysteroscopy in the detection of endometrial pathologies. Further analysis was done and presented in form of receiver operating curves (ROC). A p value of <0.05 was taken as statically significant.

3.10 Ethical Considerations

This protocol and the template informed consent form found in the Appendix 1 and any subsequent modifications to this form were reviewed and approved by the Kenyatta National Hospital/University of Nairobi Ethics Research Committee (KNH-UoN ERC) prior to the initiation of the study, with respect to scientific content and compliance with applicable research and human subjects' regulations.

Safety and progress reports were submitted to the KNH-UoN ERC, after study completion or in the case of study termination or occurrences of any adverse events. The reportsinclude the total participants enrolled in the study, the number of participants that completed the study, all changes in the research activity, and all other problems that were not anticipated that involved risks to human subjects or others. Finally, all open DSMB reports were to be provided to the KNH-UoN ERC. Approval was sought from Mediheal before inception of the study.

3.10.1 Informed Consent

We obtained written informed consent from participants. Adequate explanation and counselling were done before attaining consent. The informed consent form described the purpose of the study, the procedures to be carried out and the risks and benefits in accordance with applicable regulations. The consent form was translated into Swahili for ease of understanding for patients not proficient in the English Language.Literate patients appended their signatures at the provided space in the consent form. Non-literate participants documented their approval by marking the form using their thumbprint, in the presence of a literate third-party witness. Any other local ERC requirements for obtaining informed consent from non-literate persons were followed. Participants or their parents/ guardians were provided with a copy of their informed consent forms and this fact was documented in the participant's record.

No personal identifiers were employed for participants. A unique study identification number was assigned to each participant for purposes of identification. This identification number linked them to a log with their personal details. This information was stored in a password protected database that was only accessible to the principal investigator.

3.10.2 Risk to Subjects

We ensured the participants privacy and confidentiality was always maintained. However, it is possible that others knew of the participant's involvement in the study, we believe there will be no stigma related to this and hence no harm.

3.10.3 Benefits of the Study

The participants benefitted by receiving close monitoring throughout the study period. Besides, because all patients underwent TVS, SIS, and DH during evaluation of endometrial cavity pathology, they had an accurate diagnosis. The information may benefit others in the future.

3.10.4 Confidentiality

Information collected was handled with Belmont's principles of confidentiality (Respect for persons, Beneficence and Justice). Each participant was allocated a unique study identification number for confidentiality. The coded number identified all reports, data collection and other administrative forms. All the information on the participants and the study as a whole were stored and secured at the study site and stored in locked file cabinets

only accessible by study staff. All databases were secured with password-protected access systems. The study information of the participants was not released without the written permission of the participant, except for monitoring by the DMSB, or KNH-UoN-ERC.

3.10.5 Study Discontinuation

The study's goal was to achieve ≥ 95% participant retention. We made every reasonable effort to retain all enrolled study participants until completion of the study. Participants were allowed to withdraw from the study at any point if they were unwilling or unable to comply with the required study procedures at any point. To protect participants' safety, the principal investigator was allowed to withdraw participants from the study.A final evaluation was done for study participants who withdraw from the study before completion. The reasons for the withdrawal were recorded in the participants' records.The study could be discontinued at any time by the KNH-UoN-ERC.

3.10.6 Strengths of the Study

This is the first local study evaluating the endometrial cavity using transvaginal ultrasound and saline infusion sonohysterography and comparing it a Gold Standard - Hysteroscopy, it will therefore form a baseline for other studies in this area.

3.10.7 Study Limitations

The time period of follow-up was short and therefore both short-term and long-terms effects of TVS and SIS forevaluation of endometrial cavity pathology of women with AUB could not be assessed. It would be enriching to have a deeper understanding of such long-term outcomes.

The cohort can, therefore, be followed up in another study evaluating the long-term results.

3.11 Study Results Dissemination

All participants in the research were given a report of the findings and were encouraged to comment on them. A report of the study findings will be presented to the department of obstetrics and gynecology, University of Nairobi, and copies sent to Mediheal hospital and the KNH-UoN ERC. A manuscript will be drafted and submitted to a peer-reviewed journal.

CHAPTER 4: RESULTS

4.1 Study Flow Chart

Out of 65 patients who presented with abnormal uterine bleeding, 12 were excluded due to incomplete records, ten patients declined consent, and three patients did not fit the inclusion criteria. Therefore 40 pre-menopausal and post-menopausal patients were recruited (Figure 3).

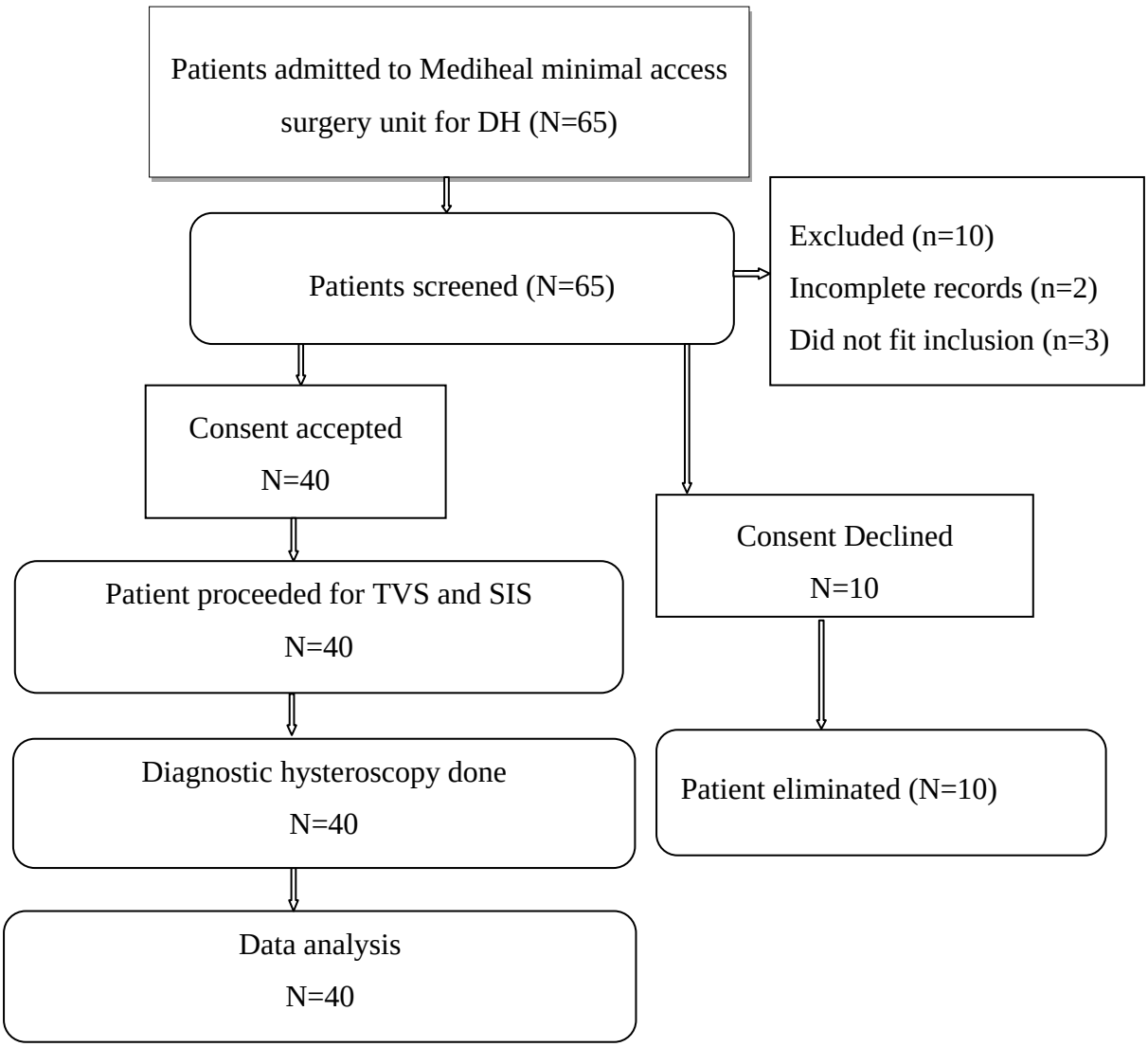

Figure 3. Study flow chart

4.2 Sociodemographic Characteristics

The mean age of participants was 38.1 years ±8.8 years, range 25-71 years. Thirty five patients(87.5%) were of a pre-menopausal age. Mean weight was 73.53 kilograms ± 16.2 kilograms, range 47-125 kilograms, while the mean BMI was 27.6±5.7, range 19.4-41.9.

Majority of the patients were Nulliparous (62.5%), of an African origin (75%) married (27, 67%), had attained higher than primary school education (92.5%), and were unemployed (52.5%) (Table 1 below).

Table 1. Sociodemographic characteristics of premenopausal and postmenopausal women in Nairobi

		Frequency (n)	***Percent (%)***
Age	mean ± SD (range)	38.1 ± 8.8 (25-71)	
Parity			
	Nulliparous	25	62.5
	Primipara	8	20.0
	Multipara	7	17.5
Ethnicity			
	African	30	75.0
	Asian	7	17.5
	Caucasian	3	7.5
BMI	mean ± SD (range)	27.6±5.7 (19.4-41.9)	
Marital status			
	Married	27	67.5
	Not married	13	32.5
Educational level			
	Primary	03	7.5
	>Primary	37	92.5
Employment status			
	Salaried	07	17.5
	Self Employed	12	30.0
	Unemployed	21	52.5

4.3 Bleeding Patterns of the Study Participants with AUB

All patients who were included in the study had a history of Abnormal Uterine Bleeding (AUB), characterized further as shown in F***igure 4***. Twenty-eight (70%) of the patients presented with a history of heavy menstrual bleeding,5 (12%) presented with post-menopausal bleeding and 3 (7.5%) presented with a history of hypomenorrhea and amenorrhea respectively

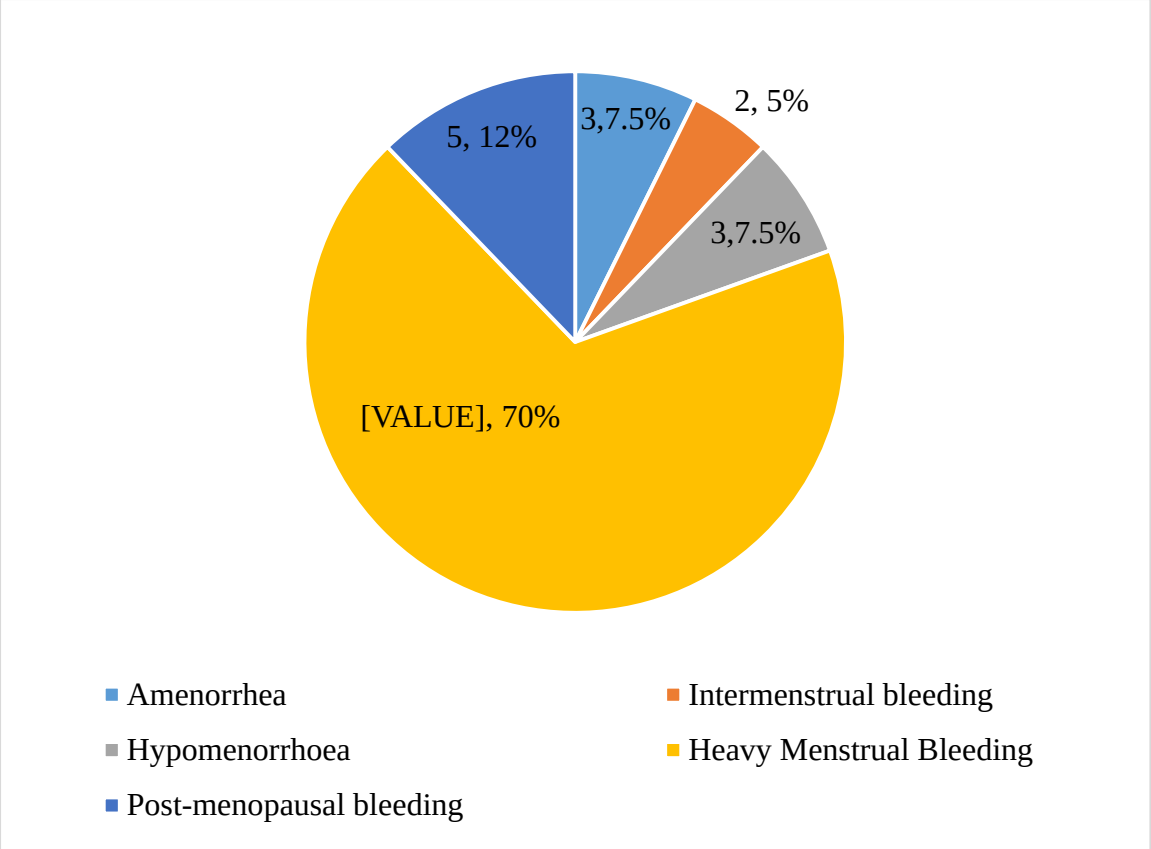

Figure 4. Bleeding patterns distribution amongst the Study Participants with ABU.

4.4 Pathologies diagnosed with TVS, SIS and Diagnostic Hysteroscopy

The pathological findings of women with AUB are summarized in Figure 5 and Table 2 below. Out of the 40 3D-transvaginal ultrasounds that were conducted prior to SIS, 27 (67.5%) showed Normal Cavity, 7 (17.5%) submucosal fibroids, and 6 (15%) endometrial polyps. TVS did not detect endometrial lesions such as endometrioid cyst (adenomyosis), cervical stenosis, Mullerian duct anomalies and synechiae. SIS evaluation showed a normal cavity in 8 (20 %) of participants, while 29 (72.5%) cases had a submucous myoma (47.5%), endometrial polyp (20.0%), uterine adhesions (7.5%), adenomyosis (endometroid cyst) (5 %) and cervical polyps (2.5%).

Two cases were diagnosed falsely with normal uterine cavity, but were diagnosed with abnormal uterine cavity on diagnostic hysteroscopy. However, hysteroscopic evaluation of the Uterine cavity showed no false negative cases as 6 (15%) cases were diagnosed with normal cavity and uterine cavity abnormalities were diagnosed in 34(85%) [52.5 % submucous myoma, 20%endometrial polyp,15% uterine adhesions, 5%adenomyosis (endometroid cyst), 2.5% cervical polyp, 2.5 with Mullerian duct anomaly].

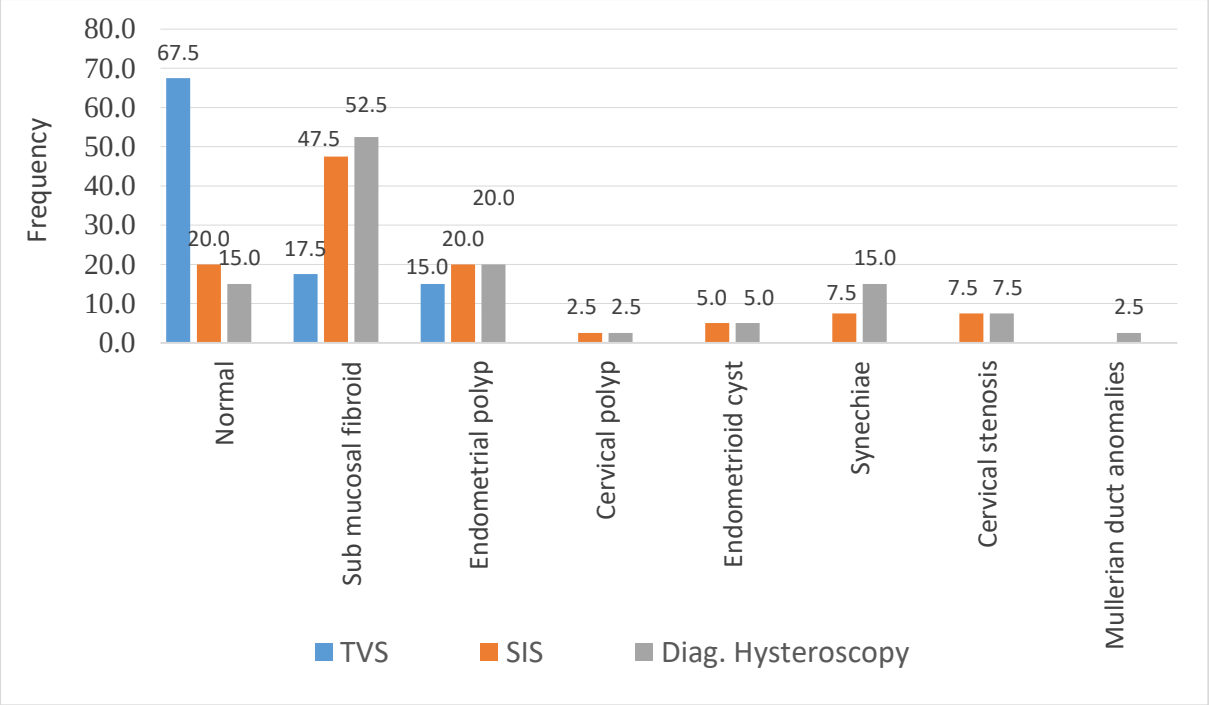

Figure 5. Distribution of pathology noted on TVS, SIS and diagnostic hysteroscopy.

Table 2. TVS, SIS, and Diagnostic hysteroscopy findings of premenopausal and postmenopausal women in Nairobi

	Frequency: n (%)		
	TVS	***SIS***	***Diag. Hysteroscopy***
Normal	27 (67.5)	8 (20.0)	6 (15.0)
Sub mucosal fibroid	7 (17.5)	19 (47.5)	21 (52.5)
Endometrial polyp	6 (15)	8 (20.0)	8 (20.0)
Cervical polyp	0 (0.0)	1 (2.5)	1 (2.5)
Endometrioid cyst	0 (0.0)	2 (5.0)	2 (5.0)
Synechiae	0 (0.0)	3 (7.5)	6 (15.0)
Cervical stenosis	0 (0.0)	3 (7.5)	3 (7.5)
Mullerian duct anomalies	0 (0.0)	0 (0.0)	1 (2.5)

4.5 Sensitivity and Specificity of TVS versus Hysteroscopy*(Gold Standard)*in Evaluation of Endometrial Pathology in Pre-menopausal and Postmenopausal Women

The overall sensitivity, specificity. PPV, NPV, and accuracy in diagnosing endometrial pathologies was 38.2%, 100%, 100%, 22.2%, and 47.5%. TVS demonstrated a low sensitivity in diagnosing submucosal fibroids (33.3%) with a specificity, PPV, and NPV of 100%, 100%, and 57.6% but a high sensitivity and specificity in diagnosing endometrial polyps(75%

and 100% respectively) as shown in ***Table 3***.The sensitivity, specificity, PPV, NPV, and accuracy for a normal endometrial pathology was 38.2%. 100%, 100%, and 100%.

Table 3.Sensitivity and specificity of TVS versus hysteroscopy in evaluation of endometrial pathology in pre- and postmenopausal women in Nairobi

Pathology	***Sensitivity***	***Specificity***	***PPV***	***NPV***	***DA***
Overall	38.2	100	100	22.2	47.5
Normal	38.2	100	100	22.2	47.5
Submucosal Fibroid	33.3	100	100	57.6	65.0
Endometrial polyp	75.0	100	100	94.1	95.0
Synechia	0	100	-	85.0	85.0
Endometrial cyst	0	100	-	95.0	95.0

TVS:Transvaginal Ultrasound; PPV, Positive Predictive Value; NPV, Negative Predictive Value; DA- diagnostic accuracy

4.6 The Sensitivity and Specificity of SIS versus Hysteroscopy *(Gold Standard)*in Evaluation of Endometrial Pathology in Pre- and Postmenopausal Women

Saline infusion sonohysterography demonstrated high sensitivity (91.2%), specificity (83.3%), PPV (96.9%), NPV (62.5%), and accuracy (90.0%)in diagnosing endometrial pathologies. In detecting endometrial polyps, the sensitivity, specificity, PPV, NPV and accuracy of SISwas 100%, 100%,100%,100%, and 100%. In detecting submucous myomas, its sensitivity, specificity, PPV and NPV were 90.5%, 100%,100%, 90.5%respectively***Table 4/Figure 6.***

Table 4. Sensitivity, Specificity PPV and NPV of SISversus Hysteroscopy

Pathology	***Sensitivity***	***Specificity***	***PPV***	***NPV***	***DA***
Overall	92.1	83.3	96.9	62.5	90.0
Normal	94.1	100	100	75.0	95.0
Sub mucosal fibroids	90.5	100	100	90.5	95.0
Endometrial polyp	100	100	100	100	100
Endometrioid cyst	100	100	100	100	100
Synechiae	50	100	100	91.9	92.5

SIS: Saline infusion Sonohysterography; HS, Hysteroscopy; PPV, Positive Predictive Value; NPV, Negative Predictive Value; DA- diagnostic accuracy

Cervical polyps and cervical stenosis were incidental findings of SIS evaluation.

4.7 Comparison of sensitivity, specificity, PPV, NPV, and accuracy of TVS and SIS

Overall, the sensitivity, NPV, and accuracy of SIS (92.1%, 62.5%, and 90.0%) was higher than TVS (38.2%, 22.2%, and 47.5%). However, TVS demonstrated a higher specificity (100%) and PPV (100%) than SIS (83.3% and 96.9%) as shown in Table 5 below.

Table 5. Overall sensitivity, specificity, PPV, NPV, and accuracy of TVS versus SIS

Pathology	***Sensitivity***	***Specificity***	***PPV***	***NPV***	***Accuracy***
TVS	38.2	100	100	22.2	47.5
SIS	92.1	83.3	96.9	62.5	90.0

SIS: Saline infusion Sonohysterography; TVS: Transvaginal ultrasound; PPV, Positive Predictive Value; NPV, Negative Predictive Value; **DA- diagnostic accuracy**

SIS demonstrated a higher sensitivity in detecting normal endocrine pathology (94.1%), sub mucosal fibroids (90.5%) and endometrial polyps (100%) that TVS (38.2%, 33.3%. and 75.0% respectively. Even though the specificity of TVS in detecting the three pathologies (100%) was comparable to SIS (100%), SIS had a higher accuracy as shown in Table 6.

Table 6. Comparison of the sensitivity and specificity of SIS and TVS in detecting individual endometrial pathologies

	SIS					***TVS***				
Pathology	***Se.***	***Sp.***	***PPV***	***NPV***	***DA***	***Se***	***Sp.***	***PPV***	***NPV***	***DA***
Normal	94.1	100	100	75.0	95.0	38.2	100	100	22.2	47.5
Sub mucosal fibroids	90.5	100	100	90.5	95.0	33.3	100	100	57.6	65.0
Endometrial polyp	100	100	100	100	100	75.0	100	100	94.1	95.0
Endometrioid cyst	100	100	100	100	100	0	100	-	85.0	85.0
Synechiae	50	100	100	91.9	92.5	0	100	-	95.0	95.0

SIS: Saline infusion Sonohysterography; TVS: Transvaginal ultrasound; PPV, Positive Predictive Value; NPV, Negative Predictive Value; DA- diagnostic accuracy

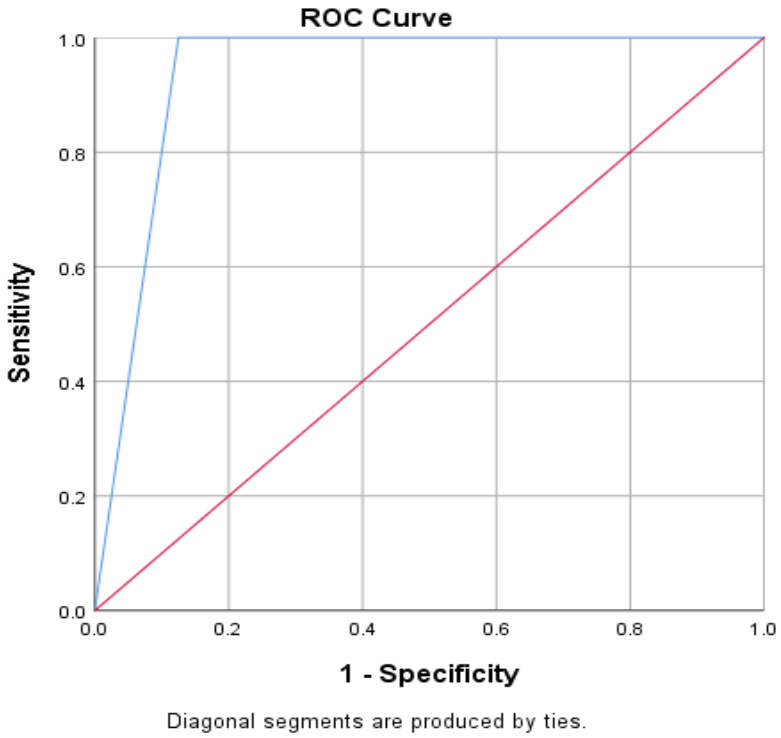

Figure 6. Receiver Operating for the Overall sensitivity of using SIS in diagnosis of AUB taking hysteroscopy as the gold standard (Area under curve: 0.938, std error 0.038, p value <0.001, C I 0.864-1.00, kappa 0.737, p<0.001)

4.8 Complications

There were no documented complications during Transvaginal scan, during or after Saline Infusion Sonohysterography whereas diagnostic hysteroscopy had 2 complications uterine perforation (fundal) and false passage created into the posterior wall. The procedure was successfully completed in 100%, 92.5%, 100% of the patients undergoing TVS, SIS and diagnostic hysteroscopy respectively.

CHAPTER 5: DISCUSSION, CONCLUSIONS, AND RECOMMENATIONS

5.1 Discussion

The management of abnormal uterine bleeding, a common symptom in women of all ages continues to pause a significant financial burden on healthcare resources. Generally, in patients with AUB, 2D and 3D US is done as an initial investigation. If the endometrium is found to be abnormal >5 mm in postmenopausal women or >12mm in a premenopausal patient, a clinical evaluation is made.If the 3D ultrasound is suspicious of thickened or distorted endometrium it is usually followed by diagnostic/therapeutic hysteroscopy, but SIS has found to be equally effective and less invasive in evaluation of endometrial cavity pathologies.

The sociodemographic characteristics of abnormal uterine bleeding have shown to have a variable pattern in different studies. The mean age and BMI of the study population presenting with AUB was 38.1 ± 8.8 (25-71), out of which only 5 were postmenopausal (12.5%). A similar study done on comparison of TVS versus SIS by Swaleh et al. (21) showed mean age to be 31.57. The difference in age might be as a result of the different settings of the studies. The study by Swaleh was in the largest referral hospital in Kenya – the Kenyatta National Hospital while our study was in a private institution, whose service cost significantly higherthan atKNH.

Out of 40 patients with abnormal uterine bleeding, 28 (70%) had Heavy Menstrual Bleeding (HMB), 5(12%) had postmenopausal bleeding, 3(7.5%) had amenorrheaand hypomenorrhea respectively, 2 (5%) had intermenstrual bleeding which wassimilar in studies conducted by Khan et al. in Saudi Arabia(1)and Rani et al. in India(30) in which HMB wasthe commonest presenting complaint at 73%.

The 3D-TVS was able to detect endometrial lesions in only 32.5% of patients with undiagnosed abnormal uterine bleeding to be suffering from uterine pathologies (13 out of 40 patients). The pathologies that were noted on TVS were submucosal fibroid and endometrial polyps other focal lesions such as endometrioid cyst, synechiae and cervical stenosis were not diagnosed with 3D- TVS. Though 2D/3D-TVS is the first imaging modality of choice for the evaluation of endometrial cavity in AUB of less than 12 weeks size uterus, it has limitations in detecting small lesions, location of myoma and in differentiating diffuse and focal lesion(30). The sensitivity and specificity of TVS, SIS in detecting intracavitary

abnormalities were 31.3 and 100%, 94.1% and 100%. Dıjkhuizen (31)reported a comparable diagnostic accuracy.

3D-Saline infusion sonohysterography was able to detect 80% of patients with undiagnosed abnormal uterine bleeding to be suffering from uterine pathologies (32 out of 40 patients). Most prevalent pathologies found in both pre- and postmenopausal age group was submucosal fibroids (47.5%) and endometrial polyps (20%) of the patient presenting with AUB. These findings were comparable to a study done in 2017 by Shaikh (32) where she documented 78% of patients who presented with undiagnosed AUB were found to have a uterine pathology with equal prevalence of polyps and submucosal fibroids.

Saline infusion sonohysterography performed well in my study for detecting endometrial pathology. Its sensitivity in detecting submucosal fibroids, endometrial polypsand endometrial lesions such as synechia, endometroid cystwas 90.5, 100, 92.5 respectively. Its specificity in detecting the same pathology was 100%, 100%, 100% respectively. The positive and negative predictive values was 100;90.5, 100;100, and 100;85.7, demonstrating a higher sensitivity compared to the overall across women for all ages. The findings demonstrate a high sensitivity and specificity in diagnosing endometrial polyps and adenomyosis (100%) but slightly lower sensitivity and specificity in diagnosing sub mucosal fibroids. These findings were comparable to other studies (23,30).

Other pathologies diagnosed with SIS were endometroid cysts (Adenomyosis), synechiae, and cervical stenosis. Cervical stenosis was a diagnosis of exclusion made when there were 3 failed SIS procedures. These 3 patients underwent a Diagnostic hysteroscopy where the diagnosis of cervical stenosis and synechia was confirmed. This was also documented in a study done by Faryal Khan et al Saudi Arabia in 2010 (1)in which he had 6 patients out of 101 patients with cervical stenosis, amongst these 1 was documented to have endometrial cancer.

Additionally, the study demonstrated a high area under curve on the ROC of 0.938, p, < 0.001 and the relatively high kappa coefficient of 0.737 further confirming accuracy of using SIS in the identification of uterine lesions in comparison to using diagnostic hysteroscopy. These findings were seen in a systemic review and meta-analysis which demonstrated a high area under ROC curve of 0.97 in detection of intrauterine pathology(33). Grimbizis et al

considered diagnostic hysteroscopy as only a complimentary procedure in case of abnormal findings detected by other methods such as hysterosalpingography, SIS and TVS.

Out of the 40 hysteroscopies that were conducted, 6 (15%) showed a normal cavity, 21 (52.5%) showed submucosal fibroids, 8 (20%) showed endometrial polyps, 2 (5%) showed adenomyosis, 6 (15%) showed synechia one had Mullerian duct anomaly on hysteroscopy. One patient had cervical polyp, three had cervical stenosis. The prevalence of the findings however differ slightly form a study done in the Saudi Arabia (1)where out of the 58 patients in whom hysteroscopy was performed, normal cavities were found in three patients (3%), endometrial polyps in 40 patients (39%), submucous fibroids in 13 patients (13%), a distorted cavity in one (1%) patient, and thickened endometrium in one patient (1%).

Overall all pathologies were detected by SIS apart from Mullerian duct abnormality. However, a study done with 3D-SIS showed perfect diagnostic accuracy (100.0%) in general detection of uterine abnormalities, compared with initial 3D-TVS and is identical to Hysteroscopy(34). Hence SIS is a more accurate than 3D-TVS in visualizing the endometrial cavity and is a better alternative to hysteroscopy(30). In the United Kingdom, Vathanan and Armar found SIS to be superior to TVS for the diagnosis of submucous fibroids and endometrial polyps and therefore suitable for assessing intracavity pathology after TVS examination (35).

SIS is superior to TVS for the diagnosis of endometrial polypsand submucous fibroids therefore should be considered as an intermediate investigation after TVS to assess intracavity pathologyand to confirm the diagnosis; hysteroscopy should be considered if there is an therapeutic intervention to be performed.

Concerns have however been raised about hysteroscopy being not only an expensive and invasive procedure, but unnecessary in 50% of the women who had normal findings, suggesting 3D SIS as an initial alternative approach in investigating women with AUB (5,11). In a meta-analysis, a total of 2228 procedures were reviewed that compared 3D SIS with hysteroscopy(36). The pooled sensitivity of 3D SIS for evaluating uterine cavity was 0.95 (95% confidence interval [CI], 0.93–0.97), and the pooled specificity was 0.88 (95% CI, 0.85–0.92). This meta-analysis suggested that SIS was an accurate means of evaluating the endometrial cavity in pre- and postmenopausal women with AUB.

In view of the above, SIS is more accurate than TVS in evaluation of intracavitary abnormalities amongst pre- post-menopausal women. Therefore, a primary approach of TVS together with SIS to evaluate an endometrial lesion would be an effective method to reduce the number of hysteroscopies.

5.2 Study Limitations

In view of the small number of women in the post-menopausal group of women were not individually assessed, it was not possible to conduct an in-depth analysis of the findings in this age group. The findings of this study may not therefore be generalizable to the post-menopausal women. Further studies that can compare accessibility of SIS and hysteroscopy.

5.3 Conclusion and Recommendations

SIS has a comparable diagnostic accuracy to DH and was superior to TVS in detecting uterine pathologies in patients presenting with abnormal uterine bleeding.

The use of SIS as an investigational technique should therefore be considered as it also has a high specificity and exceptional PPV and NPV. Hysteroscopyshould be reserved for patients with intrauterine lesions or patients with inconclusive 3D SIS.

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ANNEXES

Appendix 1Informed Consent (Appendix 1)

A written informed consent will be obtained from participants. Adequate explanation and counseling will be done before obtaining a permission. Participant's partners will be informed about the study. Participant requests for the partner's presence or advice before consenting will be granted if the partner can be located on the territory of the hospital at the request time. As a witness, the partner will then append their signature in the consent form. However, the participant's approval will be considered as tacit approval from the partner, unless specified.

The informed consent form describes the purpose of the study, the procedures to be carried out, and the risks and benefits in accordance with applicable regulations. Literate participants will append their signatures at the provided space in the consent form. Non-literate participants will document their approval by marking the form using their thumbprint, in the presence of a literate third-party witness. Any other local ERC requirements for obtaining informed consent from non-literate persons will be followed, and respondents will be given a copy and documented in the participant's record.

No personal identifiers will be employed for participants. A unique study identification number will be assigned to each participant for purposes of identification. This identification number will link them to a log with personal details. This information will be stored in a password protected database that will only be accessible to the principal investigator.

Risks of SIS

SIS is a very safe procedure and usually performed without incidents however some *common complications can be pelvic infections, cramping and spotting*

Benefits

SIS is non-invasive, temporary discomfort not painful, safe as there is no ionizing radiation, simple, minimally invasive, gives a good view of soft tissue and can also prevent unnecessary surgery

Confidentiality

Information collected will be handled according to Belmont's principle of confidentiality (Respect for persons, Beneficence, and Justice). Each participant will be allocated a unique study identification number for concealment. The coded number will identify all reports, data collected and other administrative forms. All the information on the participants and the investigation, as a whole, will be stored and secured at the research site and stored in locked file cabinets only accessible by the principal and assistant investigators. All databases will be secured with password-protected access systems. The study information of the participants will not release without the written permission of the participant, except for monitoring by the DMSB or KNH-UoN-ERC.

Study Discontinuation

The aim of this research is to achieve ≥ 95% participant retention. We will make every reasonable effort to retain any enrolled respondent until the end; however, participants are at will to withdraw from the study at any point. To ensure safety, the principal investigator may withdraw study participants from the study. Finally, the study may be discontinued at any time by the KNH-UoN-ERC.

Training

The research team involved will undertake Good Clinical Practice (GCP) training and certification. Once the study has been approved, it will be listed with the clinical trial registry and clinicaltrial.gov. Training of research assistants will take place over the duration of one week; initially, they will observe the process of obtaining informed consent and filling of the questionnaires. After that, they will work under supervision until the principal investigator is satisfied.

The principal investigator will constantly review the forms for completion. The principal investigator and two research assistants will carry out the data collection. The research assistants will be two clinical officers. A structured survey questionnaire will be used to gather obstetrical and medical details, Research assistants will undergo sensitization and training before the commencement of the study via video tutorials and clinical teachings.

2. Participant Consent Form (English)

Date (date/month/year): _____

Study Title: The Diagnostic Value of Saline Infusion Sonohysterography*vs.* Hysteroscopy in The Detection and Evaluation of Endometrial Pathology: *A Prospective, blind comparison to a Gold standard study.*

Principal Investigator:
Department of Obstetrics and Gynecology, University of Nairobi.
Telephone Number

Investigator's Statement:

We are requesting you to kindly participate in this research study. The purpose of this consent form is to provide you with the information you will need to help you decide whether to participate in the study. This process is called 'Informed Consent'. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study with which you are uncertain. You are free to ask any questions about the study. The investigator will be available to answer any questions that arise during the study and afterward.

Introduction:

Saline infusion sonohysterography (SIS) or saline ultrasound uterine scan uses a small amount of saline (salt solution) inserted into the uterus (or womb) that allows the lining of the uterus (endometrium) to be clearly seen on an ultrasound scan. Gives a virtual image of the pathology.

Hysteroscopy is a procedure that can assist a doctor give an up-close look at your cervix and uterus to help learn what's causing problems. That is done in a theatre set up. A *thin, lighted tube* that is *inserted into* the *vagina* to *examine* the *cervix* and *inside* of the *uterus*. Gives an actual image of the pathology.
Benefits of SIS

Inserting the saline fluid into the uterus allows very clear ultrasound images to be taken of the lining of the uterus, and any abnormalities, such as thickening of the endometrium or polyps,

can be easily seen. This will help to guide the discussion between you and your doctor about any further investigation or treatment that may be needed.

Risks of SIS:

The scan is very safe. The main risk is that of infection within your uterus being introduced by the procedure. This is extremely uncommon and is treated with antibiotics if it occurs. Infection may present as pelvic pain that does not settle, or you may develop an odorous vaginal discharge for which antibiotics will be prescribed.

Benefits of Hysteroscopy:

SIS is non-invasive, temporary discomfort not painful, safe as there is no ionizing radiation, simple, minimally invasive, gives a good view of soft tissue and can also prevent unnecessary surgery.

Risks of Hysteroscopy:

Infection, Bleeding, Pelvic inflammatory disease, tearing of the uterus (rare) or damage to the cervix, Complications from fluid or gas used to expand the uterus, you may have slight vaginal bleeding and cramps for a day or two after the procedure.

Voluntariness:

The study will be fully voluntary. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Refusal to participate will not compromise you or your child's care in any way.

Confidentiality:

All the information obtained from you will be held in strict confidentiality. Any information that may identify you or your child will not be published or discussed with any unauthorized persons. No specific information regarding you, your child or your family will be released to any person without your written permission. Your research number will be used in place of your names.

Access to health records

You may apply for access to your own records or may authorize third parties such as lawyers, employers, or insurance companies to do so on your behalf. The Principal Investigator can be contacted if access to health records is required.

Sharing of results

Study staff will protect your personal information closely, so no one will be able to connect your responses and any other information that identifies you. Federal or state laws may require us to show information to university or government officials (or sponsors), who are responsible for monitoring the safety of this study. Directly identifying information (e.g. names, addresses) will be safeguarded and maintained under controlled conditions. You will not be identified in any publication from this study.

Intervention

A structured survey questionnaire will be used to gather your medical details. You will be able to reach the principal investigator at any time in-between the follow-up period.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator, _____ by calling _____. If you have any questions about your rights as a research participant, you can contact the Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC) by calling ____ Ext. _____.

Consent Form: Participant's Statement:

I_____ have received adequate information regarding the study research, risks, benefits hereby AGREE / DISAGREE (Cross out as appropriate) to participate in the study with my child. I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Parent's name: _____Signature/thumb print: _____Date _____

Witness name: _____Signature/thumb print: _____Date: _____

I_____declare that I have adequately explained to the above participant, the study procedure, risks and benefits and

given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Interviewer's name and Signature: _____ Date: _____

Appendix 2: FomuYaMshirikiwa Dhana (Swahili)

Tarehe (Tarehe/Mwezi/Mwaka):

Kichwa cha Uchunguzi: The Diagnostic Value of Saline Infusion Sonohysterographyvs. Hysteroscopy in The Detection and Evaluation of Endometrial Pathology: A Prospective, blind comparison to a Gold standard study.

MtafitiMkuu:

IdaraYaMagonjwaYaUjinsia, Chuo Kikuu Cha Nairobi.

NambariYa Simu:

Taarifa ya Mpelelezi:

Tunakuomba ushiriki kwa fadhili katika utafiti huu. Madhumuni ya fomu hii ya idhini ni kukupa habari utahitaji kukusaidia kuamua ikiwa unashiriki katika utafiti. Utaratibu huu unaitwa 'Dhibitisho Iliyojulikana' Tafadhali soma habari hii ya ridhaa kwa uangalifu na uulize maswali yoyote au utafute ufafanuzi juu ya suala lolote kuhusu utafiti ambao hauna uhakika. Uko huru kuuliza maswali yoyote juu ya utafiti. Mpelelezi atapatikana kujibu maswali yoyote ambayo yanaibuka wakati wa masomo na baadaye.

Utangulizi:

Mchanganyiko wa saline infusion sonohysterografia (SIS) au suluhisho la uterine la mucine la saline hutumia kiasi kidogo cha chumvi (suluhisho la chumvi) iliyoingizwa ndani ya uterasi (au tumbo) ambayo inaruhusu bitana ya uterasi (endometrium) ionekane wazi kwenye skana ya ultrasound. Hutoa picha ya kweli ya ugonjwa.

Hysteroscopy ni utaratibu ambao unaweza kumsaidia daktari kuangalia kwa karibu kizazi chako na uterasi ili kusaidia kujua nini husababisha shida. Hiyo inafanywa katika ukumbi wa michezo ulioanzishwa. Bomba nyembamba na nyepesi ambayo imeingizwa ndani ya uke ili kuchunguza kizazi na ndani ya uterasi. Hutoa picha halisi ya ugonjwa wa ugonjwa.

Faida za SIS

Kuingiza maji ya chumvi ndani ya uterasi inaruhusu picha zilizo wazi kabisa za ultrasound zichukuliwe kwa kuwekewa kwa uterasi, na makosa yoyote, kama vile unene wa endometriamu au polyps, yanaweza kuonekana kwa urahisi. Hii itasaidia kuongoza majadiliano kati yako na daktari wako kuhusu uchunguzi wowote zaidi au matibabu ambayo yanaweza kuhitajika.

Hatari za SIS:

Scan ni salama sana. Hatari kuu ni ile ya kuambukizwa ndani ya tumbo lako inayoletwa na utaratibu. Hii ni kawaida sana na inatibiwa na dawa za viuatilifu ikiwa itatokea. Kuambukizwa kunaweza kuonyesha kama maumivu ya pelvic ambayo hayakuni, au unaweza kupata kutokwa kwa harufu ya uke ambayo dawa za kuua dawa zitaamriwa.

Faida za Hysteroscopy:

SIS sio ya kuvamizi, usumbufu wa muda sio chungu, salama kwani hakuna mionzi ya ionizing, rahisi, isiyo na uvamizi, inatoa mtazamo mzuri wa tishu laini na inaweza pia kuzuia upasuaji usiohitajika.

Hatari ya Hysteroscopy:

Kuambukizwa, Kupunguza damu, ugonjwa wa uchochezi wa Pelvic, kuvua kwa uterasi (nadra) au uharibifu wa seviksi, Matatizo kutoka kwa giligili au gesi iliyotumiwa kupanua uterasi, unaweza kuwa na damu kidogo ya uke na kusugua kwa siku moja au mbili baada ya utaratibu.

Kujitolea:

Utafiti utakuwa wa hiari kamili. Hakutakuwa na thawabu ya kifedha kwako kwa kushiriki katika utafiti. Moja ni huru kushiriki au kujiondoa kutoka kwa masomo wakati wowote. Kukataa kushiriki hakutakuangusha au utunzaji wa mtoto wako kwa njia yoyote.

Usiri:

Habari yote inayopatikana kutoka kwako itafanyika kwa usiri mkali. Habari yoyote ambayo inaweza kukutambulisha au mtoto wako haitachapishwa au kujadiliwa na watu wowote wasio ruhusa. Hakuna habari maalum kuhusu wewe, mtoto wako au familia yako itatolewa kwa mtu yeyote bila ruhusa yako ya kuandikwa. Nambari yako ya utafiti itatumika badala ya majina yako.

Upataji wa rekodi za afya

Unaweza kuomba ufikiaji wa rekodi zako mwenyewe au unaweza kuidhinisha wahusika wengine kama wanasheria, waajiri, au kampuni za bima kufanya hivyo kwa niaba yako. Mpelelezi Mkuu anaweza kuwasiliana nao ikiwa ufikiaji wa rekodi za afya unahitajika.

Kushiriki kwa matokeo

Wafanyikazi wa masomo watalinda habari yako ya kibinafsi kwa karibu, kwa hivyo hakuna mtu atakayeweza kuunganisha majibu yako na habari nyingine yoyote ambayo inakutambulisha. Sheria za shirikisho au za serikali zinaweza kututaka tuonyeshe habari kwa viongozi wa chuo kikuu au wa serikali (au wafadhili), ambao wana jukumu la kuangalia usalama wa utafiti huu. Kuainisha habari moja kwa moja (kwa mfano, majina, anwani) italindwa na kutunzwa chini ya hali inayodhibitiwa Hautatambuliwa katika chapisho lolote kutoka kwa utafiti huu.

Uingiliaji

Dodoso la utafiti lililoandaliwa litatumika kukusanya maelezo yako ya matibabu. Utaweza kufikia mpelelezi mkuu wakati wowote kati ya kipindi cha ufuatiliaji.

Shida au Maswali:

Ikiwa umewahi kuwa na maswali yoyote juu ya utafiti huo au juu ya matumizi ya matokeo unaweza kuwasiliana na mpelelezi mkuu, _____ kwa kupiga _____. Ikiwa una maswali yoyote kuhusu haki yako kama mshiriki wa utafiti, unaweza kuwasiliana na Kamati ya

Maadili na Utafiti ya Kitaifa ya Hospitali ya Kitaifa ya Kenya (KNH- ESRC) kwa kupiga ____ Ext. _____.

Fomu ya idhini: Taarifa ya Mshiriki:

Mimi _____ nimepata habari ya kutosha kuhusu utafiti, hatari, faida za KUHUSU / DUKA (Toka nje kama inafaa) kushiriki katika masomo na mtoto wangu. Ninaelewa kuwa ushiriki wetu ni wa hiari kamili na kwamba niko huru kujiondoa wakati wowote. Nimepewa nafasi ya kutosha ya kuuliza maswali na kutafuta ufafanuzi juu ya utafiti na hizi zimeshughulikiwa kwa kuridhisha.

Jina la mzazi: _____ Saini / kuchapishwa kwa kidole: _____ Tarehe _____
Jina la Shahidi: _____ Saini / kuchapa kwa thumba: _____ Tarehe: _____

Mimi_____Haadhiri kwamba nimeelezea kwa kutosha mshiriki wa hapo juu, utaratibu wa kusoma, hatari na faida na nimempa wakati wa kuuliza maswali na kutafuta ufafanuzi kuhusu utafiti. Nimejibu maswali yote yaliyoulizwa kwa uwezo wangu wote.
Jina la Mhojiwa na Saini: _____ Tarehe: _____

Asante!

Appendix 3: Inclusion and Exclusion Screening Enrolment Form (English)

Study Title: The Diagnostic Value ofSaline infusion sonohysterography*vs*. Hysteroscopy in The Detection and Evaluation of Endometrial Pathology.

Date: (date/month/year): _____

Enrolment identification number: _____

Inclusion Criteria: Answers MUST be 'yes' for these questions.

Pre-menopausal Women

- With Abnormal Uterine Bleeding.

Post- Menopausal Women

- With Abnormal Uterine Bleeding.

Exclusion criteria: If any answer is 'Yes' excluded from enrolment

- Declined consent.
- Expectant women/positive pregnancy test.
- Women below 18 years.
- Pelvic Inflammatory Disease/ Active vaginal infection.
- Congenital anomalies/structural anomalies- e.g. Rudimentary Uterus, Mullerian Agenesis, Fraser's Syndrome, McKusick Kaufman Syndrome, BardettBiedl Syndrome amongst various others.

Appendix 4: KuingizwanaKutolewakutengenezafomuyausajiliwaufuatiliaji (Swahili)

Kichwa cha Utafiti: The Diagnostic Value ofSaline infusion sonohysterographyvs. Hysteroscopy in the Detection and Evaluation of Endometrial Pathology.

Tarehe: (tarehe / mwezi / mwaka):
Nambari ya kitambulisho: _____
Viwango vya kujumuisha: Majibu lazima uwe 'NDIO' kwa maswali haya.

Wanawake:premonopausal

● Na Kutokwa na damu isiyo ya kawaida.

Wanawake: postmenopausal

● Na Kutokwa na damu isiyo ya kawaida.

Vigezo vya Kutengwa: Ikiwa jibu lolote ni 'Ndio' bila kutengwa kwa uandikishaji
● Idhini iliyokataliwa.
● Uchunguzi wa ujauzito wa wanawake / mtihani mzuri wa ujauzito.
● Wanawake walio chini ya miaka 18.
● Ugonjwa wa uchochezi wa Pelvic / maambukizo ya uke.
● Ukosefu wa kuzaliwa / anomalies ya miundo- n.k. Rudimentary Uterus, Mulirian Agenesis, Dalili ya Fraser, Dalili za McKusick Kaufman, Dalili za BardettBiedl kati ya zingine nyingi.

Appendix 5: Baseline Questionnaire

Study Title: The Diagnostic Value ofSaline infusion sonohysterography*vs.* Hysteroscopy in The Detection and Evaluation of Endometrial Pathology.

BASELINE QUESTIONNAIRE: This form will be filled by a Qualified Physician.

PART 1: Socio-demographics

DATE _____

Enrolment identification number: _____

Date of Signed Informed Consent: _____/_____/_____ *(DD/MM/YYYY)*

Copy given to patient: Yes / No …….…….

1. Age (years) …….
2. Marital Status

Single □ Widowed □

Married □ Separated □

Divorced □

3. Level of Education

Primary □ Secondary □ Tertiary □

4. Employment status

Self-employed □ Salaried employment □ Unemployed □

5. Ethnicity

African □ Asian □ Caucasian □ Multi racial □ Others please specify_____

6. Weight/ height …… BMI ……..

Part 2: Past medical/ Surgical history:

7. History of chronic illnesses/co-morbidity illnesses Yes No

If 'yes' for question 5, please state which illness (type and frequency):

……

……

8. History of blood transfusion Yes No
9. Blood Group

   ……
10. Known food or drug allergies Yes No

11. If ‘yes’ for question 8 please state which drug history (type and frequency):

……

……

Part 3: Obstetrics and Gynecology history:

Last monthly period …….

Parity …….

Last Pap smear…… Result……

Contraceptive history……...

History of Gender base violence ……

History of Sexually transmitted disease…….

Part 4:

Menorrhagia □ Oligomenorrhea □ Polymenorrhagia □ Amenorrhea □

Post- menopausal bleeding □

Part 5:

11.Characteristics of disease on Saline Infused Sonohysterography

Submucosal fibroid: Grade 1/2/3/4

Endometrial polyp

Cervical polyp

Adhesions/ Asherman Syndrome

Mullerian Duct Anomalies

Cervical Stenosis

Endometrial hyperplasia

Others

12.Characteristics of disease on Hysteroscopy

Submucosal fibroid: Grade 1/2/3/4

Endometrial polyp

Cervical polyp

Adhesions/ Asherman Syndrome

Mullerian Duct Anomalies

Cervical Stenosis

Endometrial hyperplasia

Others

13.Complications

SIS Yes No

If ‘yes’ for question 8 please state what complication……

Hysteroscopy Yes No

If ‘yes’ for question 8 please state what complication……

Appendix 6: Data Sheet for Biographical Information

The Diagnostic Value of Transvaginal ultrasound with Saline infusion sonohysterography*vs.* Hysteroscopy in the Detection and Evaluation of Endometrial Pathology.

Patient Biographical Information

Date	Name	Enrolment Number	Telephone Number

Appendix 7: Data Collection Sheet for SIS/Inpatient Hysteroscopy

The Diagnostic Value of Transvaginal ultrasound with Saline infusion sonohysterography*vs.* Hysteroscopy in The Detection and Evaluation of Endometrial Pathology.

The numbers and percentages of results for each method			
	SIS n%	HS n%	Endometrial Pathology n%
Endometrial carcinoma	X	X	X
Polypoid	X	X	X
Hyperplasia	X	X	X
Myoma	X	X	X
Other findings	X	X	X
Total	Xx	Xx	Xx
SIS, Saline infusion sonohysterography; HS, Hysteroscopy			

Appendix 8: Data Analysis Tables

TRANSVAGINAL ULTRASOUND VS DIAGNOSTIC HYSTEROSCOPY

Normal

		HYS +	HYS -		
TVS	+	13	0	13	PPV= 100.0%
	-	21	6	27	NPV= 22.2%
		34	6	40	

Sensitivity	Specificity
38.2%	100.0%

Accuracy	47.5%

Submucosal fibroid

		HYS +	HYS -		
TVS	+	7	0	7	PPV= 100.0%
	-	14	19	33	NPV= 57.6%
		21	19	40	

Sensitivity	Specificity
33.3%	100.0%

Accuracy	65.0%

Endometrial Polyp

		Gold Standard +	Gold Standard -		
Test	+	6	0	6	PPV= 100.0%
	-	2	32	34	NPV= 94.1%
		8	32	40	

Sensitivity	Specificity
75.0%	100.0%

Accuracy	95.0%

Synechia

		Gold Standard +	Gold Standard -			
Test	+	0	0	0	**PPV=**	**-**
	-	6	34	40	**NPV=**	**85.0%**
		6	34	40		

Sensitivity	**Specificity**
0.0%	**100.0%**

Accuracy **85.0%**

Endometroid cyst

		Gold Standard +	Gold Standard -			
Test	+	0	0	0	**PPV=**	**#DIV/0!**
	-	2	38	40	**NPV=**	**95.0%**
		2	38	40		

Sensitivity	**Specificity**
0.0%	**100.0%**

Accuracy **95.0%**

SALINE INFUSION SONOHYSTEROGRAPHY VS DIAGNOSTIC HYSTEROSCOPY

Normal

		HYS +	HYS -			
SIS	+	32	0	32	**PPV=**	**100.0%**
	-	2	6	8	**NPV=**	**75.0%**
		34	6	40		

Sensitivity	**Specificity**
94.1%	**100.0%**

Accuracy **95.0%**

Submucosa Fibroid

		HYS +	HYS -			
SIS	+	19	0	19	**PPV=**	**100.0%**
	-	2	19	21	**NPV=**	**90.5%**
		21	19	40		

Sensitivity	**Specificity**
90.5%	**100.0%**

Accuracy **95.0%**

Endometrial Polyp

		HYS +	HYS -			
SIS	+	8	0	8	PPV=	100.0%
	-	0	32	32	NPV=	100.0%
		8	32	40		

Sensitivity	Specificity
100.0%	100.0%

Accuracy 100.0%

Cervical Polyp

		HYS +	HYS -			
SIS	+	1	0	1	PPV=	100.0%
	-	0	39	39	NPV=	100.0%
		1	39	40		

Sensitivity	Specificity
100.0%	100.0%

Accuracy 100.0%

Endometroid cyst

		HYS +	HYS -			
SIS	+	2	0	2	PPV=	100.0%
	-	0	38	38	NPV=	100.0%
		2	38	40		

Sensitivity	Specificity
100.0%	100.0%

Accuracy 100.0%

Synechia

		HYS +	HYS -			
SIS	+	3	0	3	PPV=	100.0%
	-	3	34	37	NPV=	91.9%
		6	34	40		

Sensitivity	Specificity
50.0%	100.0%

Accuracy 92.5%

Cervical stenosis

		HYS +	HYS -			
SIS	+	3	0	3	**PPV=**	**100.0%**
	-	0	37	37	**NPV=**	**100.0%**
		3	37	40		

Sensitivity	**Specificity**
100.0%	**100.0%**

Accuracy **100.0%**

OVERALL

		HYS +	HYS -			
TVS	+	13	0	13	**PPV=**	**100.0%**
	-	21	6	27	**NPV=**	**22.2%**
		34	6	40		

Sensitivity	**Specificity**
38.2%	**100.0%**

Accuracy **47.5%**

		HYS +	HYS -			
SIS	+	31	1	32	**PPV=**	**96.9%**
	-	3	5	8	**NPV=**	**62.5%**
		34	6	40		

Sensitivity	**Specificity**
91.2%	**83.3%**

Accuracy **90.0%**

Appendix 9. Sample Diagnostic tool for Computation of Sensitivity, Specificity, PPV, NPV, and accuracy of tests

SNO	TVS TEST	GOLD STD	RESULT
1	Negative	Negative	True Negative
2	Negative	Negative	True Negative
3	Negative	Positive	False Negative
4	Negative	Positive	False Negative
5	Positive	Positive	True Positive
6	Negative	Positive	False Negative
7	Positive	Positive	True Positive
8	Negative	Positive	False Negative
9	Positive	Positive	True Positive
10	Negative	Positive	False Negative
11	Positive	Positive	True Positive
12	Negative	Positive	False Negative
24	Negative	Positive	False Negative
25	Negative	Negative	True Negative
26	Negative	Positive	False Negative
27	Negative	Positive	False Negative
28	Positive	Positive	True Positive
29	Negative	Positive	False Negative
30	Positive	Positive	True Positive
31	Negative	Positive	False Negative
32	Positive	Positive	True Positive
33	Positive	Positive	True Positive
34	Positive	Positive	True Positive
35	Negative	Positive	False Negative
36	Negative	Positive	False Negative
37	Negative	Negative	True Negative

		Gold Standard +	Gold Standard -			
Test	+	13	0	13	PPV=	100.0%
	-	21	6	27	NPV=	22.2%
		34	6	40		

Sensitivity	Specificity
38.2%	100.0%

Accuracy
47.5%