THE ACCURACY OF 2D TRANSVAGINAL ULTRASONOGRAPHY IN THE DIAGNOSIS OF BENIGN ENDOMETRIAL PATHOLOGY:

A COMPARISON BETWEEN ULTRASONOGRAPHY AND HYSTEROSCOPY

Original Research Article: original research study

BY

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DECLARATION

Declaration

I, *Khatija Hoosen Jagot (JGTKHA001)*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part of it has been, is being or is to be submitted for another degree in this or any other university.

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SIGNATURE: Signed by candidate

DATE: 25 March 2018

ABSTRACT

STUDY OBJECTIVE: To evaluate the diagnostic accuracy of transvaginal sonography compared to hysteroscopy in diagnosing benign endometrial pathology.

DESIGN: Retrospective cross-sectional study. Canadian Task force classification II – 2

SETTING: Department of Gynaecology, Groote Schuur Hospital, Cape Town, South Africa.

PATIENTS: Patients having an office hysteroscopy procedure between January 2014 and December 2016, with a record of a recent transvaginal ultrasound and endometrial histology were included in this study. All malignant cases were excluded.

INTERVENTIONS: Transvaginal ultrasound, endometrial biopsy and office hysteroscopy.

MEASUREMENTS AND MAIN RESULTS: A total of one hundred and forty two patients, pre- and postmenopausal, were included in this study. The most common indications for hysteroscopy were abnormal uterine bleeding and postmenopausal bleeding. Sensitivity, specificity, positive and negative predictive values were calculated for ultrasonography and hysteroscopy in diagnosing benign endometrial pathology by comparing them to histological diagnosis as gold standard. The most common pathologies identified at histology were polyps and fibroids.

For those patients who had a normal endometrium at ultrasound (n=59), hysteroscopy revealed 33.9% polyps, 5.1% submucosal fibroids and 49.2% normal/atrophic endometrium. The remainder of these patients demonstrated proliferative or hyperplastic endometrium, suspicious endometrium and adhesions. For those patients who had a normal hysteroscopy (n=26), ultrasound demonstrated 7.7% polyps, 7.7% submucosal fibroids, 11.5% cystic areas, 3.9% no comment on endometrium and 69.2% normal endometrium.

In diagnosing polyps, hysteroscopy had a higher sensitivity (78%) than ultrasound (37.3%). However, ultrasound had a higher specificity (85.5%), compared to that of hysteroscopy which was 71.1%. The negative predictive value of hysteroscopy for polyps was 81.9% and ultrasound, 65.7%.

In the diagnosis of submucosal fibroids, ultrasound had a higher sensitivity than hysteroscopy but they both had similar specificity. Ultrasound and hysteroscopy had high negative predictive values and low positive predictive values. The combination of ultrasound and hysteroscopy did not improve sensitivity, PPV or NPV with a small decline in specificity.

CONCLUSION: This study demonstrated that hysteroscopy was more accurate in the diagnosis of endometrial polyps than ultrasound with a higher sensitivity and negative predictive value. However hysteroscopy had a lower sensitivity when diagnosing submucosal fibroids.

ACKNOWLEDGEMENTS

I would like to acknowledge my supervisor, Dr S. Jeffery, for his continued support and guidance through each step of this research project.

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ABBREVIATIONS

TVS – TRANSVAGINAL ULTRASOUND

SIS – SALINE INFUSION SONOHYSTEROGRAPHY

PPV – POSITIVE PREDICTIVE VALUE

NPV - NEGATIVE PREDICTIVE VALUE

ROC curve – RECEIVER OPERATING CHARACTERISTIC curve

CHAPTER 1

CHAPTER 1

INTRODUCTION

DESCRIPTION OF CONDITION

Abnormal uterine bleeding is a common symptom and can be found in the pre-menopausal, peri-menopausal or postmenopausal woman (1, 2). It is the most common reason for referral to a gynaecologist and it can be debilitating for many women (1, 3). Of the many causes of abnormal uterine bleeding, intra-uterine pathology such as fibroids and polyps are significant contributing factors, occurring in more than 40% of women (3). Fibroids and polyps can also lead to infertility (4). Another important cause of bleeding in the postmenopausal woman is malignant pathology (5).

DESCRIPTION OF INTERVENTION

Endometrial pathology requires an accurate and timeous diagnosis followed by appropriate treatment (6). Previously, dilatation and curettage was regarded as the gold standard for investigating abnormal uterine bleeding but this has been shown to be inaccurate (7). The ultimate gold standard is hysterectomy but for obvious reasons it is not a feasible diagnostic modality (3).

The management of women with abnormal uterine bleeding has changed over the years with advances in ultrasound and endoscopic technology (6). Special investigations for diagnosis include transvaginal ultrasonography and hysteroscopy, of which hysteroscopy can be a diagnostic as well a therapeutic procedure (6). Transvaginal ultrasound has led to better quality imaging and predictive ability (6). It is also a straightforward and non-invasive procedure which exhibits good diagnostic accuracy for most endometrial pathologies (8). Advanced hysteroscopy offers excellent visualisation of the uterine cavity and is commonly used for diagnosis of endometrial pathology. It also enables outpatient operative surgery (6). Hysteroscopy is advantageous in that besides visualising the uterine cavity and endometrium, a directed biopsy is also possible (8). Hysteroscopy is, however, a more invasive procedure which may sometimes require anaesthesia (8). It is also associated with discomfort as well as complications, although rare, such as uterine perforation and fluid overload (3, 8, 9).

Hysteroscopy has been considered to be a gold standard in assessing the uterine cavity since a study published by Gimpelson et al in 1988 (3, 10). Since then many studies have been carried out to assess diagnostic accuracy of hysteroscopy, including a systematic review which will be further discussed in the literature review. The choice between ultrasound and hysteroscopy is based on the suspected clinical diagnosis. The clinician also needs to consider feasibility, accuracy, versatility and cost (6).

LITERATURE REVIEW

AVAILABLE EVIDENCE

A systematic review of the choice between outpatient hysteroscopy and ultrasonography in the management of endometrial disease, by TJ Clark in 2004, concluded that further research was required to ascertain which modality would best be suited to guide clinicians in the diagnosis and management of endometrial disease. The author does concede that these modalities complement each other and the choice of investigation should be individualised (6). Clark also stressed the importance of evaluating all aspects of diagnostic performance including availability, preference, feasibility, accuracy, versatility, effectiveness and cost before choosing a specific modality (6).

Feasibility of a diagnostic investigation deals with acceptability and successful completion of the investigation(6). TVS is the most acceptable modality with minimal discomfort, whilst saline infusion sonography (SIS) and outpatient hysteroscopy are associated with more discomfort but are usually acceptable to patients (6). There are negligible failure rates of TVS but SIS and hysteroscopy are occasionally not possible due to inadequate distension of the uterine cavity and patient discomfort. Hysteroscopy may fail due to a stenotic cervix, patient discomfort or inadequate visualisation due to bleeding or debris (6).

When it comes to versatility, both ultrasound and hysteroscopy have their advantages. Ultrasound allows for imaging of the endometrium as well as the myometrium and adnexa whilst hysteroscopy only provides imaging of the uterine cavity(6). Hysteroscopy allows for easier examination of the patient whilst in lithotomy and additional diagnostic tests ie. biopsies, swabs, smears can be done. It also allows for definitive management if appropriate eg. resection of fibroids or polyps (6).

Accuracy of a diagnostic test is demonstrated in the tests proficiency in identifying true positives for the disease ie. sensitivity and true negatives for the disease ie. specificity (27). A diagnostic test which achieves no false positives and no false negatives is considered an ideal diagnostic test. In order to determine the performance of a diagnostic test in a specific population, predictive values (also called post-test probabilities) and likelihood ratios are calculated (27). A more thorough statistical method when comparing two different diagnostic modalities is a ROC curve analysis (11). Area Under the Curve (AUC) assesses diagnostic performance and is the most suitable statistical method as it measures overall efficiency of a diagnostic test. It allows for comparison of different diagnostic tests by comparing the AUC (12). Likelihood ratio is clinically more valuable as it is a combination of the sensitivity and specificity of a test (12).

As early as the nineties, studies were published assessing the accuracy of transvaginal ultrasonography. In 1996, a prospective study, of 136 women with abnormal uterine bleeding, published by Dijkhuizen et al, assessed the accuracy of transvaginal ultrasonography in the diagnosis of endometrial abnormalities (13). Of the 136 women included in the study, 52% were postmenopausal and 49% were premenopausal (13). Each patient had a transvaginal ultrasound (TVS) followed by outpatient hysteroscopy where endometrial samples were taken either by suction curettage or directed biopsy. It was a single blinded study where investigators were blinded to the ultrasound findings. Previous studies had demonstrated that curettage has high false negative rates (14-16) since less than half the uterine cavity is sampled (17) therefore Dijkhuizen et al opted to add hysteroscopy to improve evaluation of the uterine cavity. The main objective was diagnostic

accuracy of transvaginal ultrasound and not hysteroscopy (13). They found that curettage did not detect abnormalities in 18 women(13.2%) who had abnormalities on hysteroscopy and three of these were postmenopausal women with myomas on hysteroscopy (13). There have been several older studies prior to Dijkhuizen et al confirming that hysteroscopy is superior to curettage in making an accurate diagnosis of endometrial pathology, such as submucosal myomas and polyps (18, 19).

A study by Abdelazim et al in 2012 assessed the diagnostic accuracy of Pipelle endometrial sampling by comparing it to dilatation and curettage as gold standard in 143 women with abnormal uterine bleeding. The failure rate was 2.1% and these patients were thus excluded. All samples obtained from dilatation and curettage were adequate whilst 2.1% samples obtained via Pipelle were inadequate. The authors found that Pipelle had 100% sensitivity, specificity and predictive values for diagnosing endometrial hyperplasia, endometrial carcinoma, proliferative and secretory endometrium however when diagnosing endometrial polyps it had 60% sensitivity, 100% specificity, 100% PPV and 89.6% NPV (20).

A recent systematic review and meta-analysis was conducted by Hanegam et al in 2015 assessing the accuracy of endometrial sampling in women with postmenopausal bleeding. This review included twelve studies of which five studies used dilatation and curettage as a reference test and seven studies used hysteroscopy. Eight studies used the Pipelle device whilst the others used Accurette, Endorette and Novak for endometrial sampling. The failure rates of endometrial sampling were 11% (range 1% -53%) and the rates of insufficient samples obtained were 31% (range 7% – 76%). Of those who had failed sampling or insufficient samples, 7% were found to have endometrial cancer (range 0 – 18%). The authors of this review concluded that endometrial sampling is not effective in ruling out disease and therefore further diagnostic work-up should be performed for focal endometrial pathology, even after a benign result in postmenopausal women (21).

Dijkhuizen et al thus concluded that transvaginal ultrasonography was excellent at excluding disease as it demonstrated high sensitivity, high negative predictive value and a low negative likelihood ratio but its use was limited in diagnosing endometrial pathology (13). Therefore, TVS is a good screening tool or a first step before deciding on invasive endometrial evaluation (13). The study noted that TVS could not exclude submucosal myomas and polyps in premenopausal women in comparison to postmenopausal women in which most endometrial pathology could be excluded with ultrasonography (13).

Based on the findings of a randomised control trial by Tahir et al, published in BJOG in 1999, the recommendation is that the first line investigations for abnormal uterine bleeding in women above 35 years should be ultrasound and endometrial biopsy. If there is further bleeding or inability to perform ultrasound and endometrial biopsy, one should proceed to hysteroscopy (7). The aims of this randomised controlled trial were “to compare the efficacy and acceptability of outpatient and inpatient procedures, and to assess if there is any additional benefit conferred by hysteroscopy following endometrial sampling” (7). Four hundred patients above the age of 35 years old with abnormal uterine bleeding were randomised to either group 1 (inpatient group - examination under anaesthesia, inpatient hysteroscopy and curettage) or group 2 (outpatient group – vaginal ultrasound, outpatient hysteroscopy and Pipelle endometrial biopsy) (7). The results showed that outpatient ultrasound, hysteroscopy and biopsy had a similar efficacy to inpatient hysteroscopy and

curettage with good patient acceptability and that fibroids and polyps missed by ultrasound and endometrial sampling will be detected by hysteroscopy (7).

In 1998, Garuti et al evaluated the accuracy of hysteroscopy and transvaginal ultrasonography in diagnosing endometrial pathology in postmenopausal women with uterine bleeding by comparing it to histology (22). The study included 419 women, who underwent transvaginal ultrasonography assessing endometrial thickness only, diagnostic hysteroscopy and endometrial biopsy. Patients with the final diagnosis of submucosal fibroids and obvious cervical pathology were excluded. The final diagnosis of polyps, seen at hysteroscopy, was only made after operative hysteroscopy or hysterectomy. Insufficient samples were considered as atrophy (22).

In this study, transvaginal ultrasonography showed a sensitivity of 95.1%, specificity of 54.8% and PPV of 63.7% at a cut off value of an endometrial thickness of more than 4mm (22). If the cut off value for endometrial thickness was adjusted to more than 8mm, transvaginal ultrasound demonstrated a sensitivity of 83.8%, specificity of 81.3% and positive predictive value of 79.4% (22). Hysteroscopy on the other hand, showed sensitivity of 96.5%, specificity of 93.6% and PPV of 92.6%. The combination of ultrasound and hysteroscopy revealed a sensitivity of 100%, specificity of 94.8% and positive predictive value of 93.3%. The authors concluded that hysteroscopy was more accurate than transvaginal ultrasound because of a higher specificity. However, due to poor patient acceptability, cost and safety, it is still clinically practical to use transvaginal ultrasound in postmenopausal women as first line investigative tool. The patient can then be triaged accordingly to hysteroscopy and biopsy (22).

A similar study in postmenopausal women by Sousa et al in 2000 reported comparable results. Their objective was to determine the diagnostic value of transvaginal ultrasonography and hysteroscopy in patients with postmenopausal bleeding (5). This was a prospective study which included 69 women with postmenopausal bleeding. For the diagnosis of endometrial cancer, the combination of the two modalities demonstrated sensitivity 100%, specificity 91.7%, PPV 64.3%, NPV 100% (5). Overall, the combination of ultrasound and hysteroscopy demonstrated a sensitivity of 97.7%, specificity 84%, positive predictive value 91.5% and negative predictive value 95.5%. The authors acknowledged that the combination of the two modalities prevented any endometrial pathology from being overlooked. The authors concluded that ultrasound should remain a first line investigation and if endometrial thickness is >4mm or other risk factors are present, the clinician should proceed to hysteroscopy (5).

In a systematic review and meta-analysis, comprising 17 studies published in 2007, van Dongen et al looked at the accuracy of diagnostic hysteroscopy in evaluating intra-uterine abnormalities in pre-menopausal and post-menopausal women with abnormal uterine bleeding (3). The primary outcome measures were the accuracy of hysteroscopy assessed by likelihood ratios and post-test probability (3). Secondary outcome measures were feasibility and accuracy of hysteroscopy in the diagnosis of polyps and fibroids (3). This systematic review demonstrated that diagnostic hysteroscopy was both accurate, with pooled sensitivity 94%, specificity 89%, PPV 85%, NPV 93% and feasible as the review also established that hysteroscopy was safe and demonstrated a small failure rate ranging between 3-5% (3).

A recent study by Vitner et al in 2013 compared ultrasonography and hysteroscopy in the diagnosis of uterine pathology to evaluate diagnostic accuracy of the two modalities. The study also attempted to determine if the number of diagnostic hysteroscopies performed could be reduced (8).

This was a retrospective study comprising of 128 patients with abnormal uterine bleeding or suspicious findings on ultrasound (8).

The study demonstrated a sensitivity of 93% for TVS in detecting uterine abnormalities but a specificity of 58%. Hysteroscopy had a sensitivity of 92% and specificity of 67.7% (8). In cases of intra-uterine polyps and fibroids, hysteroscopy was still necessary to make an accurate diagnosis (8). Hysteroscopy had a higher sensitivity for the diagnosis of uterine fibroids and TVS had a higher sensitivity in diagnosing retained products of conception (8). Although hysteroscopy showed better predictive values for diagnosing uterine polyps, the difference was not statistically significant and the combination of the two modalities did not improve the results (8). Vitner et al concluded that although hysteroscopy was still needed to make an accurate diagnosis, the number of diagnostic hysteroscopies could be reduced particularly in cases of retained products of conception (8). This, however, was a small study of 128 women which failed to show statistical significance in the diagnosis of polyps.

A more recent study by Babacan et al (2014) concluded that although it would still be reasonable to routinely use ultrasound as a primary investigative tool, hysteroscopy performed better overall, especially in the diagnosis of endometrial polyps (23). The study included 285 women with varying complaints including abnormal uterine bleeding (69.4% of patients), postmenopausal bleeding, lower abdominal pain, abnormal vaginal discharge and women who presented for a routine gynaecological examination (23). All the patients had TVS followed by hysteroscopy with biopsy taken at hysteroscopy. The most common diagnosis based on histology was endometrial polyps in 46.7% patients with 30.5% having normal histology. Overall, hysteroscopy had better specificity than ultrasound (41.4% versus 13.8%) without much difference in sensitivity between hysteroscopy 92.9% and ultrasound 96% (23). However, hysteroscopy demonstrated better sensitivity for the diagnosis of polyps particularly those less than 1cm in size. Babacan et al acknowledged that their study was limited, due to low numbers of patients with other uterine pathology besides polyps, thus not permitting direct comparisons between ultrasound and hysteroscopy (23).

As demonstrated in the above studies, transvaginal ultrasonography is a simple, non-invasive procedure of which the diagnostic accuracy is limited, particularly when diagnosing polyps or submucosal fibroids. Hysteroscopy on the other hand has been shown to demonstrate better diagnostic accuracy but it is a more invasive and expensive procedure which is at times associated with more discomfort (12). An alternative is saline infusion sonohysterography (SIS). Although not done at our centre, several studies have shown the improved diagnostic accuracy of saline infusion over standard transvaginal ultrasonography, however hysteroscopy was still shown to be superior.

Saline infusion sonohysterograpy was first introduced in the early 1980's in an endeavour to enhance imaging and thus it developed as an alternative modality in the diagnosis of endometrial pathology (23). A systematic review assessing the accuracy of transvaginal ultrasonography, saline infusion sonohysterography and diagnostic hysteroscopy when investigating abnormal uterine bleeding in premenopausal women, was conducted in 2002 by Farquhar et al. This review included 19 studies in which the outcomes that were measured included diagnosis of any uterine pathology, submucosal fibroids and endometrial hyperplasia or carcinoma. This review demonstrated that transvaginal ultrasonography has a higher rate of false negatives compared to saline infusion sonohysterography and diagnostic hysteroscopy. It also showed that when diagnosing submucosal

fibroids and endometrial hyperplasia, saline infusion sonohysterography and diagnostic hysteroscopy were both accurate but hysteroscopy was superior for diagnosing submucosal fibroids. Unfortunately, resource utilisation and reproducibility were not assessed in any of the studies included in the review (24).

The authors aptly noted that in order to make progress when assessing diagnostic tests, it may be more useful to the clinical management of these patients to rather assess clinical usefulness, such as a testing algorithm, in future research instead of only assessing diagnostic accuracy in order to make a clinical impact (24).

Another systematic review and meta-analysis was done by Kroon et al in 2003, evaluating the diagnostic accuracy of saline infusion sonohysterography in pre- and postmenopausal women with abnormal uterine bleeding (25). The main outcome measures were reliability (likelihood ratios and post-test probability) and feasibility (success rate) (25). Secondary outcome measures were the separate reliability of saline infusion sonohysterography in the diagnosis of endometrial polyps and intrauterine fibroids (25). The meta-analysis included 24 studies, 16 of which had homogenous data as they avoided verification bias. The pooled sensitivity was found to be 0.95, specificity 0.88, likelihood ratios 8.23 and 0.06 with post-test probabilities of 0.91 and 0.07. The overall success rate was 93% but the success rate was significantly lower ($p<0.01$) in postmenopausal women (86.5%) than premenopausal women (94.8%). For the diagnosis of intrauterine fibroids, the pooled sensitivity was 0.87, specificity 0.92, likelihood ratios 11 and 0.07. For the diagnosis of endometrial polyps, pooled sensitivity was 0.86 and specificity 0.81 and the likelihood ratios 5.23 and 0.12 (25).

The authors commented that there was no meta-analysis on diagnostic accuracy of diagnostic hysteroscopy but on review of studies available they concluded that the diagnostic accuracy of saline infusion sonohysterography was similar to diagnostic hysteroscopy. However, on assessing reliability of saline infusion sonohysterography for diagnosis of endometrial polyps, some endometrial polyps were missed. The authors commented that this may become clinically relevant in postmenopausal women as a malignancy may be overlooked and therefore all postmenopausal women should have endometrial sampling as well. The authors of this review concluded with the recommendation that saline infusion ultrasonography could be the standard diagnostic procedure in women with abnormal uterine bleeding (25).

Bingol et al conducted a prospective, investigator-blind study comparing diagnostic accuracy of saline infusion sonohysterography, transvaginal ultrasonography and hysteroscopy in women with postmenopausal bleeding between 2004 and 2008. The study included 137 postmenopausal women with a mean age of 61.6 years. All the patients underwent transvaginal ultrasonography, saline infusion ultrasonography and hysteroscopy, with biopsy/resection at hysteroscopy. The study demonstrated that hysteroscopy and saline infusion sonohysterography performed equally when diagnosing endometrial hyperplasia, submucosal fibroids and polyps when compared to histology as gold standard. However, transvaginal ultrasonography and hysteroscopy were shown to be more accurate than saline infusion ultrasonography in the diagnosis of endometrial cancer (26).

Grimbizis et al also conducted a prospective study, comparing diagnostic accuracy between the three modalities, but the population differed in that it included all women with abnormal uterine bleeding as well as those presenting with infertility. The study included 98 women who underwent all three diagnostic tests as well biopsy at hysteroscopy for histology. Sensitivity, specificity, positive

likelihood ratios and negative likelihood ratios were calculated as well ROC analysis performed to assess diagnostic accuracy. The final results showed that diagnostic hysteroscopy was the most accurate in diagnosing any endometrial pathology compared to saline infusion sonohysterography and transvaginal ultrasonography. This result was shown to be statistically significant. When comparing saline infusion sonohysterography to transvaginal ultrasonography in diagnosing any endometrial pathology both had similar diagnostic value (11).

The authors also sub-analysed diagnostic accuracy for endometrial hyperplasia and endometrial cancer. It was found that diagnostic hysteroscopy was superior but this was not statistically significant. Saline infusion sonohysterography and transvaginal ultrasonography performed equally in the diagnosis of endometrial hyperplasia and endometrial cancer. When diagnosing intracavitatory masses such as endometrial polyps or submucous fibroids, diagnostic hysteroscopy was found to be the more superior diagnostic test and this was shown to be statistically significant. However, in this category, saline infusion sonohysterography was found to be superior to transvaginal ultrasonography, which was also statistically significant. Grimbizis et al commented that their results were similar to other studies and concluded that saline infusion sonohysteroscopy has a role in clinical practice in patients where an intracavitatory mass is suspected on TVS. The patient may then be triaged directly to operative hysteroscopy if SIS confirms an intracavitatory mass (11).

A more recent prospective study by Soguktas et al comparing TVS, SIS and diagnostic hysteroscopy included 89 premenopuasal women with abnormal uterine bleeding. The authors found that hysteroscopy and saline infusion sonography performed similarly in diagnosing any endometrial pathology and their diagnostic value was superior to transvaginal ultrasonography. The authors recommended that SIS should be performed if there is no obvious abnormality on TVS and hysteroscopy should be performed if there are intracavitatory masses or suspicious lesions (12). This recommendation differs from Grimbizis et al but it is important to note that there were some differences in the populations studied.

The studies comparing TVS and hysteroscopy therefore indicate that TVS may be a good screening tool but that hysteroscopy provided superior diagnostic value overall. Although several studies have shown the improved diagnostic accuracy of saline infusion sonohysterography over standard transvaginal ultrasonography, hysteroscopy was still shown to be superior. Most of the studies have been small with variable outcomes and different populations which looked at both benign and malignant pathology.

The aim of this study, therefore, is to further analyse the diagnostic accuracy of transvaginal ultrasound in benign endometrial pathology by comparing it to findings at hysteroscopy using histological diagnosis as the gold standard. This is the first study of this nature to be done in our setting.

AIMS AND OBJECTIVES

To evaluate the diagnostic accuracy of transvaginal sonography compared to hysteroscopy in diagnosing benign endometrial pathology in our tertiary level referral hospital.

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CHAPTER 2

PUBLICATION READY MANUSCRIPT

COVER LETTER

25 March 2018

Dear Editor in Chief

Please accept the enclosed manuscript “THE ACCURACY OF 2D TRANSVAGINAL ULTRASOUND IN THE DIAGNOSIS OF BENIGN ENDOMETRIAL PATHOLOGY: A COMPARISON BETWEEN ULTRASONOGRAPHY AND HYSTEROSCOPY”.

Abnormal uterine bleeding is a common symptom and can be found in the pre-menopausal, peri-menopausal or postmenopausal woman. It is the most common reason for referral to a gynaecologist as it can be debilitating for many women. Endometrial pathology requires an accurate and timeous diagnosis followed by appropriate treatment. The management of women with abnormal uterine bleeding has changed over the years with advances in ultrasound and endoscopic technology. Special investigations for diagnosis include transvaginal ultrasonography and hysteroscopy, of which hysteroscopy can be a diagnostic as well a therapeutic procedure.

The purpose of this study was to evaluate the diagnostic accuracy of transvaginal sonography compared to hysteroscopy in diagnosing benign endometrial pathology in our tertiary level referral hospital. This is the first study of this nature to be done in our setting.

Our data has not been published or presented elsewhere and the manuscript is not under review at any other journal. We declare no conflict of interest.

Sincerely,

K. Jagot, FCOG(SA)

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TITLE PAGE

ORIGINAL ARTICLE

The accuracy of 2D transvaginal ultrasound in the diagnosis of benign endometrial pathology: a comparison between ultrasound and hysteroscopy

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Disclosure statement: The authors declare that they have no conflicts of interest and nothing to disclose.

PRECIS

This study demonstrated that hysteroscopy was more accurate in the diagnosis of endometrial polyps than ultrasound with a higher sensitivity and negative predictive value but lower sensitivity when diagnosing submucosal fibroids.

ABSTRACT

STUDY OBJECTIVE: To evaluate the diagnostic accuracy of transvaginal sonography compared to hysteroscopy in diagnosing benign endometrial pathology.

DESIGN: Retrospective cross-sectional study. Canadian Task force classification II – 2

SETTING: Department of Gynaecology, Groote Schuur Hospital, Cape Town, South Africa.

PATIENTS: Patients having an office hysteroscopy procedure between January 2014 and December 2016, with a record of a recent transvaginal ultrasound and endometrial histology were included in this study. All malignant cases were excluded.

INTERVENTIONS: Transvaginal ultrasound, endometrial biopsy and office hysteroscopy.

MEASUREMENTS AND MAIN RESULTS: A total of one hundred and forty two patients, pre- and postmenopausal, were included in this study. The most common indications for hysteroscopy were abnormal uterine bleeding and postmenopausal bleeding. Sensitivity, specificity, positive and negative predictive values were calculated for ultrasonography and hysteroscopy in diagnosing benign endometrial pathology by comparing them to histological diagnosis as gold standard. The most common pathologies identified at histology were polyps and fibroids.

For those patients who had a normal endometrium at ultrasound (n=59), hysteroscopy revealed 33.9% polyps, 5.1% submucosal fibroids and 49.2% normal/atrophy. The remainder of these patients demonstrated proliferative or hyperplastic endometrium, suspicious endometrium and adhesions. For those patients who had a normal hysteroscopy (n=26), ultrasound demonstrated 7.7% polyps, 7.7% submucosal fibroids, 11.5% cystic areas, 3.9% no comment and 69.2% normal endometrium.

In diagnosing polyps, hysteroscopy had a higher sensitivity (78%) than ultrasound (37.3%). However, ultrasound had a higher specificity (85.5%), compared to that of hysteroscopy which was 71.1%. The negative predictive value of hysteroscopy for polyps was 81.9% and ultrasound, 65.7%.

In the diagnosis of submucosal fibroids, ultrasound had a higher sensitivity than hysteroscopy but they both had similar specificity. Ultrasound and hysteroscopy had high negative predictive values and low positive predictive values. The combination of ultrasound and hysteroscopy did not improve sensitivity, PPV or NPV with a small decline in specificity.

CONCLUSION: This study demonstrated that hysteroscopy was more accurate in the diagnosis of endometrial polyps than ultrasound with a higher sensitivity and negative predictive value. However hysteroscopy had a lower sensitivity when diagnosing submucosal fibroids.

Keywords: Fibroids; Hysteroscopy; polyps; transvaginal ultrasound; uterine pathology

CHAPTER 2 – PUBLICATION MANUSCRIPT

INTRODUCTION

Abnormal uterine bleeding is a common symptom and can be found in the pre-menopausal, peri-menopausal or postmenopausal woman (1, 2). It is the most common reason for referral to a gynaecologist as it can be debilitating for many women (1, 3). Of the many causes of abnormal uterine bleeding, intra-uterine pathology such as fibroids and polyps are significant contributing factors, occurring in more than 40% of women (3). Fibroids and polyps can also lead to infertility (4). Another important cause of bleeding in the postmenopausal woman is malignant pathology (5).

Endometrial pathology requires an accurate and timeous diagnosis, followed by appropriate treatment (6). Previously, dilatation and curettage was regarded as the gold standard for investigating abnormal uterine bleeding but this has been shown to be inaccurate (7). The ultimate gold standard is hysterectomy, but for obvious reasons it is not a feasible diagnostic modality (3).

The management of women with abnormal uterine bleeding has changed over the years, with advances in ultrasound and endoscopic technology (6). Special investigations for diagnosis include transvaginal ultrasonography and hysteroscopy, of which hysteroscopy can be a diagnostic as well as a therapeutic procedure (6). The choice between ultrasound and hysteroscopy is based on suspected clinical diagnosis, however the clinician also needs to consider feasibility, accuracy, versatility and cost (6).

The purpose of this study was to evaluate the diagnostic accuracy of transvaginal sonography compared to hysteroscopy in diagnosing benign endometrial pathology in our tertiary level referral hospital.

MATERIALS AND METHODS

In this retrospective study, we included patients who underwent hysteroscopy at Groote Schuur Hospital outpatient hysteroscopy clinic. For inclusion, women were required to have had a previous ultrasound within six months and endometrial histology results should have been available. All women fulfilling the recruitment criteria between January 2014 and December 2016 were included in this study. All malignant cases were excluded.

Transvaginal ultrasound was performed in the Department of obstetrics ultrasound unit using ALOKA (Alpha 10) with a 1 to 15 MHz transvaginal transducer. Abnormal findings noted on ultrasound included polyps, submucosal fibroids, cystic areas on endometrium and a mass. Nil focal pathology on endometrium was classified as normal endometrium.

Hysteroscopy was performed using a 5mm Betocchi scope with a 30 degree lens by Karl Storz in the outpatient hysteroscopy clinic at Groote Schuur Hospital. Normal saline was used to distend the uterine cavity. Abnormal findings at hysteroscopy included fibroid, polyp, hyperplasia, suspicious endometrium, proliferative endometrium, offensive discharge, adhesions, fluffy endometrium and cyst on endometrium.

Statistical analysis was done using STATA software. Sensitivity, specificity, positive and negative predictive values were calculated for ultrasonography and hysteroscopy in diagnosing benign endometrial pathology, such as polyps and submucosal fibroids, by comparing it to histological diagnosis as gold standard.

RESULTS

One hundred and forty two patients were included in this cross-sectional retrospective study. The mean age of patients included in the study was 51.9 ± 10.6 years (range 29 – 84 years). The mean thickness of the endometrium in our study group was 10.15 ± 6.13mm. One of the patients recruited deviated from the protocol as the ultrasound was done 6 months and 18 days prior to hysteroscopy. Three other patients had ultrasound performed within two weeks after hysteroscopy.

The majority of patients who had hysteroscopy were women presenting with abnormal uterine bleeding (n=71, 47%) and postmenopausal bleeding (n=52, 37%). Only 2% (n=3) of patients were referred to the hysteroscopy clinic to investigate endometrial pathology as a cause of infertility or recurrent miscarriages. (See Table 1)

The common findings at ultrasound relating to the endometrium included polyps (n=34, 23.9%) and cystic areas (n=26, 18.31%). Fibroids (submucosal) were seen in 9.8% (n=14) of patients and in 41.6% (n=59) no focal endometrial pathology was identified at ultrasound.

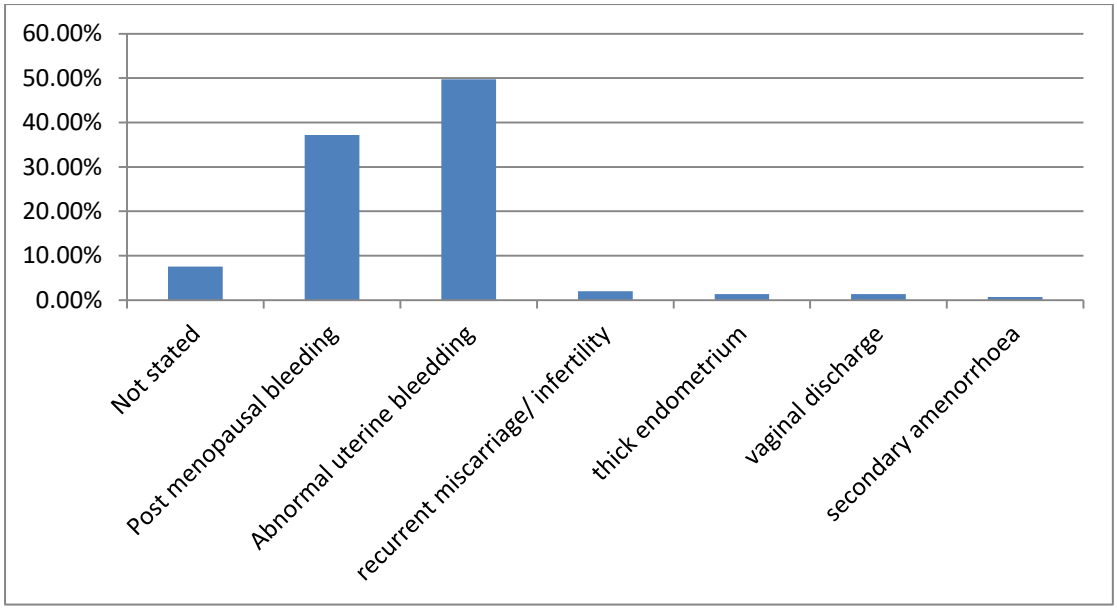

TABLE 1. INDICATIONS FOR HYSTEROSCOPY

At hysteroscopy, the common findings were polyps (n=70, 47.6%) and submucosal fibroids (n=15, 10.6%), with 17.7% (n=26) having a normal endometrium and uterine cavity. Other findings included atrophy (n=13), proliferative endometrium (n=8), hyperplastic endometrium (n=6), suspicious lesions (n=3) and adhesions (n=3). (See Table 2)

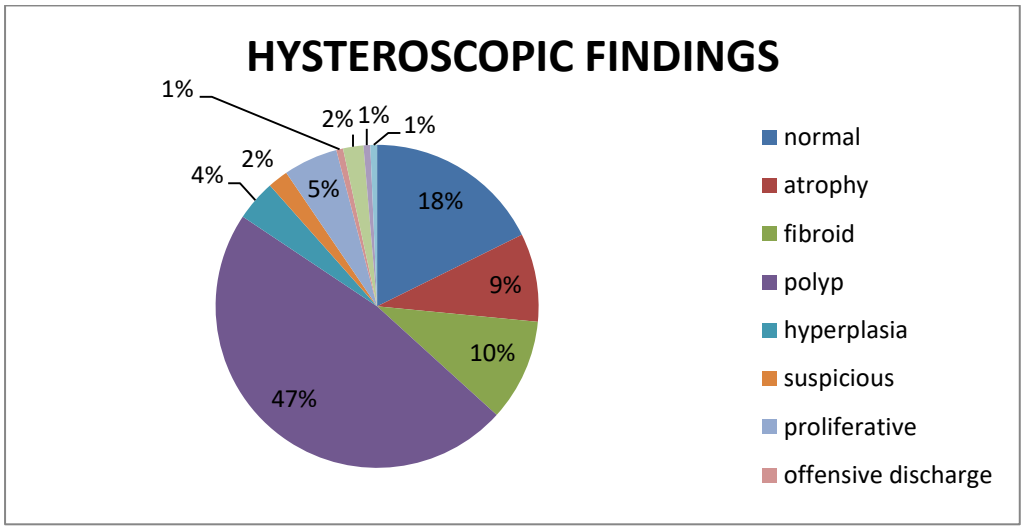

Table 2. HYSTEROSCOPIC FINDINGS

Endometrial samples were obtained via three methods: Pipelle prior to hysteroscopy or at hysteroscopy (n=72, 51%), biopsies under direct vision at hysteroscopy (n=62, 43%) and histology obtained from hysterectomy specimen (n=8, 6%).

The final histology of samples taken showed that 41.6% (n=59) of patients had polyps, 3.5% (n=5) had fibroids, 2.8% (n=4) had an atrophic endometrium, 26.8% (n=38) had a normal endometrium and 18.3% (n=26) of samples taken were inadequate for histological diagnosis.

Of the 59 women who had a normal endometrium ultrasound, 50% (n=29) had normal hysteroscopy, 34% (n=20) had polyps at hysteroscopy and 5% (n=3) had submucosal fibroids. Of the 26 patients who had normal hysteroscopy, ultrasound was normal in 69% of those patients. Of the patients who had submucosal fibroids at ultrasound, only 31% had submucosal fibroids at hysteroscopy and the rest were reported as polyps, hyperplasia, proliferative endometrium or normal endometrium (12.5%, n=2) at hysteroscopy. On analysing the patients who had normal histology (n=38) it was found that 39.5% had normal hysteroscopy, with 23.7% patients having polyps and 7.9% had fibroids at hysteroscopy.

The two most common findings at hysteroscopy (polyps and fibroids) were further analysed. The sensitivity, specificity, positive and negative predictive value for transvaginal ultrasound and hysteroscopy in the diagnosis of polyps and fibroids is summarised in Table 3. In diagnosing polyps, hysteroscopy had a higher sensitivity than ultrasound however ultrasound had a higher specificity. Both ultrasound and hysteroscopy had a similar positive predictive value for the diagnosis of polyps however hysteroscopy had a higher negative predictive value. The combination of the two modalities only improved sensitivity and negative predictive value (whereas specificity and PPV declined).

In the diagnosis of fibroids, ultrasound had a higher sensitivity than hysteroscopy, however both had similar specificity. Ultrasound and hysteroscopy had high negative predictive values and low positive predictive values for the diagnosis of fibroids. The combination of ultrasound and hysteroscopy did not improve sensitivity, PPV or NPV with a small decline in specificity. See Table 3.

	SENSITIVITY	SPECIFICITY	PPV	NPV
ENDOMETRIAL POLYPS				
ULTRASOUND	37.30%	85.50%	64.70%	65.70%
HYSTEROSCOPY	78%	71.10%	65.70%	81.90%
COMBINED	84.70%	66.30%	64.10%	85.90%
UTERINE FIBROIDS				
ULTRASOUND	80%	92.70%	28.60%	99.20%
HYSTEROSCOPY	60%	91.20%	20%	98.40%
COMBINED	80%	86.10%	17.40%	99.20%

Table 3. Sensitivity, specificity, positive predictive value and negative predictive value of ultrasound and hysteroscopy in diagnosing benign endometrial pathology – endometrial polyps and submucosal fibroids.

DISCUSSION

The aim of this study was to evaluate the diagnostic accuracy of transvaginal ultrasound when diagnosing benign endometrial pathology by comparing it to hysteroscopy. This study demonstrated that hysteroscopy was more accurate in the diagnosis of endometrial polyps than ultrasound with a higher sensitivity and negative predictive value but lower sensitivity when diagnosing fibroids.

Abnormal uterine bleeding is the most common reason for referral to a gynaecologist and transvaginal ultrasound is usually the first line of special investigations for imaging as it is quick, easy to perform and cheap with minimal discomfort to the patient. If there are abnormal findings of the endometrium on ultrasound the next step is hysteroscopy for better visualisation of the endometrium with the advantage of taking a biopsy under direct visualisation or the option of simultaneously treating the patient ie. resection of fibroids or polyps. Hysteroscopy is more invasive, expensive and at times associated with discomfort or pain which may require anaesthesia.

Studies have shown that transvaginal ultrasound has good diagnostic value and should still be used as first line before proceeding to hysteroscopy. A recent retrospective study of 123 women by Vitner et al in 2013, comparing ultrasonography and hysteroscopy in the diagnosis of uterine pathology, demonstrated a sensitivity of 93% using TVS in detecting uterine abnormalities but a specificity of 58% (8). Our study had a lower sensitivity of 71.2% and a specificity of 62.2%.

Their results also showed a sensitivity of 100% and specificity 86.9% for the diagnosis of uterine fibroids at hysteroscopy. TVS demonstrated a sensitivity of 85.7% and specificity of 73.9%(8). Although hysteroscopy showed better predictive values for diagnosing uterine polyps, the difference was not statistically significant and the combination of the two modalities did not improve the results (8). Vitner et al concluded that in cases of intrauterine polyps and fibroids, hysteroscopy was still necessary to make an accurate diagnosis (8).

Our study had a lower sensitivity of 60% but a higher specificity of 91.9% for the diagnosis of uterine fibroids at hysteroscopy, whilst TVS had a sensitivity of 80% and a specificity of 92%. Both ultrasound and hysteroscopy had poor positive predictive values but high negative predictive values, similar to that of Vitner et al. The reason for this difference in our study may be that we had a small number of patients with the final diagnosis of fibroids on histology (n=5, 3.5%). The reason for the small numbers may be due to the fact that this was a retrospective study of outpatient hysteroscopy where resection was not performed. With regards to the diagnosis of polyps, in our study hysteroscopy had higher sensitivity but lower specificity than Vitner et al, with a higher PPV of 73.3% but lower NPV 75.5% than Vitner et al.

A similar study by Babacan et al in 2014, focused on diagnosis of polyps, particularly looking at polyp size ie. >1cm and <1cm, and atrophy. Babacan et al concluded that hysteroscopy offered better overall diagnostic value, for uterine polyps in particular (23). The study included 285 women with varying complaints, including abnormal uterine bleeding, postmenopausal bleeding, lower abdominal pain and abnormal vaginal discharge. Their results indicated that hysteroscopy had a higher sensitivity in diagnosis of all polyps but it did not have an advantage over TVS in diagnosing polyps greater than 1cm. Hysteroscopy did demonstrate better specificity (23). Similarly, in our study, hysteroscopy demonstrated a higher sensitivity in the diagnosis of polyps however hysteroscopy had a lower specificity.

Saline infusion sonography is a new alternative diagnostic modality in evaluating the endometrium. Although not done at our centre, several studies have shown the improved diagnostic accuracy of saline infusion over standard TVS, however hysteroscopy was still shown to be superior (11, 12).

In a study by Soguktas et al., the authors concluded that hysteroscopy was superior to saline infusion sonography in evaluating premenopausal women with abnormal uterine bleeding, however the authors recommended that SIS should be performed if there is no obvious abnormality on TVS and hysteroscopy should be performed if there are intracavitatory masses or suspicious lesions (12).

Bingol et al compared diagnostic accuracy of SIS, TVS and HSC in women with postmenopausal bleeding only. The authors recommended that SIS should be the primary screening tool in this group of women (26). Grimbizis et al, concluded that SIS was more valuable in diagnosis of polyps and myomas and should be performed routinely prior to hysteroscopy (11).

The limitations of our study were the small numbers and missing data due to lack of consistency in reporting on ultrasound and hysteroscopy as it was a retrospective study. The generalisation of the results is limited as the study was performed in one centre with small numbers. Another limitation was that 50% of endometrial histology was obtained via pipelle in which majority of the specimens were inadequate.

CONCLUSION

In conclusion, this study demonstrated that hysteroscopy was more accurate in the diagnosis of endometrial polyps than ultrasound with a higher sensitivity and negative predictive value. The combination of the two modalities, however, did improve sensitivity and negative predictive value. For the diagnosis of submucosal fibroids, hysteroscopy and ultrasound had similar specificity, negative predictive values and positive predictive values, but hysteroscopy had a lower sensitivity and the combination of the two modalities did not improve sensitivity. Therefore hysteroscopy is still necessary for diagnosis of endometrial pathology and particularly for the diagnosis of endometrial polyps. However, saline infusion sonography should also be considered when diagnosing endometrial pathology to improve diagnostic accuracy of ultrasonography.

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APPENDICES

ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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23 December 2016

HREC REF: 775/2016

Dr S Jeffery
Obstets & Gynae
H Floor
OMB

Dear Dr Jeffery

PROJECT TITLE: THE ACCURACY OF 2D TRANSVAGINAL ULTRASOUND IN THE DIAGNOSIS OF BENIGN ENDOMETRIAL PATHOLOGY: A COMPARISON BETWEEN ULTRASONOGRAPHY AND HYSTERO$COPY (FCOG-candidate-K Jagot)

Thank you for submitting your response to the queries raised by the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website:
www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledges that the following FCOG Candidate, K Jagot, will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

TJ Burgess

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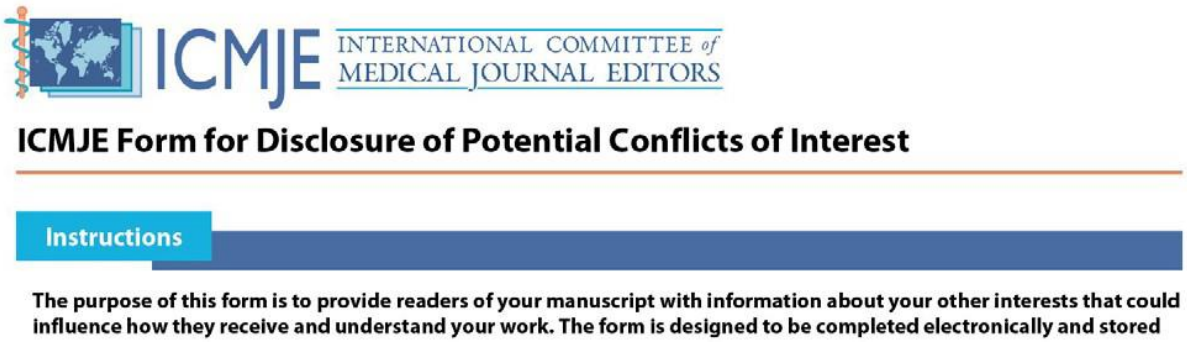
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All manuscripts must be submitted in Arial 11 point font with continuous line numbering, page numbers, and double spaced. Title must be title case. The title page must include

• Authors' full first and last (family) names, degrees

• Authors' institutional affiliations

• Conflict of interest statement

• Source of funding

• Statement of prior presentation or publications and/or abstract/poster presentation

• Corresponding author's complete contact information including complete mailing address, telephone and facsimile numbers, email address

• Clinical trial registry number

• Date and number of IRB

• Word count Title Page Sample

Keywords: include 3 to 5 words that differ from the title, in alphabetical order, separated by semi-colons.

Arrange the manuscript as follows: title page, precis, abstract, keywords, text, acknowledgments, disclosures, references, tables, and figure legends.

The precis is a one-sentence synopsis of no more than 30 words that describes the basic findings of the article. It appears in the table of contents under the author(s) name(s). **Precis Letter Sample.**

Introduction of all articles should not exceed 250 words; the discussion should not exceed 750 words.

The JMIG style now reflects AMA Manual of Style, 10th edition. Numbers are Arabic, not spelled out. Delete zeros before decimal point when reporting p values, which should not be carried out past 3 decimal places.

Scientific (generic) names of drugs should be used at all times. Weights and measures must be expressed in metric values and temperatures in Celsius (centigrade). Prior presentation as an abstract or at a professional meeting should be described fully on the title page.

It is your responsibility to obtain written permission from the original copyright holder (generally the publisher, not the author or editor) to reproduce figures, tables, and text. Permission from the Journal or book concerned must be sent with the manuscript. An appropriate credit line should appear at the end of a figure legend or in a table footnote; for example, "Reprinted with permission from reference 17." Full publication data must appear in a numbered entry in the reference list.

It is the authors' responsibility to ensure that all data are accurate and verified.

American English spelling should be used throughout the manuscript, including within illustrations.

Acknowledgments

It is reasonable to acknowledge others in acknowledgments. Please limit acknowledgments to those who are directly and scientifically involved in the preparation of the manuscript.

Electrosurgery Terminology

The JMIG has specific electrosurgery terminology:

Table 2.1. Definitions of variables commonly used in the description of RF electrosurgery that can impact effect on cells and tissue.

Variable	Definition	Units
Current (I)	Flow of electrons past a point in the circuit/unit time	Amperes (coulombs/second)
Voltage (V)	Difference in electrical potential between two points in the circuit; force required to push a charge along the circuit	Volts (joules/coulomb)
Impedance (resistance) (R)	Degree to which the circuit or a portion of the circuit impedes the flow of electrons	Ohms
Power (P)	Work; amount of energy per unit time. Product of V and I	Watts (joules/second)
Energy	Capacity of a force to do work; cannot be created or destroyed	Joules (watts/second)

From: Munro MG. Fundamentals of electrosurgery part I: principles of radiofrequency energy for surgery. In: Feldman LS, et al, eds. The SAGES Manual on the Fundamental Use of Surgical Energy (FUSE). Springer Science + Business Media, LLC. 2012:15-59.

Manuscript requirements at a glance*

Article type†	Precis, word limit	Abstract	Word limit‡	References, maximum number§	Authors, total number permitted
Original Article	30 words	300 words Structured: Study Objective, Design (Canadian Task Force Classification), Setting, Patients, Interventions, Measurements and Main Results, Conclusion	4,000 words	30	
Review Article	30 words	250 words Unstructured	5,000 words	60	
Case Report	30 words	125 words Unstructured	2,000 words	10	6 authors
Instruments and Techniques	30 words	200 words Unstructured	2,000 words	10	
Special Articles	30 words	200 words Unstructured	Per invitation	Per invitation	Per invitation
Perspectives	30 words	None	2,000 words	5	
Editorials	None	None	750 words	5	
Images in Gynecology	None	None	300 words		10
Letters to the Editor	None	None	300 words	5	
Video Article	None		250 words Structured: Study Objective, Design (Canadian Task Force Classification), Setting, Intervention, Conclusion	5	

*All manuscripts must be submitted via EES. Font must be submitted as Arial 11 point with continuous line numbering, page numbers, and double spaced. Title must be title case and title page must include Authors' full names, degrees, affiliations; conflict of interest statement; source of fundir authors complete contact information; clinical trial registry number; date and number of Institutional Review Board; word count. Keywords: include 3 to 5 words that differ from the title, in alphabetical order, separated by semi-colons. Introduction of all articles should not exceed 250 words; types are defined as Original article: original research study; Review article: a review and evaluation of current evidence and previously published literature regarding condition, diagnosis, and/or technique considering the progress toward resolution of a problem in minimally invasive gynecolog description up to 3 cases of a particular condition that reports an unusual presentation or novel diagnostic or therapeutic approach; Instruments and techniques: substantive new information concerning innovative surgical techniques; Special articles: by invitation only and peer reviewed; Persp invasive community; Editorials: a commentary or a topic assigned by the Editor in Chief; Images in gynecology: images that are novel, of high quality, and pertinent to minimally invasive gynecology; Letters to the Editor: comments and opinions regarding recently published articles in JMIG.
‡Word limit does not include title page, precis, or abstract. §References must be verified and accurate, formatted per JMIG style, complete, from peer-reviewed journals, and the majority must be no older than 8 years unless used for historic reasons (eg, Phillips DR, Nathanson HG, Milim SJ, et treatment of adenomyomata. J Am Assoc Gynecol Laparosc. 1996;4:20-24.) Acknowledgments: limit to those who are directly and scientifically involved in the preparation of the manuscript.

Manuscript Preparation, Specific

The Original Articles section of JMIG is reserved for manuscripts that represent original research. Abstracts for these manuscripts must appear in **structured format**, as follows: Study Objective, Design (Design [Canadian Task Force] Classification), Setting, Patients, Interventions, Measurements and Main Results, and Conclusion. All abstract sections must be complete.
The Design portion of abstracts are to be classified by the author according to the Canadian Task Force Classification of Study Designs (see table below).

Table Canadian Task Force Classification of Study Design

I	**Evidence obtained from a properly designed, randomized, controlled trial**
II-1	**Evidence obtained from a well-designed, controlled trial without randomization**
II-2	**Evidence obtained from well-designed cohort or case-control studies, preferably from more than one center or research group**
II-3	**Evidence obtained from several timed series with or without the intervention; dramatic results in uncontrolled experiments, such as the results of the introduction of penicillin treatment in the 1940s, could also be regarded as this type of evidence**
III	**Opinions of respected authorities based on clinical experience, descriptive studies, or a report of an expert committee**

Adapted from Woolf SH. Arch Intern Med. 1992;152:946-952.

Manuscripts that do not contain original research are placed in the section of JMIG that is most appropriate; for example, Review Articles, Case Reports, Instruments and Techniques, Special Articles, Perspectives, Editorials, Images in Gynecology, Letters to the Editor, and Video Articles.

Review articles: a review and evaluation of current evidence and previously published literature regarding condition, diagnosis, and/or technique considering the progress toward resolution of a problem in minimally invasive gynecology. The preferred reporting of systematic review article and meta-analyses should follow PRISMA guidelines (Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700) (Word limit 5,000; Reference limit 60). See PRISMA Flow Diagram and Checklist.

Case reports: a brief description up to 3 cases of a particular condition that reports an unusual presentation or novel diagnostic or therapeutic approach. (Word limit 2,000; Reference limit 10; Author limit 6)

Instruments and techniques: substantive new information concerning innovative surgical

techniques. (Word limit 2,000; Reference limit 10)

Special articles: by invitation only.

Perspectives: a short article of current interest of the minimally invasive community. (Word limit 2,000; Reference limit 5)

Editorials: a commentary or a topic assigned by the Editor in Chief. (Word limit 750; Reference limit 5; Author limit 4)

Images in gynecology: images that are novel, of high quality, and pertinent to minimally invasive gynecology. (Word limit 300; Reference limit 10)

Letters to the Editor: comments and opinions regarding recently published articles in JMIG. (Word limit 300; Reference limit 5; Author limit: 6)

When Writing Your Research Paper

Please keep in mind the following when writing your clinical manuscript. Each submission is peer reviewed and the reviewers are looking for the following to ensure that your research is of the highest value.

Title/Abstract

• Why was the study performed?

• How is this study different from others?

• Can the study be replicated?

• Will the study results and publication improve patient care? If not, the paper is not relevant.

• Is it novel and suitable to fill the gap of existing publications?

• The abstract must be able to stand alone and be understood without reading the manuscript.

• The objective must be clear.

Introduction must include

• The rationale, or motivation for the current investigation; what is the problem that the authors are trying to answer?

• Is it the next logical step in a line of an investigation or have prior studies been deficient in some way that the current study addresses?

• Coherent and comprehensive background information as to why the study was performed, including gaps in current knowledge.

• Previous relevant publications.

• Study hypothesis.

The methodology must include

• Inclusion and exclusion criteria.

• One single primary endpoint (outcome measure).

• Secondary endpoints (when appropriate).

• Tests, procedures, interventions, analyses.

• Institutional review board approval statement.

• Could another investigator replicate the study?

Results

• Logical and systemic presentation of data mirroring the same sequence as in the methods.

• If one author does not have a statistical background, a statistician should have been consulted.

• Values of measured variables to be shown with error limits (standard deviations).

• Tables and figures presented here.

Conclusion

• Summary of main findings balanced to the stated hypothesis and objectives.

• How does this article change what the reader recommends to patients?

• Comparison to other previous publications on the topic.

• Discussion of alternative explanations for the observations.

• Clinical relevance.

• Limitations of the study; explanation of unexpected findings.

• Rational defensible conclusion or take-home message.

• Is the conclusion justified by the results?

Statistics

Manuscripts dealing with comparisons between groups--cohort, case-control and/or randomized clinical trials--must use proper statistical analyses. Failure to do so may result in the manuscript being returned to the author(s) without peer review. Means or medians, depending on distribution of the data, must be accompanied by standard deviations. Confidence intervals are mandatory where applicable. Use of "p" values for comparisons between groups is not sufficient; use of probability ratios, odds ratios or hazard ratios, where appropriate are necessary. Consultation with a medical statistician *prior* to submission is advised

References

References must be cited in the order that they appear in the text in brackets inside punctuation. Every entry must have only one number; if it is cited a second time, it should have the first (original) number, not a new number, ibid, or op cit. If a new entry is inserted into an established list, it must be numbered consecutively (not, 10a, 10b, etc.), with subsequent entries renumbered both in the text and in the reference list.

To maintain relevance, timeliness, and comprehensiveness of current research, references must be verified and accurate, formatted per JMIG style, complete, from peer-reviewed

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journals, and the majority must be no older than 8 years unless used for historic reasons.

If it becomes clear that the references are cited incorrectly, are single-spaced, incomplete, unclear, or otherwise in unacceptable format, they will be returned to you to be corrected. This will delay publication of the article. You are responsible for the accuracy of references, and are reminded that inaccurate references are highly frustrating to the reader, the cited author, and indexing services. Footnotes are not acceptable JMIG style.

No unpublished data, personal communications, papers presented at meetings, manuscripts submitted for publication may be listed in the reference list.

The JMIG requests that the following formats be used for all reference lists, and that they be typed and double-spaced.

For up to 6 authors, list all authors; for 7 or more, list the first 3 authors + et al.

Journal article

1. Phillips DR, Nathanson HG, Milim SJ, et al. Laparoscopic bipolar coagulation for the conservative treatment of adenomyomata. *J Am Assoc Gynecol Laparosc*. 1996;4:20-24.

Journal article online ahead of print

2. Kumakiri, J, Phillips DR, Nathanson HG, et al. Incidence of complications during gynecologic laparoscopic surgery in patients after previous laparotomy. *J Minim Invasive Gynecol*. 2010;DOI: 10.1016/j.jmig.2010.03.004.

Book

2. Parker WH, Parker RL. *A Gynecologist's Second Opinion: The Questions and Answers You Need to Take Charge of Your Health*. New York: Penguin; 1996.

Chapter in a book

3. Steege JF. Persistent or chronic pelvic pain. In: Rock JA, Thompson JD, eds. *TeLinde's Operative Gynecology.* 8th ed. Philadelphia: Lippincott-Raven; 1997: 645-656.

Presentation

4. Wortman M, Daggett A. Serum sodium changes during hysteroscopic endomyometrial resection. Paper presented at: 23rd annual meeting of the American Association of Gynecologic Laparoscopists; October 18-24, 2015; New York, NY.

5. World Health Organization. Equitable access to essential medicine: a framework for collective action. Available at: http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.4.pdf. Published March 2004. Accessed December 6, 2016.

Unpublished observations must not be included in the reference list.

Figures, Illustrations, and Tables

Figures/tables should be of high quality, clear, concise and not redundant to the material in the paper; the purpose is to make data more understandable. Figure legends must be included in the paper only following the references and tables (not in the figure itself) and include abbreviation definitions. The editors reserve the right to limit the number of black and white illustrations that will be reproduced free of charge.

Electronic tables must be submitted as separate word files. All photographs, figures or Illustrations, images, line-art images should be submitted at a resolution of 300 dpi. Black and white photographs should be gray scale and bit map for line-art images. **Do not embed figures within documents.** Color figures are preferred, but must be submitted in high resolution (300 dpi) tiff file form. The colors must be dark enough and have enough contrast for reproduction.

Video Clips to Supplement Written Manuscripts

The Journal of Minimally Invasive Gynecology accepts electronic supplementary material to support and enhance your scientific research. Supplementary files may include movies, animations sequences, high-resolution videos, sound clips, and more. Supplementary files supplied will be published online together with the electronic version of your article in Elsevier Web products, including Science Direct.

Videos will be accepted only for an Original Article or an article for the section titled Instruments and Techniques.

The JMIG will not edit any video or computer graphics nor may reviewers suggest changes in the video or computer graphic following submission. The video will be accepted or rejected as presented without an option for revision. Videos and computer graphics will not be accepted separately from a manuscript that has been rejected; however, a manuscript may be accepted even if a video is rejected.

Maximum cumulative length of videos or animated computer graphics is approximately 6 to 8 minutes.

Files may be divided into several smaller clips not to exceed 8 minutes in total. Video files are often very large files. We ask that you submit your file to our video server and compress the file before submitting it through JMIG. Video segments cannot exceed 50MB. The submission program will timeout if the file size is larger than 50MB. To hasten the upload time, please ZIP the file and upload the ZIP file.

If the video or animation is divided into several clips, each clip should be identified at the beginning of the section, (e.g., Video Clip 1 or Graphic 1) and each clip or graphic should be saved as a separate file. Concise legends (typed on a separate page) must accompany each video clip or computer graphic presentation. A sound track is highly recommended.

The following formats for video will be accepted: MPEG-4, MPEG-1 or MPEG-2 (.mpg), QuickTime (.mov), Audio/Video Interface (.avi). *The Journal of Minimally Invasive Gynecology* provides a free conversion service that will convert your video into the appropriate format and correct size for submissions, at no charge. This service can be used by going to www.JournalVideos.com

Review Process

Three or more referees are assigned to review each full-length original article. Decisions are based on significance, originality, and validity of the material presented. If the article is accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning.

Reviewers are requested to recommend papers for publication with the greatest scientific competence and accuracy that are important to the practice of minimally invasive

gynecologic surgery and those which will have the greatest clinical, theoretical, and/or educational impact on the field.

Reviewers consider the following:

1. What is the importance of the research question or subject field of study?

2. Are the methods and experimental techniques of the highest scientific standard?

3. Can the study be replicated?

4. Are the results reliable and presented clearly?

5. Is the discussion relevant?

6. Are the conclusions justified by the results presented?

7. Are the illustrations and references appropriate and necessary?

8. Is the abstract informative and intelligible to readers not working in the specific area?

9. Is the organization of the paper sound and the writing clear?

10. Is the material original?

11. Will the paper impact the specialty?

Following Peer Review

Once the manuscript has been reviewed and comments and requests for changes have been sent via email back to the authors, the authors are requested to send back to the editorial office two Word files for revised manuscript submissions:

(1) a revised, marked manuscript Word file showing additions and deletions, using track changes; and

(2) a revised, unmarked clean manuscript Word file.

PDF files will not be accepted; please submit Microsoft Word files only.

Response to the Reviewers

A point-by-point response to the Editors' and reviewers' comments indicating what changes were made to the manuscript must be submitted.

For each comment the authors must provide the following three items:

1. Each of the Editor's or reviewer's comments.

2. The author(s) response.

3. A statement about what changes have been made to the manuscript (or an explanation why no changes were made).

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