The use of the Myometrial-Cervical Ratio in the Ultrasound Diagnosis of Adenomyosis – a Validation Study.

Running title: Myometrial-Cervical Ratio to diagnose adenomyosis.

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The use of the Myometrial-Cervical Ratio in the Ultrasound Diagnosis of Adenomyosis – a Validation Study.

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Abstract:

Background: Adenomyosis is a benign disorder defined by ectopic endometrial glands within the uterine myometrium. A study by Mooney et al. reported the myometrial-cervical ratio (MCR), a novel ultrasound measurement that was found to improve the pre-operative diagnosis of adenomyosis.

Aims: To validate the association between sonographic MCR and adenomyosis confirmed on histopathology in an independent patient group.

Materials and Methods: Single-centre retrospective cohort study including women who underwent hysterectomy between the 1st of January 2016 and the 31st of December 2018 for a benign, non-obstetric indication with an ultrasound at the study centre prior to surgery. Clinical details and histopathology were extracted. Ultrasound images were reviewed by a gynaecology ultrasound subspecialist blinded to histological findings.

Results: 887 patients underwent hysterectomy in the study period for eligible indications, 317 had an ultrasound at the study centre and were included. There was no statistically

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significant association between the MCR and adenomyosis on histology when all patients were included; however, increased MCR was associated with adenomyosis when those with fibroids on ultrasound were excluded. The area under the receiver operating characteristic for this model was 0.614 (95% CI: 0.53 to 0.69). The optimal MCR cut-point in this subgroup was 1.79, which achieved 55.6% sensitivity and 62.8% specificity, with 58.5% correctly classified. There was no significant difference in MCR compared to traditional ultrasound markers of adenomyosis.

Conclusions: In a population undergoing hysterectomy for benign and non-obstetric indications, the MCR applied to pre-operative ultrasound was only weakly associated with a histological diagnosis of adenomyosis.

Introduction

Adenomyosis is a benign uterine disorder defined by ectopic endometrial glands within the myometrium.[1] Women typically present with abnormal uterine bleeding and pelvic pain, although approximately a third are asymptomatic.[2] The estimated incidence varies markedly, with a range of 5-70%.[3–6] This is, in part, due to definitive diagnosis requiring hysterectomy to obtain a pathological specimen.[7] An accurate, non-invasive means of diagnosing adenomyosis is crucial for guiding management in women wishing to preserve fertility, those who are ineligible for surgery, and for preoperative planning.

Pelvic sonography has been increasingly utilised to diagnose adenomyosis over the last 40 years.[8,9] Whilst there is no clear consensus regarding the definitive ultrasound features of adenomyosis, current techniques rely on markers such as asymmetric thickening of the myometrium, presence of a 'globular uterus', myometrial cysts, linear striations radiating from the endometrium, loss of the endomyometrial border, thickening of the junctional zone and increased heterogeneity of the myometrium.[10,11] Using these markers, there is still a wide range in the reported sensitivity and specificity of pelvic sonography which remains highly operator dependant.[9,12]

A study by Mooney et al published in 2021, explored the use of a sonographic myometrial-cervical ratio (MCR) in the diagnosis of adenomyosis.[13] The MCR is an objective

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measurement proposed to reflect smooth muscle hyperplasia that occurs in adenomyosis, producing the 'globular uterus'. It requires minimal experience in gynaecological ultrasound to perform and can be retrospectively applied to images. The study found that a greater MCR was associated with a histopathological diagnosis of adenomyosis in patients without uterine fibroids (OR: 5.79, 95% CI: 2.15, 15.62, p=0.001). Using an MCR cut-off at 1.74, the sensitivity was found to be 67.2% and specificity 66.2%, with 66.7% of samples correctly classified. These results indicate that the MCR may be a valuable addition to current ultrasound markers of adenomyosis. This validation study aims to assess the association between sonographic MCR and adenomyosis confirmed on histopathology.

Materials and Methods

This retrospective cohort study included women who underwent a hysterectomy at a tertiary obstetrics and gynaecological hospital in Melbourne, Australia, between the 1st of January 2016 and the 31st of December 2018 for benign and non-obstetric indications. Patients were required to have had an ultrasound at the study centre in the two years prior to surgery and were identified using a centralised database.

Data Collection

Medical records were reviewed by a single examiner. Data points collected were identical to the study by Mooney et al.[13] Demographics, including age, time between ultrasound and surgery, menopausal status, presenting complaint, gravidity and parity, previous twin pregnancy, previous cervical or myometrial surgery and hormonal treatment at the time of ultrasound. Histopathological diagnosis was extracted from the pathologist report and recorded as adenomyosis present or absent. All specimens were reported by pathologists within the same laboratory.

Ultrasound images were retrospectively reviewed by a gynaecological ultrasound subspecialist blinded to the chart review findings and the original scan report. Ultrasound were performed on a Phillips Epiq 7 machine using a transvaginal probe and reviewed using ViewPoint™6 (GE Healthcare) picture archiving and communication system. Studies were excluded if imaging was limited to the transabdominal approach or if image quality was

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inadequate to accurately calculate the MCR. The MCR was calculated by author 5, using the same technique as Mooney et al. to ensure uniform image review between the two studies. As previously described,[13] a single standard sagittal view was used where the uterine body and cervix filled 75% of the screen. Two perpendicular measurements were performed, one at the mid-point in the cervical canal and a second at the greatest anterior posterior diameter of the myometrium at the fundus. Fibroids were included in the myometrial component unless they were pedunculated and could be easily excluded. The images were also examined for the volume of the uterus; presence of adenomyosis using traditional markers as outlined in the Morphological Uterus Sonographic Assessment (MUSA) group criteria;[14] and fibroids.

Statistical analysis

Statistical analyses were conducted using Stata/IC v16.1 (StataCorp LLC, College Station, Texas, USA). Participant characteristics grouped by presence or absence of adenomyosis on histopathology were compared using independent sample t-tests for continuous variables (or rank-sum tests for non-normally distributed variables), and chi-squared tests for categorical variables. Logistic regression was used to estimate the association (odds ratios with 95% confidence intervals) between MCR and histopathology diagnosis of adenomyosis, with the area under the receiver operating characteristic (ROC) curve calculated. The optimal MCR cut-point was identified to maximise model sensitivity and specificity (with 95% confidence intervals determined from 10,000 bootstrapped samples) using the 'cutpt' package.[15] Performance (as area under ROC) was compared to a previously described out-of-sample MCR cut-point of 1.74[13] using the algorithm proposed by DeLong, DeLong, and Clarke-Pearson (1988)[16] as implemented in Stata. Logistic regression was used to calculate the performance of models including MCR alone and traditional ultrasound measurements A sub-group analysis was then performed excluding samples where fibroids were present on ultrasound. Statistical significance for all comparisons was set at $p<0.05$.

Ethics

Ethics approval was obtained from the Royal Women's Hospital Human Research Ethics Committee (approval number AQA 20/31).

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Results

Study cohort

During the study period, 1,523 patients had hysterectomies, with 887 performed for benign or non-obstetric indications. Of these, 368 had ultrasounds available for review of which 51 (13.9%) were excluded due to poor quality. The remaining 317 became the final study cohort. The mean age at ultrasound was 47.5 (SD 10.0), 73.8% (234) were premenopausal and 20.2% (64) were nulliparous (Table 1). The median time from ultrasound to surgery was 88 days (interquartile range 53, 210). The most common indications for surgery were heavy menstrual bleeding (51.7%, 164) and pelvic pain (51.7%, 164), followed by pelvic organ prolapse (19.9%, 63). Hormonal contraception was used by 26.2% (83) of women, with 71.1% (59) of these taking progesterone only contraception such as the Mirena intrauterine device. On histopathology, adenomyosis was found in 55.8% (177) of women, fibroids were found in 59.0% (187), whilst 30.9% (98) had both adenomyosis and fibroids. 45.7% (145) of women had uterine fibroids identified on ultrasound, 23 of these were pedunculated and not included in the MCR measurements. In total, 61.5% (195) of patients had an MCR not including uterine fibroids in the measurements.

Adenomyosis was found on histopathology in 61.3% (155) of parous women and 34.4% (22) of nulliparous women ($p<0.001$). Women with fibroids on ultrasound had decreased rates of adenomyosis on histopathology (71/145, 49.0%) compared to women with no fibroids on ultrasound (106/172, 61.6%; $p=.02$). There was no significant difference in rates of adenomyosis on histopathology between pre and postmenopausal women, women with previous myometrial or cervical surgery, women taking hormonal therapy or those with pelvic organ prolapse or heavy menstrual bleeding (Table 1). The prevalence of adenomyosis on histopathology was 61.1% (44/72) amongst women who had a caesarean section compared to 61.3% (111/181) for women who had vaginal deliveries.

When comparing our study cohort to that of Mooney et al., there was no statistically significant difference in the rate of adenomyosis on histopathology ($p=.11$), fibroids on ultrasound ($p=0.50$), menopausal status ($p=.40$) or previous myometrial or cervical surgery ($p=.50$). Our study had a marginally younger cohort, with an average age of 47.5 (SD=10) compared to 50.1 (SD=11.3). Our cohort had fewer women on hormonal supplementation,

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with 26.2% (83/317) compared to 34.5% (81/235; p=.04) and a greater percentage of nulliparous women (20.2% vs 8.4%; p<0.001). There was no difference in women undergoing surgery for pelvic organ prolapse (p=.62), heavy menstrual bleeding (p=.62) or pelvic pain (p=.16).

Performance of MCR

There was no statistically significant association between the MCR and adenomyosis on histopathology for the entire study cohort (OR: 0.89, 95% CI: 0.71 to 1.13; p=.33). The area under the receiver operator curve (AUROC) for this model is 0.486 (Figure 1a). When observations that included fibroids in the MCR measurement were excluded, there was statistical evidence of an association between MCR and adenomyosis (OR: 2.44, 95% CI: 1.26 to 4.71; p=.008). The AUROC for this model was 0.614 (95% CI: 0.53 to 0.69; Figure 1b). The optimal MCR cut-point in this subgroup was 1.79, which achieved 55.6% sensitivity and 62.8% specificity, with 58.5% of samples correctly classified (Table 2). Using the previously described cut-point of 1.74[13] achieved 59.0% sensitivity, 59.0% specificity, and 59.0% correct classification. There was no statistical evidence of a difference in the AUROC using either cut-point (p=.88).

In women without fibroids on ultrasound, subgroup analysis found that there was a statistically significant (p=0.012) improvement in performance of the MCR amongst women having hysterectomies for postmenopausal bleeding (n=19; AUROC: 0.84, 95%CI: 0.66, 1.00) when compared to those having hysterectomies for other reasons (n=176; AUROC: 0.58, 95%CI: 0.50, 0.67). There was no significant difference for other indications for surgery including pelvic organ prolapse (p=.18), heavy menstrual bleeding (p=.90), dysmenorrhoea (p=.58), other pelvic pain (0=.51), urinary incontinence (p=.09) and cancer risk reduction (p=.93). Demographic subgroup analysis found no significant difference in sensitivity and specificity of MCR for diagnosing adenomyosis. Subgroups analysed include: pre vs postmenopausal women (p=.92), use of hormonal therapy (p=.74), parity (p=.16) and history of myometrial or cervical surgery (p=.51).

Excluding patients where fibroids were included in the MCR measurement, traditional ultrasound markers for adenomyosis achieved a sensitivity and specificity of 53.8% and

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66.2%, respectively, with 58.8% classified correctly (Table 2). When both MCR and traditional ultrasound markers are combined (i.e. if either MCR or traditional ultrasound markers are positive), sensitivity is 57.3%, specificity is 64.9%, with 60.3% of cases correctly classified. The change in sensitivity and specificity with the addition of MCR is not statistically significant (p=.20). In patients with fibroids excluded, there is a weak association between uterine volume and adenomyosis on histopathology, with an AUROC 0.631. There is no statistically significant difference between rates of adenomyosis on histopathology when using the MCR compared to the uterine volume (p=.56).

Discussion

Accurate preoperative diagnosis of adenomyosis provides the patient information, aids surgical decision-making, and guides management for women who are not candidates for hysterectomy.[6] The current reliance on post-hysterectomy histopathology for diagnosis limits both our understanding and management of this disease. Ultrasound is an easily accessible imaging modality; however, its use is currently limited by a wide range in reported sensitivity and specificity for diagnosis of adenomyosis.[12]

Mooney et al showed an association between MCR and histological diagnosis of adenomyosis when samples with fibroids in the MCR measurement were excluded.[13] Using an MCR cut-point of 1.74 achieved a sensitivity of 67.2% and specificity of 66.2%. Our study identified a cut-point of 1.79 as providing the optimum AUROC, which generated a weaker, but statistically significant, association with a sensitivity of 55.6% and specificity of 62.8%. These findings suggest that the MCR has limited utility as a standalone ultrasound marker of adenomyosis.

Mooney et al showed that the MCR outperforms traditional markers for adenomyosis when there were no fibroids on ultrasound.[13] Our study does not support this finding with similar findings for both traditional ultrasound markers and the MCR. When MCR is used in addition to other ultrasound markers there is an increase in sensitivity to 57.3% whilst specificity fell to 64.9%. The poor performance of traditional ultrasound measures in our cohort highlights the difficulty of preoperative diagnosis and the need for improved ultrasound markers. These results demonstrate that the MCR, in its current form, does not have a role in this

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context. However, all ultrasounds were performed at a specialist women's ultrasound centre and retrospectively reviewed by an experienced obstetrician and gynaecologist with subspecialty training in ultrasound. This may overestimate the effectiveness of traditional ultrasound markers, and therefore underestimate the benefit of the MCR.

It is well established that the specificity and sensitivity of ultrasound is operator dependent and the interpretation of many ultrasound signs subjective.[18,19] Despite the limitations of ultrasound in the diagnosis of adenomyosis, it is the first line investigation for patients presenting with many of the associated symptoms. As such, it is likely to remain a core part of preoperative workup; however, a greater understanding of its diagnostic performance is required to best complement clinical assessment. Diagnostic models which incorporate ultrasound markers with clinical signs and symptoms, such as described by Tellum et al, may help improve accuracy[11] Whilst MRI has been shown as a potential alternative to ultrasound,[20] the cost and limited access remain barriers to its widespread use.

A 'globular uterus' is reported as the best single measure of adenomyosis on ultrasound;[21] however, it is subjective and requires an experienced ultrasound operator to reliably assess. In our cohort there was no significant difference between MCR and uterine volume in the diagnosis of adenomyosis. In addition to being a more objective measurement, the MCR is easier to record than uterine volume - requiring fewer measurements in only one plane. Therefore, it may have value as an objective, easily recordable marker of a 'globular uterus' that can be retrospectively applied.

There were statistically significant differences between our cohort and the cohort examined by Mooney et al[13]. Our cohort had an increased number of nulliparous women and fewer women on hormonal supplementation pre-operatively. This may reflect differing practices and documentation between hospitals, or the demographic backgrounds of the patients referred to each centre. Subgroup analysis of the accuracy of the MCR found no significant changes in performance of the MCR, except for women undergoing hysterectomy for postmenopausal bleeding. Thus, the degree to which the differing demographics between the two study centres would influence the results is unknown. Given the small sample size

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of the postmenopausal bleeding subgroup (19), these results should be considered with caution. Post-hysterectomy specimen review was not standardised. Whilst histopathology was used as the gold-standard diagnostic test, it is well recognised that there is a lack of standardised histological criteria for the diagnosis of adenomyosis,[17].

Adenomyosis is often found in the presence of other pathologies such as fibroids. A clear weakness of the MCR is its limited use in women with fibroids which distort the myometrium. We did not show a statistically significant association between the MCR and the presence of histologically confirmed adenomyosis when patients with uterine fibroids were included in the analysis, supporting the findings of Mooney et al. This is particularly limiting given 45.7% of our patients had fibroids seen on ultrasound.

This study employed similar research methodology to the work of Mooney et al., using the same ultrasound subspecialist and statistician to ensure uniform interpretation of imaging and data. This adds to its strength as a validation study, despite the limitations posed by its retrospective study design. Patients required hysterectomy for inclusion and only 35.7% (317/887) of eligible patients had available pre-operative ultrasound, increasing the risk of selection bias. A prospective study would enable standardised documentation, sonography and review of pathology.

As the use of traditional ultrasound markers to diagnose adenomyosis remains subjective and operator dependent, the MCR offers an objective measure that requires minimal training in gynaecological imaging to apply. Whilst the results of this study demonstrate an association between MCR and adenomyosis on histopathology, this association is not sufficiently strong for it to be used in isolation. Further research exploring the MCR, and other methods of preoperative ultrasound diagnosis of adenomyosis will aid management of women with adenomyosis.

TABLES AND FIGURES

Table 1: Patient characteristics and association with adenomyosis on histopathology

Characteristic	Adenomyosis on histopathology

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	Full sample (N=317)	No (n=140)	Yes (n=177)	p-value
Age at ultrasound (years), mean (SD)	47.5 (10.0)	47.4 (10.8)	47.6 (9.4)	0.85
Age at surgery (years), mean (SD)	47.9 (10.1)	47.7 (10.9)	48.0 (9.4)	0.83
Days between ultrasound and surgery, median (IQR)	88 (53, 210)	83.5 (49.5, 168)	99 (57, 248)	0.062
Menopause status at ultrasound				0.97
Premenopausal	234 (73.8%)	104 (74.3%)	130 (73.4%)	
Postmenopausal	81 (25.6%)	35 (25.0%)	46 (26.0%)	
Unknown	2 (0.6%)	1 (0.7%)	1 (0.6%)	
Parity - Categorical				**<0.001**
Nulliparous	64 (20.2%)	42 (30.0%)	22 (12.4%)	
Parous	253 (79.8%)	98 (70.0%)	155 (87.6%)	
Prior Myometrial or Cervical Surgery	90 (28.4%)	39 (27.9%)	51 (28.8%)	0.85
Myometrial / Cervical Surgery Type				0.54
Caesarean section	72 (80.0%)	28 (71.8%)	44 (86.3%)	
Myomectomy	9 (10.0%)	5 (12.8%)	4 (7.8%)	
Other	9 (10.0%)	6 (15.4%)	3 (5.8%)	
Hormonal Suppression				0.87
No	234 (73.8%)	104 (74.3%)	130 (73.4%)	
Yes	83 (26.2%)	36 (25.7%)	47 (26.6%)	
Hormonal Suppression Type				0.65
Combined oral contraceptive pill	14 (16.9%)	6 (16.7%)	8 (17.0%)	
Progesterone only contraception	59 (71.1%)	25 (69.4%)	34 (72.3%)	
Other	10 (12.0%)	5 (13.9%)	5 (10.6%)	
Fibroids on ultrasound				**0.024**
No	172 (54.3%)	66 (47.1%)	106 (59.9%)	
Yes	145 (45.7%)	74 (52.9%)	71 (40.1%)	
Uterus volume, median (IQR)	127.5 (71.5, 234.5)	116.0 (64.0, 268.0)	135.0 (77.0, 217.0)	0.72
Presenting condition^				
Heavy Menstrual Bleeding	164 (51.7%)	71 (50.7%)	93 (52.5%)	0.75
Pelvic Pain	164 (51.7%)	76 (54.3%)	88 (49.7%)	0.43
Pelvic Organ Prolapse	63 (19.9%)	23 (16.4%)	40 (22.6%)	0.17
Urinary Incontinence	45 (14.2%)	14 (10.0%)	31 (17.5%)	0.057

Non-parametric (Wilcoxon rank-sum) tests were performed for variables were medians (IQRs) are presented.

^ Presenting conditions are not mutually exclusive; up to two presenting conditions were available per participant.

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Table 2: Performance of the MCR compared to traditional ultrasound markers.

Cohort (N)	MCR cut point	Sensitivity	Specificity	Correctly identified
Entire cohort (317)	1.89	60.5%	46.4%	54.3%
Cohort, excluding fibroids in the MCR measurements (195)	1.79	55.6%	62.8%	58.5%
Cohort, excluding fibroids in the MCR measurements - Mooney et al cut-point (195).	1.74	59.0%	59.0%	59.0%
Traditional ultrasound measures (195)	-	53.8%	66.2%	58.8%
Traditional ultrasound measures in addition to MCR (195)	-	57.3%	64.9%	60.3%

Figure 1:

Figure 1a: Area under receiver operator curve for MCR in the entire cohort (n=317).

Figure 1b: Area under receiver operator curve for MCR excluding observations with fibroids included in MCR calculation (n=195).

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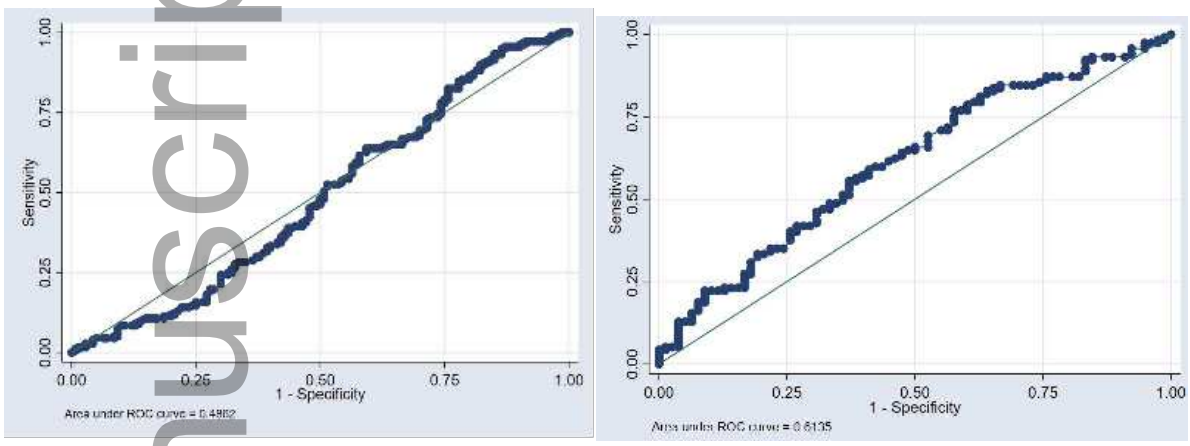
Figure 1:

Figure 1a: Area under receiver operator curve for MCR in the entire cohort (n=317).

Figure 1b: Area under receiver operator curve for MCR excluding observations with fibroids included in MCR calculation (n=195).



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