Variability in the quality of ultrasound reporting for uterine fibroids in Canada: results from a prospective cohort registry

Olga Bougie MD MPH, Mohamed A. Bedaiwy MD PhD, Philippe Laberge MD ACGE, Gerald Lebovic PhD, Nicholas Leyland MD MHCM, Mostafa Atri MD, Ally Murji MD MPH, on behalf of the CAPTURE Steering Committee

Affiliations: Department of Obstetrics and Gynaecology, Queen's University, Kingston, Ontario (Bougie), Department of Obstetrics and Gynecology, The University of British Columbia, Vancouver, British Columbia (Bedaiwy), Department of Obstetrics and Gynecology, CHU de Québec, Laval University, Québec City, Québec (Laberge), Applied Health Research Centre, LKSKI, St. Michael's Hospital, Toronto, Ontario (Lebovic), Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario (Leyland), Department of Medical Imaging, University of Toronto, Toronto, Ontario (Atri), Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario (Murji), Canada

Correspondence to: Olga Bougie, Department of Obstetrics and Gynaecology, Queen's University, Victory 4, 76 Stuart St., Kingston, Ontario, K7L 2V7, Canada. Tel.: 613-548-7840; fax: 613-548-1330; e-mail: olga.bougie@kingstonhsc.ca

Funding: Sponsored by Allergan Inc., Markham, Canada. Editorial assistance was provided to the authors by Natalie Prior, PhD, of Complete HealthVizion and funded by Allergan plc, Dublin, Ireland. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Competing interests: Olga Bougie has presented continuing medical education events sponsored by Allergan Canada, Bayer, Hologic and AbbVie. Mohamed A. Bedaiwy is a member of advisory boards for AbbVie and Allergan. Philippe Laberge is the Chair of the CAPTURE study and a consultant for Allergan, AbbVie, Hologic, Medtronic, Minerva and Olympus. Gerald Lebovic has no conflicts to declare. Nicholas Leyland has received research support from Allergan and AbbVie. Mostafa Atri has no conflicts to declare. Ally Murji is a member of Speaker Bureaus and advisory boards for AbbVie, Allergan, Bayer and Hologic.

ABSTRACT

BACKGROUND: Uterine fibroids are common in women and their management is heavily influenced by information gathered through imaging. We aimed to evaluate the type of imaging performed for fibroids in Canada.

METHODS: Pre-menopausal women with symptomatic fibroids were enrolled in a prospective, non-interventional, observational registry at 19 Canadian sites (CAPTURE). Clinical characteristics were extracted from the baseline visit. Ultrasound reporting quality criteria were evaluated using the Morphological Uterus Sonographic Assessment guideline.

RESULTS: Of 1493 women, 1148 had ultrasound, 135 had magnetic resonance imaging (MRI), 80 had other imaging types and 130 did not have imaging reported at the baseline visit. After adjusting for demographic and clinical characteristics, patients who received MRI had larger fibroids (OR per 1-cm increase 1.11; 95% CI 1.05–1.17) and more numerous fibroids (1 v. > 1) (OR 1.74; 95% CI 1.14–2.64) compared to those with ultrasound only. For ultrasound reporting, quality criteria were met by 268/1148 (23.3%) reports. There was a difference in the quality of reporting between the 19 sites ($p < 0.0001$). Logistic regression model accounting for within-site variability showed that ultrasounds in the province of Québec were less likely to meet all quality criteria (OR 0.20; 95% CI 0.06–0.66) and those from sites in more populated cities (≥ 400,000 inhabitants) were more likely to do so (OR 6.15; 95% CI 2.20–17.18).

INTERPRETATION: Imaging modality for fibroids is associated with patient characteristics. The quality of fibroid ultrasound reporting in Canada falls short of internationally endorsed guidelines and needs improvement.

Trial registration: ClinicalTrials.gov: NCT02580578.

Keywords: magnetic resonance imaging; ultrasonography; ultrasound; uterine fibroids

Introduction

Uterine fibroids are benign smooth muscle tumors with a prevalence of up to 70–80% in women by the age of 50 years.[1] Approximately half of women with uterine fibroids will experience symptoms of abnormal uterine bleeding, pressure and reproductive issues.[1] Although ultrasound is the mainstay for the diagnosis and monitoring of uterine fibroids, magnetic resonance imaging (MRI) can also be used.[2] There are no clinical practice guidelines to help determine when an MRI should be ordered and many fibroid guidelines de-emphasize the role of MRI.[3] Nonetheless, the decision to order MRI is often based on patient and provider characteristics, and likely to be dependent on the practice setting. Little is known about the real-world choices for fibroid-imaging modalities. Regardless of the choice of modality, it is essential that imaging provides the clinician with details on fibroid characteristics to help guide the management approach. Hence, the quality of imaging may be even more important than the modality itself. In 2015, the International Society of Ultrasound in Obstetrics and Gynecology endorsed the Morphological Uterus Sonographic Assessment (MUSA) consensus statement, which described the sonographic features and terminology for reporting on uterine fibroids.[4] This document called for standardized reporting to reduce the variability in the evaluation of fibroids. The goal of systematic standardization was to improve the quality of reporting and thereby optimize clinical management of this condition. The uptake of this guideline in clinical settings has not been previously evaluated.

A prospective, non-interventional, multi-site, observational registry of pre-menopausal women with symptomatic uterine fibroids (CAPTURE) was established in Canada in 2015. This registry provides an opportunity to describe practice patterns

in the diagnosis and management of fibroids across diverse geographic and practice settings. The study had 2 objectives: 1) describe factors associated with the use of MRI to evaluate uterine fibroids; 2) evaluate the quality of, and variation in, ultrasound reporting within the Canadian health-care system.

Methods

The CAPTURE registry comprised a cohort of women with uterine fibroids from 19 study sites across Canada (ClinicalTrials.gov: NCT02580578). The registry methods have been previously published.[5] The study sites represented all regions in Canada and were a mix of academic and community centers. This was a non-interventional study in which physicians were not required to perform any medical procedure that was outside their routine clinical practice. All investigations were ordered at the physicians' discretion and performed/interpreted at various clinical practice locations based on provider and patient preference. Approval was obtained from research ethics boards at each participating study site (see Table S1 in Appendix). Included in the registry were pre-menopausal female patients aged ≥ 18 years with symptoms associated with uterine fibroids who were being observed (watchful waiting), currently being treated or initiating treatment (drug intervention, procedure intervention or a combination of both). Patients were required to provide written, informed consent prior to or at the initial study visit. Exclusion criteria included known or suspected significant pelvic pathology not associated with uterine fibroids and patients undergoing an emergency hysterectomy at initial visit.

Imaging type, as well as uterine and fibroid characteristics described in the imaging reports, were extracted from the patient chart. Imaging for uterine fibroids performed within 12 months of the baseline visit was recorded in the

registry. Patients who had MRI or other imaging may have also undergone ultrasound. Furthermore, patient demographic information, medical history and evaluation of past and current symptomatology were extracted. Baseline measures of patient-reported outcomes were extracted using the Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire[6,7] and the Aberdeen Menorrhagia Severity Scale (AMSS) (Ruta score) bleeding score.[8] Characteristics of the medical practice in which the patient was seen were also recorded, including geographic region within Canada (Western Ontario, Central Ontario, Eastern Ontario, Québec, Western Canada), academic versus community practice and city size based on population (small city is < 400,000 inhabitants). Data were recorded in the Research Electronic Data CAPTURE database. Data quality assurance included real-time flagging of missing data, flagging of values outside pre-established ranges and quarterly site visits by central research teams to ensure accuracy of data entry for each patient chart.

Ultrasound reporting quality criteria

Each ultrasound report was assigned a quality rating based on 5 criteria that were adapted from the MUSA consensus statement, as described below.

1. Fibroid number – If the report mentioned a specific number of fibroids, it met the quality standard. If it reported "multiple" or "unspecified" number of fibroids, then it did not meet the quality standard.

2. Fibroid dimensions – If all 3 dimensions of the largest fibroid were reported, the report met the quality standard.

3. Uterine dimensions – If all 3 uterine dimensions or a uterine volume were reported, the report met the quality standard.

4. Fibroid type – A report describing any of the following for the largest fibroid met the quality standard: submucosal (International Federation of Gynecology and Obstetrics type 0, 1, 2, unknown type), intramural, subserosal, cervical, pedunculated.

5. Fibroid location – A report describing any of the following for the largest fibroid location met the quality standard: anterior, lateral, posterior, fundal.

An ultrasound report was considered to be of high quality if it met all 5 quality standards.

Statistical analysis

Descriptive analyses of demographic and clinical variables of interest were conducted. Continuous data were summarized using mean and standard deviation or median and interquartile range. Categorical variables were summarized using counts and percentage. Chi-square tests or Fisher exact tests, as appropriate, were used to test for unadjusted differences in categorical variables between imaging groups. Parametric or non-parametric *t*-tests, as appropriate, were used to test for unadjusted differences in continuous variables between imaging groups. Unadjusted and adjusted logistic regression models examined the association between demographic and clinical variables of interest with regard to imaging type. A generalized linear mixed model was used to examine associations between hypothesis-generating covariates and the outcome of having a quality ultrasound. This model adjusted for the following characteristics: age; body mass index (BMI); ethnicity; gravidity (any v. none);

history of infertility (yes, no, unknown); previous medical or surgery intervention; geographic region; community versus academic center; city population size. A random effect was placed in the model to account for correlation arising within clinical site. The median odds ratio (OR), a measure of heterogeneity that is adjusted for patient-level covariates, was computed from the adjusted model.[9]

Results

The study included 1493 women from across 19 practice sites in Canada. For 1148 (76.9%) women, ultrasound was the only imaging modality recorded. At baseline visit, an MRI report was available for 135 (9.0%) women, 80 (5.4%) had another imaging modality and 130 (8.7%) did not have imaging reported. Of the 130 women without imaging reported at baseline, 104 (80%) did have imaging diagnosis of fibroids that was performed more than 12 months before the baseline visit. These 130 women were excluded from further analysis. Baseline characteristics of women who had ultrasound only and MRI are shown in Table 1.

After adjusting for demographic and clinical characteristics, patients with MRI were more likely to have larger fibroids (OR per 1-cm increase in fibroid diameter 1.11; 95% confidence interval [CI] 1.05–1.17) and more numerous fibroids (OR of 1 v. > 1 fibroid 1.74; 95% CI 1.14–2.64) compared to those with ultrasound only. Older patients were less likely to have an MRI (OR per 5-year age increase 0.73; 95% CI 0.64–0.84). Patients having MRI reported lower menstrual bleeding scores (OR for 10-point increase in AMSS score 0.89; 95% CI 0.81–0.98). There was no difference in the odds of having an MRI based on BMI (OR per 1-unit increase in BMI 1.01; 95% CI 0.98–1.04), gravidity (> 0 v. 0) (OR 0.89; 95% CI 0.58–1.35), infertility (OR 1.17; 95% CI 0.75–1.83) or ethnicity/race (p = 0.02).

The quality of ultrasound reporting is shown in Table 2. Overall, 268 (23.3%) ultrasound reports met all 5 quality criteria. Four quality criteria were met by 365 (31.8%) reports, 3 quality criteria were met by 326 (28.4%) and 2 quality criteria were met by 162 (14.1%). Twenty-seven (2.4%) reports did not meet any quality criteria. The proportion of ultrasound reports meeting each individual quality criterion is depicted in Figure 1.

An adjusted generalized linear mixed model including 1128 patients was used to examine the association of patient and institutional characteristics with receiving an ultrasound that met all 5 quality standards. There were no patient characteristics that were associated with having a high-quality ultrasound report. However, compared to patients from Central Ontario (referent group) those from Québec (OR 0.20; 95% CI 0.06–0.66) were less likely to have a high-quality report. Patients from study sites in more populated cities (≥ 400,000 inhabitants) were more likely to receive a high-quality ultrasound report (OR 6.15; 95% CI 2.20–17.18).

After adjusting for institutional and patient characteristics (described above), the median OR across study sites was 1.66. In other words, the odds of receiving a high-quality ultrasound were 1.66 times greater if the same patient had imaging at 1 random study site as opposed to another. This inter-hospital variation was not explained by patient characteristics and only partially by region and city size. The logistic regression model above explained 42% of the observed variation in quality rates and had good discrimination (c = 0.78). Similarly, a logistic regression that did not account for variability between sites explained 38% of the variation and had only slightly lower discrimination (c = 0.75). When 19 study sites were compared with their rates of high-quality ultrasound, there was considerable variation. There was a

difference ($p < 0.0001$) in the quality of reporting between the 19 sites (best site had 56/111 [50.5%] scans meeting all criteria v. the worst site with 0/19 [0.0%]). The median rate of high-quality ultrasound report was 16.8 per 100 ultrasounds (range 0–50.9). Figure 2 shows the variation in high-quality ultrasounds across sites.

Interpretation

Ultrasound is the first-line imaging modality for uterine fibroids. Our study determined the situations in which MRI was utilized in clinical practice. We found that after adjusting for patient demographics and clinical practice characteristics, MRI was more likely to be obtained in cases of larger and more numerous fibroids. These results are consistent with previously published literature demonstrating that the capacity of ultrasound for accurate fibroid mapping falls short of MRI in large (> 375 mL) multi-fibroid (> 4) uteri.[2] Due to the cost differential between these imaging modalities, standardized algorithms that incorporate the cost-effectiveness of each modality would be helpful to guide clinicians in their decision to order MRI.

We identified significant limitations in the quality and variability of ultrasound reporting in Canada. In this prospective cohort of 1148 women who underwent an ultrasound evaluation for uterine fibroids, only 23% of ultrasound reports met all quality criteria, as recommended by the MUSA guidelines. Furthermore, there was considerable inter-site variation in the quality of ultrasound reports, which was not explained by patient characteristics and only partially by region and city size. It is sobering that the odds of a Canadian woman with uterine fibroids receiving a high-quality ultrasound were 1.66 times greater if the same patient had imaging at 1 random institution as opposed to another. These findings are reflective of the limited focus on the importance of standardized imaging for the evaluation of uterine

fibroids within our clinical practice guidelines.[10,11] In fact, much of the focus of international guidelines on uterine fibroids is on providing guidance on management rather than thorough evaluation of the condition.[10–12] However, accurate diagnosis and assessment of uterine fibroids is essential to guide optimal selection of treatment strategies, particularly since fibroid characteristics are unique between patients. We observed that fibroid number, type and location were more consistently reported accurately than uterine or fibroid size.

It is important to mention that the MUSA guidelines were established by a European team performing high-quality endovaginal ultrasonography,[4] not transabdominal ultrasonography as is mostly the case in the Canadian context. The CAPTURE database did not collect information about the route of ultrasonography that was performed and transvaginal ultrasonography is sometimes a second-line examination in many parts of the country. Currently, there are no Canadian-specific guidelines/standards for ultrasound reporting of uterine fibroids. Another underlying reason for the variability in ultrasound reporting across Canada may be a variation between provinces as to who performs the scan, where they are performed and remuneration structures. In larger cities in the province of Ontario, ultrasound technologists perform the majority of scans and prepare initial reports with accompanying measurements on saved images. The use of ultrasound technologists differs across the country, but they are least utilized in Québec and in smaller centers, where the physician will often directly perform and report on the ultrasound. Furthermore, there are differences in the specialty/training of physicians who can perform and interpret ultrasound. In certain provinces it is exclusively the domain of radiology, while in other regions gynecologists may also be involved. These

differences in the practitioners involved in obtaining and reporting imaging may be driving the variability in quality across the country.

Limitations

The findings of our study must be interpreted within the context of study design. One of the challenges of using data from a non-interventional registry is that data may be available in a heterogeneous manner based on local practice patterns. Unfortunately, the registry did not collect data on imaging characteristics such as route of ultrasound (transabdominal or transvaginal), the specialty of the reporting physician (radiologist or gynecologist) and whether a technologist was involved in obtaining the images. It would be important to evaluate these variables in detail in future projects and before initiating quality-improvement initiatives. The training received by gynecologists or radiologists who are performing sonographic imaging of uterine fibroids should also be evaluated and standardized in accordance with unified international guidelines.[13,14]

Conclusion

Our findings hold important implications for the evaluation and treatment of women with uterine fibroids, a condition that affects up to 80% of women of reproductive age.[1] The results also shed light on optimizing resource allocation in the evaluation of this common gynecologic condition. Characteristics defined through high-quality imaging and standardized reporting may guide selection of medical versus surgical management of fibroids. Furthermore, if surgical management is chosen, accurate evaluation of fibroid topography will have implications for surgical planning (route, time, incision, etc) and patient counselling. As this is the first study to evaluate the uptake of MUSA guidelines and quality of imaging in uterine fibroids, we propose that prompt evaluation of factors influencing imaging quality are necessary. Factors

limiting quality of ultrasound reporting may include lack of knowledge, dissemination of imaging practice guidelines, limited training and time/resource restraints, as well as patient characteristics (i.e., elevated BMI). Identifying such limitations can focus areas of improvement. Furthermore, we suggest that national clinical practice guidelines for uterine fibroids should include guidance on choice of imaging modality and identify standards with respect to imaging quality for fibroid evaluation.

References

1. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188:100–7.

2. Dueholm M, Lundorf E, Hansen ES, et al. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. *Am J Obstet Gynecol* 2002;186:409–15.

3. Marret H, Fritel X, Ouldamer L, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. *Eur J Obstet Gynecol Reprod Biol* 2012;165:156–64.

4. Van den Bosch T, Dueholm M, Leone FPG, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. *Ultrasound Obstet Gynecol* 2015;46:284–98.

5. Bedaiwy MA, Janiszewski P, Singh SS, et al. A patient registry for the management of uterine fibroids in Canada: protocol for a multicenter, prospective, noninterventional study. *JMIR Res Protoc* 2018;7:e10926.

6. Coyne KS, Margolis MK, Bradley LD, et al. Further validation of the uterine fibroid symptom and quality-of-life questionnaire. *Value Health* 2012;15:135–42.

7. Spies JB, Coyne K, Guaou Guaou N, et al. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol* 2002;99:290–300.

8. Ruta DA, Garratt AM, Chadha YC, et al. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? *Qual Life Res* 1995;4:33–40.

9. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005;161:81–8.

10. Vilos GA, Allaire C, Laberge PY, et al. The management of uterine leiomyomas. *J Obstet Gynaecol Can* 2015;37:157–78.

11. Pérez-López FR, Ornat L, Ceausu I, et al. EMAS position statement: management of uterine fibroids. *Maturitas* 2014;79:106–16.

12. Agency for Healthcare Research and Quality. Comparative Effectiveness Review Number 195. Management of Uterine Fibroids. 2017. Available: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-195-uterine-fibroids-final_0.pdf (accessed 2018 Dec. 19).

13. Leonardi M, Murji A, D'Souza R. Ultrasound curricula in obstetrics and gynecology training programs. *Ultrasound Obstet Gynecol* 2018;52:147–50.

14. Abuhamad A, Minton KK, Benson CB, et al. Obstetric and gynecologic ultrasound curriculum and competency assessment in residency training programs: consensus report. *Am J Obstet Gynecol* 2018;218:29–67.

Contributors: All authors contributed to the conception/design of the work. Dr. Lebovic performed the data analysis for this study. Drs. Bougie, Murji and Bedaiwy interpreted the data from the analysis. All authors were involved in drafting the manuscript and in the critical revisions for intellectual content, and all authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

Acknowledgments: The authors greatly acknowledge the following members of the CAPTURE Steering Committee: Dr. Sari Kives, Dr. George Vilos, Dr. Joshua Polsky and Dr. Liane Belland. This manuscript was reviewed by the CAPTURE Steering Committee, which also contributed to the development of the study goals.

Table 1: Demographics based on imaging modality

	Ultrasound (n = 1148)	MRI (n = 135)	p value
Mean (SD) age, years	43.22 (6.69)	40.24 (7.30)	**< 0.001**
Mean (SD) BMI	27.28 (6.29)	27.20 (7.04)	0.891
Nulliparous, *n* (%)	483 (42.1)	91 (67.4)	**< 0.001**
Nulligravid, *n* (%)	358 (31.2)	61 (45.2)	**0.001**
Family history of fibroids, *n* (%)	401 (34.9)	46 (34.1)	0.072
Previous procedural intervention for fibroid, *n* (%)	251 (21.9)	29 (21.5)	0.883
History of bulk symptoms, *n* (%)	663 (57.8)	90 (66.7)	0.116
Mean (SD) maximum fibroid diameter, mm	75.56 (36.01)	90.15 (34.67)	**< 0.001**
Number of fibroids, *n* (%)			**< 0.001**
1	408 (35.5)	35 (25.9)	
2	191 (16.6)	20 (14.8)	
3	135 (11.8)	6 (4.4)	
4	45 (3.9)	5 (3.7)	
> 4	101 (8.8)	17 (12.6)	
Multiple/not specified	268 (23.3)	52 (38.5)	
Mean (SD) UFS-QOL score	50.25 (23.41)	46.45 (22.77)	0.076
Mean (SD) HRQoL score	50.45 (25.23)	52.05 (26.39)	0.493

Mean (SD) AMSS score	37.07 (18.89)	31.85 (20.74)	**0.003**
Academic center, *n* (%)	622 (54.2)	84 (62.2)	0.092
Region, *n* (%)			0.076
Western Ontario	160 (14.1)	16 (12.1)	
Eastern Ontario	131 (11.5)	24 (18.2)	
Central Ontario	264 (23.3)	29 (22.0)	
Québec	267 (23.5)	21 (15.9)	
Western Canada	313 (27.6)	42 (31.8)	
Small city size, *n* (%)	437 (38.1)	41 (30.4)	0.098

Note: SD = standard deviation; UFS-QOL = Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire; HRQoL = health-related quality of life; AMSS = Aberdeen Menorrhagia Severity Scale.

Table 2: Quality of ultrasound reports

Quality criterion, *n* (%)	Patients (*n* = 1148)
Fibroid number	
Meets standard	880 (76.7)
Fibroid dimensions	
Meets standard	667 (58.1)
2 dimensions reported	179 (15.6)
1 dimension reported	275 (24.0)
0 dimensions reported	27 (2.4)
Uterine dimensions	
Meets standard	504 (43.9)
2 dimensions reported	3 (0.3)
1 dimension reported	5 (0.4)
0 dimensions reported	636 (55.4)
Fibroid type	
Meets standard	1120 (97.6)
Fibroid location	
Meets standard	907 (79.0)
5 criteria meeting quality standard	**268 (23.3)**

Figure legends

Figure 1: Distribution of ultrasound reports meeting each quality criterion.

Figure 2: Site-specific rates (in ascending order) of high-quality ultrasound reporting (per 100 ultrasounds).

Figure 1

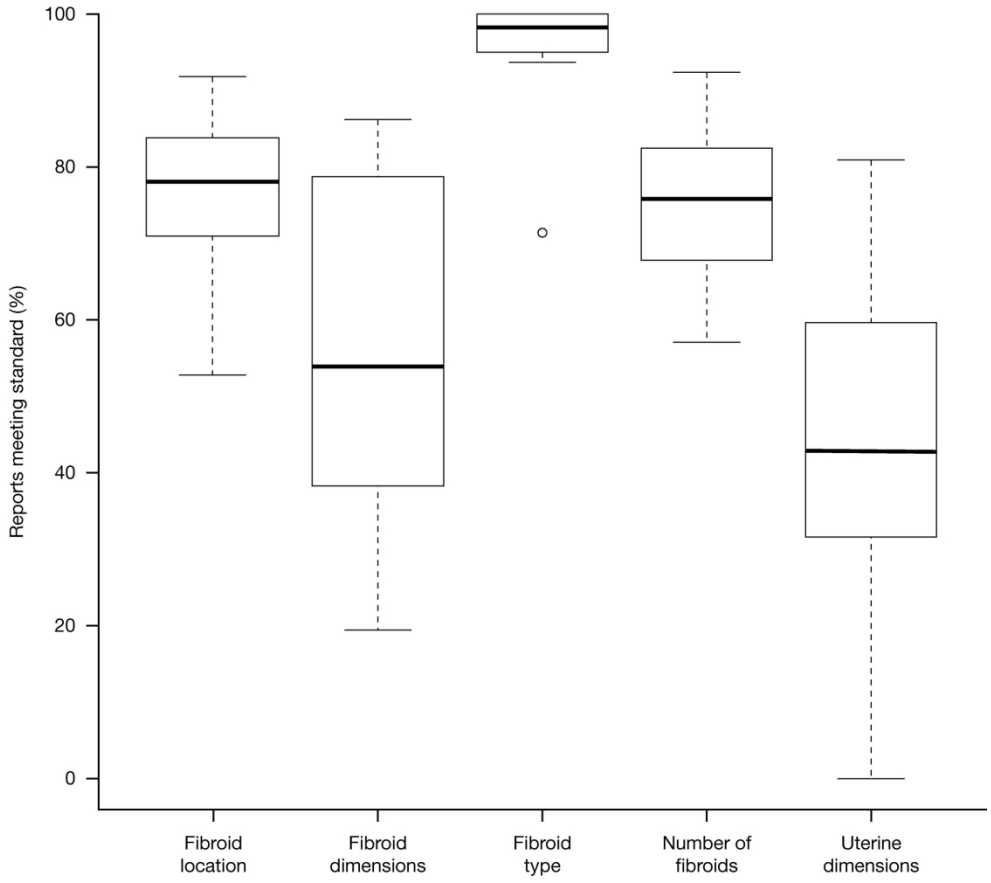

Figure 1: Distribution of ultrasound reports meeting each quality criterion.

187x194mm (300 x 300 DPI)

Figure 2

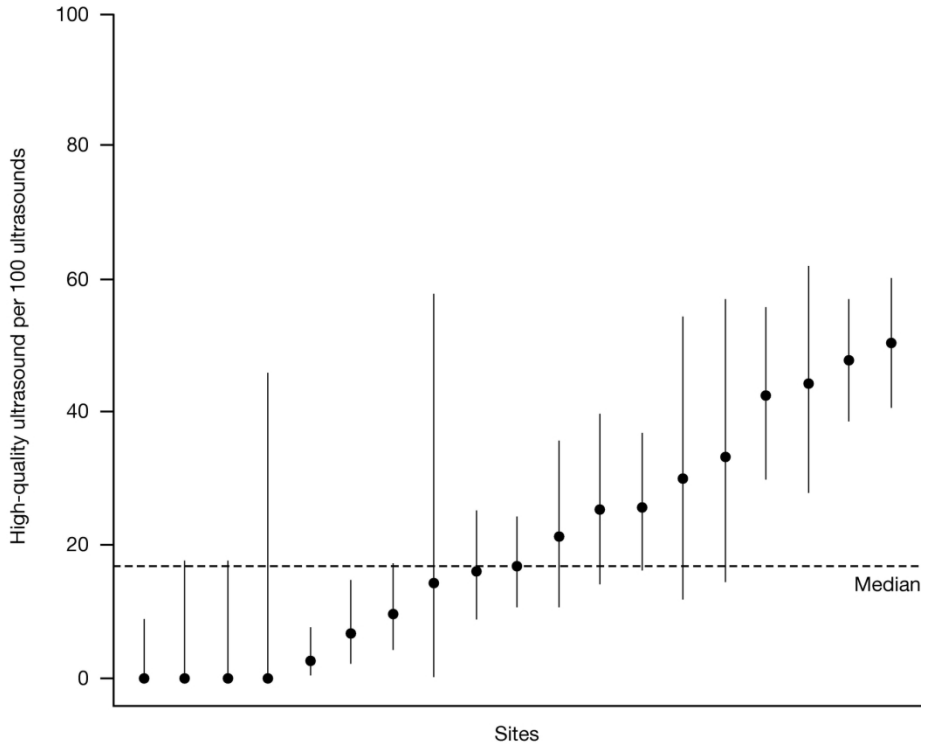

Figure 2: Site-specific rates (in ascending order) of high-quality ultrasound reporting (per 100 ultrasounds).

174x147mm (300 x 300 DPI)

Supplementary material

Table S1: Listing of the site names, research ethics board names and registration numbers for the 19 CAPTURE registry study sites across Canada

Site name	Research ethics board name	Registration number
Capital City Women's Center, Edmonton, Alberta	Health Research Ethics Board – Health Panel	Pro00063537
Centre Gynecologie et Maternité, LaSalle, Québec	IRB Institutional Review Board Services	Pro00012844
CHU de Québec, Université Laval, Québec City	Comité d'éthique de la recherche CHU de Québec	R-00-768
Clinique de Gynécologie & Obstétrique Pierre Boucher, Longueil, Québec	IRB Institutional Review Board Services	Pro00012844
Complexe Medical Saint Laurant – Dr. Robert Sabbah Inc., Saint-Laurent, Québec	IRB Institutional Review Board Services	Pro00012844
Department of Obstetrics and Gynaecology, St. Michael's Hospital, Toronto, Ontario	St. Michael's Hospital Research Ethics Office	15-286

Department of Obstetrics and Gynecology, BC Women's Hospital & Health Centre, Vancouver, British Columbia	University of British Columbia Children's and Women's Research Ethics Board	H15-03372
Department of Obstetrics and Gynecology, Mount Sinai Hospital, Toronto, Ontario	Mount Sinai Hospital Research Ethics Board	15-0206-E
Dr. Barry Sanders, Inc., Vancouver, British Columbia	IRB Institutional Review Board Services	Pro00012844
Hamilton Health Sciences, Hamilton, Ontario	Hamilton Integrated Research Ethics Board	0620
IWK Health Centre, Halifax, Nova Scotia	IWK Research Ethics Board (IWK-REB)	1021698
Kingston General Hospital, Kingston, Ontario	Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB)	6021528
Ottawa Hospital Research Institute, Ottawa, Ontario	Ottawa Health Science Network Research Ethics Board	20150671-01H

Regina Medical Centre, Regina, Saskatchewan	University of Saskatchewan Research Ethics Office	Bio 16-87 / RQHR 16-26
Southern Health Centre, White Rock, British Columbia	IRB Institutional Review Board Services	Pro00012844
South Windsor Women's Health, Windsor, Ontario	IRB Institutional Review Board Services	Pro00012844
Strand Clinic, St. John's, Newfoundland	Newfoundland and Labrador Health Research Ethics Board	File# 20170665 Ref# 2016.228
The Fertility Clinic, Victoria Hospital London Health Sciences Centre, London, Ontario	IRB Institutional Review Board Services	Pro00012844
University of Calgary, Calgary, Alberta	Conjoint Health Research Ethics Board	REB 16-0547

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 (reference to previous publication); Table S1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6 N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	18-19 (Table 1)
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11, Table 2, Figure 1, Figure 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.