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Can magnetic resonance imaging at 3.0-Tesla reliably detect patients with endometriosis? Initial results

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Abstract

Aim: The aim of this study was to determine whether an optimized 3.0-Tesla magnetic resonance imaging (MRI) protocol is sensitive and specific enough to detect patients with endometriosis.

Material and Methods: This was a prospective cohort study with consecutive patients. Forty consecutive patients with clinical suspicion of endometriosis underwent 3.0-Tesla MRI, including a T2-weighted high-resolution fast spin echo sequence (spatial resolution = $0.75 \times 1.2 \times 1.5$ mm^3) and a 3D T1-weighted high-resolution gradient echo sequence (spatial resolution = $0.75 \times 1.2 \times 2.0$ mm^3). Two radiologists reviewed the dataset with consensus reading. During laparoscopy, which was used as reference standard, all lesions were characterized according to the revised criteria of the American Fertility Society. Patient-level and region-level sensitivities and specificities and lesion-level sensitivities were calculated.

Results: Patient-level sensitivity was 42% for stage I (5/12) and 100% for stages II, III and IV (25/25). Patient-level specificity for all stages was 100% (3/3). The region-level sensitivity and specificity was 63% and 97%, respectively. The sensitivity per lesion was 61% (90% for deep lesions, 48% for superficial lesions and 100% for endometriomata). The detection rate of obliteration of the cul-the-sac was 100% (10/10) with no false positive findings. The interreader agreement was substantial to perfect (kappa = 1 per patient, 0.65 per lesion and 0.71 for obliteration of the cul-the-sac).

Conclusions: An optimized 3.0-Tesla MRI protocol is accurate in detecting stage II to stage IV endometriosis.

Key words: 3.0-Tesla, endometriosis, magnetic resonance imaging.

Introduction

Endometriosis is characterized by development of ectopic endometrial tissue causing cyclic abdominal pain and subfertility.[1] The incidence of endometriosis in the general population is estimated to be 12–45%.[2]

Development of a non-invasive test for endometriosis has long been an important priority in endometriosis research because the delay that precedes an accurate diagnosis of endometriosis seems to be substantial.[3,4] As most of these patients are in their reproductive life span but also may have significant pain symptoms, this will have a significant influence on fertility chances and quality of life. The reference standard for the diagnosis of endometriosis is currently still a diagnostic laparoscopy, an invasive procedure with known complications.[5]

So far, several non-invasive tests have been developed for detecting patients with endometriosis. Inflammatory markers in either the peritoneal fluid or blood

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as evidence of induction of systemic inflammatory responses in women with endometriosis are depicted with limited success.[6–9] Similarly, tests with tumor markers like cancer antigen (CA)-125 and CA-19-9 showed disappointing results so far.[7–11] Ultrasonography can only detect deep lesions and therefore is unreliable to depict lower stages, which are mainly characterized by superficial lesions.[12,13]

Recent literature shows that magnetic resonance imaging (MRI) using a 3.0-Tesla (T) scanner can reliably detect deep endometriosis.[14] Studies on MRI of endometriosis so far have mainly focused on the preoperative setting in order to map the locations of deep endometriosis. Such mapping allows the gynecologist to plan the operation, should this be performed. However, the use of MRI to make the diagnosis of endometriosis, irrespective of the presence and extent of deep or superficial endometriosis, has not fully been addressed until now.

The purpose of this study was to explore whether an optimized 3.0-Tesla MRI protocol for endometriosis may be sufficiently sensitive to detect the disease in a clinical setting, compared to laparoscopic exploration.

Methods

Patients

The study protocol was approved by the institutional medical ethical review board (MERB). Sixteen patients gave written informed consent and for the other 24 patients informed consent was waived by the MERB because they underwent MRI for clinical purposes (preoperative imaging). The consecutive group of 40 patients with clinical suspicion of endometriosis was scheduled to undergo laparoscopy during a period of 2 years from November 2010 to December 2012. Exclusion criteria were the use of contraceptives or hormonal suppressive medication (like gonadotrophin-releasing hormones), contraindication to MRI (pacemaker, different metallic bodies, claustrophobia), age younger than 18 and postmenopausal status.

Patients were included from the Division of Gynecology for pain complaints and from the Division of Reproductive Medicine with subfertility as major complaint and with specific symptoms suspicious for endometriosis.

MRI

After inclusion, the MRI was performed between the ninth and 15th day of the menstrual cycle. Buscopan (butylscopolamine 40 mg, Boehringer Ingelheim) was administered intravenously. In order to suppress bowel motion for at least half an hour, Buscopan was administered at double dose (40 mg instead of 20 mg) in a very slow drip-infusion of 50 cc Natrium chloride. No intravenous MRI contrast was used.

Scans were acquired on a 3.0-Tesla scanner (GE Healthcare) using a whole-body radio frequency (RF) coil transmitter and an 8-channel cardiac phased array coil for signal reception. After a 3-plane localizer, a 2-D T2-weighted fast spin echo (FSE) sequence was performed in the axial orientation with the following imaging parameters: TR/TE = 12 000/70 ms; echo train length (ETL) = 10; readout bandwidth (BW) = 50 kHz; number of excitations (NEX) = 2, 100 sections; spatial resolution = $0.75 \times 1.2 \times 1.5$ mm^3; and field of view (FOV) = 24×24 cm^2. The acquisition time was around 8 min.

The examination was followed by an axial 3-D fat-suppressed T1-weighted fast RF spoiled gradient echo (SPGR) sequence. The imaging parameters used were: TR = 13/1.3 ms; flip angle = 30; BW = 31.2 kHz; NEX = 2, 80 sections; spatial resolution = $0.75 \times 1.2 \times 2.0$ mm^3; and FOV = 24×24 cm^2. The acquisition time was around 7 min.

Laparoscopy

Within 2 months after the MRI scan was performed, all patients underwent a diagnostic laparoscopy. Laparoscopic findings were used as reference standard to evaluate the MR findings. The location and size of each peritoneal lesion and endometrioma found during laparoscopy was recorded with digital video (avi) and reviewed by two experienced gynecologists (blinded). Both gynecologists were highly qualified and had extensive practical experience with laparoscopy and especially qualified in detecting endometriosis. Interobserver agreement with consensus reading was performed. The pelvic locations include the cul-the-sac, uterus, torus uterinus, recto-sigmoid, bladder, pelvic sidewalls, right uterosacral ligament, left uterosacral ligament, left ovary, right ovary, and their respective ovarian fossa. Lesions were categorized by depth according to the revised American Fertility Society (rAFS) criteria. The approximation of the depth of the lesion categorization according to Stratton *et al*. was used with different depths (<2 mm, 2–4 mm, >4 mm).[15] A lesion was classified as superficial if it was stated as no deeper than 4 mm below the peritoneal surface.[15,16] Because this is difficult to assess, a consensus reading was performed. On a clarifying drawing and in a table,

the gynecologists, blinded to the MRI findings, were asked to write down the location of the lesions.

Obliteration of the cul-the-sac was mentioned if the cul-the-sac was not accessible from the peritoneal space, due to the presence of adhesions.

Finally, patients were categorized according to the rAFS criteria in stage I (minimal), II (mild), III (moderate) and IV (severe).

Image analysis

Two experienced radiologists (blinded), with 13 and 12 years of experience in abdominal MRI, respectively, analyzed independently and blindly the data from the MRI on a PACS workstation (iSITE, Philips). They had no information regarding clinical data. On a clarifying drawing and in a table they were asked to identify the location of the lesions.

The diagnosis of an endometrioma in the ovary was based on shading on T2-weighted images and hyperintensity on T1-weighted images.[17] Fibrotic-like tissue on T2-weighted images was stated as deep endometriosis. Focal T1-weighted hyperintense foci without T2-weighted abnormalities were considered as superficial endometriotic lesions.[17]

The presence of obliteration without a definable mass is based on the visibility of adhesions between the uterus and bowel loops as previously mentioned by Kataoka *et al*.[18]

Statistical analysis

The diagnostic performance of MRI for the detection of patients with endometriosis was compared with the findings on laparoscopy, the reference standard test. The estimated measures were sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and were calculated per patient and per region separately. These diagnostic parameters were expressed with a 95% confidence interval (CI) for per-region analysis and 97.5%CI using exact test for the per-patient analysis. The per-patient calculations included classification according to the rAFS stage.

The pelvis was divided into 12 regions similar to those used in the laparoscopy (see above). For the per-region calculations the estimated measures and corresponding 95%CI were calculated by using variance estimates that take into account the correlated data owing to the multiple regions within a patient and were based on the generalized estimating equations (GEE) method with an independent working correlation matrix.[19]

In addition, the sensitivity and PPV were calculated per-lesion (superficial lesions, deep lesions, endometriomata) and for the presence of obliteration of the cul-the-sac. These diagnostic parameters were also expressed with a 95%CI for per-lesion analysis and 97.5%CI using exact test for obliteration of the cul-the-sac. Specificity and the NPV are dependent on the number of true negatives, and therefore these parameters can only be meaningfully determined in the per-patient and per-region analysis but not in the per-lesion analysis.

Based on the presence of obliteration, endometriomata, deep lesions and superficial lesions, patients are categorized as having more pronounced endometriosis (higher stages, III and IV) or less pronounced endometriosis (lower stages, I and II). A classification tree was developed to determine the optimal algorithm for classification into the higher and lower stages as compared to the reference standard test in our dataset.

Interobserver agreement was assessed using the kappa value (k). A $k \leq 0.20$ was interpreted as slight agreement; 0.21–0.40 was fair agreement; 0.41–0.60 was moderate agreement; 0.61–0.80 was substantial agreement; and ≥0.81 was almost perfect agreement.[20] Final results were based on consensus agreement between the two readers.

All statistical analyses were performed using SPSS 16.0, and STATA 11.0.

Results

A total of 40 patients were included in this study with a median age of 25 (range: 18–39) years. During laparoscopy, three patients were diagnosed without having endometriosis, 12 patients had stage I endometriosis, eight patients had stage II endometriosis, two patients had stage III endometriosis, and 15 had stage IV endometriosis. Eighteen endometriomata, 29 deep lesions and 126 superficial lesions were found.

The per-patient calculations of detection of endometriosis by MRI compared to laparoscopy as reference standard had a sensitivity of 81% (30/37; 97.5%CI: 65–92%), a specificity of 100% (3/3; 97.5%CI: 29–100%), a PPV of 100% (30/30; 97.5%CI: 88–100%) and an NPV of 70% (7/10; 97.5%CI: 29–100%) for all stages combined. Table 1 shows the sensitivity of detecting endometriosis by stage. There were seven patients with false negative findings on MRI, all diagnosed with stage I endometriosis according to the laparoscopic findings. In these seven patients, only some small spots of superficial endometriosis were seen by laparoscopy. In

Table 1 Patient-level analysis: Detection of patients with endometriosis according to the stage of endometriosis based on laparoscopy

	Laparoscopy+†				Laparoscopy–‡
	Stage I	Stage II	Stage III	Stage IV	
MRI+§	5	8	2	15	0
MRI–¶	7	0	0	0	3
Sensitivity	42%	100%	100%	100%	

†Patient positive for endometriosis based on consensus reading of two laparoscopists. ‡Patient negative for endometriosis based on consensus reading of two laparoscopists. §Patient positive for endometriosis based on consensus reading of two radiologists. ¶Patient negative for endometriosis based on consensus reading of two radiologists.

Table 2 Region-level analysis: Sensitivity, specificity, NPV and PPV according to the 12 regions in the pelvis

	Bladder	Fossa ov left	Fossa ov right	SUL left	SUL right	Torus	Rectum	Douglas	Pelvic wall	Ov left	Ov right	Uterus
Sensitivity	0.65	0.65	0.59	0.56	0.53	0.86	0.88	0.5	0.87	1	1	0.9
Specificity	1	0.92	0.92	0.92	0.92	0.92	1	1	1	1	1	0.96
NPV	0.53	0.65	0.61	0.6	0.57	0.96	0.96	0.65	0.92	1	1	0.96
PPV	1	0.92	0.91	0.91	0.91	0.75	1	1	1	1	1	0.9

NPV, negative predictive value; Ov, ovarian; PPV, positive predictive value; SUL, sacrouterine ligament.

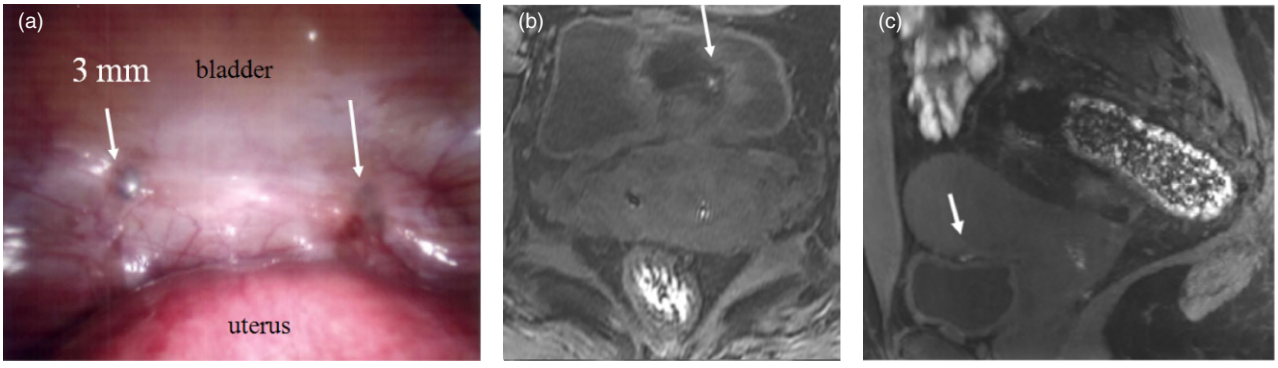

Figure 1 Laparoscopic view and magnetic resonance imaging of a patient with endometriosis in the plica vesico-uterina. (a) Endoscopic view with two brown superficial lesions on the bladder, both with an estimated depth of less than 4 mm. (b) Axial high resolution 3-D T1-weighted gradient image of the same patient showing a hyperintense spot on the bladder dome (e.g. plica vesico-uterina). Due to partial volume effect, this lesion is mainly surrounded by peritoneal fat. (c) Reconstructed sagittal high-resolution 3-D T1-weighted gradient image of the same patient visualizes the second lesion also in the plica vesico-uterina.

eleven patients, MRI found only superficial lesions, which were confirmed by laparoscopy. Four of them were laparoscopically classified as stage I and seven as stage II, based on a combination of superficial lesions, and fibrotic strands.

The per-region calculations of detection of endometriosis by MRI using the GEE method had similar estimates as the per-region calculations without GEE. However, the 95%CI were slightly wider with a sensitivity of 63% (95%CI: 54–70%), a specificity of 97% (95%CI: 94–98%), a PPV of 92% (95%CI: 86–96%) and an NPV of 82% (95%CI: 78–85%) (Table 2).

The sensitivity for deep lesions of 90% (26/29; 95%CI: 78–100%) was significantly higher in comparison to smaller lesions (Fig. 1) (48%; 61/126; 95%CI: 41–59%) (*P*-value <0.001) (Table 3). Three deep lesions were missed: one was visible retrospectively (sacrouterine ligament), one lesion was in the anterior abdominal wall and outside the scan, and the last one was not clearly visible retrospectively. The PPV for

Table 3 Lesion-level analysis: Detection of lesions according to laparoscopic findings based on lesion depth and presence of ovarian lesions (endometriomata)

	Laparoscopy+†				Laparoscopy−‡
	<2 mm	2–4 mm	>4 mm	Ovarian lesion	
MRI+§	24	37	26	18	9
MRI−¶	33	32	3	0	n/a
Sensitivity	42%	54%	90%	100%	

†Per lesion positive findings based on consensus reading of two laparoscopists. ‡Per lesion negative findings based on consensus reading of two laparoscopists. §Per lesion positive for finding based on consensus reading of two radiologists. ¶Per lesion negative finding based on consensus reading of two radiologists.

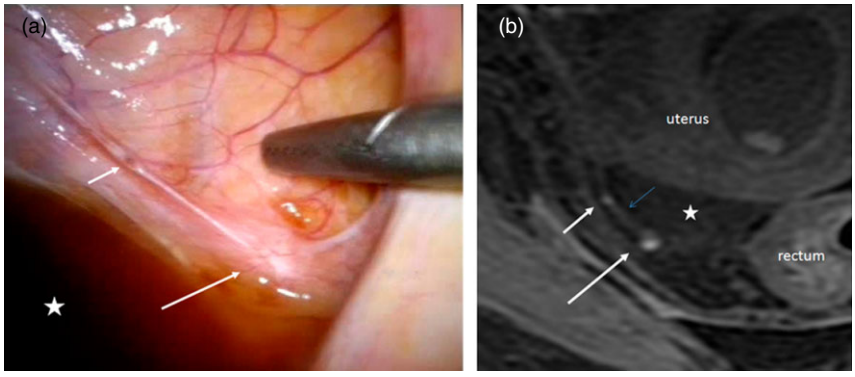

Figure 2 Laparoscopic view and magnetic resonance imaging of a patient with endometriosis in the cul-the-sac. (a) Endoscopic view shows two spots of superficial endometriosis in the pelvic sidewall with a fibrotic strand. The larger lesion is white (right arrow) and the very small lesion is brown (left arrow). (b) Axial high-resolution 3-D T1-weighted gradient image of the same region shows very superficial bright spots in the cul-the sac (large white arrow). Asterisk: ascites; small blue arrow: peritoneal surface.

detecting deep lesions was 100% (26/26; 97.5%CI: 87–100) and higher than that for superficial lesions (Fig. 2) (87%; 61/70; 95%CI: 79–95%), although not statistically significant (*P*-value = 0.06). There were nine false positive findings in 114 detected lesions (deep, superficial lesions and endometriomata) (Table 3). These false positive findings consisted of one lesion on the bladder dome, three lesions on the sacrouterine ligament, three lesions on the ovariae and two lesions in the fossa ovarica.

The sensitivity and PPV in detecting lesions unrelated to the size was 61% (105/173; 95%CI: 53–68%) and 92% (105/114; 95%CI: 87–97%), respectively.

The sensitivity, specificity, PPV and NPV of detecting obliteration of the cul-the-sac were 100% (10/10; 97.5%CI: 69–100%), 100% (30/30; 97.5%CI: 88–100%), 100% (10/10; 97.5%CI: 69–100%) and 100% (30/30; 97.5%CI: 88–100%), respectively.

The classification tree of patients having lower-stage endometriosis (I and II) versus higher-stage endometriosis (III and IV) is reflected in an algorithm (Fig. 3). In the presence of obliteration, one endometrioma or more than one deep lesion on MRI, a patient is classified as having higher stage of endometriosis.

The per-patient interobserver agreement for radiologists was perfect (k = 1). The per-lesion interobserver agreement was substantial (k = 0.65). The interobserver agreement for the detection of obliteration was substantial (k = 0.71). The per-region interobserver was not measured as the data for the per-region analysis were derived from the consensus findings per lesion.

Discussion

The current study provides evidence that MRI is accurate in detecting patients with mild, moderate or severe

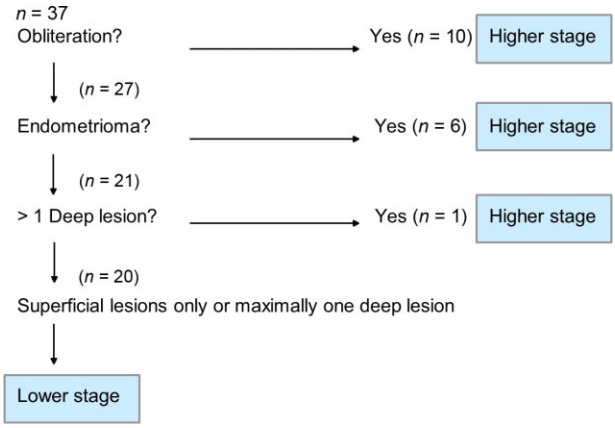

Figure 3 Classification tree: Explorative algorithm in order to classify patients as having lower-stage (stage I or II) or higher-stage (stage III or IV) endometriosis on magnetic resonance imaging. (>1 deep lesion: more than one deep lesion).

endometriosis (stages II–IV) with perfect interreader agreement. In patients with minimal endometriosis (stage I), MRI is unable to detect the disease.

During laparoscopy, endometriosis is classified according the rAFS into four different stages: minimal, mild, moderate and severe (stage I–IV).[16] It is of importance to detect all stages of endometriosis, including the lower stages, as pain and infertility are not always related to the severity of the disease as classified by the rAFS. Regarding endometriosis-related pain conditions, it is known that patients can suffer from severe dysmenorrhea caused by mild endometriosis and that complaints can be minimal in cases of severe endometriosis.[21] Concerning subfertility, it is known that all stages can cause fecundity problems. Although higher stages probably cause more infertility, detection of the lower stages are very important as fertility may be improved with surgical intervention mainly in this subgroup, as shown by a recent meta-analysis.[22]

Stage III and IV endometriosis according to the AFS classification reflects usually deep endometriosis, endometriomata or cul-the-sac obliteration. Our results in detecting deep endometriosis and endometriomata are in concordance with previously reported studies.[14,17] The largest study is by Bazot *et al*., where they detected around 90% deep lesions using a 1.5-Tesla scanner.[17]

As a consequence of our findings, the detection of higher stages of endometriosis (stage III and IV) can be performed with high sensitivity as these are mainly affected by deep lesions, endometriomata, or cul-the-sac obliteration. Our protocol utilizing a 3.0-Tesla MRI scanner seems to be an improvement in comparison to a previous protocol using 1.5-Tesla MR scanner, which had lower resolution.[15] In the previous study using a 1.5-Tesla scanner, the investigators detected only 10 of 15 patients with stage III and IV endometriosis, whereas we had no false negatives.

It is also of importance to depict the lower stages I and II of endometriosis. These lower stages reflect fewer deep lesions and more superficial endometriosis. On MRI, superficial lesions are mainly detected by bright spots on T1-weighted sequences, corresponding to local blood residues on the peritoneal surface. Earlier reports found a very low sensitivity in depicting superficial lesions (between 5 and 15%).[15,17] Our results were better, but still only 50% of the superficial lesions were detected. Even though we detected only half of all superficial lesions, we were able to make the diagnosis in all patients with stage II endometriosis, including seven patients with only superficial endometriosis. The detection of minimal endometriosis, reflecting sporadic superficial lesions (stage I), is still unsatisfactory.

The lower sensitivity of previous studies, regarding superficial endometriosis, might be related, apart from the lower scan field, to the use of a 2-D technique for T1-weighted imaging. With a 2-D technique, small vessels in the pelvis can be bright due to slow flow phenomenon, hence making it very difficult to differentiate it from superficial endometriosis spots. Using a 3-D gradient sequence, these pseudo-lesions are optimally suppressed. This provided us the opportunity to classify every bright spot on T1-weighted images as endometriosis with only nine false positive findings in a total of 174 detected lesions and a specificity of 97% based on a per region analysis. Note that specificity has no meaning in the lesion-level analysis.

To be able to predict whether a patient has a lower stage of endometriosis (stage I and II) versus a higher stage of endometriosis (stage III and IV) an explorative algorithm was developed. The cut-off between lower versus higher stage of endometriosis was arbitrarily chosen because of the small dataset. Not surprisingly, cul-the-sac obliteration on MRI strongly predicted the presence of higher stage endometriosis. Furthermore, the presence of an endometrioma or at least two deep lesions was found to be indicative for a higher stage of endometriosis. We emphasize that this algorithm could be useful to stage patients based on MRI but it needs to be validated in a larger patient population.

Our findings, although preliminary, could have impact for clinical practice, in patients with subfertility

and pain. In the case of subfertility it would be very useful to have a non-invasive test which could detect endometriosis. Instead of a diagnostic laparoscopy in order to rule out endometriosis, this could result in advice to add MRI as a tool to detect endometriosis early in the fertility screening on a routine basis.

Another implication for MRI is its use in pain-related conditions. Endometriosis can cause serious morbidity. Complaints can often be atypical with a doctor delay as consequence. A survey from 2006 showed that the mean diagnostic delay of patients suffering from dysmenorrhea is approximately 11 years, and that most patients had visited more than five doctors before a final diagnosis could be made.[23] A non-invasive test like MRI could lead to treatment in an earlier stage of the disease and hence prevent or slow down progression of the disease and symptoms.

A limitation of our study is the relatively small patient group and the patient selection based on clinical suspicion of having endometriosis. Our study indicates that it is possible to detect all stages of endometriosis except minimal endometriosis. Using this protocol it has to be determined if the results can be replicated in a larger patient population and in patients with a weaker clinical suspicion of having endometriosis.

Our patient group was also limited to patients without hormonal suppression. This was performed in order to enhance the visibility of active lesions on T1-weighted images. In the fertility screening, most patients do not take any hormonal medication that might suppress the cycle, but in other situations the influence of hormonal suppression on the detection of endometriosis has to be further evaluated.

This study focused on lesions visually diagnosed by two experienced gynecologists on laparoscopy instead of only pathologically proven lesions as a reference standard. It was considered that direct visualization with laparoscopy was a more realistic test to use as reference standard. Furthermore, the European Society of Human Reproduction and Embryology stated in 2005 that visual inspection of the pelvis on laparoscopy can be used as the 'gold' standard investigation for a definite diagnosis of endometriosis.[5]

In conclusion, using an optimized protocol, MRI seems reliable to detect all patients with endometriosis higher than stage I. Further studies have to be performed in larger patient populations and in patients with a low suspicion of the disease to confirm our findings.

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Disclosure

None of the authors have relationships with companies that may have a financial interest in the information contained in the manuscript.

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