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Three-dimensional saline infusion sonohysterography for the diagnosis of focal intracavitary lesions (Protocol)

Nieuwenhuis LL, Hermans FJR, Bij de Vaate AJM, Leeflang MMG, Brölmann HAM, Mol BWJ, Clark TJ, Huirne JAF

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[Diagnostic Test Accuracy Protocol]

Three-dimensional saline infusion sonohysterography for the diagnosis of focal intracavitary lesions

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the diagnostic accuracy of 3D SIS in comparison to 2D SIS in the diagnosis of focally growing lesions (polyps or fibroids) in women with abnormal uterine bleeding or subfertility with hysteroscopy as a reference test.

In addition we will evaluate the diagnostic accuracy of 2D+3D SIS (compared to 2D SIS) in the diagnosis of focally growing lesions (polyps or fibroids) in women with abnormal uterine bleeding or subfertility with hysteroscopy as a reference test. In this case, any abnormality on any of the two modalities will be regarded as a positive result ('OR' approach).

The secondary objective is, where possible, to evaluate the diagnostic accuracy of 3D SIS in comparison to 2D SIS in type of abnormality (to differentiate between polyps and fibroids) in women with abnormal uterine bleeding or subfertility using histology as a reference.

In addition we will evaluate, where possible, the diagnostic accuracy of 2D+3D SIS in type of abnormality (to differentiate between polyps and fibroids) in women with abnormal uterine bleeding or subfertility using histology as a reference.

BACKGROUND

Target condition being diagnosed

Abnormal uterine bleeding affects about 22% of healthy premenopausal women aged above 35 years (Gath 1987). Apart from hormonal imbalance, intracavitary abnormalities are the leading cause. Intracavitary abnormalities are (usually) focally growing benign formations (polyps, fibroids, adhesions) inside the cavity of the uterus that can cause several complaints including abnor-

mal uterine bleeding, dysmenorrhoea and subfertility. Tur-Kaspa (Tur-Kaspa 2006) reported that 39.6% of patients with abnormal uterine bleeding were diagnosed with an intracavitary abnormality (polyp 29.8%, fibroid 9%, or adhesions 0.7%) and in a recent Cochrane review the overall prevalence of intracavitary abnormalities in asymptomatic women prior to in vitro fertilisation (IVF) or intracytoplasmic sperm insemination (ICSI) was 11% (Fatemi HM 2010). Our target condition is focally growing lesions (polyps or fibroids) inside the uterine cavity.

Index test(s)

Sonohysterography is a procedure in which fluid (saline or gel) is instilled transcervically into the uterine cavity to provide enhanced visualisation of the endometrial lining during transvaginal ultrasound examination. Two-dimensional saline infusion sonography (2D SIS) and diagnostic hysteroscopy are techniques for detection of intrauterine abnormalities. The study from Dijkhuizen (Dijkhuizen 2003) revealed that SIS and hysteroscopy had the highest number of successfully diagnosed women for menorrhagia. Both saline infusion sonohysterography (SIS) and gel installation sonohysterography (GIS) are simple, safe, well tolerated and accurate techniques in the assessment of intrauterine abnormalities (Beemsterboer 2008; Bij de Vaate 2010). Although 2D SIS has become the diagnostic test of choice in most clinical practice, diagnostic hysteroscopy (with histology) still is the golden standard to confirm the absence or presence of an intrauterine abnormality. The introduction of three-dimensional (3D) SIS enhances visualisation of the uterine cavity and is reported to be highly accurate (Abou Salem 2010; de Kroon 2004; La Torre 1999; Lee 2006; Makris 2007; Salim 2005; Sylvestre 2003; Terry 2009). The 3D SIS allows the examination of the uterus from any angle and in any plane, which allows the examiner to more accurately measure fibroid size and the extent of protrusion of submucous fibroids into the uterine cavity. Since 3D SIS is reported to be accurate, it may be of additional value to 2D SIS or may even replace it. This review focuses on studies in which 3D SIS alone (index test 1) or 2D+3D SIS (index test 2) was compared with 2D SIS (comparator test), with hysteroscopy (and histology) as the reference test to identify or classify intrauterine abnormalities.
Index tests: 3D SIS and 2D+3D SIS.

Clinical pathway

In most clinics (of developed countries) women with abnormal uterine bleeding who are suspected to have an intracavitary abnormality on transvaginal sonography (TVS) will have planned 2D SIS. If an intracavitary abnormality is seen during 2D SIS, a therapeutic hysteroscopy will be scheduled. Though hysteroscopy is a relatively safe operation with minor complications, it is a more expensive and burdensome procedure for the patient compared to SIS (Dongen 2011; Widrich 1996). If a normal cavity is seen at 2D SIS, women will first be treated with expectant management or hormonal therapy.

Rationale

SIS is an appropriate technique for the detection of focally growing lesions (polyps and fibroids) (Bij de Vaate 2010; de Kroon 2003). A meta-analysis of the accuracy of 2D SIS (with hysteroscopy as the gold standard) in abnormal uterine bleeding reported a pooled sensitivity and specificity of 95% and 88%, respectively (de Kroon 2003). High sensitivity in 2D SIS means that further more burdensome and expensive diagnostic methods (such as diagnostic hysteroscopy) may be avoided if a normal uterine cavity is detected using SIS (negative predictive value of 95%). However, 5% of the uterine cavity abnormalities were missed (post-test probability of a negative test 0.05) and 12% (specificity 88%) of the women without abnormalities were scheduled for unnecessary hysteroscopy due to a false positive test result (they were found to have a normal uterine cavity). The 2D SIS may not be fully accurate in the assessment of the type and classification of intrauterine abnormalities (Kroon 2006). The introduction of 3D SIS enhances visualisation of the uterine cavity and the 3D SIS advantage (over 2D SIS) lies in the fact that it can measure the size and extent of protrusion of submucous fibroids into the uterine cavity very accurately (Lee 2006; Mavrelos 2011; Wamsteker 1993). Both parameters are important determinants for the planning of hysteroscopic procedures in terms of applied anaesthetics, instruments used and the required level of experience of the surgeon (Betjes 2009). Though 3D SIS is reported to be highly accurate in the diagnosis of uterine abnormalities (de Kroon 2004), 2D SIS is mainly used in clinical practice. The 3D SIS may have an additional role to 2D SIS in the detection and classification of focally growing lesions, which might result in fewer unnecessary hysteroscopies or missed abnormalities.

OBJECTIVES

To evaluate the diagnostic accuracy of 3D SIS in comparison to 2D SIS in the diagnosis of focally growing lesions (polyps or fibroids) in women with abnormal uterine bleeding or subfertility with hysteroscopy as a reference test.

In addition we will evaluate the diagnostic accuracy of 2D+3D SIS (compared to 2D SIS) in the diagnosis of focally growing lesions (polyps or fibroids) in women with abnormal uterine bleeding or subfertility with hysteroscopy as a reference test. In this case, any abnormality on any of the two modalities will be regarded as a positive result ('OR' approach).

Secondary objectives

The secondary objective is, where possible, to evaluate the diagnostic accuracy of 3D SIS in comparison to 2D SIS in type of abnormality (to differentiate between polyps and fibroids) in women with abnormal uterine bleeding or subfertility using histology as a reference.

In addition we will evaluate, where possible, the diagnostic accuracy of 2D+3D SIS in type of abnormality (to differentiate between polyps and fibroids) in women with abnormal uterine bleeding or subfertility using histology as a reference.

METHODS

Criteria for considering studies for this review

Types of studies

All diagnostic test accuracy studies, randomised controlled trials and prospective cohort studies of sufficient methodological quality in which 2D SIS and 3D SIS were evaluated with the results of hysteroscopy as the reference will be eligible for inclusion. Secondly, all studies in which 2D SIS or 3D SIS alone were evaluated will be eligible for inclusion. We prefer to use studies that have reported both 2D SIS and 3D SIS. If we find enough studies which have reported both, studies that report only 2D SIS or only 3D SIS will be excluded. Both 2D SIS and 3D SIS should be obtained in the same setting, regardless of performance sequence. Prospective cohort studies will be included if enrolment was performed consecutively. Case-control, case-report and retrospective cohort studies will be excluded.

Participants

The populations of interest are premenopausal women with abnormal uterine bleeding or subfertility and postmenopausal women with abnormal uterine bleeding.

Index tests

Studies evaluating the diagnostic accuracy of 3D SIS alone (index test 1) or 2D+3D SIS (index test 2) in comparison with 2D SIS (comparator test) will be included.

Target conditions

Women will be tested for the presence of intracavitary abnormalities. The target condition is the presence of a focally growing lesion in the uterine cavity (polyp or fibroid). If reported, we will differentiate between polyps and fibroids. Smoothly margined echogenic masses with an homogenous texture are classified as polyps, while structures of mixed echogenicity disrupting the endometrial continuity are described as submucous fibroids (Parsons 1993).

Reference standards

Diagnostic hysteroscopy will be the reference standard to confirm the absence or presence of the target condition. When reported, we will also use histology as a reference standard to differentiate between the type of abnormality (polyp or fibroid). We expect that in some studies not all women will have received a hysteroscopy (reference standard) due to a negative test result with 2D SIS (meaning no suspicion of abnormality). Because the sensitivity for 2D SIS is high, it may sometimes be considered unethical to perform hysteroscopy in this group of women. The calculation of false negatives may not always be possible.

Search methods for identification of studies

Electronic searches

The databases of CENTRAL, MEDLINE and EMBASE will be searched in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator Marian Showell. All studies will be screened for eligibility from inception until present. The full search strategies for the databases are listed in the appendices (Appendix 2; Appendix 3; Appendix 4).

We will also search PubMed to find recent published trials not yet indexed in MEDLINE.

The following additional electronic sources of trials will be used: DARE, the MDSG Specialised Register and the MDSG Diagnostic Test Accuracy (DTA) Specialised Register.

To find ongoing trials we will search the trial registries: clinicaltrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

Searching other resources

We will handsearch the reference lists of all included articles and contact experts in the field to obtain additional data. We will also handsearch conference abstracts that are not covered in the MDSG Specialised Register, in liaison with the Trials Search Co-ordinator. The number and sources of studies will be depicted in a flow diagram.

Data collection and analysis

Selection of studies

Two authors (LLN and FJRH) will independently read all the potentially included references after doing a first screening by title and abstract. Disagreements on decisions for inclusion will be resolved by discussion between both authors; when agreement is not reached a third author will be consulted.

Data extraction and management

Two authors (LLN and FJRH) will independently extract data from eligible studies using a data extraction form (see Appendix 6). Disagreements will be resolved by discussion between both authors; when agreement is not reached a third author will be consulted. If required, we will correspond with study investigators for further data on methods and results.

Assessment of methodological quality

Studies will be assessed by two authors (working independently) for methodological quality using QUADAS-2 (see Appendix 6). The QUADAS-2 tool will be supplemented with review-specific questions. For example, in the domain 'index test' we added the question whether the level of experience of the (index) test performer was reported. We added in the domain 'reference test and target condition' the question whether the target condition was specified or not and in what categories.

Statistical analysis and data synthesis

The main outcome of this review and meta-analysis is the accuracy of 3D SIS (compared to 2D SIS); a secondary outcome is the accuracy of 2D and 3D SIS combined. We expect to include studies that have evaluated 2D SIS and 3D SIS against the reference standard, and studies that evaluated the combination of 2D SIS and 3D SIS against the reference standard. Only if there are fewer than 10 of these latter studies we will also include studies evaluating 2D SIS or 3D SIS only. From all included studies 2 x 2 tables will be constructed.

In studies where multiple index tests (2D SIS or 3D SIS alone and 2D+3D SIS together) were performed, we will also construct a series of 2 x 2 tables where the results of investigations are combined provided that they are derived from the total study population and that the definition of a positive result is given for one of the tests.

To describe and visualise the data, forest plots showing pairs of sensitivity and specificity together with 95% confidence intervals from each study will be produced in RevMan, as well as raw receiver operating characteristic (ROC) plots. Paired analyses (studies that have tested both 2D SIS and 3D SIS, and studies that have tested both 2D SIS and 2D+3D SIS) will be displayed in a ROC plot by linking the sensitivity-specificity pairs from each study with a dashed line (Leeflang 2008).

To compare 3D SIS with 2D SIS, we will use a generalized linear mixed model (binomial family) approach for bivariate meta-analysis of sensitivity and specificity (Reitsma 2005), restricted to those studies that report 2 x 2 tables for both tests. Test type will be added to the model as a covariate. To analyse the addition of 3D SIS to 2D SIS, we will include studies that report the accuracy for the combination of these two techniques. In this case, any abnormality on any of the two modalities will be regarded as a positive result ('OR' approach).

A secondary objective is to assess the accuracy of these tests to differentiate between polyps and fibroids. In this case the same analyses will be used as described above but the target condition will be polyp (versus no polyp) or fibroid (versus no fibroid), depending on what is reported.

Results will be presented as the summary sensitivity and specificity, and additionally as likelihood ratios. The graphical display will be a false positive (1 - specificity) versus sensitivity plot (ROC plot) showing individual study results including the individual study estimates, the summary operating point (summary values for sensitivity and specificity) and the 95% confidence region on the operating point.

Investigations of heterogeneity

Heterogeneity will be addressed by adding variables to the bivariate model as covariates. To evaluate heterogeneity, the following clinical characteristics will be collected: age, body mass index, premenopausal or postmenopausal state, clinical symptoms, parity and race. Subgroup analyses will be performed in premenopausal and postmenopausal women as these are distinct patient populations. Other subgroup analyses will be performed in symptomatic (where womens' menstrual complaints were an indication for SIS) versus asymptomatic women (SIS was performed for screening, mostly in subfertile women).

Sensitivity analyses

We will consider whether the clinical and methodological characteristics (as assessed by the QUADAS-2 tool) of the included studies are sufficiently similar for meta-analyses to provide a clinically meaningful summary. Therefore, we will conduct sensitivity analyses to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility of studies and the analyses performed. Missing or uninterpretable data will be classified as positive test results. Studies where the results can not be confirmed in subsequent publications will not be excluded but will be used in the meta-analysis.

Assessment of reporting bias

We will aim to minimise potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data.

ACKNOWLEDGEMENTS

We would like to thank the DTA Working Group and the Menstrual Disorders and Subfertility Group for their specialist peer review comments and we thank Marian Showell (Trials Search Coordinator) for her help with the search strategy.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MDSG search strategy

Title CONTAINS “three dimensional” or “3d” or “3 dimensional” or Keywords CONTAINS “three dimensional” or “3d” or “3 dimensional”

Appendix 2. CENTRAL search strategy

Database: Ovid EBM Reviews - Cochrane Central Register of Controlled Trials inception until present
Search Strategy:

1 (uter$ adj2 abnormal$).tw.
2 abnormal vagina$ bleeding.tw.
3 (intrauter$ adj2 abnormal$).tw.
4 (endometri$ adj2 abnormal$).tw.
5 (uterine adj2 anomal$).tw.
6 (endometri$ adj2 anomal$).tw.
7 (intrauterine adj2 anomal$).tw.
8 (uterine adj2 anomal$).tw.
9 abnormal uter$ bleeding.tw.

10 dysfunctional uter$ bleeding.tw.
11 DUB.tw.
12 heavy menstrual bleeding.tw.
13 (postmenopaus$ adj2 bleed$).tw.
14 (perimenopaus$ adj2 bleed$).tw.
15 exp uterine hemorrhage/
16 uter$ haemorrhag$.tw.
17 uter$ hemorrhag$.tw.
18 menorrhagi$.tw.
19 metrorrhagi$.tw.
20 (endometri$ adj2 lesion$).tw.
21 (endometri$ adj2 adhesion$).tw.
22 (uter$ adj2 lesion$).tw.
23 (uter$ adj2 adhesion$).tw.
24 (ovar$ adj2 adhesion$).tw.
25 (intrauter$ adj2 adhesion$).tw.
26 (intrauter$ adj2 lesion$).tw.
27 polyp$.tw.
28 endometrio$.tw.
29 adnexal mass$.tw.
30 adenomyosis.tw.
31 exp leiomyoma/ or exp myoma/
32 infertil$.tw.
33 subfertil$.tw.
34 myoma$.tw.
35 leiomyoma$.tw.
36 fibroid$.tw.
37 (septate adj2 uterus).tw.
38 arcuate uter$.tw.
39 (endometri$ adj2 thick$).tw.
40 (uter$ adj2 malformation$).tw.
41 (bicornuate adj2 uterus).tw.
42 intracavity abnormal$.tw.
43 (uter$ adj2 contour).tw.
44 (uter$ adj3 sept$).tw.
45 endometri$ atroph$.tw.
46 (endometri$ adj2 tumor$).tw.
47 (endometri$ adj2 tumour$).tw.
48 ((uter$ adj2 malignan$) or (uter$ adj2 cancer$)).tw.
49 ((endometri$ adj2 malignan$) or (endometri$ adj2 cancer$)).tw.
50 ((ovar$ adj2 malignan$) or (ovar$ adj2 cancer$)).tw.
51 (uterus adj2 disorder$).tw.
52 (uterine adj2 disorder$).tw.
53 (uterus adj2 disease$).tw.
54 (uterine adj2 disease$).tw.
55 (endometri$ adj2 neoplasm$).tw.
56 (uterine adj2 neoplasm$).tw.
57 (uterus adj2 neoplasm$).tw.
58 (uterine adj2 patholog$).tw.
59 (uterus adj2 patholog$).tw.
60 (endometri$ adj2 patholog$).tw.
61 Adenomyoma/
62 Adenomyo$.tw.

63 fibroma.tw.
64 fibromyoma$.tw.
65 Infertility, Female/
66 exp endometriosis/ or exp uterine diseases/
67 Polyps/
68 Endometrial Hyperplasia/
69 (Endometri$ adj3 Hyperplasia).tw.
70 exp Ovarian Diseases/
71 (ovar$ adj2 mass$).tw.
72 (ovar$ adj2 tumo?r).tw.
73 (ovar$ adj2 cyst$).tw.
74 Gynecology/
75 (gynecolog$ or gynaecolog$).tw.
76 uter$ cavit$.tw.
77 endometrial cavity.tw.
78 intracav$ lesion$.tw.
79 intracav$ abnormal$.tw.
80 (uter$ adj2 volume).tw.
81 (ovar$ adj2 volume$).tw.
82 (intrauter$ adj2 patholog$).tw.
83 or/1-82
84 Imaging, Three-Dimensional/
85 (Three-Dimensional and imag$).tw.
86 (3D and imag$).tw.
87 (3 D and imag$).tw.
88 (Three-Dimensional and sonogra$).tw.
89 (3D and sonogra$).tw.
90 (3 D and sonogra$).tw.
91 3dus.tw.
92 3 dus.tw.
93 (Three-Dimensional and ultraso$).tw.
94 (3D and ultraso$).tw.
95 (3 D and ultraso$).tw.
96 3D US.tw.
97 three dimension.tw.
98 3 dimension.tw.
99 (3d and multiplanar).tw.
100 (3 dimension$ and multiplanar).tw.
101 (three dimension$ and multiplanar).tw.
102 (three dimensional or 3d or 3 d).ti,ab,hw. and us.fs.
103 or/84-102
104 Ultrasonography/
105 limit 104 to yr="1990 -Current"
106 103 or 105
107 (3D and hystero$).tw.
108 (3 D and hystero$).tw.
109 (Three-Dimensional and sonohysterogra$).tw.
110 (3D and sonohysterogra$).tw.
111 (3 D and sonohysterogra$).tw.
112 (Three-Dimensional and SIS).tw.
113 (3D and SIS).tw.
114 (3 D and SIS).tw.
115 (Three-Dimensional and hystero$).tw.

116 (3d and hycosy).tw.
117 (3 d and hycosy).tw.
118 (three dimension$ and hycosy).tw.
119 or/107-118
120 83 and 106
121 119 or 120
122 exp animals/ not humans.sh.
123 121 not 122

Appendix 3. EMBASE search strategy

Database: Ovid Embase inception until present
Search Strategy:

1 (uter$ adj2 abnormal$).tw.
2 (intrauter$ adj2 abnormal$).tw.
3 (endometri$ adj2 abnormal$).tw.
4 (uterine adj2 anomalies).tw.
5 (endometri$ adj2 anomal$).tw.
6 (intrauterine adj2 anomal$).tw.
7 (uterine adj2 anomal$).tw.
8 abnormal uter$ bleeding.tw.
9 dysfunctional uter$ bleeding.tw.
10 abnormal vagina$ bleeding.tw.
11 DUB.tw.
12 heavy menstrual bleeding.tw.
13 intrauterine patholog$.tw.
14 adnexal mass$.tw.
15 (uter$ adj2 malformation$).tw.
16 exp uterus bleeding/ or uterine body disease/
17 exp menorrhagia/ or "menorrhagia and metrorrhagia"/
18 uter$ haemorrhag$.tw.
19 uter$ hemorrhag$.tw.
20 menorrhagi$.tw.
21 metrorrhagi$.tw.
22 (endometri$ adj2 lesion$).tw.
23 (endometri$ adj2 adhesion$).tw.
24 (uter$ adj2 lesion$).tw.
25 (uter$ adj2 adhesion$).tw.
26 (intrauter$ adj2 lesion$).tw.
27 (intrauter$ adj2 adhesion$).tw.
28 polyp$.tw.
29 arcuate uter$.tw.
30 endometrio$.tw.
31 endometrial cavity.tw.
32 (endometri$ adj2 chang$).tw.
33 exp leiomyoma/
34 exp uterus myoma/ or exp myoma/
35 infertil$.tw.
36 subfertil$.tw.
37 myoma$.tw.
38 fibroid$.tw.

39 leiomyoma$.tw.
40 (septate adj2 uterus).tw.
41 (bicornuate adj2 uterus).tw.
42 intracavity abnormal$.tw.
43 (uter$ adj2 contour).tw.
44 (uter$ adj3 sept$).tw.
45 endometri$ atroph$.tw.
46 (endometri$ adj2 tumor$).tw.
47 (endometri$ adj2 tumour$).tw.
48 ((uter$ adj2 malignan$) or (uter$ adj2 cancer$)).tw.
49 ((endometri$ adj2 malignan$) or (endometri$ adj2 cancer$)).tw.
50 ((ovar$ adj2 malignan$) or (ovar$ adj2 cancer$)).tw.
51 (uterus adj2 disorder$).tw.
52 (uterine adj2 disorder$).tw.
53 (uterus adj2 disease$).tw.
54 (uterine adj2 disease$).tw.
55 (endometri$ adj2 neoplasm$).tw.
56 (uterine adj2 neoplasm$).tw.
57 (uterus adj2 neoplasm$).tw.
58 (uterine adj2 patholog$).tw.
59 (uterus adj2 patholog$).tw.
60 (endometri$ adj2 patholog$).tw.
61 (endometri$ adj2 thick$).tw.
62 exp adenomyoma/
63 Adenomyo$.tw.
64 fibroma.tw.
65 fibromyoma$.tw.
66 exp female infertility/
67 endometriosis/
68 exp uterus disease/
69 exp endometrium tumor/
70 polyp/ or endometrium polyp/
71 endometrium hyperplasia/
72 Endometrial Hyperplasia.tw.
73 exp ovary disease/
74 (ovar$ adj2 mass$).tw.
75 (ovar$ adj2 tumo?r).tw.
76 uter$ cavit$.tw.
77 intracavity lesion$.tw.
78 (postmenopaus$ adj2 bleed$).tw.
79 (perimenopaus$ adj2 bleed$).tw.
80 (uter$ adj2 volume).tw.
81 (ovar$ adj2 volume$).tw.
82 gyn?ecology.tw.
83 or/1-82
84 three dimensional imaging/
85 limit 84 to yr="1990 -Current"
86 (Three-Dimensional adj2 imag$).tw.
87 (3 D adj2 imag$).tw.
88 (Three-Dimensional adj2 sonogra$).tw.
89 (3D adj2 sonogra$).tw.
90 (3 D adj2 sonogra$).tw.
91 3dus.tw.

92 3 dus.tw.
93 (Three-Dimensional adj2 ultraso$).tw.
94 (3D adj2 ultraso$).tw.
95 3D US.tw.
96 (3d adj2 multiplanar).tw.
97 (3 dimension$ adj2 multiplanar).tw.
98 (three dimension$ adj2 multiplanar).tw.
99 or/85-98
100 (Three-Dimensional and sonohysterogra$).tw.
101 (3D and sonohysterogra$).tw.
102 (3 D and sonohysterogra$).tw.
103 (Three-Dimensional and SIS).tw.
104 (3D adj2 SIS).tw.
105 (3 D and SIS).tw.
106 (Three-Dimensional adj2 hystero$).tw.
107 (3D adj2 hystero$).tw.
108 (3 D and hystero$).tw.
109 (3d and hycosy).tw.
110 (3 d and hycosy).tw.
111 (three dimension$ and hycosy).tw.
112 echography/
113 Three dimensional.tw.
114 3dus.tw.
115 3D.tw.
116 113 or 114 or 115
117 112 and 116
118 99 or 117
119 83 and 118
120 or/100-111
121 119 or 120

Appendix 4. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) inception until present
Search Strategy:

1 (uter$ adj2 abnormal$).tw.
2 abnormal vagina$ bleeding.tw.
3 (intrauter$ adj2 abnormal$).tw.
4 (endometri$ adj2 abnormal$).tw.
5 (uterine adj2 anomal$).tw.
6 (endometri$ adj2 anomal$).tw.
7 (intrauterine adj2 anomal$).tw.
8 (uterine adj2 anomal$).tw.
9 abnormal uter$ bleeding.tw.
10 dysfunctional uter$ bleeding.tw.
11 DUB.tw.
12 heavy menstrual bleeding.tw.
13 (postmenopaus$ adj2 bleed$).tw.
14 (perimenopaus$ adj2 bleed$).tw.
15 exp uterine hemorrhage/

16 uter$ haemorrhag$.tw.
17 uter$ hemorrhag$.tw.
18 menorrhagi$.tw.
19 metrorrhagi$.tw.
20 (endometri$ adj2 lesion$).tw.
21 (endometri$ adj2 adhesion$).tw.
22 (uter$ adj2 lesion$).tw.
23 (uter$ adj2 adhesion$).tw.
24 (ovar$ adj2 adhesion$).tw.
25 (intrauter$ adj2 adhesion$).tw.
26 (intrauter$ adj2 lesion$).tw.
27 polyp$.tw.
28 endometrio$.tw.
29 adnexal mass$.tw.
30 adenomyosis.tw.
31 exp leiomyoma/ or exp myoma/
32 infertil$.tw.
33 subfertil$.tw.
34 myoma$.tw.
35 leiomyoma$.tw.
36 fibroid$.tw.
37 (septate adj2 uterus).tw.
38 arcuate uter$.tw.
39 (endometri$ adj2 thick$).tw.
40 (uter$ adj2 malformation$).tw.
41 (bicornuate adj2 uterus).tw.
42 intracavity abnormal$.tw.
43 (uter$ adj2 contour).tw.
44 (uter$ adj3 sept$).tw.
45 endometri$ atroph$.tw.
46 (endometri$ adj2 tumor$).tw.
47 (endometri$ adj2 tumour$).tw.
48 ((uter$ adj2 malignan$) or (uter$ adj2 cancer$)).tw.
49 ((endometri$ adj2 malignan$) or (endometri$ adj2 cancer$)).tw.
50 ((ovar$ adj2 malignan$) or (ovar$ adj2 cancer$)).tw.
51 (uterus adj2 disorder$).tw.
52 (uterine adj2 disorder$).tw.
53 (uterus adj2 disease$).tw.
54 (uterine adj2 disease$).tw.
55 (endometri$ adj2 neoplasm$).tw.
56 (uterine adj2 neoplasm$).tw.
57 (uterus adj2 neoplasm$).tw.
58 (uterine adj2 pathолog$).tw.
59 (uterus adj2 pathолog$).tw.
60 (endometri$ adj2 pathолog$).tw.
61 Adenomyoma/
62 Adenomyo$.tw.
63 fibroma.tw.
64 fibromyoma$.tw.
65 Infertility, Female/
66 exp endometriosis/ or exp uterine diseases/
67 Polyps/
68 Endometrial Hyperplasia/

69 (Endometri$ adj3 Hyperplasia).tw.
70 exp Ovarian Diseases/
71 (ovar$ adj2 mass$).tw.
72 (ovar$ adj2 tumo?r).tw.
73 (ovar$ adj2 cyst$).tw.
74 Gynecology/
75 (gynecolog$ or gynaecolog$).tw.
76 uter$ cavit$.tw.
77 endometrial cavity.tw.
78 intracav$ lesion$.tw.
79 intracav$ abnormal$.tw.
80 (uter$ adj2 volume).tw.
81 (ovar$ adj2 volume$).tw.
82 (intrauter$ adj2 patholog$).tw.
83 or/1-82
84 Imaging, Three-Dimensional/
85 (Three-Dimensional and imag$).tw.
86 (3D and imag$).tw.
87 (3 D and imag$).tw.
88 (Three-Dimensional and sonogra$).tw.
89 (3D and sonogra$).tw.
90 (3 D and sonogra$).tw.
91 3dus.tw.
92 3 dus.tw.
93 (Three-Dimensional and ultraso$).tw.
94 (3D and ultraso$).tw.
95 (3 D and ultraso$).tw.
96 3D US.tw.
97 three dimension.tw.
98 3 dimension.tw.
99 (3d and multiplanar).tw.
100 (3 dimension$ and multiplanar).tw.
101 (three dimension$ and multiplanar).tw.
102 (three dimensional or 3d or 3 d).ti,ab,hw. and us.fs.
103 or/84-102
104 Ultrasonography/
105 limit 104 to yr="1990 -Current"
106 103 or 105
107 (3D and hystero$).tw.
108 (3 D and hystero$).tw.
109 (Three-Dimensional and sonohysterogra$).tw.
110 (3D and sonohysterogra$).tw.
111 (3 D and sonohysterogra$).tw.
112 (Three-Dimensional and SIS).tw.
113 (3D and SIS).tw.
114 (3 D and SIS).tw.
115 (Three-Dimensional and hystero$).tw.
116 (3d and hycosy).tw.
117 (3 d and hycosy).tw.
118 (three dimension$ and hycosy).tw.
119 or/107-118
120 83 and 106
121 119 or 120

122 exp animals/ not humans.sh.
123 121 not 122

Appendix 5. Eligibility form

INCLUSION FORM for DTA review '3D SIS for the diagnosis of intrauterine abnormalities in women with abnormal uterine bleeding'

1. Name assessing author

o Lotte Nieuwenhuis o Frederik Hermans o …….

2. Study ID (= Name first author + Year of publication)

…….....

3. Study design (Prospective cohort study, RCT)

o Yes o no o unclear

4. Index test(s) of interest (3D GIS or 2D+3D GIS)

o Yes o no o unclear

5. Reference test (hysteroscopy and or histology)

o Yes o no o unclear

6. Disease of interest (intra uterine abnormality)

o Yes o no o unclear

7. Population of interest (Women with abnormal uterine bleeding, dysmenorroe or infertility)

o Yes o no o unclear

---

8. If one of the above questions is answered with 'no', study will be excluded from review.

o Inclusion o exclusion

9. Comments ……..

……...

10. Is study included by both assessing authors?

Yes? à Data extraction form can be completed.
No? à Discussion between both authors needs to take place.

Appendix 6. Data extraction form (using QUADAS 2)

DATA EXTRACTION AND QUALITY ASSESMENT* FORM for DTA review '3D SIS for the diagnosis of intrauterine abnormalities in women with abnormal uterine bleeding'
(*quality assessment using QUADAS 2 tool)

1. Name assessing author

o Lotte Nieuwenhuis o Frederik Hermans o ……...

1. Study ID (= Name first author + Year of publication)

…….....

Patient selection

3. What type of study design (patient sampling) was used?
o RCT o Prospective cohort study o Other…….....

4. How was patient enrolment performed?
o Consecutive o Random sample

5. How was participant recruitment arranged?
o Based on presenting symptoms o Results from previous test
o Participants received index test or golden standard

6. Were the selection criteria clearly described?
o Yes o No o Unclear/ Not reported

7. Was a case-control design avoided?
o Yes o No o Unclear/ Not reported

8. Did the study avoid inappropriate exclusions?
o Yes o No o Unclear/ Not reported
9. Could the selection of patients have introduced bias?
o Yes o No o Unclear/ Not reported

10. Are there concerns that the included patients and setting do not match the review question?
o Yes o No o Unclear/ Not reported

11. Presentation or symptoms
o Pre menopausal abnormal uterine bleeding (AUB) o Post menopausal AUB
o Sub or-Infertility o Dysmenorrhoea o Other……..

Index test 3D SIS

12. Were the index test results interpreted without knowledge of the results of the reference standard?
o Yes o No o Unclear/ Not reported

1. If a threshold was used, was it pre-specified?
o Yes ,……. o No o Unclear/ Not reported

14. Was the execution of the index test described sufficiently to permit replication of the test?
o Yes o No o Unclear/ Not reported

15. Were criteria for different index test findings well defined?
o Yes o No o Unclear/ Not reported

16. Is the amount of experience/ training of the persons executing and reading the index tests specified?
o Yes ,……. o No o Unclear/ Not reported

1. Where complications with the index test registered?
o Yes ,……. o No o Unclear/ Not reported

1. Could the conduct or interpretation of the index test have introduced bias?
o Yes ,……. o No o Unclear/ Not reported

1. Are there concerns that the index test, its conduct, or interpretation differ from the review question?
o Yes ,……. o No o Unclear/ Not reported

Index test : 2D + 3D SIS

20. Were the index test results interpreted without knowledge of the results of the reference standard?
o Yes o No o Unclear/ Not reported

1. If a threshold was used, was it pre-specified?
o Yes ,……. o No o Unclear/ Not reported

22. Was the execution of the index test described sufficiently to permit replication of the test?
o Yes o No o Unclear/ Not reported

23. Were criteria for different index test findings well defined?

o Yes o No o Unclear/ Not reported

24. Is the amount of experience/ training of the persons executing and reading the index tests specified?
o Yes ,……. o No o Unclear/ Not reported

1. Where complications with the index test registered?
o Yes ,……. o No o Unclear/ Not reported

1. Could the conduct or interpretation of the index test have introduced bias?
o Yes ,……. o No o Unclear/ Not reported

1. Are there concerns that the index test, its conduct, or interpretation differ from the review question?
o Yes ,……. o No o Unclear/ Not reported

Index test : 2D SIS

28. Were the index test results interpreted without knowledge of the results of the reference standard?
o Yes o No o Unclear/ Not reported

1. If a threshold was used, was it pre-specified?
o Yes ,……. o No o Unclear/ Not reported

30. Was the execution of the index test described sufficiently to permit replication of the test?
o Yes o No o Unclear/ Not reported

31. Were criteria for different index test findings well defined?
o Yes o No o Unclear/ Not reported

32. Is the amount of experience/ training of the persons executing and reading the index tests specified?
o Yes ,……. o No o Unclear/ Not reported

1. Where complications with the index test registered?
o Yes ,……. o No o Unclear/ Not reported

1. Could the conduct or interpretation of the index test have introduced bias?
o Yes ,……. o No o Unclear/ Not reported

1. Are there concerns that the index test, its conduct, or interpretation differ from the review question?
o Yes ,……. o No o Unclear/ Not reported

Reference standard: hysteroscopy
Target condition: intra uterine abnormality

1. Is the reference standard likely to correctly classify the target condition?
o Yes o No o Unclear/ Not reported

1. Were the reference standard results interpreted without knowledge of the results of the index tests?
o Yes o No o Unclear/ Not reported

1. Did all patients receive the (same) reference standard?
o Yes o No, random sample o No, non random sample o Unclear/ Not reported

1. Could the reference standard, its conduct, or its interpretation have introduced bias?
o Yes o No o Unclear/ Not reported

1. Are there concerns that the target condition as defined by the reference standard does not match the question?
o Yes o No o Unclear/ Not reported

1. Was the target condition specified?
o Yes o No o Unclear/ Not reported

1. If 'Yes', which of the following were reported
o fibroid o polyp o adhesions o endometrial folds
o suspect for malignancy o anomalies o none
oother……..

43. Is the amount of experience/ training of the persons executing and reading the reference test specified?
o Yes ,……. o No o Unclear/ Not reported

Flow and timing

1. Was there an appropriate interval (= less than 3 months (??)) between index test and reference standard?
o Yes o No o Unclear/ Not reported

1. Did all patients receive the same reference standard?
o Yes o No o Unclear/ Not reported

1. Were all patients included in the analysis?
o Yes o No o Unclear/ Not reported

1. Were withdrawals from the study explained?

o Yes o No o Unclear/ Not reported

1. Could the patient flow have introduced bias?

o Yes o No o Unclear/ Not reported

Data extraction

49. Number of study participants

…….....

50. Mean (SD) age of study participants

……..

51. Time interval between index test and reference standard

o < 1month o >1 <3 months o > 3 months o > 6 months

52. Can a 2x2 table be reconstructed?

o Yes o No o Unclear/ Not reported

1. **2x2 table index test 1 :**

	Reference test+	Reference test -	
Index test +			Sens:
Index test -			Spec:
	PPV:	NPV:	

1. **2x2 table index test 2 :**

	Reference test+	Reference test -	
Index test +			Sens:
Index test -			Spec:
	PPV:	NPV:	

1. **2x2 table index test 3 :**

	Reference test+	Reference test -	
Index test +			Sens:
Index test -			Spec:
	PPV:	NPV:	

1. Other measures of accuracy

o Sensitivity……
o Specificity……
o Other……

1. Is interobserver or intraobserver agreement reported?

o Yes o No o Unclear/ Not reported

1. Interobserver……

……

.....

……

……

1. Intraobserver ……...

……

……

……

……

……

Final conclusion

1. Can this study be included in the review?

o Yes o No
If 'No', Reason for exclusion:……..

1. How was agreement for inclusion found?
o Both authors included the study
o Inclusion after discussion and agreement between both authors
o Inclusion after discussion and agreement with a third author

Comments……

……

……

……

……

……

……

……...

CONTRIBUTIONS OF AUTHORS

LL Nieuwenhuis: co-ordinating the protocol, designing search strategies, providing a methodological perspective, writing the protocol.

FJR Hermans: providing a methodological perspective, writing the protocol.

AJM Bij de Vaate: conceiving the protocol, providing general advice on the protocol.

MMG Leeflang: providing a methodological perspective, providing general advice on the protocol.

HAM Brölmann: providing a clinical perspective; providing a policy perspective; providing a consumer perspective, providing general advice on the protocol, performing previous work that was the foundation of the current protocol.

BWJ Mol: providing a clinical perspective; providing a policy perspective; providing a consumer perspective, providing general advice on the protocol.

TJ Clark: providing general advice on the protocol.

JAF Huirne: conceiving the protocol, co-ordinating the protocol, providing a clinical perspective; providing a policy perspective; providing a consumer perspective, providing general advice on the protocol, performing previous work that was the foundation of the current protocol.

DECLARATIONS OF INTEREST

The authors have no conflicts of interest or financial ties to disclose.

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Internal sources

- VU University Medical Center, Netherlands.

Salary for Lotte Nieuwenhuis

External sources

- None, Not specified.