

## Tables

**Table 1 – Characteristics of studies reporting on the detection of structural anomalies in low risk and unselected populations using first trimester ultrasound.**

Notes:

(i). In studies where both TA and TV ultrasound were used, the number in parentheses adjacent to the ultrasound modality refers to the percentage of the study population which received this screening test (when available).

(ii). In studies where aneuploid fetuses were included, the percentage of the study population confirmed by karyotyping as aneuploid was indicated in parentheses (where available).

(iii). The subgroup analysis column identifies the group(s) in which the respective study's data was analyzed.

\* Highlights studies where TV ultrasound was only performed in situations where visualization with TA ultrasound was deemed suboptimal.

\*\*Cardiac exam performed at time of first trimester scan, but cardiac malformations excluded from study analysis.

\*\*\*For the purposes of this review, only the cohort of known euploid fetuses was included in analysis (as insufficient data was provided on the entire cohort reported in the study).

Group	Year	N	Gestation (weeks)	Population	Health-Care Setting	Aneuploid Included?	Index Test	Anatomy Checklist	Cardiac Exam Done?	Subgroup for data Analysis
Achiron <sup>(62)</sup>	1991	800	9-13	Mixed indications: vaginal bleeding, dating and early anomaly screening	Unclear	Yes	TV/TA	Basic	Yes	2
Hernadi <sup>(37)</sup>	1997	3991	11-14	Unselected	Unclear	Yes (0.2%)	TV	Basic	No	1

Bilardo <sup>(25)</sup> (Low risk)	1998	1543	10-14	Consecutive, Singleton pregnancies, Normal NT (<3.0mm),	University Hospital	No	TA/TV	None	Unclear	2
Whitlow <sup>(32)</sup>	1999	6443	11-14 <sup>+6</sup>	Unselected, consecutive recruitment	University Hospital	Yes (0.7%)	TA/ TV(20.1%)	Detailed	Yes	1
Carvalho <sup>(44)</sup>	2002	2853	11-14	Unselected	University Hospital, tertiary care	Yes (0.9%)	TA/TV*	Basic	No**	2
Drysdale <sup>(43)</sup>	2002	917	12-14	Unselected	District General Hospital	Yes	TA/TV	None	No	1
Taipale <sup>(34)</sup>	2003	20,751	11-15 <sup>+6</sup>	Unselected, consecutive recruitment	Local hospital	Yes (0.3%)	TV/ TA(<1%)	Detailed	Yes**	1
McAuliffe <sup>(46)</sup>	2005	325	11-13 <sup>+6</sup>	Unselected	University Hospital, tertiary care	No	TA/TV (24.6%)*	Detailed	Yes	2
Cedergren <sup>(39)</sup>	2006	2708	11-14	Unselected, consecutive recruitment	University Hospital	Yes (0.3%)	TA	None	Unclear	1
Souka <sup>(30)</sup>	2006	1148	11-14	Unselected	Unclear	Yes	TA/TV	Detailed	Yes	1
Saltvedt <sup>(24)</sup>	2006	18053	11 <sup>+5</sup> -13 <sup>+5</sup>	Unselected	Multi- centre (8)	No	TA/TV*	Detailed	Yes	1

Dane <sup>(29)</sup>	2007	1290	11-14	Unselected	Research hospital	Yes	TA/TV	Basic	No	1
Li <sup>(28)</sup>	2008	2232	11-14	Unselected, consecutive recruitment	Unclear	Yes	TA/TV (2.0%)*	None	Unclear	1
Chen <sup>(19)</sup> (Control group)	2008	3693	10-14 <sup>+6</sup>	Unselected, consecutively randomized,	Multi-centre (one university & one regional hospital)	Yes	TA/TV*	None	No	1,2
Chen <sup>(19)</sup> (Study group)	2008	3949	12-14 <sup>+6</sup>	Unselected, consecutively randomized	Multi-centre (One university & one regional hospital)	Yes	TA/TV*	Detailed	Yes	1,2
Oztekin <sup>(42)</sup>	2009	1085	11-14	Unselected	Research hospital	Yes	TA/TV*	Detailed	Yes	1
Hildebrand <sup>(21)</sup>	2010	6692	11-15	Unselected, consecutive recruitment	University Hospital	Yes (0.2%)	TA	None	No	1,2
Abu-Rustum <sup>(38)</sup>	2010	1370	11-13 <sup>+6</sup>	Unselected, retrospective	Private Practice	Yes (4.4%)	TA/TV*	Detailed	Yes	1,2
Syngelaki <sup>(14)</sup>	2011	44,859	11-13 <sup>+6</sup>	Unselected, Retrospective	University Hospital, tertiary care	N	TA/TV(1%)	Detailed	Y	2

Jakobsen <sup>(22)</sup>	2011	9324	11-15	Unselected, Retrospective	University Hospital	Yes	TA/TV*	None	No	1,2
Vavilala <sup>(63)</sup>	2011	7916	11-13+6	Unselected	Tertiary Care	Yes	TA/TV*	Detailed	Yes	1
Grande <sup>(23)</sup>	2012	13723	11-14	Unselected retrospective	Tertiary Care	No	TA/TV	Detailed	Yes	1,2
Pilalis <sup>(27)</sup>	2012	3902	11-14	Unselected, retrospective	Private maternity hospital	Yes	TA/TV	Detailed	No	1
Becker <sup>(64)</sup>	2012	6544	11-13 <sup>+6</sup>	Normal NT ( $\leq$ 95th centile)	University Hospital	Yes (0.6%)*	TA/TV* (23.4%)	Detailed	Yes	1
Iliescu <sup>(41)</sup>	2013	5472	12-13 <sup>+6</sup>	Unselected	Multi-centre (2)	Yes (0.4%)	TA/TV(7.8%)	Detailed	Yes	2
Wang <sup>(33)</sup>	2013	2822	11-14	Not stated	University Hospital	Yes	TA	Detailed	Yes	2
Natu <sup>(26)</sup> (Low Risk)	2014	551	11-14wks	Low risk: age<30, no FH, no co-morbidity	Unclear	Yes	Unclear	Detailed	Yes	2

n – Number of fetuses included in the study population. TA – Transabdominal Ultrasound. TV – Transvaginal Ultrasound. FH – Family history. NT – Nuchal Translucency.

**Table 2 – Characteristics of studies reporting on the detection of all types of fetal structural abnormalities using first trimester ultrasound in high risk pregnancies.**

<b>Group</b>	<b>Year</b>	<b>N</b>	<b>Gestation (weeks)</b>	<b>Population</b>	<b>Health-Care Setting</b>	<b>Aneuploid Included?</b>	<b>Index Test</b>	<b>Anatomy Checklist</b>	<b>Cardiac Exam Done?</b>	<b>Types of Anomalies Included</b>
Pandya <sup>(65)</sup>	1995	565	10-14	Euploid fetuses with raised NT ( $\geq 3.0\text{mm}$ )	University Hospital, tertiary care	No	TA	None	No	Not specified
Bilardo <sup>(25)</sup> (High risk)	1998	47	10-14	Euploid fetuses with raised NT ( $\geq 3.0\text{mm}$ )	University Hospital	No	TA/TV	None	Unclear	Not specified
Den Hollander <sup>(35)</sup>	2002	101	11-14	Women with previously affected infants (92%), fetuses with parental consanguinity	Tertiary care	Yes	TA/TV	Detailed	Yes	Not specified
Chen <sup>(31)</sup>	2004	1609	12-14wks	Women aged $\geq 35$ years	University Hospital	Yes	TA/TV	Detailed	Yes	Not specified
Bronshtein <sup>(45)</sup>	2008	23	11-14wks	Fetuses with raised NT ( $\geq 3.5\text{mm}$ )	Unclear	Yes	TV	Used, but not provided	Yes	All anomalies

Natu <sup>(26)</sup> (High Risk)	2014	496	11-14wks	Mixed indications including age >30, prev. affected child, FHx of anomalies, multiple pregnancy, hx of smoking/ETOH, maternal RF.	Unclear	Yes	Unclear	Detailed	Yes	All anomalies
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n - Number of fetuses included in the study population. NT – Nuchal Translucency. TA – Transabdominal Ultrasound. TV – Transvaginal Ultrasound.

**Table 3 – Summary of results from studies assessing the sensitivity of first trimester ultrasound for the detection of major fetal structural abnormalities in low risk/unselected pregnancies (Subgroup 1)**

Group	Number of Anomalies Present Within Study per 100 fetuses [95% C.I.]	Prevalence of Affected Fetuses within Study Population* (%) [95% C.I.]	Anomalies Detected in 1 <sup>st</sup> Trimester (TP)	Total Anomalies Present in Study (TP+FN)	False Positives Detected during 1 <sup>st</sup> Trimester USS (FP)	Sensitivity of 1 <sup>st</sup> Trimester USS for Anomaly Detection (%) [95% C.I.]	Sensitivity of 1 <sup>st</sup> Trimester USS for Detection of Affected Fetuses* (%) [95% C.I.]	Antenatal Diagnoses Made Within 1st Trimester** (%)
Hernadi	1.30 [0.97-1.71]	1.08 [0.78-1.45]	20	52	NA	38.46 [25.30-52.98]	32.56 [19.08-48.54]	48.78 [32.88-64.87]
Whitlow	1.20 [0.94-1.49]	0.85 [0.64-1.11]	38	77	3	49.35 [37.76-61.00]	52.73 [38.80-66.35]	57.58 [44.79-69.66]
Drysdale	4.14 [2.95-5.64]	2.94 [1.95-4.26]	5	38	1	13.16 [4.41-28.09]	18.52 [6.30-38.08]	11.76 [3.30-27.45]
Taipale	0.34 [0.27-0.43]	0.32 [0.25-0.41]	37	71	2	52.11 [39.92-64.12]	52.24 [39.67-64.60]	NA
Cedergren	1.11 [0.75-1.58]	1.07 [0.72-1.53]	11	30	NA	36.67 [19.93-56.14]	34.48 [17.94-54.33]	NA
Souka	1.30]1 [0.73-2.15]	1.22 [0.67-2.04]	7	15	3	46.67 [21.27-73.41]	50.00 [23.04-76.96]	50.00 [23.04-76.96]
Saltvedt	0.74 [0.62-0.87]	NA	42	133	2	31.58 [23.80-40.20]	NA	34.43 [26.06-43.57]
Dane	2.71 [1.90-3.75]	1.71 [1.07-2.57]	23	35	NA	65.71 [47.79-80.87]	68.18 [45.13-86.14]	71.88 [53.25-86.25]
Li	1.16 [0.76-1.70]	0.99 [0.62-1.49]	13	26	NA	50.00 [29.93-70.07]	54.55 [32.21-75.61]	65.00 [40.78-84.61]
Chen	1.19	0.73	9	44	NA	20.45	29.63	20.45

(Control group)	[0.87-1.60]	[0.48-1.06]				[9.80-35.30]	[13.75-50.18]	[9.80-35.3]
Chen (Study group)	1.75 [1.36-2.21]	1.44 [1.10-1.87]	41	69	NA	59.42 [46.92-71.09]	43.86 [30.74-57.64]	61.19 [48.50-72.86]
Oztekin	1.81 [1.11-2.78]	1.75 [1.06-2.72]	13	20	NA	65.00 [40.78-84.61]	63.16 [38.36-83.71]	72.22 [46.52-90.31]
Hildebrand	0.49 [0.34-0.69]	NA	13	33	NA	39.39 [22.91-57.86]	NA	NA
Abu-Rustum	1.17 [0.67-1.89]	NA	10	16	1	62.50 [35.43-84.80]	NA	66.67 [38.38-88.18]
Jakobsen	1.07 [0.87-1.30]	NA	16	100	NA	16.00 [9.43-24.68]	NA	33.33 [20.40-48.41]
Vavilala	0.99 [0.78-1.23]	NA	69	78	NA	88.46 [79.22-94.59]	NA	NA
Grande	1.39 [1.20-1.60]	1.39 [1.20-1.60]	92	191	NA	48.17 [40.90-55.50]	48.17 [40.90-55.50]	51.11 [43.57-58.62]
Pilalis	1.54 [1.18-1.97]	NA	26	60	NA	43.33 [30.59-56.76]	NA	44.07 [31.16-57.60]
Becker	1.18 [0.93-1.47]	NA	44	77	NA	57.14 [45.35-68.37]	NA	64.71 [52.17-75.92]
Total Included	1.01 [0.95-1.07]	0.93 [0.85-1.00]	529	1165	12	46.10 [36.88-55.46]	45.25 [38.44-52.14]	53.47 [43.42-63.37]

TP – True positives. FP – False Positives, FN – False Negatives. USS – Ultrasound. NA – Not available.

\*Those studies which did not provide data on the number of affected fetuses within their cohorts were not included in the pooled estimates of ‘Prevalence of affected fetuses’ and of ‘Sensitivity of 1<sup>st</sup> trimester USS for detection of affected fetuses’.

\*\*Those studies which only performed one antenatal USS on fetuses during pregnancy were not included in the pooled estimate of ‘Antenatal anomalies diagnosed during the 1<sup>st</sup> trimester’.



Note: The specificity of first trimester ultrasound for major anomaly detection was not calculated due to the small numbers of studies, which provided data on false positive diagnoses.

**Table 4 – Summary of results from studies assessing the sensitivity of first trimester ultrasound for the detection of all types of fetal structural abnormalities in a low risk/unselected pregnancies (Subgroup 2).**

Group	Number of Anomalies Present Within Study per 100 fetuses [95% C.I.]	Prevalence of Affected Fetuses within Study Population* (%) [95% C.I.]	Anomalies Detected in 1 <sup>st</sup> Trimester (TP)	Total Anomalies Present in Study (TP+FN)	False Positives Detected during 1 <sup>st</sup> Trimester USS (FP)	Sensitivity of 1 <sup>st</sup> Trimester USS for Anomaly Detection (%) [95% C.I.]	Sensitivity of 1 <sup>st</sup> Trimester USS for Detection of Affected Fetuses* (%) [95% C.I.]	Antenatal Diagnoses Made with 1st Trimester USS** (%)
Achiron	2.12 [1.24-3.38]	1.50 [0.78-2.61]	8	17	NA	47.06 [22.98-72.19]	50.00 [21.09-78.91]	53.33 [26.59-78.73]
Bilardo (Low risk)	1.56 [1.00-2.31]	1.23 [0.74-1.92]	6	24	NA	25.00 [9.77-46.71]	31.58 [12.58-56.55]	37.50 [15.20-64.57]
Carvalho	4.98 [4.21-5.84]	NA	30	142	NA	21.13 [14.73-28.77]	NA	29.13 [20.59-38.90]
McAuliffe	1.85 [0.68-3.97]	1.85 [0.68-3.97]	1	6	1	16.67 [0.42-64.12]	16.67 [0.42-64.12]	20.00 [0.51-71.64]
Chen (Control)	2.11 [1.67-2.63]	1.41 [1.05-1.84]	9	78	NA	11.54 [5.41-20.78]	15.38 [6.88-28.08]	16.36 [7.77-28.80]
Chen (Study)	2.30 [1.86-2.82]	1.44 [1.10-1.87]	44	91	NA	48.35 [37.74-59.07]	43.86 [30.74-57.64]	61.97 [49.67-73.24]
Abu-Rustum	2.41 [1.66-3.37]	NA	12	33	1	36.36 [20.40-54.87]	NA	37.50 [21.10-56.31]
Hildebrand	1.79 [1.49-2.14]	NA	14	120	NA	11.67 [6.53-18.80]	NA	NA
Syngelaki	1.18 [1.09-1.29]	1.09 [0.99-1.19]	222	531	62	41.81 [37.57-46.13]	43.65 [39.19-48.18]	42.86 [38.55-47.25]

Jakobsen (All)	1.92 [1.65-2.22]	NA	23	179	NA	12.85 [8.32-18.65]	NA	21.90 [14.42-31.03]
Grande (All)	NA	3.18 [2.89-3.48]	NA	NA	NA	NA	22.48 [18.64-26.69]	NA
Iliescu	4.77 [4.22-5.37]	2.98 [2.54-3.46]	132	261	187	50.57 [44.34-56.80]	39.88 [32.30-47.83]	53.44 [47.01-59.79]
Wang	1.24 [0.87-1.72]	0.82 [0.52-1.22]	23	35	3	65.71 [47.79-80.87]	56.52 [34.49-76.81]	69.70 [51.29-84.41]
Natu (Low risk)	0.73 [0.20-1.85]	NA	2	4	0	50.00 [6.76-93.24]	NA	50.00 [6.76-93.24]
Pooled Results	1.81 [1.72-1.90]	1.63 [1.54-1.72]	526	1521	254	32.35 [22.45-43.12]	35.56 [26.27-45.44]	41.10 [32.13-50.38]

TP – True positives. FP – False Positives, FN – False Negatives. USS – Ultrasound. NA – Not available.

Note: The specificity of first trimester ultrasound for major anomaly detection was not calculated due to the small numbers of studies, which provided data on false positive diagnoses.

\*Those studies which did not provide data on the number of affected fetuses within their cohorts were not included in the pooled estimates of ‘Prevalence of affected fetuses’ and of ‘Sensitivity of 1<sup>st</sup> trimester USS for detection of affected fetuses’.

\*\*Those studies which only performed one antenatal USS on fetuses during pregnancy were not included in the pooled estimate of ‘Antenatal anomalies diagnosed during the 1<sup>st</sup> trimester’.

**Table 5 – Summary of results from studies assessing the sensitivity of first trimester ultrasound for the detection of all types of fetal structural abnormalities in high risk pregnancies (Subgroup 3).**

Group	Number of Anomalies Present Within Study per 100 fetuses [95% C.I.]	Prevalence of Affected Fetuses within Study Population* (%) [95% C.I.]	Anomalies Detected in 1 <sup>st</sup> Trimester (TP)	Total Anomalies Present in Study (TP+FN)	False Positives Detected during 1 <sup>st</sup> Trimester USS (FP)	Sensitivity of 1 <sup>st</sup> Trimester USS for Anomaly Detection (%) [95% C.I.]	Sensitivity of 1 <sup>st</sup> Trimester USS for Detection of Affected Fetuses* (%) [95% C.I.]	Antenatal Diagnoses Made with 1st Trimester USS (%)
Pandya	6.37 [4.50-8.71]	5.66 [3.91-7.90]	12	36	NA	33.33 [18.56-50.97]	34.38 [18.57-53.19]	35.29 [19.75-53.51]
Bilardo (High risk)	19.15 [9.15-33.26]	14.89 [6.2-28.31]	2	9	NA	22.22 [2.81-60.01]	28.57 [3.67-70.96]	33.33 [4.33-77.72]
Den Hollander	26.73 [18.41-36.46]	10.89 [5.56-18.65]	20	27	0	74.07 [53.72-88.89]	81.82 [48.22-97.72]	83.33 [62.62-95.26]
Chen	3.42 [2.59-4.43]	1.55 [1.01-2.29]	32	55	5	58.18 [44.11-71.35]	52.00 [31.31-72.20]	64.00 [49.19-7.08]
Bronshtein	94.87 [82.68-99.37]	33.33 [19.09-50.22]	36	37	2	97.30 [85.84-99.93]	100.00 [75.29-100.00]	97.30 [85.84-99.93]
Natu (High Risk)	4.44 [2.80-6.64]	NA	14	22	0	63.64 [40.66-82.80]	NA	63.64 [40.66-82.80]
Pooled Results	6.55 [5.66-7.52]	3.75 [3.02-4.60]	116	186	7	61.18 [37.71-82.19]	62.42 [33.40-87.24]	66.29 [43.47-85.69]

Abbreviations: TP – True positives. FP – False Positives, FN – False Negatives. USS – Ultrasound. NA – Not available.

\*Those studies which did not provide data on the number of affected fetuses within their cohorts were not included in the pooled estimates of ‘Prevalence of affected fetuses’ and of ‘Sensitivity of 1<sup>st</sup> trimester USS for detection of affected fetuses’.

**Table 6 – Summary of Results from Meta-Analysis**

Subgroup	Population/Anomaly Type	Outcomes		
		<b>Number of Anomalies Present Within Study per 100 fetuses [95% C.I.]</b>	<b>Sensitivity of 1<sup>st</sup> Trimester USS for Anomaly Detection (%) [95% C.I.]</b>	<b>Antenatal Diagnoses Made with 1st Trimester USS (%) [95% C.I.]</b>
1	Major Anomalies in a Low Risk/Unselected Population	1.01 [0.95-1.07]	46.10 [36.88-55.46]	53.47 [43.42-63.37]
2	All Types of Anomalies in a Low Risk/Unselected Population	1.81 [1.72-1.90]	32.35 [22.45-43.12]	41.10 [32.13-50.38]
3	All Types of Anomalies in a High Risk Population	6.55 [5.66-7.52]	61.18 [37.71-82.19]	66.29 [43.47-85.69]

Supplement A: Search strategy for systematic review of diagnostic accuracy of first trimester two-dimensional ultrasound for fetal structural abnormalities.

The search was conducted using Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)[OvidSP](1946-present), Embase [OvidSP](1974-2014 July 17), Cochrane Central Register of Controlled Trials [Cochrane Library, Wiley](Issue 6 of 12, 2014), Database of Abstracts of Reviews of Effects [Cochrane Library, Wiley](Issue 2 of 4, 2014), Science Citation Index-Expanded [Web of Science Core Collection, Thomson Reuters](1945-present).

Search #	Searches Conducted	Results
1	Ultrasonography, Prenatal/	24571
2	Prenatal diagnosis/ and exp ultrasonography/	6667
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*).ti,ab.	350062
4	((fetal or foetal or fetus or foetus or prenatal* or pre-nat* or prepart* or pre-part*) adj3 (screen* or scan* or structural assessment* or structural survey*)).ti,ab.	4946
5	1 or 2 or 3 or 4	363227
6	Pregnancy Trimester, First/	13090
7	(1st trimester or first trimester).ti,ab.	17031
8	(early pregnan* or early gestation*).ti,ab.	14840
9	(10 week? or 11 week? or 12 week? or 13 week? or 14 week?).ti,ab.	95426
10	(10week? or 11week? or 12week? or 13week? or 14week?).ti,ab.	535
11	((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week?).ti,ab.	5950
12	6 or 7 or 8 or 9 or 10 or 11	131973
13	exp *Congenital Abnormalities/	368002
14	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal*).ti,ab.	46663
15	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal*).ti,ab.	7081
16	(structural adj2 (defect? or malformation? or abnormalit* or anomal*).ti,ab.	12112
17	((non-chromosomal or nonchromosomal) adj2 (defect? or malformation? or abnormalit* or anomal*).ti,ab.	80
18	13 or 14 or 15 or 16 or 17	405021
19	5 and 12 and 18	2386
20	((fetal or foetal or fetus or foetus) adj (anatomy or defect? or malformation? or abnormalit* or anomal*) adj5 (ultrasound* or	891

	ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.	
21	exp Congenital Abnormalities/us [Ultrasonography]	16703
22	20 or 21	17312
23	12 and 22	1383
24	((early pregnan* or early gestation* or 1st trimester or first trimester) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.	2264
25	((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.	1150
26	((10week? or 11week? or 12week? or 13week? or 14week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.	10
27	((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week? adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.	34
28	24 or 25 or 26 or 27	3332
29	18 and 28	1113
30	19 or 23 or 29	2744
31	limit 30 to "reviews (maximizes specificity)"	44

## Supplement B - QUADAS -2 Assessment Tool:

### Defining the review question:

1. What is the sensitivity of first trimester ultrasound for structural fetal malformations?

Is it a sensitive enough tool for use in daily clinical practice?

2. What factors might impact detection rates?

-Patient selection: pregnant women with gestational age prior to 14 weeks, mothers with all levels of risk and with either singleton or multiple pregnancies were included

-Index Test: Transvaginal and/or Transabdominal 2D Ultrasound prior to 14 weeks gestational age.

-Reference Standard: Postnatal examination of fetus for structural abnormalities, or postmortem of fetus for structural abnormalities.

-Target condition: all types of congenital fetal structural anomalies (lethal, severe, moderate, and minor as defined by the RCOG).

### Domain 1: Patient Selection

A. Risk of Bias : Could the selection of patients have introduced bias?

LOW/HIGH/UNCLEAR

i. Was a consecutive or random sample of patients enrolled?

YES/NO/UNCLEAR

ii. Did the study avoid inappropriate exclusions?

YES/NO/UNCLEAR

B. Applicability

i. Are there concerns that the included patients and setting do not match the review question (i.e. severity of the target condition, demographic features, presence of co-morbidity, setting)?

LOW/HIGH/UNCLEAR



## **Domain 2: Index Test**

A. Risk of Bias - Could the conduct or interpretation of the index test have introduced bias?

LOW/HIGH/UNCLEAR

i. Were sonographers blinded to the history (risk profile) of the patients?

YES/NO/UNCLEAR

ii. Were all major anatomical organs included in the index test examination?

YES/NO/UNCLEAR

iii. Did the study adequately and clearly specify what types of abnormalities were to be assessed by 1<sup>st</sup> term USS?

YES/NO/UNCLEAR

B. Applicability

i. Are there concerns that the index test, its conduct, or interpretation differ from the review question?

LOW/HIGH/UNCLEAR

## **Domain 3: Reference Standard**

A. Risk of Bias – Could the reference standard, its conduct, or its interpretation have introduced bias?

LOW/HIGH/UNCLEAR

i. Was an appropriate reference standard used to correctly classify the target condition?

YES/NO/UNCLEAR

B. Applicability

i. Are there concerns that the target condition as defined by the reference standard does not match the question?

LOW/HIGH/UNCLEAR

## **Domain 4: Flow and Timing**

A. Risk of Bias – Could the patient flow have introduced bias?

LOW/HIGH/UNCLEAR

i. Was a reference standard performed for all appropriate patients enrolled in the study?  
(including post-mortems for still-births/TOPs in those with diagnosed malformations)

YES/NO/UNCLEAR

ii. Were all patients enrolled in the study (and who had complete follow-up data)  
included in the analysis?

YES/NO/UNCLEAR

iii. Were all measures of 1<sup>st</sup> trimester ultrasound detection accuracy (eg. TP, FP, TN, FN)  
reported?

YES/NO/UNCLEAR

Supplement C: Table of studies included and details regarding which subgroup analysis they contributed to:

Chen et al. (2008) <sup>(19)</sup> , Abu-Rustum et al. (2010) <sup>(20)</sup> , Hildebrand et al. (2010) <sup>(21)</sup> , Jakobsen et al. (2011) <sup>(22)</sup> and Grande et al. (2012) <sup>(23)</sup>	Data on fetuses with major abnormalities and on those with a wider range of anomalies were presented, allowing these studies to be analyzed as part of both subgroups 1 and 2.
Saltvedt et al. (2006) <sup>(24)</sup>	Reported on the detection of all types of abnormalities. However, they only provided a breakdown of major abnormalities and as such was evaluated as part of subgroup 1.
Chen et al. (2008) <sup>(19)</sup>	In this prospective randomized control trial, which compared the first term detection rates between a control group (randomized to receive only a nuchal scan at 10-14+6 weeks) and a study cohort (randomized to receive a nuchal scan at 10-14+6 weeks in addition to a detailed anomaly scan at 12-14+6 weeks). We collated data on the two population cohorts of this study separately, as one group had a detailed

	<p>first trimester anomaly scan with the use of an anatomical checklist, whereas the other did not.</p>
<p>Bilardo et al. (1998)<sup>(25)</sup></p>	<p>Provided data on both a cohort of euploid fetuses with normal nuchal scans (low risk) and a cohort of euploid fetuses with raised nuchal translucency (high risk), which were analyzed separately in subgroups 2 and 3 respectively.</p>
<p>Natu et al.(2014)<sup>(26)</sup></p>	<p>Assessed unspecified types of anomalies in both low risk and high risk populations and therefore data from this study was analyzed in both subgroups 2 and 3.</p>