National Institute for Health and Care Excellence

Draft for consultation

Twin and Triplet Pregnancy

[A3] Evidence review for ultrasound screening for twin anaemia polycythaemia sequences

NICE guideline tbc

Evidence reviews

March 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

Contents

Ultrasound screening for Twin Anaemia Polycythaemia Sequences

Review question

What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Introduction

The aim of this review is to determine what is the most accurate screening strategy for complicated, uncomplicated and post laser TAPS in monochorionic twin and triplet pregnancies considering the optimum frequency and gestational age of ultrasound scans.

Summary of the protocol

Table 1 summarises the Population, Index test, Reference standard and Outcome (PIRO) characteristics of this review.

Table 1: Summary of protocol (PIRO table)

Population	**For twin pregnancies:** • Monochorionic diamniotic • Monochorionic monoamniotic **For triplet pregnancies:** • Monochorionic triamniotic • Dichorionic, diamniotic (in relation to the monochorionic pair) • Monochorionic monoamniotic Setting: Secondary or tertiary care centres
Index Test	Ultrasound scan at 16 weeks onwards: • Doppler studies (fetal middle cerebral arterial peak systolic velocity [MCA-PSV]) • Umbilical artery doppler velocity (UA-AREDV) • Ductus venosus atrial systolic velocity (DV-RAV) • Hydrops or fetal effusion or ascites skin oedema The above tests will be considered in isolation or in combination. Details regarding frequency and duration of testing throughout pregnancy presented in included studies will be recorded
Reference Standard	Recognised postnatal diagnostic criteria reference standard for TAPS
Outcome	**Diagnostic value of tests** **Critical outcomes** • Sensitivity (detection rate) • Specificity Sensitivity was regarded as the more important measure for decision making as these are primarily screening diagnostic tests **Important outcomes** • area under curve (AUC)

TAPS: twin anaemia-polycythaemia sequences

For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from March 2017 until March 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Two prospective cohort studies (Fishel-Bartal 2016; Veujoz 2015) and 1 retrospective cohort study (Tollenaar 2018) were included. All studies used ultrasound (US) fetal middle cerebral arterial peak systolic velocity (MCA-PSV) to detect postnatally diagnosed TAPS in monochorionic diamniotic (MCDA) twins, using the reference test of inter-twin haemoglobin (Hb) discordance at birth.

One study (Veujoz 2015) reported sensitivity and specificity based on 9 cases of MCDA twin pregnancies, from an initial 20 cases of TAPS (only 9 cases had MCA-PSV scans within the assigned 48 hour period before birth), assessed prenatally within 48 hours of birth. One study (Tollenaar 2018) reported sensitivity and specificity based on 35 MCDA twins with TAPS, assessed prenatally within one-week of birth. In this study the authors used 2 different cut-offs for ultrasound MCA-PSV discordancy, that is >1.5 and >0.5 multiples of the median.

Another study (Fishel-Bartel 2016) reported area under the curve (AUC) for TAPS based on 69 MCDA twin pregnancies, assessed prenatally within 1 week of birth.

The clinical studies included in this evidence review are summarised in Table 2.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D and GRADE profiles in appendix F.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies for twin pregnancy

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study
Fishel-Bartal 2016 [1] Prospective cohort	N=69/162 [2] MCDA twin pregnancies (138 twins: n=131 neonates	Ultrasound MCA-PSV discordancy: MCA-PSV >1.5 MoM in one twin	Inter-twin Hb difference >8g/dL, combined with reticulocyte count ratio	Diagnostic accuracy of ultrasound MCA-PSV discordancy (AUC)	Fortnightly (every 2 weeks) until complications were noted (for example,

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study
France	analysed [7 excluded due to fetal death or selective reduction])	(anaemic/donor), and concordant decrease MCA-PSV (<1.0) MoM in the co-twin (polycythaemic/ recipient)	>1.7 or finding of infra-millimetric anastomoses		IUGR, discordant fetal growth, fluid volumes, Doppler flow in MCA-PSV), then "surveillance was intensified accordingly" no other detail
Tollenaar 2018 Retrospective cohort The Netherlands	N=35 twins with TAPS, N=45 uncomplicated monochorionic twins	Ultrasound MCA-PSV discordancy: MCA-PSV >1.5 or >0.5 MoM in one fetus (anaemic/donor), and MCA-PSV <1 or >0.5 MoM in the other (polycythaemic/ recipient)	Inter-twin Hb difference >8 g/dL combined with reticulocyte count ratio > 1.7 or finding of minuscule anastomoses (diameter <1.0 mm) on the placental surface, detected through placental colour dye injection	Diagnostic accuracy of ultrasound MCA-PSV discordancy (sensitivity and specificity)	Ultrasound doppler measurement was performed in both twins within 1 week before birth
Veujoz 2015 [1] Prospective cohort France	N=9/20 [3] MCDA twin pregnancies with TAPS	Ultrasound MCA-PSV discordancy: MCA-PSV > 1.5 MoM in one foetus, and MCA-PSV < 1 MoM in the other	Inter-twin Hb difference > 8g/dL, combined with reticulocyte ratio > 1.7 or finding of infra-millimetric anastomoses	Diagnostic accuracy of ultrasound MCA-PSV discordancy (sensitivity and specificity)	Fortnightly (every 2 weeks)

AUC: area under the curve; Hb: haemoglobin; IUGR: intrauterine growth restriction; MCA-PSV: middle cerebral artery peak systolic velocity; MCDA: monochorionic diamniotic; MoM: multiples of the median; N: number of women; TAPS: twin anaemia-polycythaemia sequences

1 In both studies, a proportion were treated 'in utero' using transfusion or laser – it is not clear whether these were reported as no longer having TAPS or as false positives or other method of analysis

2 N=69/162: only 69 MCDA twin pregnancies were analysed out of a total of 162 as the MCA-PSV screening had to be within 1-week before birth for accurate comparison

3 N=9/20: only 9 included in analysis as MCA-PSV screening had to be within 48 hours before birth for accurate comparison

See appendix D for the full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for the full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

See the appendix B for the economic search strategy and appendix G for the economic evidence selection flow chart for further information.

Excluded studies

No economic studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Only sensitivity and specificity values are provided in the evidence statements below. When assessing the diagnostic accuracy of sensitivity and specificity the following thresholds were used: high accuracy: more than 90%; moderate accuracy: 75% to 90%; and, low accuracy: less than 75%. AUC up to 70% are described as having poor ability to discriminate and AUC of 71% and above would be described as having moderate (71 to 80%), good (81 to 90%), or excellent (91 to 100%) ability to discriminate. Estimates are reported for information in appendix D and appendix F. For further details see the methods described in supplement document C.

Sensitivity and Specificity

Very low quality evidence from 1 study (N=9) showed the sensitivity and specificity for prenatal middle cerebral artery peak systolic velocity (MCA-PSV) inter-twin discordancy (MCA-PSV >1.5 multiple of the median [MoM] in 1 fetus; and MCA-PSV <1 MoM in the other) for monochorionic diamniotic (MCDA) twins was 71% (29 to 96) and 50% (1 to 99) to detect TAPS (defined as post-natal Hb inter-twin discordance of >8g/dL and one of: reticulocyte count ratio>1.7, or placenta with only small vascular anastomoses [diameter<1mm]).

Moderate quality evidence from 1 study (N=35 twins with TAPS and N=45 without TAPS) showed that the sensitivity and specificity for prenatal MCA-PSV (MCA-PSV >1.5 MoM in 1 fetus and <1 MoM in another fetus) inter-twin discordancy for MCDA twins was 46% (30 to 62) and 100% (92 to 100) to detect TAPS (defined as an inter-twin haemoglobin difference > 8 g/dL and at least one of the following: reticulocyte count ratio > 1.7 or the presence of minuscule anastomoses (diameter < 1.0 mm) on the placental surface, detected through placental colour dye injection). Very low quality evidence from the same study showed that the sensitivity and specificity for prenatal MCA-PSV (MCA-PSV >0.5 MoM) inter-twin discordancy for MCDA twins was 83% (67 to 93) and 100% (92 to 100).

Area under the curve

Low quality evidence from 1 study (N=69) showed the AUC for prenatal MCA-PSV inter-twin discordancy (MCA-PSV >1.5 MoM in 1 fetus; and MCA-PSV <1 MoM in the other) for MCDA

twins was 87.1% (75.7 to 98.5) to detect TAPS (defined as post-natal Hb inter-twin discordance of >8g/dL and one of: reticulocyte count ratio>1.7 or placenta with only small vascular anastomoses (diameter<1mm)).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Sensitivity and specificity were regarded as critical outcomes, and AUC was an important outcome.

Sensitivity was regarded as the more critical measure (compared to specificity) for decision making, as these tests are primarily screening diagnostic tests. The committee prioritised the diagnostic accuracy measure of sensitivity because it is important to identify women with twin or triplet pregnancy who have TAPS, to potentially treat or manage where possible.

Area under the curve was rated as an important rather than critical outcome because it does not provide precise information on the false positive or false negative rates that would have the biggest impact on patient level outcomes.

The quality of the evidence

The evidence was assessed using modified GRADE criteria. Of the 3 identified studies, 2 studies had very serious risks of bias due to lack of clarity whether the reference standard was interpreted without knowledge of the index tests. There was also uncertainty around the estimate because the populations were small which meant that the evidence was downgraded for imprecision. One study contained a study pre-selected sample (all of the twins had TAPS) and the reference standard was poorly described.

Due to these limitations accuracy outcomes were assessed as very low to moderate quality according to modified GRADE criteria.

Benefits and harms

Simultaneous monitoring

There are several complications that are restricted to monochorionicity (feto-fetal transfusion syndrome and TAPS) and others, such as intrauterine growth restriction, are more common in monochorionic babies. All of these are monitored by ultrasound. The committee highlighted that measurements from one ultrasound would be used to monitor for all complications simultaneously (such as feto-fetal transfusion syndrome, intrauterine growth restriction and TAPS) rather than having separate ultrasound scans for each because they are not mutually exclusive conditions. An explanation about the relative likelihood of each complication and when they can occur during her pregnancy should be given to the woman so that she knows the reasons for the different ultrasound measurements that are taken.

Diagnostic monitoring for TAPS

The committee noted that the evidence base for TAPS was limited by study design (retrospective cohorts, timing of assessment), sample size, and heterogeneity in results. Variation in study design and the small number of studies included, meant meta-analysis was not possible. The evidence was also restricted to only one diagnostic test (MCA-PSV). They therefore had little confidence in the evidence and based their recommendations on their experience and expertise.

The committee discussed whether to make a recommendation against screening for twin anaemia polycythaemia sequence in uncomplicated monochorionic pregnancies. However, they decided against this because the natural history of antenatally diagnosed TAPS based purely on MCA-PSV measurements is unknown. Additionally the evidence showed that the antenatal diagnosis of TAPS based on MCA-PSV measurements has a false positive rate of approximately 17% and therefore may be associated with neonatal morbidity from iatrogenic preterm birth. It was therefore not deemed to be beneficial to screen all monochorionic pregnancies as the risk of unnecessary intervention was high, but to focus on the particular subgroup of twin or triplet pregnancies (those involving monochorionic babies who had additional complications) where risks of all complications (including TAPS) are higher. Despite the large variability in the results, and the low quality of the available evidence, ultrasound using MCA-PSV was deemed potentially useful when compared to no screening at all, in these specific populations. The committee therefore made a recommendation to screen for TAPS in monochorionic twin sets who had additional complications (that had potential to increase the chance of developing TAPS) only.

The committee decided that in cases where there were complicated monochorionic pregnancies it was beneficial to screen for TAPS because the risk of complications including fetal death and neonatal morbidity and mortality would outweigh the harms of intervention including preterm birth and in utero transfusion. Given the seriousness of the outcomes the committee decided that strong recommendations were warranted for this group despite the limited evidence base.

The committee agreed that cases of suspected TAPS should be managed in a tertiary fetal medicine centre. The benefit of managing complicated monochorionic pregnancies in this setting outweighed potential risks of inconvenience of travel and transfer to units away from home.

Further research

The prenatal diagnosis of TAPS is currently based on discordant measurements of the MCA-PSV (>1.5 multiples of the median [MoM] in donors and 8 g/dL), and at least 1 of the following: reticulocyte count ratio >1.7 or minuscule placental anastomoses. However, it is unclear whether these are the most accurate measurements (inter-twin discordancy: MCA-PSV >1.5 MoM in 1 fetus and MCA-PSV <1 MoM in the other; or MCA-PSV inter-twin discordancy >0.5 MoM) because evidence is very limited and the committee's confidence in the evidence was low. The committee therefore drafted a research recommendation which would investigate whether this is the most accurate combination of test measures or whether other additional measures could also be useful (on their own or in combination). The committee agreed that finding an accurate diagnostic test would lead to better detection and potentially earlier treatment. Since there is uncertainty about the accuracy for screening measures for TAPS for all monochorionic twins types (including uncomplicated pregnancies) the committee recommended this research, despite making a strong recommendation for screening using MCA-PSV measurement for those twins who are at greatest risk. For further details related to the research recommendation see appendix L.

Cost effectiveness and resource use

In the absence of any economic evidence or de novo analysis, the committee made a qualitative assessment about the cost effectiveness of screening and diagnostic monitoring for TAPS.

The committee acknowledged that there could be a small resource impact to the NHS arising from their recommendations with a potential increase in the number of assessments and referrals in women with complicated monochorionic pregnancies. However, they thought any resource impact would be relatively small given the small population of women with twin or triplet pregnancy to which the recommendations apply. Furthermore, they considered that the

recommendations would be cost-effective as reductions in the risk of fetal death, neonatal morbidity and mortality from diagnosis and intervention would be worth any costs of detection.

References

Fishel-Bartal 2016

Fishel-Bartal, M, Weisz, B, Mazaki-Tovi, S, *et al*. Can middle cerebral artery peak systolic velocity predict polycythemia in monochorionic-diamniotic twins? Evidence from a prospective cohort study. Ultrasound in Obstetrics & Gynaecology 48 (4): 470-475, 2016

Tollenaar 2018

Tollenaar LSA, Lopriore E, Middeldorp JM, Haak MC, Klumper FJ, Oepkes D, Slaghekke F. Improved antenatal prediction of twin anemia-polycythemia sequence by delta middle cerebral artery peak systolic velocity: a new antenatal classification system. Ultrasound Obstet Gynecol. 2018 Aug 20 [Epub ahead of print]

Veujoz 2015

Veujoz, M, Sananes, N, Severac, F, *et al*. Evaluation of prenatal and postnatal diagnostic criteria for twin anemia-polycythemia sequence. Prenatal Diagnosis 35 (3): 281-8, 2015

Appendices

Appendix A – Review protocols

1.3: Review protocol – diagnostic component for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Table 3: Review protocol for ultrasound screening / diagnostic monitoring for twin anaemia polycythaemia sequences (TAPS)

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?
II	Type of review question	Diagnostic accuracy
III	Objective of the review	To determine what is the most accurate screening strategy for complicated, uncomplicated and post laser TAPS in monochorionic twin and triplet pregnancies considering the optimum frequency and gestational age of ultrasound scans
IV	Eligibility criteria – population/disease/condition/issue/domain	**For twin pregnancies:** • Monochorionic diamniotic • Monochorionic monoamniotic **For triplet pregnancies:** • Monochorionic triamniotic • Dichorionic, diamniotic (in relation to the monochorionic pair) • Monochorionic monoamniotic Setting: Secondary or tertiary care centres
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Index tests** Ultrasound scan at 16 weeks onwards: • Doppler studies (fetal middle cerebral arterial peak systolic velocity [MCA-PSV]) • Umbilical artery Doppler velocity (UA-AREDV) • Ductus venosus atrial systolic velocity (DV-RAV) • Hydrops or fetal effusion or ascites skin oedema The above tests will be considered in isolation or in combination. Details regarding frequency and duration of testing throughout pregnancy presented in included studies will be recorded
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Reference standard** Recognised postnatal diagnostic criteria reference standard for TAPS
VII	Outcomes and prioritisation	Diagnostic value of tests **Critical** • Sensitivity (detection rate) • Specificity Sensitivity was regarded as the more important measure for decision making as these are primarily screening diagnostic tests **Important** • area under curve (AUC)

ID	Field (based on PRISMA-P)	Content
VIII	Eligibility criteria – study design	Systematic reviews of diagnostic accuracy studies Individual diagnostic accuracy studies including • Cross-sectional studies • Cohort studies Prospective cohort studies will be prioritised. If insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered Conference abstracts will not be considered
IX	Other inclusion exclusion criteria	Exclude: • studies that report on quadruplet or higher-order multiple pregnancies • studies that do not report results specifically for twin and/or triplet pregnancies • studies that include <5 pregnant women • structural or chromosomal anomalies • intra-uterine death at study entry Studies where 95% CIs for point estimates are not presented or where 95% CI for point estimates cannot be calculated
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • twin pregnancies • triplet pregnancies **For twin pregnancies:** • Women with uncomplicated TAPS • Women with complicated TAPS • Women who have had feto-fetal transfusion syndrome (FFTS) laser treatment **For triplet pregnancies:** • Women with uncomplicated TAPS • Women with complicated TAPS • Women who have had FFTS laser treatment
XI	Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question (as it has not been prioritised for economic analysis), although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair
XII	Data management (software)	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists Meta-analyses will be performed using Cochrane Review Manager (RevMan5) and WinBUGS if available data permit

ID	Field (based on PRISMA-P)	Content
		A modified 'GRADE' method will be used to assess the quality of evidence for each index test. A full description of this is provided in the methods in supplementary material C
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Consider cut-off dates if an update Date limit searches: 2005
XIV	Identify if an update	This is not an update of a review
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or H (economic evidence tables)
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix G (clinical evidence tables) or H (economic evidence tables)
XX	Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • QUADAS II for cross sectional or cohort studies reporting diagnostic outcomes For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXII	Methods for analysis – combining studies and exploring (in)consistency	A full description of this is provided in the methods in supplementary material C
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014

ID	Field (based on PRISMA-P)	Content
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Anthony Pearson in line with section 3 of Developing NICE guidelines: the manual 2014 Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. A full description of this is provided in the methods in supplementary material C
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Appendix B – Literature search strategies

Literature search for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Clinical searches

Date of initial search: 03/04/18

Database(s): Embase Classic+Embase 1947 to 2018 April 02, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase Classic+Embase 1947 to 2018 September 06, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emczd
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic* or dichorionic* or trichorionic*).tw.
5	Diseases in Twins/ use ppez
6	exp twins/ use emczd
7	or/1-6
8	Polycythemia/ use ppez
9	(Anemia/ and Placenta/) use ppez
10	polycythemia/ use emczd
11	(anemia/ and placenta/) use emczd
12	twin anemia polycythemia sequence/ use emczd
13	TAPS.tw.
14	or/8-13
15	7 and 14
16	twin* an?emi* polycyth?emi* sequence*.tw.
17	twin* an?emia*.tw.
18	15 or 16 or 17
19	Letter/ use ppez
20	letter.pt. or letter/ use emczd
21	note.pt.
22	editorial.pt.
23	Editorial/ use ppez
24	News/ use ppez
25	exp Historical Article/ use ppez
26	Anecdotes as Topic/ use ppez
27	Comment/ use ppez

#	Searches
28	Case Report/ use ppez
29	case report/ or case study/ use emczd
30	(letter or comment*).ti.
31	or/19-30
32	randomized controlled trial/ use ppez
33	randomized controlled trial/ use emczd
34	random*.ti,ab.
35	or/32-34
36	31 not 35
37	animals/ not humans/ use ppez
38	animal/ not human/ use emczd
39	nonhuman/ use emczd
40	exp Animals, Laboratory/ use ppez
41	exp Animal Experimentation/ use ppez
42	exp Animal Experiment/ use emczd
43	exp Experimental Animal/ use emczd
44	exp Models, Animal/ use ppez
45	animal model/ use emczd
46	exp Rodentia/ use ppez
47	exp Rodent/ use emczd
48	(rat or rats or mouse or mice).ti.
49	or/36-48
50	18 not 49
51	limit 50 to english language
52	remove duplicates from 51

Date of initial search: 03/04/2018

Database(s): The Cochrane Library, issue 4 of 12, April 2018

Date of updated search: 06/09/2018

Database(s): The Cochrane Library, issue 9 of 12, September 2018

ID	Search
#1	MeSH descriptor: [Pregnancy, Multiple] explode all trees
#2	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) near/3 (birth* or pregnan* or gestation* or foetus* or fetus or foetal or fetal))
#3	(chorionicity or monochorionic or dichorionic or trichorionic)
#4	MeSH descriptor: [Diseases in Twins] this term only
#5	MeSH descriptor: [Twins] explode all trees
#6	{or #1-#5}
#7	MeSH descriptor: [Polycythemia] this term only
#8	MeSH descriptor: [Anemia] this term only
#9	MeSH descriptor: [Placenta] this term only

ID	Search
#10	#8 and #9
#11	#7 or #10
#12	#6 and #11
#13	(twin* anemia* polycythemia* sequence*)
#14	(twin* anaemia* polycythaemia* sequence*)
#15	(twin* anemia* or twin* anaemia*)
#16	{or #12-#15}

Health Economics Searches

(For the Cochrane Library, see above)

Date of initial search: 04/04/18

Database(s): Embase Classic+Embase 1947 to 2018 April 03, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase Classic+Embase 1947 to 2018 September 06, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emczd
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic* or dichorionic* or trichorionic*).tw.
5	Diseases in Twins/ use ppez
6	exp twins/ use emczd
7	or/1-6
8	Polycythemia/ use ppez
9	(Anemia/ and Placenta/) use ppez
10	polycythemia/ use emczd
11	(anemia/ and placenta/) use emczd
12	twin anemia polycythemia sequence/ use emczd
13	TAPS.tw.
14	or/8-13
15	7 and 14
16	twin* an?emi* polycyth?emi* sequence*.tw.
17	twin* an?emia*.tw.
18	15 or 16 or 17
19	Letter/ use ppez

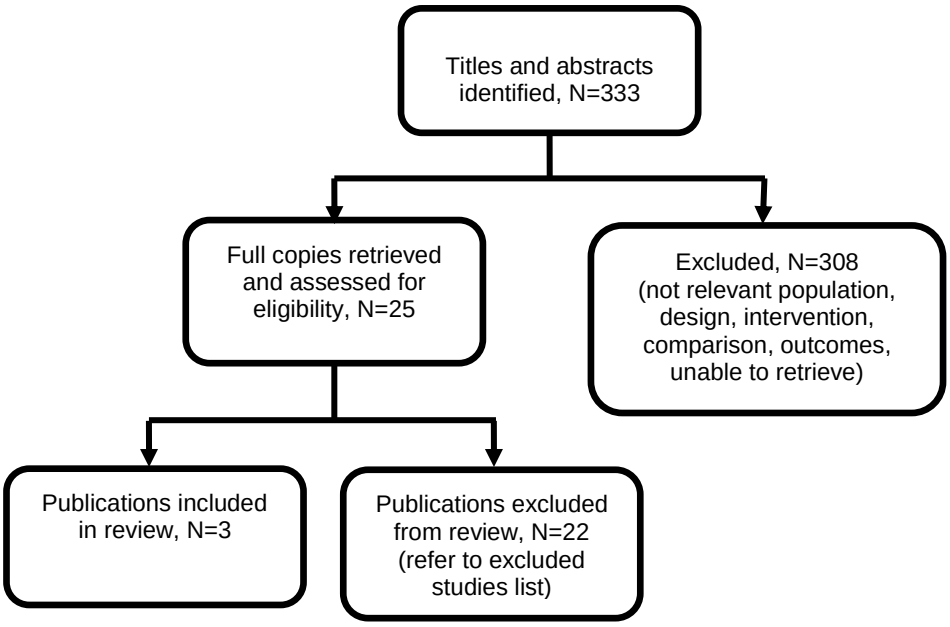
#	Searches
20	letter.pt. or letter/ use emczd
21	note.pt.
22	editorial.pt.
23	Editorial/ use ppez
24	News/ use ppez
25	exp Historical Article/ use ppez
26	Anecdotes as Topic/ use ppez
27	Comment/ use ppez
28	Case Report/ use ppez
29	case report/ or case study/ use emczd
30	(letter or comment*).ti.
31	or/19-30
32	randomized controlled trial/ use ppez
33	randomized controlled trial/ use emczd
34	random*.ti,ab.
35	or/32-34
36	31 not 35
37	animals/ not humans/ use ppez
38	animal/ not human/ use emczd
39	nonhuman/ use emczd
40	exp Animals, Laboratory/ use ppez
41	exp Animal Experimentation/ use ppez
42	exp Animal Experiment/ use emczd
43	exp Experimental Animal/ use emczd
44	exp Models, Animal/ use ppez
45	animal model/ use emczd
46	exp Rodentia/ use ppez
47	exp Rodent/ use emczd
48	(rat or rats or mouse or mice).ti.
49	or/36-48
50	18 not 49
51	limit 50 to english language
52	remove duplicates from 51
53	Economics/
54	Value of life/
55	exp "Costs and Cost Analysis"/
56	exp Economics, Hospital/
57	exp Economics, Medical/
58	Economics, Nursing/
59	Economics, Pharmaceutical/
60	exp "Fees and Charges"/
61	exp Budgets/
62	(or/53-61) use ppez
63	health economics/

#	Searches
64	exp economic evaluation/
65	exp health care cost/
66	exp fee/
67	budget/
68	funding/
69	(or/63-68) use emczd
70	budget*.ti,ab.
71	cost*.ti.
72	(economic* or pharmaco?economic*).ti.
73	(price* or pricing*).ti,ab.
74	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
75	(financ* or fee or fees).ti,ab.
76	(value adj2 (money or monetary)).ti,ab.
77	or/70-75
78	62 or 69 or 77
79	52 and 78

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Figure 1: Flow diagram of clinical article selection for the optimal screening programme to detect TAPS in twin and triplet pregnancy



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
Full citation Fishel-Bartal, M, Weisz, B, Mazaki-Tovi, S, Ashwal, E, Chayen, B, Lipitz, S, Yinon, Y., Can middle cerebral artery peak systolic velocity predict polycythemia in monochorionic-diamniotic twins? Evidence from a prospective cohort study, Ultrasound in Obstetrics & Gynaecology, 48, 470-475, 2016 **Ref Id** 794778 **Country/ies where the study was carried out** Israel	**Sample size** n=69/162 MCDA twin pregnancies (138 twins) scanned within one week of birth n=131 neonates analysed (7 excluded due to fetal death or selective reduction) **Characteristics** Characteristics based on n=69 MCDA twin pregnancies - presented as median (range) Maternal age: 32.4 (22-43) years Parity: 2.4 (1-8) GA at birth: 33.6 (24.6-38.3) weeks	**Tests** **Index test:** Ante-natal diagnosis of TAPS: US MCA-PSV discordancy >1.5 MoM in one twin (anaemic donor) and concordant decrease (<1.0) in the co-twin (polycythaemic recipient). NB: Lower cut-off reported at both <0.8 MoM and <1.0 MoM **Reference Standard:** Post-natal diagnosis of TAPS: inter-twin Hb difference >8g/dL, and elevated reticulocyte count ratio in anaemic twin >1.7 (described by Lopriore 2010, Slaghekke 2010) or	**Methods** Identifying appropriate population: first trimester US to determine chorionicity. Fortnightly (every 2 weeks) assessment from 18 weeks GA: standard biometry for fetus size and age; amniotic fluid volume per sac; anatomical survey to exclude morphological anomalies; Doppler flow at umbilical artery, MCA-PSV, ductus venosus. MCA-PSV measurement: MCA located using colour or power Doppler US. Insonation angle close to 0 degrees (never >30 degrees). Sample volume placed close to internal fetal carotid artery. 1.5 MoM used as cut-off for moderate or severe fetal anaemia. Management uncomplicated MCDA pregnancies:	**Results** MCDA cases assessed within one week of birth: n=69 TAPS: n=9 (n=2/9 post-laser, n=7/9 spontaneous) n=6/9 diagnosed prenatally by US MCA-PSV n=4/6 managed expectantly, n=2/6 treated with intrauterine blood transfusion In TAPS group: n=6 polycythaemic twins MCA-PSV <1 MoM, n=2 <0.8 MoM TAPS AUC =0.871 95%CI [0.757,0.985], n=9 – described as "*good performance*"	**Limitations** **QUADAS-II** **A. Risk of Bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK LOW **B. Concerns regarding applicability** Is there concern that the included patients do not match the review question? CONCERN: Low

Study type Prospective cohort study **Aim of the study** Assess whether fetal MCA-PSV can predict polycythaemia in MCDA twin pregnancies **Study dates** January 2011 - June 2014 **Source of funding** Not reported	Birth <32 weeks: n=11 (15.9%) Birth weight: 1878 (460-3445) grams Pregnancy complications: Uncomplicated: n=30 (43.5%); TTTS: n=17 (24.6%); selective IUGR: n=13 (18.8%) TAPS: n=9 (13.0%) (n=2/9 post-laser, n=7/9 spontaneous) TAPS: n=6/9 diagnosed prenatally by US MCA-PSV n=4/6 managed expectantly, n=2/6 treated with intrauterine blood transfusion **Inclusion Criteria** All MCDA twin pregnancies recruited at 14-16 weeks gestation from a single tertiary care centre. **Exclusion Criteria** None reported (but 7 neonates were excluded from some analyses when one or both twins	finding of infra millimetric anastomoses	antenatal evaluation every 2 weeks until complications were noted (e.g. IUGR, discordant fetal growth, fluid volumes, Doppler flow in MCA-PSV) when "surveillance *was intensified accordingly*" No other detail was reported.		Index test (pre-natal MCA-PSV US measurement) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? RISK: LOW **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **Reference Standard** **A. Risk of Bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct, or its

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
	had fetal death or selective reduction).				interpretation have introduced bias? RISK: LOW **B. Concerns regarding applicability** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test(s) and reference standard? Yes - data analysed from n=69 MCDA cases (for AUC), the MCA-PSV measurement was less than one week before birth Did all patients receive a reference standard? No - only 131/138 neonates had reference standard and index test available (7 babies died in utero) Did patients receive the same reference standard? Yes Were all patients included in the analysis? unclear - n=69 cases of MCDA twin

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
					pregnancies, but 7 neonates were excluded from analysis, and so unclear how many complete twin sets were in final analysis for TAPS Could the patient flow have introduced bias? RISK: UNCLEAR
Full citation Tollenaar LSA, Lopriore E, Middeldorp JM, Haak MC, Klumper FJ, Oepkes D, Slaghekke F. Improved antenatal prediction of twin anemia-polycythemia sequence by delta middle cerebral artery peak systolic velocity: a new antenatal classification system. Ultrasound Obstet Gynecol. 2018 Aug 20 [Epub ahead of print] **Ref Id** 898051 **Country/ies where the study was carried out**	**Sample size** N=35 MCDA twins with TAPS and N=45 without TAPS scanned within 1 week of birth **Characteristics** GA at birth (median (IQR)): TAPS group = 32 (29-34), no TAPS group = 35 (33-36); Birthweight discordance (%, median (IQR)): TAPS group = 14.5 (7.9-20.8), no TAPS group = 11.6 (5.9-17.3); Birthweight discordance (≥20%, n/N): TAPS group = 12/35 (34), no TAPS group = 4/45 (9); Inter-twin Hb difference (g/dL, median (IQR)): TAPS group = 12.7	**Tests** **Index test:** US MCA-PSV discordancy: MCA-PSV > 1.5 or >0.5 MoM in 1 fetus (anaemic/donor), and MCA-PSV <1 or >0.5 MoM in the other (polycythaemic/ recipient) **Reference standard:** Post-natal diagnosis of TAPS: inter-twin Hb difference >8 g/dL combined with reticulocyte count ratio >1.7 or finding of minuscule anastomoses (diameter <1.0 mm) on the placental surface, detected through placental colour dye injection	**Methods** All consecutive uncomplicated MCDA twin pairs, and those with post-natal TAPS, managed between 2003 and 2017 in the Dutch national referral centre for fetal therapy were included in this study. Cases in which MCA-PSV US Doppler measurements were performed in both fetuses within 1 week before birth were included in the analysis. The postnatal diagnosis of TAPS was based on an inter-twin Hb difference >8 g/dL and at least 1 of the following: reticulocyte count ratio >1.7 or the presence of minuscule anastomoses (diameter <1.0 mm) on the placental surface, detected through	**Results** Pre-natal US MCA-PSV discordancy (MCA-PSV >1.5 MoM in 1 fetus; and MCA-PSV <1 MoM in the other): sensitivity (95% CI): 46% (30-62), specificity (95% CI): 100% (92-100) Pre-natal US MCA-PSV discordancy (>0.5 MoM): sensitivity (95% CI): 83% (67-93), specificity (95% CI): 100% (92-100)	**Limitations** **QUADAS-II** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: LOW **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
The Netherlands **Study type** Retrospective cohort study **Aim of the study** To investigate the predictive value of delta MCA-PSV >0.5 MoM compared to cut-off values (>1.5 MoM in the donor and <1.0 MoM in the recipient for the diagnosis of TAPS **Study dates** 2003–2017 **Source of funding** Not reported	(10.8-15.1), no TAPS group = 1.2 (0.3-3.6) **Inclusion criteria** Cases in which MCA-PSV US Doppler measurements were performed in both fetuses within 1 week before birth. **Exclusion criteria** Cases with incomplete postnatal Hb values were excluded from the analysis.		placental colour dye injection. MCA-PSV values were retrospectively obtained from obstetric records. MCA-PSV was measured according to the technique described by Mari et al. 2000. Reference ranges for MCDA twin pregnancies published by Klaritsch et al. 2009 were used to convert MCA-PSV (cm/s) values to MoM. When twins exceeded both cut-off values, i.e. >1.5 MoM in one twin and <1.0 MoM in the co-twin, this was named a 'cut-off MCA-PSV diagnosis'. In case of an inter-twin difference in MCA-PSV >0.5 MoM, the term "delta MCA-PSV >0.5 MoM diagnosis" was used.		do not match the review question? CONCERN: LOW **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
					knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: UNCLEAR **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? CONCERN: LOW **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW
Full citation Veujoz, M, Sananes, N, Severac, F, Meyer,	**Sample size** n = 20 (maternal) cases of TAPS: N=10	**Tests** **Reference standard**	**Methods** Every MCDA pregnancy managed at the centre within	**Results** Sensitivity and specificity values based on only N=9	**Limitations** **QUADAS-II** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
N, Weingertner, A. S, Kohler, M, Guerra, F, Gaudineau, A, Nisand, I, Favre, R., Evaluation of prenatal and postnatal diagnostic criteria for twin anemia-polycythemia sequence, Prenatal Diagnosis, 35, 281-8, 2015 **Ref Id** 795698 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Aim of the study** Analyse the pre-natal and post-natal diagnostic parameters of TAPS (twin anaemia-polycythaemia sequence) Compare diagnostic parameters between	spontaneous, N=10 iatrogenic (post-laser) TAPS Sensitivity and specificity values based on only N=9 out of all 20 cases, all of whom had TAPS - though some were treated in utero (N=433 MCDA twin pregnancy during the inclusion period, 4.6% incidence rate) **Characteristics** Characteristics unavailable for sample used for this review, so all N=20 cases described below Total (spontaneous + iatrogenic TAPS): Maternal (N=20) and pre-natal diagnostic (N=17) data Maternal age: 29.3±4 years Null parity: 9/20 (45%) GA at diagnosis: 174±41 days	Postnatally: inter-twin Hb difference > 8g/dL, combined with reticulocyte ratio > 1.7, or finding of infra-millimetric anastomoses Index test (antenatal Ultrasound) Absence of TOPS with MCA-PSV > 1.5 multiple of the median (MoM) in one fetus (anaemic/donor), and MCA-PSV < 1 MoM in the other (polycythaemic/recipient) - using the MCA-PSV measurement technique described by Mari et al (2000), using Voluson 730 or E8 General Electric devices. Nomograms (established by Mari et al, 1995) were used to calculate MoM from MCA-PSV. Every MCDA pregnancy had an US every 2 weeks to check for symptoms/signs of complications	the test period had an US every 2 weeks (fortnightly) to check for symptoms/signs of complications, such as TTTS and TAPS. Case management when TAPS diagnosed in utero/antenatally: Before 32 weeks' GA: If TAPS was diagnosed using the pre-natal test (US of MCA-PSV), treatment was offered in utero for TAPS Stage 3 or 4, and aggressive Stage 1 or 2 (intervention: fetoscopy with laser coagulation of placental anastomoses, or in utero transfusion). Follow-up ultrasound performed at 24 hours, 48 hours, 1 week, and fortnightly post-operatively. After 32 weeks' GA: If TAPS was diagnosed using the pre-natal test (ultrasound of MCA-PSV), treatment was expectant management or birth. Measurement for outcome measures (including diagnostic accuracy):	out of all 20 cases, all of whom had TAPS - though may have been treated in utero (N=433 MCDA twin pregnancy during the inclusion period, 4.6% incidence rate) Sensitivity: 71% 95%CI [0.29, 0.96]* Specificity: 50% 95%CI [0.01, 0.99]* TP=5, FP=1, TN=1, FN=2, total N=9 *calculated by NGA team based on information provided within the paper	**Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: LOW **B. Concerns regarding applicability** Patient characteristics and setting. Are there concerns that the included patients and setting do not match the review question? CONCERN: HIGH-sensitivity and specificity values based on only n=9 out of all 20 cases, all of whom had TAPS Index test (pre-natal MCA-PSV US measurement) **Index Test** **A. Risk of Bias** Were the index test results interpreted without

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
spontaneous and post-laser (iatrogenic) TAPS **Study dates** December 2006 - August 2013 **Source of funding** Not reported	Anaemic MCA-PSV at diagnosis (MoM): 1.8±0.3 Polycythaemic MCA-PSV at diagnosis (MoM): 0.7±0.1 Neonatal data: N=17 cases, 34 children (3 cases excluded from post-natal analysis due to in utero fetal demise of one (N=2) or both fetuses (N=1)) Live births: 19 polycythaemic (or formerly polycythaemic), and 16 anaemic (or formerly anaemic) infants GA at birth: 225±13 days Anaemic body weight: 1370±384 grams Polycythaemic body weight: 1628±386 grams Anaemic Hb: 9.2±4.8 g/dL Polycythaemic Hb: 19.5±3.8 g/dL Reticulocyte ratio: 1.30±0.57 No TAPS: 6/17 (35.3%) - these cases may or may		US measurement: used MCA-PSV measurements from before in utero transfusion, or within the 48 hours before birth. Hb assay: used sample taken during each in utero transfusion procedure, and at birth		knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? RISK: LOW **B. Concerns regarding applicability** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **Reference Standard** **A. Risk of Bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
	not be included in the analysis presented, due to unclear reporting **Inclusion Criteria** All MCDA twin pregnancies complicated by TAPS, diagnosed prenatally or postnatally, managed at the Strasbourg University Teaching Hospitals between December 2006 and August 2013. Selected diagnostic criteria: Prenatally: Absence of TOPS with MCA-PSV> 1.5 multiple of the median (MoM) in 1 fetus (anaemic/donor), and MCA-PSV <1 MoM in the other (polycythaemic/recipient) Postnatally: inter-twin Hb difference >8g/dL, combined with reticulocyte count ratio >1.7, or finding of infra-millimetric anastomoses Cases with Hb inclusion criteria, but no other post-natal criteria were also included in the study				Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: HIGH - Cases with Hb inclusion criteria, but no other post-natal criteria were also included in the study if there was "a strong clinical impression including no evidence for an acute peripartum TTTS (characterised by normal reticulocyte count for anaemic twin and constant presence of superficial anastomoses)" **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test(s) and reference standard? Yes- data analysed from n=9 patients (for specificity and sensitivity), the MCA-PSV measurement was less than 48 hours before birth Did all patients receive a reference standard? No - only 9/20 had reference

Bibliographic details	Participants	Tests	Methods	Outcomes and Results	Comments
	if there was "*a strong clinical impression including no evidence for an acute peripartum TTTS (characterised by normal reticulocyte count for anaemic twin and constant presence of superficial anastomoses)*" **Exclusion Criteria** None reported				standard and index test available Did patients receive the same reference standard? Yes - but interpretation of reference standard may have varied (see Reference Standard B) Were all patients included in the analysis? No - 20 original cases, 17 included in postnatal assessment, 9 cases analysed for diagnostic accuracy Could the patient flow have introduced bias? RISK: HIGH

AUC: area under the curve; CI: confidence interval; GA: gestational age; Hb: haemoglobin; IQR: interquartile range; MCA-PSV: middle cerebral artery peak systolic velocity; MCDA: monochorionic diamniotic; MoM: multiples of the median; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; TAPS: twin anaemia polycythaemia sequences; TOPS: twin oligo-polyhydramnios sequence; US: ultrasound

Appendix E – Forest plots

Forest plots for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

No forest plots were included in this review.

Appendix F – GRADE tables

GRADE profile for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Table 4: Clinical evidence profile for screening to identify TAPS in twin pregnancy in the second trimester

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95% CI)	Quality of the evidence (GRADE)	Importance
TAPS defined as post-natal inter-twin Hb discordance											
Pre-natal US MCA-PSV discordancy (MCA-PSV >1.5 MoM in 1 fetus; and MCA-PSV <1 MoM in the other)	1	9 twin sets	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	71% (29 to 96)	50% (1 to 99)	-	⨁⊖⊖⊖ VERY LOW	CRITICAL
Pre-natal US MCA-PSV discordancy (MCA-PSV >1.5 MoM in 1 fetus; and MCA-PSV <1 MoM in the other)	1	35 twins with TAPS and 45 without TAPS	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	46% (30 to 62)	100% (92 to 100)	-	⨁⨁⨁⊖ MODERATE	CRITICAL
Pre-natal US MCA-PSV discordancy (>0.5 MoM)	1	35 twins with TAPS and 45 without TAPS	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[3]	83% (67 to 93)	100% (92 to 100)	-	⨁⊖⊖⊖ VERY LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95% CI)	Quality of the evidence (GRADE)	Importance
TAPS defined as post-natal inter-twin Hb discordance											
Pre-natal US MCA-PSV discordancy (MCA-PSV >1.5 MoM in 1 fetus; and MCA-PSV <1 MoM in the other)	1	69 twin sets	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	-	-	0.871 (0.757 to 0.985)	⨁⨁⨀⨀ LOW	IMPORTANT

AUC: area under the curve; CI: confidence interval; Hb: haemoglobin; MCA-PSV: middle cerebral artery peak systolic velocity; MID: minimally important difference; MoM: multiples of the median; N: number of women; QUADAS-2: Quality Assessment Tool for Diagnostic Accuracy Studies 2; TAPS: twin anaemia-polycythaemia sequence; US: ultrasound

1 The quality of the evidence was downgraded by 2 levels because: 3 areas with high risk of bias (patient selection (part B); reference standard (part B); flow and timing – based on QUADAS2

2 The quality of the evidence was downgraded by 1 level because: Indirectness in Populations - the use of n=20 TAPS cases as complete population, when this is really the subset, and the target population should be all monochorionic diamniotic twin pregnancies to determine diagnostic accuracy of the US MCA-PSV test

3 The judgement of precision was based on the CI of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results are judged to be very seriously imprecise

4 Unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

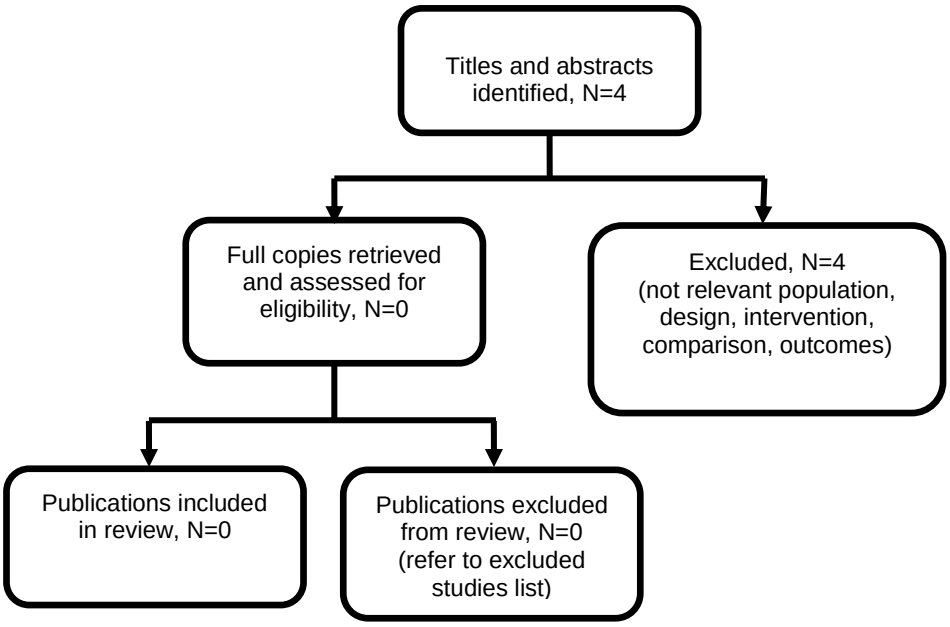
5 The quality of the evidence was downgraded by 2 levels for imprecision as the 95%CI crossed 2 thresholds above and below the estimate (AUC 80% and AUC 90%)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Figure 2: Flow diagram of economic article selection for the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix J –Economic analysis

Economic analysis for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Clinical studies

Study	Reason for Exclusion
Ashwal, E., Yinon, Y., Fishel-Bartal, M., Tsur, A., Chayen, B., Weisz, B., Lipitz, S., Twin Anemia-Polycythemia Sequence: Perinatal Management and Outcome, Fetal Diagnosis and Therapy, 40, 28-34, 2016	No relevant diagnostic accuracy data reported. The article describes the management and short-term neonatal outcomes in monochorionic twins with twin anaemia polycythaemia sequence (TAPS)
Bamberg, C, Diemert, A, Glosemeyer, P, Hecher, K., Quantified discordant placental echogenicity in twin anemia-polycythemia sequence (TAPS) and middle cerebral artery peak systolic velocities, Ultrasound in Obstetrics & Gynecology, 27, 27, 2017	No relevant diagnostic accuracy data reported. The article examines sonographic placental echogenicity in TAPS and its correlation with doppler middle cerebral artery peak systolic velocity (MCA-PSV) findings in twins
Baschat, A. A, Oepkes, D., Twin anemia-polycythemia sequence in monochorionic twins: implications for diagnosis and treatment, American Journal of Perinatology, 31 Suppl 1, S25-30, 2014	A narrative article about the pathophysiology, diagnosis, and management of TAPS
Gucciardo, L., Lewi, L., Vaast, P., Debska, M., De Catte, L., Van Mieghem, T., Done, E., Devlieger, R., Deprest, J., Twin anemia polycythemia sequence from a prenatal perspective, Prenatal Diagnosis, 30, 438-442, 2010	No relevant diagnostic accuracy data reported. The article describes the prevalence, management and outcome of TAPS in monochorionic twin pregnancies. Also includes a description of 3 cases.
Ishii, K., Murakoshi, T., Hayashi, S., Matsuoka, K., Sago, H., Matsushita, M., Shinno, T., Naruse, H., Torii, Y., Anemia in a recipient twin unrelated to twin anemia-polycythemia sequence subsequent to sequential selective laser photocoagulation of communicating vessels for twin-twin transfusion syndrome, Prenatal Diagnosis, 28, 262-263, 2008	Case report
Lopriore, E, Slaghekke, F, Oepkes, D, Middeldorp, J. M, Vandenbussche, F. P, Walther, F. J., Hematological characteristics in neonates with twin anemia-polycythemia sequence (TAPS), Prenatal Diagnosis, 30, 251-5, 2010	No ultrasound / doppler (index) tests
Lucewicz, A, Fisher, K, Henry, A, Welsh, A. W., Review of the correlation between blood flow velocity and polycythemia in the fetus, neonate and adult: appropriate diagnostic levels need to be determined for twin anemia-polycythemia sequence, Ultrasound in Obstetrics & GynecologyUltrasound Obstet Gynecol, 47, 152-7, 2016	Systematic review - references checked for relevance to protocol
McDonald, R, Hodges, R, Knight, M, Teoh, M, Edwards, A, Neil, P, Wallace, E. M, DeKoninck, P., Optimal Interval between Ultrasound Scans for the Detection of Complications in Monochorionic Twins, Fetal Diagnosis & Therapy, 41, 197-201, 2017	n=2 TAPS, cannot separate TAPS data from other "complications" aimed to compare monochorionic diamniotic (MCDA) twins at the research institution with and without twin-twin transfusion syndrome (TTTS),

Study	Reason for Exclusion
	selective intrauterine growth restriction (IUGR), TAPS and fetal demise, and then examine whether their antenatal ultrasound surveillance differed
Nakayama, S, Ishii, K, Kawaguchi, H, Yamamoto, R, Murata, M, Hayashi, S, Mitsuda, N., Perinatal complications of monochorionic diamniotic twin gestations with discordant crown-rump length determined at mid-first trimester, Journal of Obstetrics & Gynaecology Research, 40, 418-23, 2014	The article examines the value of discordance of crown rump length at mid-first trimester to predict adverse outcomes in twin gestations
Pappas, A., Delaney-Black, V., Differential diagnosis and management of polycythemia, Pediatric Clinics of North America, 51, 1063-1086, 2004	A narrative review on the differential diagnosis, clinical presentation and management of neonatal polycythaemia
Robyr,R., Lewi,L., Salomon,L.J., Yamamoto,M., Bernard,J.P., Deprest,J., Ville,Y., Prevalence and management of late fetal complications following successful selective laser coagulation of chorionic plate anastomoses in twin-to-twin transfusion syndrome, American Journal of Obstetrics and Gynecology, 194, 796-803, 2006	Not diagnostic, cases reported for sensitivity use in utero or at birth diagnosis (instead of reference test of US postnatally)
Rossi, A. C, Prefumo, F., Perinatal outcomes of twin anemia-polycythemia sequence: a systematic review, Journal of Obstetrics & Gynaecology Canada: JOGCJ Obstet Gynaecol Can, 36, 701-7, 2014	Systematic review of case series - references checked for relevant studies
Sen, D, Newcastle twin antenatal programme (TAP) an RCT study, National research register, 2003	Not relevant question as the study is examining whether a complex intervention involving attendance at a twin clinic and provision of additional antenatal education, information, and support by a specialist midwife improve psychosocial outcomes after twin birth.
Slaghekke, F, Kist, W. J, Oepkes, D, Pasman, S. A, Middeldorp, J. M, Klumper, F. J, Walther, F. J, Vandenbussche, F. P, Lopriore, E., Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome, Fetal Diagnosis & Therapy, 27, 181-90, 2010	A narrative review on the pathogenesis, incidence, diagnostic criteria, management options and outcome in TAPS
Slaghekke, F, Pasman, S, Veujoz, M, Middeldorp, J. M, Lewi, L, Devlieger, R, Favre, R, Lopriore, E, Oepkes, D., Middle cerebral artery peak systolic velocity to predict fetal hemoglobin levels in twin anemia-polycythemia sequence, Ultrasound in Obstetrics & Gynecology, 46, 432-6, 2015	Reference standard is not relevant to the protocol (based on fetal anaemia definition rather than postnatal definition in protocol)
Slaghekke, F., Lopriore, E., Lewi, L., Middeldorp, J. M., Van Zwet, E. W., Weingertner, A. S., Klumper, F. J., DeKoninck, P., Devlieger, R., Kilby, M. D., Rustico, M. A., Deprest, J., Favre, R., Oepkes, D., Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: An open-label randomized controlled trial, Obstetrical and Gynecological Survey, 69, 569-571, 2014	Abstract only

Study	Reason for Exclusion
Suzuki, S., Perinatal Outcomes of Monochorionic-Diamniotic Twin Pregnancies Uncomplicated at 28 Weeks of Gestation, Japanese Clinical Medicine, 7, 15-7, 2016	The article examines the prevalence of TTTS and TAPS in uncomplicated MCDA twin pregnancies
Tollenaar, L. S, Slaghekke, F, Middeldorp, J. M, Klumper, F. J, Haak, M. C, Oepkes, D, Lopriore, E., Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome, Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies, 19, 222-33, 2016	A narrative review on the epidemiology, pathogenesis, diagnostic criteria, management options, and short- and long-term outcome in TAPS
Turan, S., Turan, O. M., Arterial and Venous Doppler in Evaluation of the "at-Risk" Fetus, Clinical Obstetrics and Gynecology, 60, 668-678, 2017	The article describes the application of arterial and venous Doppler techniques in assessing and managing various diseases and conditions for high-risk fetuses
Wang, Q., Zhou, Y., Xu, H., Qin, G., Diagnosis of abnormal pregnancy and outcomes by color doppler ultrasound, Biomedical Research (India), 28, 3063-3065, 2017	n=3 TAPS cases no specificity/sensitivity/AUC
Yokouchi, T, Murakoshi, T, Mishima, T, Yano, H, Ohashi, M, Suzuki, T, Shinno, T, Matsushita, M, Nakayama, S, Torii, Y., Incidence of spontaneous twin anemia-polycythemia sequence in monochorionic-diamniotic twin pregnancies: Single-center prospective study, Journal of Obstetrics & Gynaecology Research, 41, 857-60, 2015	Not diagnostic - assesses incidence rate from postnatal diagnosis only N=3 cases to prospectively estimate the incidence of spontaneous TAPS at Seirei Hamamatsu General Hospital, Shizuoka, Japan
Zhao, D, Slaghekke, F, Middeldorp, J. M, Duan, T, Oepkes, D, Lopriore, E., Placental share and hemoglobin level in relation to birth weight in twin anemia-polycythemia sequence, Placenta, 35, 1070-4, 2014	Not diagnostic (no sensitivity/specificity) does not use US (index test) - looks at placental share only

AUC: area under the curve; IUGR: intrauterine growth rate; MCA-PSV: middle cerebral artery peak systolic velocity; MCDA: monochorionic diamniotic; TAPS: twin anemia polycythemia sequence; TTTS: twin-to-twin transfusion syndrome; US: ultrasound

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal screening programme to detect twin anaemia polycythaemia sequences (TAPS) in twin and triplet pregnancy?

Research recommendation:

What is the most accurate prenatal screening marker for TAPS, including MCA-PSV?

Why this is important

Monochorionic twins share a single placenta and are connected to each other through vascular anastomoses, allowing inter-twin blood transfusion. Unbalanced net inter-twin blood transfusion can lead to various disorders, including chronic feto-fetal transfusion syndrome (FFTSS), acute peripartum TTTS and TAPS.

TAPS is characterised by a chronic and slow blood transfusion from donor to recipient through miniscule vascular anastomoses during the course of pregnancy, causing the donor to become anaemic and the recipient to become polycythaemia, without discordances in amniotic fluid. TAPS may occur spontaneously (spontaneous TAPS) in 2% of the monochorionic twin pregnancies or in any monochorionic twin complications, especially after laser surgery for chronic TTTS (post-laser TAPS) in 3–16% of the chronic TTTS cases (Slaghekke F et al, Fetal Diagn Ther. 2010; 27(4):181-90).

Short-term neonatal outcome ranges from isolated inter-twin haemoglobin (Hb) differences to severe neonatal morbidity and neonatal death. Long-term neonatal outcome in post-laser TAPS is comparable with long-term outcome after treated TTTS.

The prenatal diagnosis of TAPS is currently based on discordant measurements of the middle cerebral artery peak systolic velocity (MCA-PSV; >1.5 multiples of the median [MoM] in donors and 8 g/dL), and at least one of the following: reticulocyte count ratio >1.7 or minuscule placental anastomoses. However, it is unclear whether these are the most accurate measurements because evidence is very limited. Finding an accurate diagnostic test would lead to better detection and potentially earlier treatment.

Table 5: Research recommendation rationale

Research question	What is the most accurate prenatal screening marker for TAPS, including MCA-PSV?
Importance to 'patients' or the population	• Improve the antenatal detection of TAPS • Avoid false positive prenatal diagnosis of TAPS and possible unnecessary intervention or iatrogenic premature birth • Enable a more accurate ascertainment of the natural history of TAPS • Reduce unnecessary parental anxiety
Relevance to NICE guidance	The ability to more accurately diagnose TAPS prenatally is relevant to this guidance because it would allow earlier detection.
Relevance to the NHS	• Reduce perinatal mortality and morbidity associated with TAPS • Reduce unnecessary intervention or iatrogenic premature birth • Reduce costs from unnecessary intervention arising from false positive diagnosis • Reduce costs from adverse perinatal outcomes associated with TAPS, such as neurodevelopmental impairment
National priorities	• Reduce stillbirth in twin pregnancies

Research question	What is the most accurate prenatal screening marker for TAPS, including MCA-PSV?
	• Reduce prematurity in twin pregnancies • Reduce unnecessary intervention in twin pregnancies
Current evidence base	Current evidence was not clear and was graded as very low quality with high rates of imprecision.
Equality	This applies to all women with monochorionic twin pregnancies

MCA-PSV: middle cerebral artery peak systolic velocity; TAPS: twin anaemia polycythaemia sequence

Table 6: Research recommendation modified PIRO table

Criterion	Explanation
Population	Monochorionic twin pregnancies: • Monochorionic diamniotic pregnancies • Monochorionic monoamniotic pregnancies
Index test	• MCA-PSV • The detection of fetal effusions in the anaemic co-twin • Prenatal ultrasound surveillance for placental dichotomy and /or 'starry sky' liver The above tests could be used in isolation or in combination.
Reference standard	Recognised postnatal diagnostic criteria reference standard for TAPS Postnatal diagnostic criteria of TAPS: • Inter-twin Hb difference ≥8.0 g/dL • and at least one of the following criteria: o reticulocyte count ratio ≥1.7 o small anastomoses (<1 mm) at the placental surface
Outcome	• True positive • False positive • True negative • False negative
Study design	Multicentre large observational cohort study
Timeframe	3-5 years
Additional information	The diagnosis of TAPS is for the most part is a 'prenatal diagnosis'. The diagnostic criteria are based upon each ultrasound test (MCA-PSV) that one is evaluating.

Hb: haemoglobin; MCA-PSV: middle cerebral artery peak systolic velocity; TAPS: twin anaemia polycythaemia sequence