National Institute for Health and Care Excellence

Draft for consultation

Inducing labour

[A] Induction of labour for suspected fetal macrosomia

NICE guideline CG70 (update)

Evidence review underpinning recommendations 1.2.22 and 1.2.23 in the NICE guideline

May 2021

Draft for consultation

This evidence review was developed by the National Guideline Alliance which is a part of 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:

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Induction of labour for suspected fetal macrosomia

Review question

What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Introduction

Fetal macrosomia is a term used when a fetus is larger than expected for gestational age, and is usually defined by an absolute weight (for example an estimated fetal weight of more than 3500g at 36 weeks) or in relation to centiles (for example, an estimated fetal weight above the 95th percentile at or after 36 weeks of gestation). Birth of a large baby can lead to problems for both mother and baby - including perineal tears, an increased risk of caesarean birth, shoulder dystocia, brachial plexus injury and severe perinatal morbidity or even death. Induction of labour may lead to earlier birth, and hence a baby who is smaller than if they had continued growing until natural labour commenced.

The aim of this review is to determine if induction of labour for suspected fetal macrosomia at or after 35 weeks of gestation has benefits, and reduces the risk of adverse outcomes for the mother and the baby, compared to expectant management.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women with suspected fetal macrosomia (as defined by study authors) at/near term (≥35^{+0} weeks). • Include: primiparous and multiparous women • Exclude: women with treated diabetes (pre-existing or gestational on medication/insulin)
Intervention	Any method of induction of labour (or combination of methods)
Comparison	Watchful waiting/expectant management
Outcomes	**Critical outcomes:** • Third/fourth degree perineal tears • Shoulder dystocia (as defined by study authors) • Perinatal death **Important outcomes:** • Hypoxic ischaemic encephalopathy (HIE) • Maternal satisfaction/HRQoL • Brachial plexus injury • Caesarean birth

HIE: Hypoxic ischaemic encephalopathy; HRQoL: health-related quality of life

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Please see the methods chapter for further details. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest 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 Register of Interests).

Clinical evidence

Included studies

One Cochrane systematic review (Boulvain 2016) including 4 RCTs was included in this review, (N=1190) (Boulvain 2015, Gonen 1997, Kean unpublished data [LIBBY 1998], Tey 1995). No RCTs were retrieved for full-text screening.

The included studies are summarised in Table 2.

Participants consisted of women with suspected fetal macrosomia at/near term (≥ 35^{+0} weeks). Data on the specific outcomes relevant to this protocol were extracted from the review, and used for meta-analysis where appropriate.

The individual studies included in the Cochrane review were checked to confirm that no other relevant outcomes were reported, with the exception of Kean, which is an unpublished study.

One of the largest studies (Boulvain 2015) included in Boulvain 2016, included women with diet-controlled gestational diabetes, who constituted 10.02% of the total population of the study. As a result, separate analyses were carried out with and without this study included, as pre-specified in the review protocol. Studies including women with treated diabetes (pre-existing or gestational on medication/insulin) were excluded from this review, as this group of women was not covered by the guideline scope.

The classification of macrosomia varied across studies. Based on the trial inclusion criteria, macrosomia was defined as follows:

- Boulvain 2015: fetus weighing more than the 90th percentile using either fundal height or fetal weight estimated with the Leopold manoeuvres were then assessed sonographically with Hadlock's formula. On that subsequent assessment, those with an estimated weight above the 95th percentile (3500 g at 36 weeks of gestation, 3700 g at 37 weeks, and 3900 g at 38 weeks) were included.
- Gonen 1997: ultrasonic fetal weight estimation between 4000 and 4500 g.
- Kean, unpublished data: ultrasonic fetal weight estimation above the 97th percentile (as defined with the charts of fetal size presented in Chitty 1994, https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-0528.1994.tb13077.x).
- Tey 1995: ultrasonic fetal weight estimation between 4000 and 4750 g.

Shoulder dystocia was only defined in one of the studies included (Boulvain 2015) as: interval of 60 seconds or more between the delivery of the head and the body. The remaining studies did not provide a definition for shoulder dystocia.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

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

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Participants	Intervention	Control	Outcomes
Boulvain 2016 Cochrane systematic review Belgium, France, Switzerland, Israel, UK, USA	K=4 (Boulvain 2015, Gonen 1997, Kean unpublished data, Tey 1995) N=1190 women with suspected fetal macrosomia at/near term 35^{+0} weeks	<u>Induction of labour</u> <u>Boulvain 2015</u> Induction method was at the discretion of the treating physician and according to local protocol. Those with unfavourable cervix* received misoprostol or prostaglandins followed by oxytocin. <u>Gonen 1997</u> Oxytocin or prostaglandins, according to cervical readiness. <u>Kean, unpublished data</u> Oxytocin or prostaglandins. <u>Tey 1995</u> Prostaglandin gel if Bishop's score <6, followed by oxytocin.	<u>Expectant management (EXP)</u> <u>Boulvain 2015</u> EXP until labour started spontaneously. Labour was induced if women were diagnosed with a condition that required induction or if the pregnancy continued beyond 41 weeks GA. <u>Gonen 1997</u> EXP until labour started spontaneously. Labour was induced if the pregnancy continued beyond 42 weeks GA. <u>Kean, unpublished data</u> EXP until labour started spontaneously. Labour was induced if the pregnancy continued beyond 42 weeks GA.	• Third/fourth degree perineal tears • Shoulder dystocia • Perinatal death • Brachial plexus injury • Caesarean birth

Study	Participants	Intervention	Control	Outcomes
			Tey 1995 No further details were provided	

*Bishop's score was not reported
GA: gestational age; K: number of studies; N: number of participants.

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the evidence profiles in appendix F.

Economic evidence

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

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

Comparison 1. Induction of labour versus expectant management

Critical outcomes

Third/fourth degree perineal tears

Overall estimate

Two RCTs (N=858) provided low quality evidence to show that those who received induction of labour experienced a clinically important increase in the number of third/fourth degree perineal tears, as compared to those who received expectant management.

Women without diabetes

One RCT (N=40) provided very low quality evidence to show that, for women without diabetes, no third/fourth degree perineal tears occurred in those who received induction of labour or expectant management.

Shoulder dystocia

Overall estimate

Four RCTs (N=1190) provided low quality evidence to show that those who received induction of labour experienced a clinically important decrease in the incidence of shoulder dystocia, as compared to those who received expectant management.

Women without diabetes

Three RCTs (N=372) provided very low quality evidence to show that, for women without diabetes, there was no clinically important difference in the incidence of

shoulder dystocia between those who received induction of labour or expectant management.

Perinatal death

Overall estimate

Three RCTs (N=917) provided very low quality evidence to show that no perinatal deaths occurred in those who received induction of labour or expectant management.

Women without diabetes

Two RCTs (N=99) provided moderate quality evidence to show that, for women without diabetes, no perinatal deaths occurred in those who received induction of labour or expectant management.

Important outcomes

Hypoxic ischaemic encephalopathy

No evidence was identified to inform this outcome.

Maternal satisfaction/HRQoL

No evidence was identified to inform this outcome.

Brachial plexus injury

Overall estimate

Four randomised controlled trials (N=1190) provided moderate quality evidence to show that there was no clinically important difference in the occurrence of brachial plexus injury in the infants of those who received induction of labour or expectant management.

Women without diabetes

Three randomised controlled trials (N=372) provided low quality evidence to show that, for women without diabetes, there was no clinically important difference in the occurrence of brachial plexus injury in the infants of those who received induction of labour or expectant management.

Caesarean birth

Overall estimate

Four randomised controlled trials (N=1190) provided low quality evidence to show that there was no clinically important difference in the number of caesarean births between those who received induction of labour or expectant management.

Women without diabetes

Three randomised controlled trials (N=372) provided very low quality evidence to show that, for women without diabetes, there was no clinically important difference in the number of caesarean births between those who received induction of labour or expectant management.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to assess the benefits and harms of induction of labour in women with suspected fetal macrosomia. The committee therefore designated 3 critical outcomes: third/fourth degree perineal tears, shoulder dystocia and perinatal death. These outcomes were selected as the most direct indicators of the efficacy and safety of induction of labour in women with suspected fetal macrosomia.

The committee identified 4 further outcomes as important: hypoxic ischaemic encephalopathy, maternal satisfaction/ HRQoL, brachial plexus injury and caesarean birth. Caesarean birth was an important outcome because if a baby is too large to allow safe vaginal delivery, then it may be necessary for the mother to be offered a caesarean birth instead. Hypoxic ischaemic encephalopathy (HIE) and brachial plexus injury were important because they can put babies at significant risk of morbidity and mortality. The committee also identified maternal satisfaction as an important outcome, and one that was likely to be strongly correlated with the incidence of shoulder dystocia, third/fourth degree tears and perinatal outcomes.

The quality of the evidence

One Cochrane systematic review was included in this review. The quality of the evidence for the individual outcomes ranged from very low to moderate as assessed by GRADE.

The main reason for downgrading the quality of the evidence was the risk of bias due to studies failing to report how randomisation was concealed, or because women, investigators and assessors were aware of treatment allocation (although the committee noted that blinding was less relevant for objective outcomes like perinatal death and took this into account in their decision making). The evidence for some outcomes was also downgraded because of imprecision, as the trials had few women included, and therefore the 95% confidence intervals (CIs) around the estimate for each of the outcomes were wide.

Benefits and harms

Suspected large for gestational age babies (or babies with suspected macrosomia) are at an increased risk of having difficult births. Preventing babies from getting too large by having an earlier birth may mitigate the associated risks, however the available evidence was not sufficient to recommend inducing labour and having an early birth over managing the pregnancy expectantly and waiting until birth started spontaneously.

The evidence showed that induction of labour was associated with an increased risk of third and fourth degree perineal tears, but a reduction in the risk of shoulder dystocia.

The committee noted that the increase in third and fourth degree perineal tears with induction of labour was unexpected, as induction would normally lead to the earlier birth of a smaller baby and less need for an instrumental delivery, and therefore a reduced risk of tears. The committee noted that the meta-analysis showed a lower mean birthweight with induction, and a lower incidence of instrumental delivery with induction (although these had not been outcomes prioritised for inclusion in the review). The committee reviewed the evidence and noted that for the outcome third

and fourth degree perineal tears, there was little knowledge about the true effect of the interventions on this outcome because the 95% CIs for the point estimate were very wide, which indicates great uncertainty. Furthermore, the committee noted that in the original publication on the trial conducted by Boulvain 2015, there were no significant differences between induction of labour and expectant management for the outcome third degree perineal tear (anal sphincter tear), and this outcome was only statistically significant when reported as a composite with fourth degree tears in the Cochrane review. So while the evidence did suggest that routine induction of labour was associated with an increased risk of third and fourth degree tears, there was considerable uncertainty around this finding.

The committee also discussed how the definition of shoulder dystocia provided by Boulvain 2015 ("interval of 60 seconds or more between the delivery of the head and body") was not routinely used, and it was uncertain how a more widely used definition[1] could have affected the outcome. Nonetheless, they highlighted that in Boulvain 2015, it was described that "the estimated benefit did not change when the definition of the primary outcome (significant shoulder dystocia, delay of ≥60 seconds, fracture, brachial plexus injury, intracranial haemorrhage, death) excluded the interval of 60 seconds or more between the delivery of the head and body".

No perinatal deaths occurred in any of the trials included, therefore it was uncertain whether induction of labour had any effect on this outcome, and no trials reported on the outcome of health-related quality of life/maternal satisfaction or hypoxic ischaemic encephalopathy.

The trials varied in their definition of macrosomia, therefore no subgroup analysis was possible according to estimated fetal weight. While all trials reported that they estimated the fetal weight with ultrasound, different definitions were used. Two trials used estimates based on centile (>95th or 97th centile) and two used estimated fetal weight (4000-4500g and 4000-4750g). The committee specified that these recommendations apply to an estimated weight of the fetus above the 95th percentile at or after 36 weeks of gestation, which is in line with Boulvain 2015. The committee also noted that is important to assess the fetal weight with ultrasound rather than estimating it clinically by measuring the fundal height as this is inaccurate.

The largest trial included (Boulvain 2015) had a proportion of women (approximately 10%) with diet-controlled gestational diabetes. Data for the two subgroups (women with and without diabetes) were not reported separately, therefore data from this trial were removed from the stratified analysis considering only women without diabetes. As there are existing recommendations on the management of fetal macrosomia in diabetes (NG3), these recommendations apply to women who do not have treated diabetes.

Cost effectiveness and resource use

No relevant studies were identified in a systematic review of the economic evidence and no new economic evaluation was undertaken for this guideline.

The committee considered that there was not strong clinical evidence to support induction of labour as preferable to expectant management in women with suspected fetal macrosomia. They recognised that induction of labour is more expensive than a spontaneous vaginal birth. However, they considered that induction of labour might reduce the risk of shoulder dystocia which also has potential implications for cost and health related quality of life. Given the paucity of clinical evidence they did not

[1] "A vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed" (RCOG green-top guideline no 42)

consider the cost effectiveness of either induction of labour or expectant management was demonstrated in women with fetal macrosomia. They therefore thought it reasonable to base the choice of care on the women's circumstances and their personal preferences especially as that represents common current practice. The committee considered that these recommendations would not lead to an increase in resource use as they reflect standard practice for the majority of centres.

Other factors the committee took into account

The committee discussed the fact that the evidence presented was low quality, and that the Cochrane systematic review (Boulvain 2016) was conducted by the same author as the largest trial included (Boulvain 2015). The committee agreed that whilst this was not atypical, it could represent a possible conflict of interest and a challenge for the systematic review authors to approach all included evidence identically. Indeed, the Cochrane systematic review included an outcome (the composite outcome of third and fourth degree perineal tears) from the study described in Boulvain 2015, which was not reported in the original publication.

Due to the paucity of data in the field, the committee considered whether further trials comparing the benefits and harms of induction of labour versus expectant management were needed. However, it was decided not to make a research recommendation because the committee were aware of the ongoing National Institute of Health Research (NIHR) 'Big Baby' clinical trial, which will address this question.

The committee were aware of the recommendations for large-for-gestational-age babies in the NICE clinical guideline on intrapartum care (NG121), however they noted that these apply to women in labour, and where the evidence appraised looked at emergency (unscheduled or unplanned) caesarean birth versus continuation of labour, whereas this review assessed induction of labour versus expectant management.

The committee were aware that this evidence review only included women without diabetes but that large babies were more common in women with pre-existing or gestational diabetes, and so cross-referred to the NICE guideline on diabetes in pregnancy.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.22 and 1.2.23 in the NICE guideline.

References

Boulvain 2015

Boulvain M, Senat MV, Perrotin F, Winer N, Beucher G, Subtil D, Bretelle F, Azria E, Hejaiej D, Vendittelli F, Capelle M. Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. The Lancet. 2015 Jun 27;385(9987):2600-5.

Boulvain 2016

Boulvain M, Irion O, Dowswell T, Thornton JG. Induction of labour at or near term for suspected fetal macrosomia. Cochrane Database of Systematic Reviews. 2016(5).

Cochrane risk of bias tool

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.

Gonen 1997

Gonen O, Rosen DJ, Dolfin Z, Tepper R, Markov S, Fejgin MD. Induction of labor versus expectant management in macrosomia: a randomized study. Obstetrics & Gynecology. 1997 Jun 1;89(6):913-7.

Kean, unpublished data

Kean, L.H., Leave alone or induce for the big baby (LIBBY). National Research Register, UK. ISRCTN Registry number ISRCTN98146741 [Unpublished data referenced in Cochrane Review (Boulvain 2016)].

RCOG Green-top guideline no 42

Shoulder dystocia. Green-top Guideline No. 42. Green-top Guideline. 2012(42.2012).

ROBIS checklist

Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005. PubMed PMID: 26092286; PubMed Central PMCID: PMC4687950.

Tey 1995

Tey A, Eriksen NL, Blanco JD. A prospective randomized trial of induction versus expectant management in nondiabetic pregnancies with fetal macrosomia. Am J Obstet Gynecol. 1995;172(1 Pt 2):293.

Appendices

Appendix A – Review protocols

Review protocols for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Table 3: Protocol for benefits and harms associated with induction of labour in women with suspected fetal macrosomia

Field (based on PRISMA-P)	Content
Actual review question	What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?
Type of review question	Intervention
Objective of the review	To determine if induction of labour in women with suspected fetal macrosomia can improve maternal and neonatal outcomes compared to expectant management
Eligibility criteria – **population**/disease/condition/issue/domain	Women with suspected fetal macrosomia (as defined by study authors) at/near term (≥35 weeks 0 days) include primiparous and multiparous women
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Any method of induction of labour (or combination of methods)
Eligibility criteria – **comparator**(s)/control or reference (gold) standard	Watchful waiting/expectant management
Outcomes and prioritisation	**Critical outcomes:** Third/fourth degree perineal tears Shoulder dystocia (as defined by trialists) Perinatal death **Important outcomes:** Hypoxic ischaemic encephalopathy (HIE) Maternal satisfaction/HRQOL Brachial plexus injury Caesarean birth

Field (based on PRISMA-P)	Content
Eligibility criteria – **study design**	Only published full text papers Systematic reviews of RCTs RCTs
Other **exclusion criteria**	Exclude women with treated diabetes (pre-existing or gestational on medication/insulin)
Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	If possible – conduct subgroup analysis for women without diabetes (i.e. excluding data from women with diet-controlled diabetes, where this has been included) If heterogeneity is identified, subgroup analysis to be performed according to estimated fetal weight 4000 – 4500g >4500g 90th 95th 97th centiles If heterogeneity is identified, subgroup analysis will be performed according to the method of induction of labour (where possible).
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADE' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations, study sifting, data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched:

Field (based on PRISMA-P)	Content
	Medline EMBASE Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment [HTA] database Study design will be limited to systematic reviews and RCTs. As this protocol has been modified from the existing review, no date limit will be applied to the search. No supplementary search techniques will be used. Key papers: Cochrane Database Syst Rev. 2016 May 22;(5) Induction of labour at or near term for suspected fetal macrosomia. Boulvain M1, Irion O, Dowswell T, Thornton JG.
Identify if an update	Yes – relevant evidence included in the existing guideline will be considered against the inclusion/exclusion criteria for this protocol.
Author contacts	Developer: National Guideline Alliance nga-enquiries@rcog.org.uk
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence will 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/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important difference: Any statistically significant difference will be used for the following outcomes: Perinatal death Brachial plexus injury For all other outcomes, GRADE default values will be used of 0.8 and 1.25 for relative risk of dichotomous outcomes; 0.5 times SD of the control group for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. Consider exploring publication bias for review questions where it may be more common, such as pharmacological questions, certain disease areas, etc. Describe any steps taken to mitigate against publication bias, such as examining trial registries.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA 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. For details please see the methods chapter of the full guideline.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

1 *CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HIE: hypoxic ischaemic encephalopathy; HRQoL: health-related quality of life; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; ROBIS: risk of bias I systematic reviews; SD: standard deviation*

Appendix B – Literature search strategies

Search strategies for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 12/05/2020

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	LABOR, INDUCED/
21	(labo?r adj5 induc$).ti,ab.
22	(induc$ adj3 (birth$ or born or deliver$)).ti,ab.
23	induction?.ti,ab.
24	CERVICAL RIPENING/
25	(cervi$ adj3 ripen$).ti,ab.
26	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
27	((bishop$ or cerv$) adj3 scor$).ti,ab.
28	or/20-27
29	FETAL MACROSOMIA/
30	macrosomi$.ti,ab.
31	(large? adj3 gestational$ adj3 age?).ti,ab.
32	(large? adj3 date?).ti,ab.
33	LGA.ti,ab.
34	or/29-33
35	28 and 34
36	limit 35 to english language
37	LETTER/
38	EDITORIAL/
39	NEWS/
40	exp HISTORICAL ARTICLE/
41	ANECDOTES AS TOPIC/
42	COMMENT/
43	CASE REPORT/
44	(letter or comment*).ti.
45	or/37-44
46	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
47	45 not 46
48	ANIMALS/ not HUMANS/
49	exp ANIMALS, LABORATORY/
50	exp ANIMAL EXPERIMENTATION/
51	exp MODELS, ANIMAL/
52	exp RODENTIA/
53	(rat or rats or mouse or mice).ti.
54	or/47-53
55	36 not 54
56	10 and 55

#	Searches
57	19 and 55
58	or/56-57

Databases: Embase; and Embase Classic

Date of last search: 12/05/2020

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	LABOR INDUCTION/
23	(labo?r adj5 induc$).ti,ab.
24	(induc$ adj3 (birth$ or born or deliver$)).ti,ab.
25	induction?.ti,ab.
26	UTERINE CERVIX RIPENING/
27	(cervi$ adj3 ripen$).ti,ab.
28	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
29	((bishop$ or cerv$) adj3 scor$).ti,ab.
30	or/22-29
31	MACROSOMIA/
32	macrosomi$.ti,ab.
33	(large? adj3 gestational$ adj3 age?).ti,ab.
34	(large? adj3 date?).ti,ab.
35	LGA.ti,ab.
36	or/31-35
37	30 and 36
38	limit 37 to english language
39	letter.pt. or LETTER/
40	note.pt.
41	editorial.pt.
42	CASE REPORT/ or CASE STUDY/
43	(letter or comment*).ti.
44	or/39-43
45	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
46	44 not 45
47	ANIMAL/ not HUMAN/
48	NONHUMAN/
49	exp ANIMAL EXPERIMENT/
50	exp EXPERIMENTAL ANIMAL/
51	ANIMAL MODEL/
52	exp RODENT/
53	(rat or rats or mouse or mice).ti.
54	or/46-53
55	38 not 54
56	11 and 55
57	21 and 55
58	or/56-57

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

Date of last search: 12/05/2020

#	Searches
#1	MeSH descriptor: [LABOR, INDUCED] this term only
#2	((labor or labour) near/5 induc*):ti,ab
#3	(induc* near/3 (birth* or born or deliver*)):ti,ab
#4	Induction*:ti,ab
#5	MeSH descriptor: [CERVICAL RIPENING] this term only
#6	(cervi* near/3 ripen*):ti,ab
#7	((unfavorabl* or un-favorabl* or unfavourabl* or un-favourabl* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#8	((bishop* or cerv*) near/3 scor*):ti,ab
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [FETAL MACROSOMIA] this term only
#11	macrosomi*:ti,ab
#12	(large* near/3 gestational* near/3 age?):ti,ab
#13	(large* near/3 date?):ti,ab
#14	LGA:ti,ab
#15	#10 or #11 or #12 or #13 or #14
#16	#9 and #15

Databases: Database of Abstracts of Reviews of Effects; and Health Technology Assessment

Date of last search: 12/05/2020

#	Searches
1	MeSH descriptor: LABOR, INDUCED
2	((labor or labour) near5 induc*):ti,ab
3	(induc* near3 (birth* or born or deliver*)):ti,ab
4	Induction*:ti,ab
5	MeSH descriptor: CERVICAL RIPENING
6	(cervi* near3 ripen*):ti,ab
7	((unfavorabl* or un-favorabl* or unfavourabl* or un-favourabl* or unripe* or un-ripe*) near3 cervi*):ti,ab
8	((bishop* or cerv*) near3 scor*):ti,ab
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10	MeSH descriptor: FETAL MACROSOMIA
11	macrosomi*:ti,ab
12	(large* near3 gestational* near3 age*):ti,ab
13	(large* near3 date*):ti,ab
14	LGA:ti,ab
15	#10 or #11 or #12 or #13 or #14
16	#9 and #15

Health economic search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 12/05/2020

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.

#	Searches
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	LABOR, INDUCED/
23	(labo?r adj5 induc$).ti,ab.
24	(induc$ adj3 (birth$ or born or deliver$)).ti,ab.
25	induction?.ti,ab.
26	CERVICAL RIPENING/
27	(cervi$ adj3 ripen$).ti,ab.
28	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
29	((bishop$ or cerv$) adj3 scor$).ti,ab.
30	or/22-29
31	FETAL MACROSOMIA/
32	macrosomi$.ti,ab.
33	(large? adj3 gestational$ adj3 age?).ti,ab.
34	(large? adj3 date?).ti,ab.
35	LGA.ti,ab.
36	or/31-35
37	30 and 36
38	limit 37 to english language
39	LETTER/
40	EDITORIAL/
41	NEWS/
42	exp HISTORICAL ARTICLE/
43	ANECDOTES AS TOPIC/
44	COMMENT/
45	CASE REPORT/
46	(letter or comment*).ti.
47	or/39-46
48	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
49	47 not 48
50	ANIMALS/ not HUMANS/
51	exp ANIMALS, LABORATORY/
52	exp ANIMAL EXPERIMENTATION/
53	exp MODELS, ANIMAL/
54	exp RODENTIA/
55	(rat or rats or mouse or mice).ti.
56	or/49-55
57	38 not 56
58	21 and 57

Databases: Embase; and Embase Classic

Date of last search: 12/05/2020

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16

#	Searches
18	LABOR INDUCTION/
19	(labo?r adj5 induc$).ti,ab.
20	(induc$ adj3 (birth$ or born or deliver$)).ti,ab.
21	induction?.ti,ab.
22	UTERINE CERVIX RIPENING/
23	(cervi$ adj3 ripen$).ti,ab.
24	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
25	((bishop$ or cerv$) adj3 scor$).ti,ab.
26	or/18-25
27	MACROSOMIA/
28	macrosomi$.ti,ab.
29	(large? adj3 gestational$ adj3 age?).ti,ab.
30	(large? adj3 date?).ti,ab.
31	LGA.ti,ab.
32	or/27-31
33	26 and 32
34	limit 33 to english language
35	letter.pt. or LETTER/
36	note.pt.
37	editorial.pt.
38	CASE REPORT/ or CASE STUDY/
39	(letter or comment*).ti.
40	or/35-39
41	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
42	40 not 41
43	ANIMAL/ not HUMAN/
44	NONHUMAN/
45	exp ANIMAL EXPERIMENT/
46	exp EXPERIMENTAL ANIMAL/
47	ANIMAL MODEL/
48	exp RODENT/
49	(rat or rats or mouse or mice).ti.
50	or/42-49
51	34 not 50
52	17 and 51

Database: Cochrane Central Register of Controlled Trials

Date of last search: 12/05/2020

#	Searches
#1	MeSH descriptor: [Economics] this term only
#2	MeSH descriptor: [Value of Life] this term only
#3	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#4	MeSH descriptor: [Economics, Hospital] explode all trees
#5	MeSH descriptor: [Economics, Medical] explode all trees
#6	MeSH descriptor: [Resource Allocation] explode all trees
#7	MeSH descriptor: [Economics, Nursing] this term only
#8	MeSH descriptor: [Economics, Pharmaceutical] this term only
#9	MeSH descriptor: [Fees and Charges] explode all trees
#10	MeSH descriptor: [Budgets] explode all trees
#11	budget*:ti,ab
#12	cost*:ti,ab
#13	(economic* or pharmaco?economic*):ti,ab
#14	(price* or pricing*):ti,ab
#15	(financ* or fee or fees or expenditure* or saving*):ti,ab
#16	(value near/2 (money or monetary)):ti,ab
#17	resourc* allocat*:ti,ab
#18	(fund or funds or funding* or funded):ti,ab
#19	(ration or rations or rationing* or rationed) .ti,ab.
#20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	MeSH descriptor: [Labor, Induced] this term only
#22	((labor or labour) near/5 induc*):ti,ab
#23	(induc* near/3 (birth* or born or deliver*)):ti,ab
#24	Induction*:ti,ab
#25	MeSH descriptor: [Cervical Ripening] this term only
#26	(cervi* near/3 ripen*):ti,ab
#27	((unfavorabl* or un-favorabl* or unfavourabl* or un-favourabl* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#28	((bishop* or cerv*) near/3 scor*):ti,ab

#	Searches
#29	#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30	MeSH descriptor: [Fetal Macrosomia] this term only
#31	macrosomi*:ti,ab
#32	(large* near/3 gestational* near/3 age?):ti,ab
#33	(large* near/3 date?):ti,ab
#34	LGA:ti,ab
#35	#30 or #31 or #32 or #33 or #34
#36	#29 and #35
#37	#20 and #36

Databases: Health Technology Assessment; and NHS Economic Evaluation Database

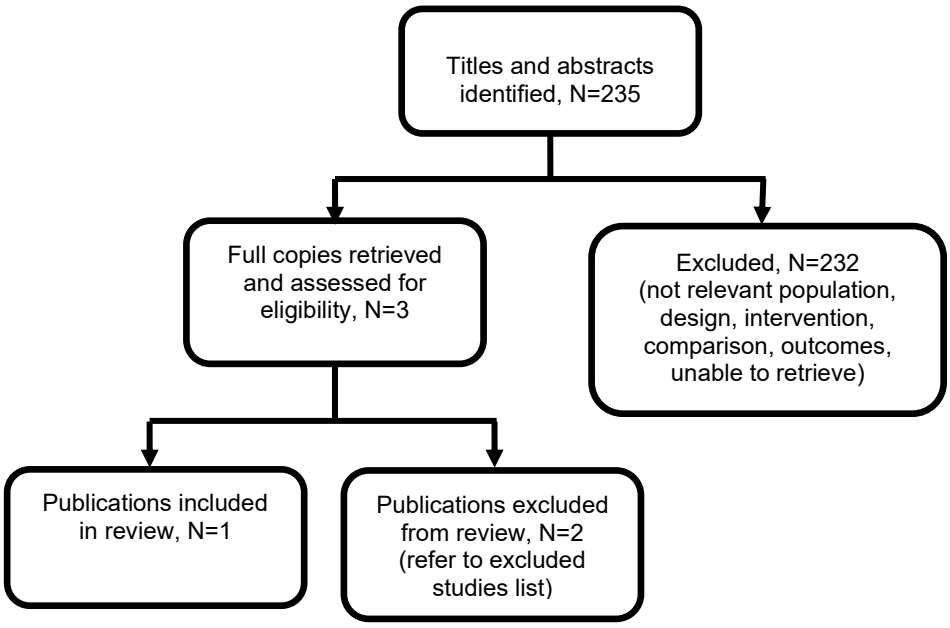
Date of last search: 12/05/2020

#	Searches
1	MeSH descriptor: LABOR, INDUCED
2	((labor or labour) near5 induc*):ti,ab
3	(induc* near3 (birth* or born or deliver*)):ti,ab
4	Induction*:ti,ab
5	MeSH descriptor: CERVICAL RIPENING
6	(cervi* near3 ripen*):ti,ab
7	((unfavorabl* or un-favorabl* or unfavourabl* or un-favourabl* or unripe* or un-ripe*) near3 cervi*):ti,ab
8	((bishop* or cerv*) near3 scor*):ti,ab
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10	MeSH descriptor: FETAL MACROSOMIA
11	macrosomi*:ti,ab
12	(large* near3 gestational* near3 age*):ti,ab
13	(large* near3 date*):ti,ab
14	LGA:ti,ab
15	#10 or #11 or #12 or #13 or #14
16	#9 and #15

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Figure 1: Flow diagram of clinical article selection for benefits and harms associated with induction of labour in women with suspected fetal macrosomia



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Table 4: Clinical evidence tables for benefits and harms associated with induction of labour in women with suspected fetal macrosomia

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Boulvain, Michel, Irion, Olivier, Dowswell, Therese, Thornton, Jim G., Induction of labour at or near term for suspected fetal macrosomia, The Cochrane database of systematic reviews, CD000938, 2016

Ref Id

889027

Countries where the study was carried out

Belgium, France, Israel,</td>
<td>Sample size

K=4 RCTs (N=1190)

Characteristics

<u>Boulvain 2015*</u>
<table>
<tr><th></th><th>Induction of labour

(N=407)</th><th>Expectant management

(N=411)</th></tr>
<tr><td>Age, mean (SD)</td><td>29.2 (5.3)</td><td>29.8 (5.3)</td></tr>
<tr><td>Gestational age, 36+0 to ≤37 weeks, N (%)</td><td>42 (10)</td><td>44 (11)</td></tr>
<tr><td>Gestational age, 37 to ≤38 weeks, N (%)</td><td>177 (44)</td><td>181 (44)</td></tr>
<tr><td>Gestational age, 38</td><td>187 (46)</td><td>184 (45)</td></tr>
</table></td>
<td>Interventions

<u>Boulvain 2015</u>

Intervention: labour was induced at the discretion of the treating physician and according to local protocol. Women with unfavourable cervix (Bishop’s score not reported) had cervical ripening with misoprostol or prostaglandins followed by oxytocin to induce the contractions
Comparison: Expectant management continued until labour started spontaneously. Labour was induced if the woman was diagnosed with a condition requiring</td>
<td>Details

A literature search was done in the Cochrane Pregnancy and Childbirth's Trials Register, hand searches of journals and the proceedings of major conferences wer e also searched. No language restrictions were applied.
Two review authors assessed all potentially eligible studies. Disagreements were resolved with consensus. Two review authors</td>
<td>Results

Third/ fourth degree perineal tears

<u>Boulvain 2015</u>

Induction of labour: 11/407

Expectant management: 3/411

<u>Tey 1995</u>

Induction of labour: 0/19

Expectant management: 0/21

Shoulder dystocia

<u>Boulvain 2015</u></td>
<td>Limitations

Systematic review limitations assessed with the ROBIS checklist

<u>Identifying concerns in the review process</u>

Domain 1: concerns regarding specification of study eligibility criteria: low

Domain 2: concerns regarding methods used to identify and/or select studies: low

Domain 3: concerns regarding methods used to collect data and</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Switzerland, UK, USA

Study type
Cochrane systematic review

Aim of the study

To assess the benefits and harms of labour induction as compared to expectant management in women with suspected fetal macrosomia

Study dates

The initial search was performed in January 2016; review content was assessed as up-to-date by the authors in January 2016

Source of funding

Funding for one of the</td>
<td>
<table>
<tr><td>to ≤39 weeks, N (%)</td><td></td><td></td></tr>
<tr><td>Estimated fetal weight, mean grams, sonography (SD)</td><td>3964 (229)</td><td>3971 (238)</td></tr>
<tr><td>Gestational diabetes¥, N (%)</td><td>39 (10)</td><td>43 (11)</td></tr>
</table>
¥Diet control only

Gonen 1997*

<table>
<tr><td></td><td>Induction of labour

(N=134)</td><td>Expectant management

(N=139)</td></tr>
<tr><td>Age, mean (SD)</td><td>30.8 (5)</td><td>29.5 (5.2)</td></tr>
<tr><td>Gestational age, mean days (SD)</td><td>284.1 (6.4)</td><td>284.4 (5.7)</td></tr>
<tr><td>Estimated fetal weight, mean grams, sonography (SD)</td><td>4160 (126.3)</td><td>4159.4 (126.5)</td></tr>
</table>
Kean, unpublished data</td>
<td>induction of labour according to the hospital's policy (for example, PROM occurred, or pregnancy continuing beyond 41 weeks)

Gonen 1997

Intervention: induction of labour using oxytocin or prostaglandins according to cervical status

Comparison: expectant management until labour started spontaneously. Labour was induced if the pregnancy continued beyond 42 weeks or if fetal distress was suspected

Kean, unpublished data
Intervention: induction of labour using oxytocin or prostaglandins
Comparison: expectant management until labour started spontaneously. Labour</td>
<td>extracted data, and authors of the original reports were contacted if any information was unclear. Risk of bias was assessed by 2 authors.

Definition of shoulder dystocia

Boulvain 2015*: Interval of 60 seconds or more between the delivery of the head and the body

Gonen 1997*: Not reported

Kean, unpublished data: Not reported

Tey 1995*: Not reported</td>
<td>Induction of labour: 15/407

Expectant management: 32/411

Gonen 1997

Induction of labour: 5/134

Expectant management: 6/139

Kean, unpublished data

Induction of labour: 0/30

Expectant management: 0/29

Tey 1995

Induction of labour: 4/19

Expectant management: 3/21

Perinatal death

Boulvain 2015</td>
<td>appraise studies: low

Domain 4: concerns regarding the synthesis and findings: low

Risk of bias in the review

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?: yes

B. Was the relevance of identified studies to the review's research questions appropriately considered?: yes

C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?: yes

Risk of bias in the review: LOW</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
reviewers: National Institute for Health Research (NIHR) Cochrane Programme Funding for the Cochrane Editorial Group: National Institute for Health Research, Cochrane Infrastructure funding, Cochrane Programme Grant funding (13/89/05) to Cochrane Pregnancy and Childbirth.	<table><tr><td></td><td>Induction of labour (N=30)</td><td>Expectant management (N=29)</td></tr><tr><td>Age, mean (SD)</td><td colspan="2">Not reported</td></tr><tr><td>Gestational age, mean (SD)</td><td colspan="2">42 completed weeks of gestation</td></tr><tr><td>Estimated fetal weight</td><td colspan="2">Above the 97th percentile</td></tr></table> Tey 1995* <table><tr><td></td><td>Induction of labour (N=19)</td><td>Expectant management (N=21)</td></tr><tr><td>Age, mean (SD)</td><td colspan="2">Not reported</td></tr><tr><td>Gestational age, mean weeks (SD)</td><td>39.8 (1.1)</td><td>40.1 (1.4)</td></tr><tr><td>Estimated fetal weight, mean grams (SD)</td><td>4250 (317)</td><td>4253 (338)</td></tr></table> **Inclusion criteria**	was induced if the pregnancy continued beyond 42 weeks Tey 1995 ***Intervention:*** induction of labour using PGE2 gel if Bishop score <6, followed by oxytocin ***Comparison:*** expectant management (no further details were provided)		*Induction of labour:* 0/407 *Expectant management:* 0/411 Kean, unpublished data *Induction of labour:* 0/30 *Expectant management:* 0/29 Tey 1995 *Induction of labour*: 0/19 *Expectant management:* 0/21 **Brachial plexus injury** Boulvain 2015 *Induction of labour:* 0/407 *Expectant management:* 0/411	**Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool** Boulvain 2015 **Random sequence generation:** Low risk (randomisation performed by centralised computer with permuted blocks) **Allocation concealment:** Low risk (central randomisation, participants and clinicians had no access to the randomisation) **Blinding of participants and personnel:** High risk (blinding was not possible) **Blinding of outcome assessment:** Unclear risk (assessment of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	RCTs of published and unpublished studies of women randomised to induction of labour versus expectant management. Studies should have included women with suspected fetal macrosomia at term (37 to 40 weeks gestational age) with no other indication of induction of labour than the suspected fetal macrosomia. ***Definition of macrosomia (based on trial inclusion criteria):*** Boulvain 2015* Two-step procedure: fetus weighing more than the 90th percentile using either fundal height or fetal weight estimated with the Leopold manoeuvres were assessed sonographically with Hadlock's formula. Those with an estimated weight above the 95th percentile (3500 g at 36 weeks of gestation, 3700 g at 37 weeks, and 3900 g at 38 weeks) were included. Gonen 1997* Ultrasonic fetal weight estimation between 4000 and 4500 g. Kean, unpublished data Ultrasonic fetal weight estimation above the 97th percentile (as defined with the charts of fetal size presented in Chitty 1994, https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-0528.1994.tb13077.x). Tey 1995* Ultrasonic fetal weight estimation between 4000 and 4750 g **Exclusion criteria**			Gonen 1997 *Induction of labour:* 0/134 *Expectant management:* 2/139 Kean, unpublished data *Induction of labour:* 0/30 *Expectant management:* 0/29 Tey 1995 *Induction of labour:* 0/19 *Expectant management:* 0/21 **Caesarean birth** Boulvain 2015 *Induction of labour:* 114/407 *Expectant management:* 130/411	primary outcome done by investigators masked to group allocation) **Incomplete outcome data:** Low risk (<20% lost to follow-up) **Selective reporting:** Unclear risk (some of the outcomes were reported in a slightly different way in the final publication as compared to the protocol and others were not pre-specified in either the registry or the protocol) **Other bias:** Unclear risk (baseline differences in weight gain) Gonen 1997 **Random sequence generation**: Low risk (computer

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Quasi-randomised trials and studies using a cross-over design			Gonen 1997 *Induction of labour:* 26/134 *Expectant management:* 30/139 Kean, unpublished data *Induction of labour:* 11/30 *Expectant management:* 8/29 **Tey 1995** *Induction of labour:* 6/19 *Expectant management:* 8/21	generated table of random numbers) **Allocation concealment:** Uncl ear risk (not reported) **Blinding of participants and personnel:** High risk (blinding was not possible) **Blinding of outcome assessment:** High risk (blinding was not possible) **Incomplete outcome data:** Low risk (<20% lost to follow-up) **Selective reporting:** Low risk Other bias: Low risk Kean, unpublished data **Random sequence generation:** Low risk (computer-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					generated table of random numbers) **Allocation concealment:** Low risk (sealed, opaque consecutively-numbered envelopes) **Blinding of participants and personnel:** High risk (blinding was not possible) **Blinding of outcome assessment:** High risk (not reported, it is likely that the outcome assessors were not blinded to treatment allocation) **Incomplete outcome data:** Low risk (<20% lost to follow-up) **Selective reporting:** Unclear risk (unclear, unpublished data) **Other bias:** Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					risk (unclear, unpublished data) Tey 1995 **Random sequence generation:** Low risk (computer-generated table of random numbers) **Allocation concealment:** Low risk (sealed opaque envelopes were used) **Blinding of participants and personnel:** High risk (blinding was not possible) **Blinding of outcome assessment:** High risk (not reported, it is likely that the outcome assessors were not blinded to treatment allocation) **Incomplete outcome data:** Unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					(unclear, published as an abstract) **Selective reporting:** Unclear risk (unclear, published as an abstract) **Other bias:** Unclear risk (unclear, published as an abstract) **Other information** The data presented in this evidence table has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies were retrieved for accuracy and to check if other outcomes of interest were reported. The risk of bias assessment was reported in the Cochrane review.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Data extracted by the NGA technical team from the original study has been marked with an *. Kean, unpublished data is quoted as LIBBY 1998 throughout this Cochrane systematic review. This has been quoted differently to be consistent with the other references and because being an unpublished trial, the year of publication is not definite.

Appendix E – Forest plots

Forest plots for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Comparison 1. Induction of labour versus expectant management

Critical outcomes

Figure 2: Third/fourth degree perineal tears

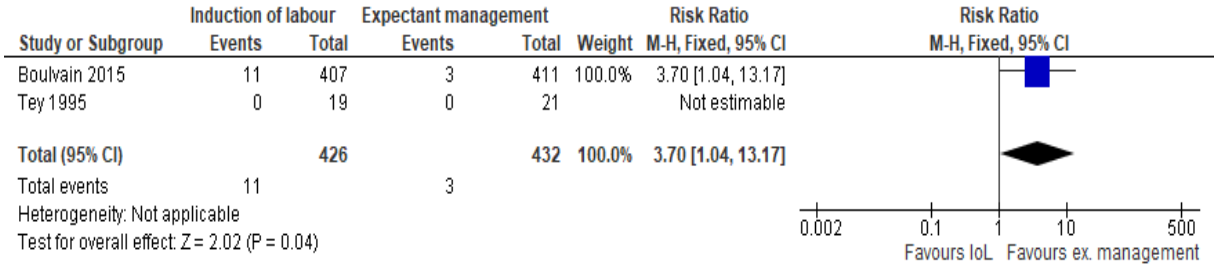
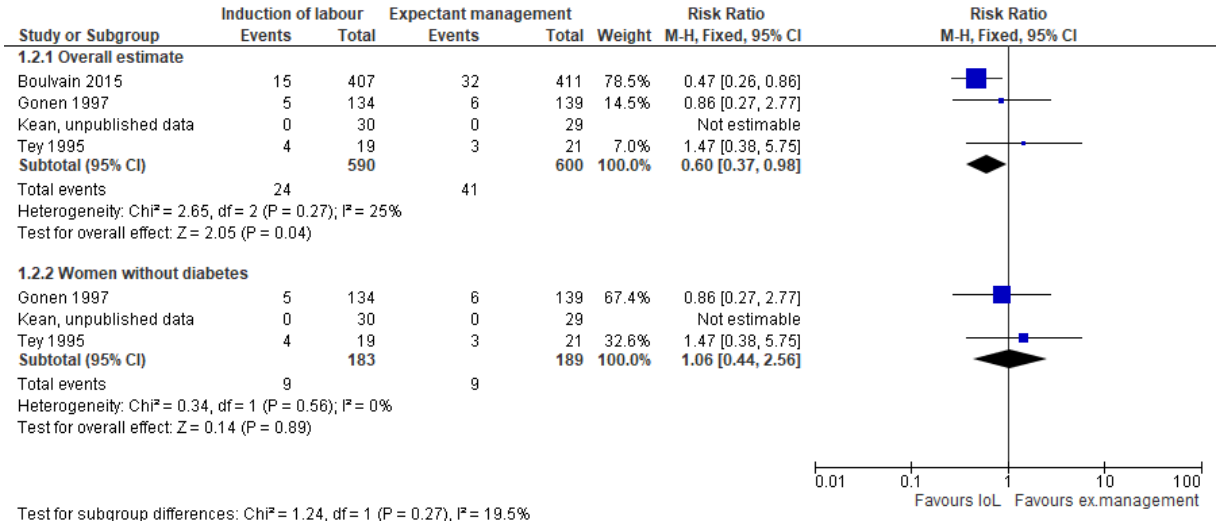


Figure 3: Shoulder dystocia



Important outcomes

Figure 4: Perinatal death

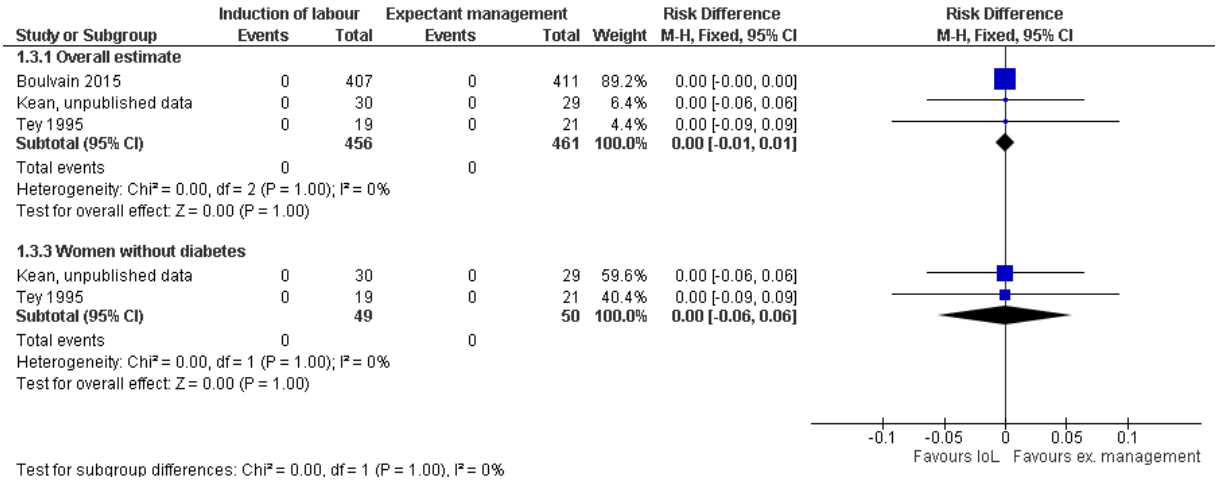


Figure 5: Brachial plexus injury

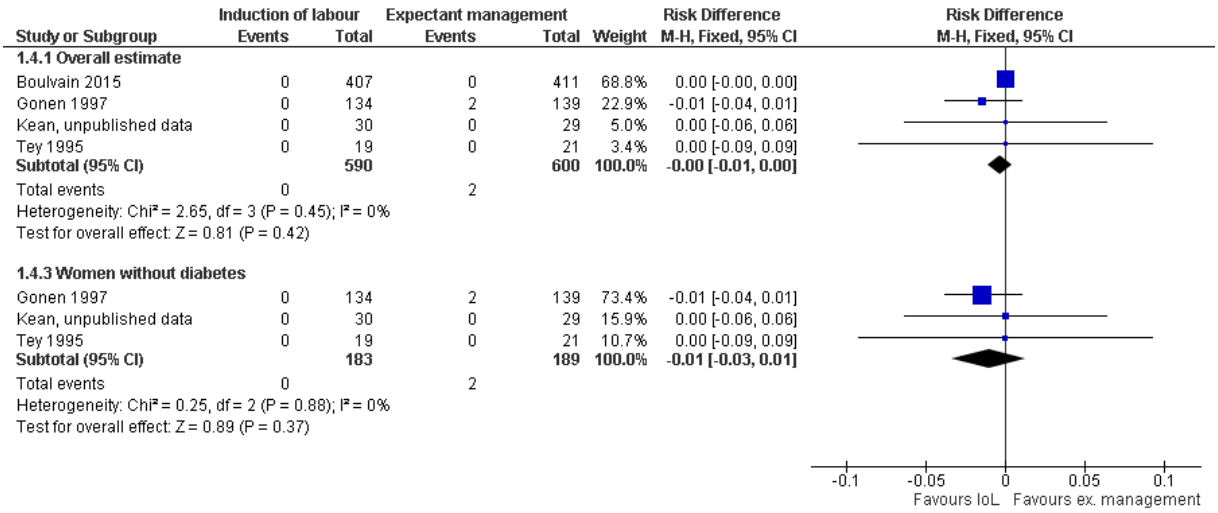
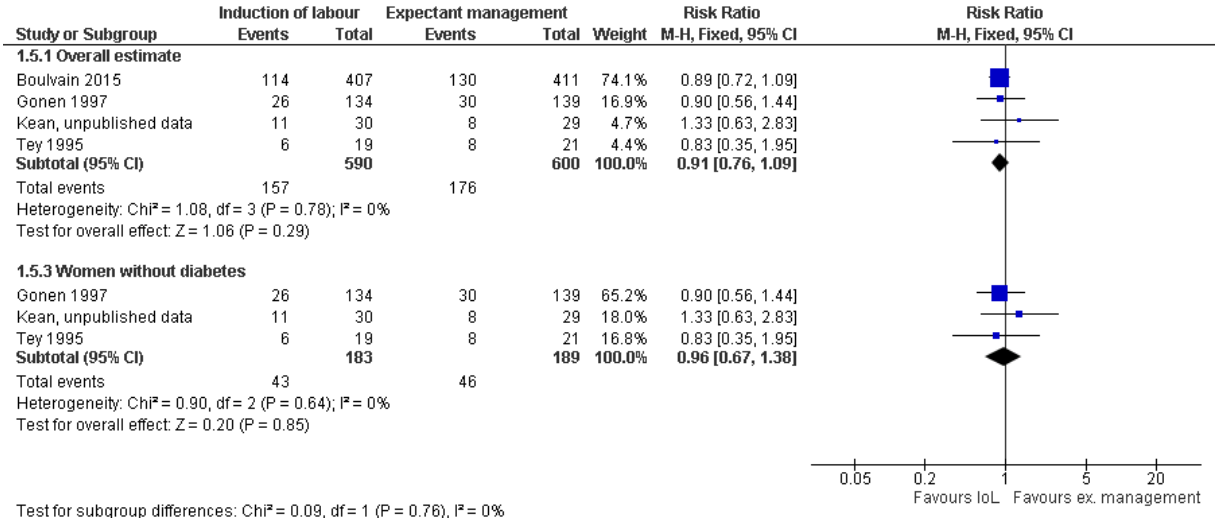


Figure 6: Caesarean birth



Appendix F – GRADE tables

GRADE tables for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Table 5: Comparison 1. Induction of labour versus expectant management

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction of labour	Expectant management	Relative (95% CI)	Absolute		
Third/ fourth degree perineal tears - Overall estimate												
2 (Boulvain 2015, Tey 1995)	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11/426 (2.6%)	3/432 (0.69%)	RR 3.7 (1.04 to 13.17)	19 more per 1000 (from 0 more to 85 more)	LOW	CRITICAL
Third/ fourth degree perineal tears - Women without diabetes												
1 (Tey 1995)	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/19 (0%)	0/21 (0%)	RD 0.00 (0.09 to 0.09)	0 per 1000 (from 90 fewer to 90 more)	VERY LOW	CRITICAL
Shoulder dystocia - Overall estimate												
4 (Boulvain 2015, Gonen 1997, Kean unpublished data, Tey 1995)	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	24/590 (4.1%)	41/600 (6.8%)	RR 0.6 (0.37 to 0.98)	27 fewer per 1000 (from 1 fewer to 43 fewer)	LOW	CRITICAL
Shoulder dystocia - Women without diabetes												
3 (Gonen 1997, Kean unpublished data, Tey 1995)	RCT	Serious[7]	No serious inconsistency	No serious indirectness	Very serious[8]	None	9/183 (4.9%)	9/189 (4.8%)	RR 1.06 (0.44 to 2.56)	3 more per 1000 (from 27 fewer to 74 more)	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction of labour	Expectant management	Relative (95% CI)	Absolute		
Perinatal death - Overall estimate												
3 (Boulvain 2015, Kean unpublished data, Tey 1995)	RCT	Serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/456 (0%)	0/461 (0%)	RD 0.00 (0.01 to 0.01)	0 per 1000 (from 10 fewer to 10 more)	MODERATE	CRITICAL
Perinatal death - Women without diabetes												
2 (Kean unpublished data, Tey 1995)	RCT	Serious[10]	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/49 (0%)	0/50 (0%)	RD 0.00 (0.06 to 0.06)	0 per 1000 (from 60 fewer to 60 more)	VERY LOW	CRITICAL
Brachial plexus injury - Overall estimate												
4 (Boulvain 2015, Gonen 1997, Kean unpublished data, Tey 1995)	RCT	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/590 (0%)	2/600 (0.33%)	RD 0.00 (-0.01 to 0)	3 fewer per 1000 (from 3 fewer to 3 fewer)	MODERATE	IMPORTANT
Brachial plexus injury - Women without diabetes												
3 (Boulvain 2015, Kean unpublished data, Tey 1995)	RCT	Serious[7]	No serious inconsistency	No serious indirectness	Serious[11]	None	0/183 (0%)	2/189 (1.1%)	RD -0.01 (-0.03 to 0.01)	11 fewer per 1000 (from 10 fewer to 11 fewer)	LOW	IMPORTANT
Caesarean birth - Overall estimate												
4 (Boulvain 2015, Gonen 1997, Kean unpublished data, Tey 1995)	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	157/ 590 (26.6%)	176/600 (29.3%)	RR 0.91 (0.76 to 1.09)	26 fewer per 1000 (from 70 fewer to 26 more)	LOW	IMPORTANT
Caesarean birth - Women without diabetes												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction of labour	Expectant management	Relative (95% CI)	Absolute		
3 (Gonen 1997, Kean unpublished data, Tey 1995)	RCT	Serious[7]	No serious inconsistency	No serious indirectness	Very serious[8]	None	43/183 (23.5%)	46/189 (24.3%)	RR 0.96 (0.67 to 1.38)	10 fewer per 1000 (from 80 fewer to 92 more)	VERY LOW	IMPORTANT

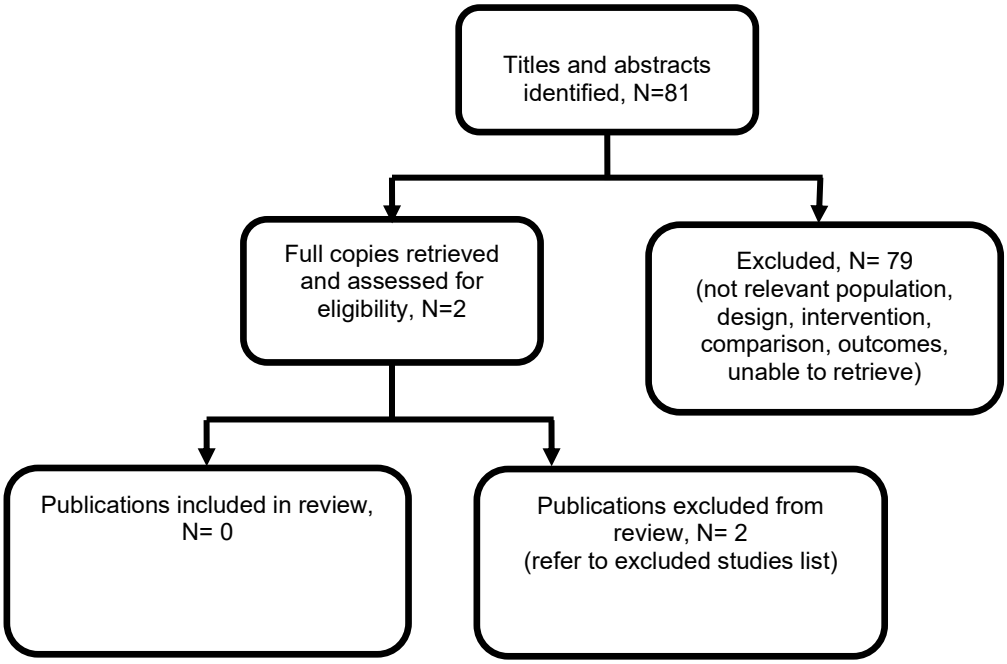
[1] The quality of the evidence was downgraded by one level due to high risk of blinding of participants and personnel in two studies; unclear risk of blinding of outcome assessors in one study; high risk of blinding of outcome assessors in one study; unclear risk of selective reporting in two studies and unclear risk of other bias in two studies
[2] The quality of the evidence was downgraded by one level as the 95% CI crossed 1 default MID threshold (1.25)
[3] The quality of the evidence was downgraded by one level due to high risk of blinding of participants and personnel; high risk of blinding of outcome assessors; unclear risk of incomplete outcome data and unclear risk of other bias
[4] The quality of the evidence was downgraded by two levels as there were no events and the sample size was less than 300
[5] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in one study; high risk of blinding of participants and personnel in four studies; high risk of blinding of outcome assessors in three studies; unclear risk of blinding of outcome assessors in one study; unclear risk of incomplete outcome data in one study; unclear risk of selective reporting in three studies and unclear risk of other bias in three studies
[6] The quality of the evidence was downgraded by one level as the 95% CI crossed 1 default MID threshold (0.8)
[7] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in one study; high risk of blinding of participants and personnel in three studies; high risk of blinding of outcome assessors in three studies; unclear risk of selective reporting in two studies and unclear risk of other bias in two studies
[8] The quality of the evidence was downgraded by two levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
[9] The quality of the evidence was downgraded by one level due to high risk of blinding of participants and personnel in three studies; high risk of blinding of outcome assessors in two studies; unclear risk of blinding of outcome assessors in one study; unclear risk of incomplete outcome data in one study; unclear risk of selective reporting in three studies and unclear risk of other bias in three studies
[10] The quality of the evidence was downgraded by one level due to high risk of blinding of participants and personnel in two studies; high risk of blinding of outcome assessors in two studies; unclear risk of incomplete outcome data in one study; unclear risk of selective reporting in two studies and unclear risk of other bias in two studies
[11] The quality of the evidence was downgraded by one level as there were no events in both arms in some studies and the total sample size was less than 500 but greater than 300

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

No economic evidence was identified for this review question.

Figure 7: Flow diagram of economic evidence article selection for benefits and harms associated with induction of labour in women with suspected fetal macrosomia



Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Health economic analysis for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

No health economic analysis was carried out for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

Table 6: Clinical studies

Study	Reason for Exclusion
Magro-Malosso, E. R., Saccone, G., Chen, M., Navathe, R., Di Tommaso, M., Berghella, V., Induction of labour for suspected macrosomia at term in non-diabetic women: a systematic review and meta-analysis of randomized controlled trials, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 414-421, 2017	The relevant studies have already been included in Boulvain 2016
Sanchez-Ramos L, Bernstein S, Kaunitz A M, Expectant management versus labor induction for suspected fetal macrosomia: a systematic review, Obstetrics and Gynecology, 100, 997-1002, 2002	The relevant studies have already been included in Boulvain 2016

Table 7: Studies excluded from the economic review

Study	Reason for Exclusion
Herbst,M.A., Treatment of suspected fetal macrosomia: a cost-effectiveness analysis, American Journal of Obstetrics and Gynecology, 193, 1035-1039, 2005	Model did not address important maternal outcomes
Lee, V. R., Niu, B., Kaimal, A., Caughey, A. B., Induction of labor for suspected macrosomia: A cost-effectiveness analysis, Obstetrics and Gynecology, 125, 103S, 2015	Conference abstract

Appendix L – Research recommendations

Research recommendations for review question: What are the benefits and harms of induction of labour in women with suspected fetal macrosomia?

No research recommendations were made for this review question.