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Fetal and umbilical Doppler ultrasound in high-risk pregnancies.

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Fetal and umbilical Doppler ultrasound in high-risk pregnancies

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ABSTRACT

Background

Abnormal blood flow patterns in fetal circulation detected by Doppler ultrasound may indicate poor fetal prognosis. It is also possible false positive Doppler ultrasound findings could encourage inappropriate early delivery.

Objectives

The objective of this review was to assess the effects of Doppler ultrasound used to assess fetal well-being in high-risk pregnancies on obstetric care and fetal outcomes.

Search methods

We updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 30 September 2013.

Selection criteria

Randomised and quasi-randomised controlled trials of Doppler ultrasound for the investigation of umbilical and fetal vessels waveforms in high-risk pregnancies compared with no Doppler ultrasound.

Data collection and analysis

Two review authors independently assessed the studies for inclusion, assessed risk of bias and carried out data extraction. Data entry was checked.

Main results

Eighteen completed studies involving just over 10,000 women were included. The trials were generally of unclear quality with some evidence of possible publication bias. The use of Doppler ultrasound in high-risk pregnancy was associated with a reduction in perinatal deaths (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.52 to 0.98, 16 studies, 10,225 babies, 1.2% versus 1.7 %, number needed to treat (NNT) = 203; 95% CI 103 to 4352). There were also fewer inductions of labour (average RR 0.89, 95% CI 0.80 to 0.99, 10 studies, 5633 women, random-effects) and fewer caesarean sections (RR 0.90, 95% CI 0.84 to 0.97, 14 studies, 7918 women). No difference was found in operative vaginal births (RR 0.95, 95% CI 0.80 to 1.14, four studies, 2813 women), nor in Apgar scores less than seven at five minutes (RR 0.92, 95% CI 0.69 to 1.24, seven studies, 6321 babies).

Authors' conclusions

Current evidence suggests that the use of Doppler ultrasound in high-risk pregnancies reduced the risk of perinatal deaths and resulted in less obstetric interventions. The quality of the current evidence was not of high quality, therefore, the results should be interpreted with some caution. Studies of high quality with follow-up studies on neurological development are needed.

PLAIN LANGUAGE SUMMARY

Doppler ultrasound of fetal vessels in pregnancies at increased risk of complications

Whilst in high-income countries most babies grow well in the womb, sometimes the mother might have a medical problem, such as diabetes, high blood pressure, heart or kidney problems, that impacts on the growth of the baby. Also, sometimes babies just do not grow well for reasons we do not fully understand. These babies with poor growth can be at increased risk of complications which can result in increased mortality or morbidity. Doppler ultrasound detects changes in the pattern of blood flow through the baby's circulation. It may be that problems for the baby could be identified through these changes. Interventions, like early delivery, might then be able to reduce the mortality and morbidity. However, it may also be that the use of Doppler ultrasound could increase the use of caesarean section.

The review of trials identified 18 studies involving just over 10,000 women. These studies compared the use of Doppler ultrasound of the babies vessels in utero with no Doppler or with cardiotocography (CTG sometimes known as electronic fetal monitoring). There was a reduction in the number of babies who died, fewer caesarean sections and operative deliveries, but the quality of the studies was not high and there remains some uncertainty here. Further studies of high quality would, therefore, be helpful.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Fetal and umbilical Doppler ultrasound compared to no Doppler ultrasound for pregnant women at increased risk of fetal complications						
Patient or population: pregnant women at increased risk of fetal complications Settings: antenatal clinics or inpatient wards Intervention: Fetal and umbilical Doppler ultrasound Comparison: no Doppler ultrasound						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no Doppler ultrasound	Fetal and umbilical Doppler ultrasound				
Any perinatal death after randomisation	Study population		RR 0.71 (0.52 to 0.98)	10225 (16 studies)	⊕○○○ very low ^{1,2,3}	
	17 per 1000	12 per 1000 (9 to 17)				
	Medium-risk population					
	15 per 1000	11 per 1000 (8 to 15)				
Serious neonatal morbidity - singleton pregnancy	Study population		RR 0.12 (0.02 to 0.99)	500 (1 study)	⊕○○○ very low ^{1,4}	
	12 per 1000	1 per 1000 (0 to 12)				
	Medium-risk population					
	32 per 1000	4 per 1000 (1 to 32)				

Serious neonatal morbidity - multiple pregnancy	See comment	See comment	Not estimable	0 (0)	See comment	No studies have looked at serious neonatal morbidity in multiple pregnancies when comparing fetal and umbilical Doppler ultrasound with no Doppler ultrasound
Cae-sarean section (elective and emergency)	Study population		RR 0.9 (0.84 to 0.97)	7918 (14 studies)	⊕⊕○○ low ^{1,5}	
	0 per 1000	0 per 1000 (0 to 0)				
	Medium-risk population					
	280 per 1000	252 per 1000 (235 to 272)				
Induction of labour	Study population		RR 0.89 (0.8 to 0.99)	5633 (10 studies)	⊕⊕○○ low ^{1,6,7}	
	334 per 1000	297 per 1000 (267 to 331)				
	Medium risk population					
	341 per 1000	303 per 1000 (273 to 338)				
Apgar < 7 at 5 minutes	Study population		RR 0.92 (0.69 to 1.24)	6321 (7 studies)	⊕⊕○○ low ^{1,8,9}	
	29 per 1000	27 per 1000 (20 to 36)				
	Medium-risk population					

	24 per 1000	22 per 1000 (17 to 30)				
Long-term infant neurodevelopmental outcome	See comment	See comment	Not estimable	0 (0)	See comment	There has been no comparative long term follow-up of babies exposed to Doppler ultrasound in pregnancy in women at increased risk of complications

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Too much missing information.

² The 153 events are below the recommended level of 300 needed for precision.

³ Funnel plot asymmetry test gives $P = 0.057$, suggesting significant asymmetry thus indicating publication bias.

⁴ The nine events are very seriously below the recommended 300 needed for precision.

⁵ Funnel plot asymmetry test is just non-significant ($P = 0.12$), but guidance from a statistician suggests visually there appears to be small studies missing indicating some publication bias.

⁶ There was evidence of heterogeneity with $T\text{-squared} = 0.01$; $\text{Chi}^2 P = 0.08$; $I^2 = 41\%$.

⁷ Funnel plot asymmetry test gives $P = 0.35$ - so not significant.

⁸ The 174 events is below the recommended level of 300 needed for precision.

⁹ Funnel plot symmetry test is $P = 0.76$, so not significant.

BACKGROUND

The previous version of this review (Neilson 1996) was split into two separate reviews, for which new protocols were prepared. This present review covers Doppler ultrasound of fetal vessels including umbilical arteries in women at high risk of fetal compromise. The other review covers Doppler ultrasound of utero-placental circulation (*Utero-placental Doppler ultrasound for improving pregnancy outcome*; Stampalija 2010). In addition, we will update the review of 'routine' use of Doppler ultrasound in low-risk pregnant women (*Fetal and umbilical Doppler ultrasound in normal pregnancy*; Alfirevic 2010b).

Description of the condition

When it comes to the provision of antenatal care or research, pregnant women tend to be divided into low- and high-risk populations; however, the boundaries between the groups are often blurred. For most researchers, 'high-risk status' includes maternal conditions associated with increased perinatal mortality and morbidity such as diabetes, hypertensive disorders (chronic hypertension and pre-eclampsia), cardiac, renal and autoimmune disorders (Fisk 2001; Graves 2007; Westergaard 2001). More recently, thrombophilias (congenital and acquired) have been added to this list (Alfirevic 2002; Greer 1999).

Of the conditions specific to pregnancy, fetal growth restriction, antepartum haemorrhage, multiple pregnancy and prolonged pregnancy tend to be regarded as 'high risk' (Bernstein 2000; Westergaard 2001).

It is important to stress that the fetal growth restriction is often confused with the concept of being small-for-gestational age. Some fetuses are constitutionally small and they do not have increased perinatal morbidity and mortality. Our inability to distinguish easily between small, but healthy fetuses and those who are failing to reach their growth potential has hampered attempts to find appropriate treatment for growth restriction. Growth restricted fetuses, who may or may not be small for dates are at increased risk of mortality and serious morbidity (intraventricular haemorrhage, bronchopulmonary dysplasia, necrotising enterocolitis, infection, pulmonary haemorrhage, hypothermia and hypoglycaemia) (Fisk 2001). Early antenatal detection, treatment where appropriate, and timely delivery could minimise the risks significantly.

In multiple pregnancies, most of the excess morbidity and mortality can be attributed to preterm birth and to pathology associated with twin-to-twin transfusion syndrome (TTTS) in monochorionic pregnancies. However, growth discordance or selective intrauterine growth restriction (IUGR) are more common than TTTS (Ortibus 2009). The pathophysiological nature of the TTTS differs from other placental pathology with specific impact on the fetal haemodynamics. Different monitoring and treatment strategies are needed for this condition and for this reason we

planned to exclude this subgroup of multiple pregnancies from this review if such information is available.

The most commonly used methods for the assessment of fetal well-being in high-risk pregnancies include fetal cardiotocography (CTG) (Pattison 1999), biophysical profile (Lalor 2008) and Doppler studies of the fetal circulation. This review focuses on the role of fetal and umbilical Doppler ultrasound as a test of fetal well-being in high-risk pregnancies.

Description of the intervention

The use of Doppler ultrasound to investigate the pattern of waveforms in the umbilical artery during pregnancy was first reported in 1977 from Dublin (Fitzgerald 1977). The waveforms were derived from the changes in the ultrasound frequency of the Doppler signal, which targeted circulating fetal blood within the umbilical artery. Such flow velocity waveforms (FVW) from the fetoplacental circulation are dependent on the fetal cardiac contraction force, density of the blood, the vessel wall elasticity and peripheral or downstream resistance (Giles 1985; Owen 2001). It was suggested that the FVWs should be obtained with the mother in a semi-recumbent position during a period of fetal inactivity, as the impedance indices are moderated by fetal breathing and elevated fetal heart rates (Mires 2000).

Different types of measurements have been described in an attempt to quantify the Doppler signals accurately and reproducibly (Chen 1996; Mari 2009; Owen 2001). The indices are calculated as ratios between peak systolic velocity (A), end-diastolic peak velocity (B) and mean velocity (mean). The most common in clinical practice are pulsatility index ($PI = (A - B)/\text{mean}$) and resistant index ($RI = (A - B)/A$) (Burns 1993). Ideally, the measurements have to be done on several consecutive identical wave forms with the angle of the insonation as close to zero as possible (Burns 1993).

Observational studies have demonstrated that in the presence of normal placental function the umbilical artery waveform has a pattern compatible with a low-resistance system, displaying forward blood flow throughout the cardiac cycle (Neilson 1987).

Initial studies have focused on umbilical arteries and veins, but better equipment has allowed studies of carotid and intracranial arteries, aorta, coronary circulation (Baschat 2002), mesenteric artery and the venous circulation (ductus venosus, inferior vena cava and vena Galena) (Cheema 2004; Owen 2001). The assessment of utero-placental arteries has also been investigated (Trudinger 1985a; Trudinger 1985b) and has been reviewed in a separate Cochrane review (*Utero-placental Doppler ultrasound for improving pregnancy outcome*; Stampalija 2010).

When inadequate vascularisation of the placenta occurs (placental insufficiency), the haemodynamic changes in the fetoplacental circulation develop, often in a progressive fashion. Doppler indices from the umbilical artery start to increase when approximately 60% to 70% of the placental vascular tree is not functioning (Thompson 1990). This tends to be followed by a decrease in

the impedance to blood flow in the middle cerebral artery as a consequence of “brain sparing effect” (Hecher 2001), while the resistance increases in aortic blood flow (Ferrazzi 2002; Hecher 2001). This redistribution of the blood flow allows preferential oxygenation of fetal vital organs such as brain and heart. Late Doppler changes include absent or reverse end diastolic flow in the umbilical artery (Al-Ghazali 1990; Nicholaides 1988) and increase in the resistance of venous blood flow (ductus venosus and inferior vena cava) (Baschat 2001; Ferrazzi 2002). Higher resistance in venous circulation reflects the elevation of right heart afterload and increase of the intraventricular pressure caused by hypoxaemia of the myocardium. Those changes correlate well with fetal acidosis (Bilardo 1990; Weiner 1990).

How the intervention might work

The time scale over which placental insufficiency and fetal compensatory changes develop varies and depends on underlying maternal and fetal pathology and gestational age. It is, therefore, difficult to apply the same management protocol to all women with abnormal Doppler findings. Normal Doppler findings do provide some reassurance and may, in some circumstances, reduce the need for hospitalisation and additional fetal monitoring, but this is not always the case. There is also some suggestion that normal umbilical artery Doppler ultrasound cannot be assumed to mean low risk where the fetus is small (Figueras 2008). An abnormal Doppler finding tends to trigger management protocols that vary significantly, not only between low- and high-income countries, but also from unit to unit in the same country. The most important factors that determine subsequent management are gestation, availability of additional monitoring methods (computerised CTG, biophysical profile, colour Doppler) and neonatal intensive care availability.

The GRIT study showed that although the delay in delivery (around four days) may lead to more stillbirths, overall number of perinatal deaths is not reduced by an immediate delivery (GRIT 2003). Importantly, the study showed that at the two years follow-up, the immediate delivery group showed a trend towards more neurological disability (GRIT 2004).

Recently, considerable interest has been generated by observations that ductus venos flow may be a good predictor of perinatal outcome (Baschat 2001; Bilardo 2004; Ferrazzi 2002). The ongoing TRUFFLE study has been designed to compare reduced short-term variation on CTG, early ductus venosus changes or late ductus venosus changes as a trigger for delivery of the growth restricted babies (Lees 2005).

Ultimately, the goal of any Doppler-triggered management protocol is to improve perinatal mortality and morbidity. An unnecessary early intervention may result in excess morbidity from prematurity, whilst a delay may result in a stillbirth or severely compromised newborn (GRIT 2003).

Why it is important to do this review

The first meta-analysis of umbilical artery Doppler in high-risk pregnancies was published in 1995 (Alfirevic 1995; Neilson 1995), demonstrating improvement with Doppler in a number of clinical outcomes and possible reduction in perinatal deaths (Neilson 1995). Since then, ultrasound technology has moved on and much more complex assessment of fetal circulation has become standard clinical practice in fetal medicine units worldwide. However, the potential for benefit from the new methods has to be balanced with the potential for harm (inappropriate interventions, or lack of them).

Another Cochrane review has analysed the role of Doppler ultrasound in routine practice (Bricker 2007), and doubts have been expressed about its benefit as a screening tool in all pregnancies. The use of utero-placental Doppler ultrasound is the subject of another Cochrane review (*Utero-placental Doppler ultrasound for improving pregnancy outcome*; Stampalija 2010). However, when both fetal and utero-placental Doppler assessments are used in high-risk pregnancies, the study will be included here because clinical judgements tends to rest on the fetal assessment.

OBJECTIVES

To assess whether the use of fetal and umbilical Doppler ultrasound in high-risk pregnancies improves subsequent obstetric care and fetal outcome.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials and quasi-randomised studies comparing Doppler ultrasound (fetal and umbilical circulations) in pregnancies considered to be at high risk of fetal compromise.

Types of participants

Women with pregnancies considered to be at ‘high risk’ for fetal compromise, e.g. intrauterine growth restriction, post-term pregnancies, previous pregnancy loss, women with hypertension, women with diabetes or other maternal pathology (e.g. thrombophilia). We planned to include twin pregnancies, separating monochorionic and dichorionic pregnancies where possible.

Types of interventions

Doppler ultrasound of the fetal and umbilical vessels for fetal assessment in pregnancies in high-risk populations. We have excluded utero-placental Doppler studies (as these are assessed in a separate review). However, where umbilical artery or fetal Doppler was combined with utero-placental Doppler, the study has been included in this review.

Comparisons

1. Doppler ultrasound of fetal vessels versus no Doppler ultrasound of fetal vessels (including comparisons of Doppler ultrasound of fetal vessels revealed versus Doppler ultrasound of fetal vessels concealed).
2. Doppler ultrasound of fetal vessels versus other forms of monitoring, e.g. cardiotocography, biophysical profile.
3. Comparison of different forms of Doppler ultrasound of fetal vessels versus other types of Doppler ultrasound of fetal vessels.
4. Combination of umbilical artery or fetal Doppler with utero-placental Doppler (uterine artery Doppler) versus either no other monitoring or additional monitoring.

Types of outcome measures

We have selected outcome measures with the help of a proposed core data set of outcome measures ([Devane 2007](#)).

Primary outcomes

1. Any perinatal death after randomisation.
2. Serious neonatal morbidity - composite outcome including hypoxic ischaemic encephalopathy, intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC).

Secondary outcomes

1. Stillbirth.
2. Neonatal death.
3. Any potentially preventable perinatal death*.
4. Fetal acidosis.
5. Apgar score less than seven at five minutes.
6. Caesarean section (both elective and emergency).
7. Spontaneous vaginal birth.
8. Operative vaginal birth.
9. Induction of labour.
10. Oxytocin augmentation.
11. Neonatal resuscitation required.
12. Infant requiring intubation/ventilation.
13. Neonatal fitting/seizures.
14. Preterm labour (onset of labour before 37 completed weeks of pregnancy).

15. Gestational age at birth.
16. Infant respiratory distress syndrome.
17. Meconium aspiration.
18. Neonatal admission to special care or intensive care unit, or both.
19. Hypoxic ischaemic encephalopathy (a condition of injury to the brain).
20. IVH.
21. BPD.
22. NEC.
23. Infant birthweight.
24. Length of infant hospital stay.
25. Long-term infant/child neurodevelopmental outcome.
26. Women's views of their care.

* Perinatal death excluding chromosomal abnormalities, termination of pregnancies, birth before fetal viability (as defined by trialists) and fetal death before use of the intervention.

Non-prespecified outcomes are also reported if we consider them to be important.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to update the update the search of the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2013)

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We also planned to look for additional studies in the reference lists of the studies identified.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review (Alfirevic 2010), see Appendix 1.

In this 2013 update, no new trial reports were identified. In future updates, if trials are identified for inclusion, we will use the methods outlined in Appendix 2.

RESULTS

Description of studies

Results of the search

The search identified 29 studies of which 18 have been included involving 10,156 women, 10 have been excluded and one study is ongoing (Lees 2005). For further details of trial characteristics, please refer to the tables of [Characteristics of included studies](#), [Characteristics of excluded studies](#) and [Ongoing studies](#). The updated search in September 2013 retrieved no new studies.

Included studies

Most studies included Doppler assessments in both experimental and control groups, with the Doppler results being revealed to clinicians only in the 'Doppler group' (Burke 1992; Biljan 1992; de Rochambeau 1992; Giles 2003; Johnstone 1993; Neales 1994; Newnham 1991; Nienhuis 1997; Nimrod 1992; Norman 1992; Ott 1998; Pattinson 1994; Trudinger 1987; Tyrrell 1990). Doppler ultrasound was used as an addition to the standard fetal

monitoring (e.g. cardiotocography (CTG), biophysical profile, fetal biometry).

Seven of these studies involved singleton pregnancies only (de Rochambeau 1992; Biljan 1992; Neales 1994; Nienhuis 1997; Ott 1998; Trudinger 1987; Tyrrell 1990) and one study of 539 women involved twin pregnancies only (Giles 2003). Two studies assessed a mixture of singleton and multiple pregnancies with 40/2289 (1.7%) being twin pregnancies in Johnstone 1993 and 40/505 (7.9%) being twin pregnancies in Newnham 1991. Four studies did not state whether they included just singleton pregnancies or not (Burke 1992; Nimrod 1992; Norman 1992; Pattinson 1994). Four studies compared Doppler ultrasound alone versus CTG alone in women whose pregnancies were considered at increased risk of problems (Almstrom 1992; Haley 1997; Hofmeyr 1991; Williams 2003). Of these, three involved singleton pregnancies only (Almstrom 1992; Haley 1997; Williams 2003) and one study did not specify (Hofmeyr 1991).

Gestational age for inclusion in studies was not reported on in six studies, and the remainder of the studies varied in the gestational ages they included from 24 weeks' gestation to those studies looking at the value of Doppler ultrasound when women have gone beyond 40 weeks ([Characteristics of included studies](#)).

Excluded studies

Ten of the 29 potentially eligible studies were excluded. In five studies, the participants were described as 'unselected populations' (Davies 1992; Newnham 1993; Omtzigt 1994; Schneider 1992; Whittle 1994); in one study the participants were women considered at low risk of complications (Mason 1993); one study was not a randomised study (McCowan 1996); in one study the full report was not available and there were no data in the conference abstract (Gonsoulin 1991) and in two studies the information was considered unreliable (McParland 1988; Pearce 1992).

Risk of bias in included studies

The quality of the 18 completed included studies was difficult to assess due to lack of information, particularly in terms of randomisation and concealment of allocation ([Figure 1](#)).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Almstrom 1992	?	?	?	?	+	?	-
Biljan 1992	?	?	?	?	?	-	?
Burke 1992	?	?	?	?	+	?	+
de Rochambeau 1992	?	?	?	?	?	?	?
Giles 2003	?	+	?	?	+	?	+
Haley 1997	+	+	?	?	+	?	+
Hofmeyr 1991	+	+	?	?	?	?	-
Johnstone 1993	?	+	?	?	+	?	+
Neales 1994	?	?	?	?	+	-	?
Newnham 1991	?	+	?	+	?	?	+
Nienhuis 1997	+	+	?	+	?	?	-
Nimrod 1992	?	?	?	?	?	?	?
Norman 1992	?	?	?	?	?	?	+
Ott 1998	+	?	?	?	?	?	+
Pattinson 1994	?	?	?	?	+	?	-
Trudinger 1987	?	?	?	?	+	?	+
Tyrrell 1990	?	?	?	?	?	?	?
Williams 2003	+	?	?	?	?	?	+

Allocation

Only three studies had adequate sequence generation and concealment allocation (Haley 1997; Hofmeyr 1991; Nienhuis 1997). Two studies had adequate sequence generation but allocation concealment was unclear (Ott 1998; Williams 2003). In three studies, concealment allocation was judged as adequate, but sequence generation was unclear (Giles 2003; Johnstone 1993; Newnham 1991). The remaining nine studies had both unclear sequence generation and unclear concealment allocation (Almstrom 1992; Biljan 1992; Burke 1992; de Rochambeau 1992; Neales 1994; Nimrod 1992; Norman 1992; Pattinson 1994; Trudinger 1987; Tyrrell 1990).

Blinding

Blinding women and/or staff in these trials was not generally feasible. Even in the studies where Doppler ultrasound was either revealed or concealed, some outcomes, such as induction of labour and caesarean section are clearly going to be influenced by the knowledge of Doppler results, but it may not be possible to avoid bias in neonatal assessment. Unfortunately, the information on the attempts to protect against biased assessment was often not available. In two studies (Newnham 1991; Nienhuis 1997), assessors of neonatal outcomes were indeed blind to Doppler results.

Incomplete outcome data

Incomplete outcome data were addressed adequately in eight studies (Almstrom 1992; Burke 1992; Giles 2003; Haley 1997; Johnstone 1993; Neales 1994; Pattinson 1994; Trudinger 1987) and unclear in 10 studies (Biljan 1992; de Rochambeau 1992; Hofmeyr 1991; Newnham 1991; Nienhuis 1997; Nimrod 1992; Norman 1992; Ott 1998; Tyrrell 1990; Williams 2003). Only a few studies provided full information on the number of women approached to take part in the studies, the numbers eligible for inclusion, and the overall refusal rate. While not sources of bias as such, high exclusion and refusal rates may affect the generalisability of the findings and the interpretation of the results.

Selective reporting

Almost all the studies, except two, were assessed as unclear because we did not assess the trial protocols. Two studies were considered to have some degree of selective reporting bias (Biljan 1992; Neales 1994).

Other potential sources of bias

Nine studies were judged to be free of other sources of bias (Burke 1992; Giles 2003; Haley 1997; Johnstone 1993; Newnham

1991; Norman 1992; Ott 1998; Trudinger 1987; Williams 2003); five studies were unclear (Biljan 1992; de Rochambeau 1992; Neales 1994; Nimrod 1992; Tyrrell 1990); and four studies were considered to have some other source of bias (Almstrom 1992; Hofmeyr 1991; Nienhuis 1997; Pattinson 1994).

Sensitivity analyses

For sensitivity analyses by quality of studies, we have used both adequate labelled sequence generation and adequate allocation concealment as essential criteria for high quality. Only three of the 18 studies met these criteria (Haley 1997; Hofmeyr 1991; Nienhuis 1997), see Figure 1.

Effects of interventions

See: [Summary of findings for the main comparison Fetal and umbilical Doppler ultrasound compared with no Doppler ultrasound for pregnant women at increased risk of fetal complications](#)

This review includes 18 studies involving 10,156 women and has 58 meta-analyses.

1) Doppler ultrasound versus no Doppler ultrasound (18 studies, 10,156 women)

We have included here all 18 completed studies, including those that compared Doppler ultrasound alone versus CTG alone, as we wished to get an overall assessment of whether using Doppler ultrasound was beneficial. A separate comparison of studies where Doppler was used as an alternative to CTG was also undertaken, and these findings are reported below under 2) 'Doppler ultrasound alone versus CTG alone'.

As mentioned above, the quality of the studies included in this comparison was often unclear, particularly in terms of randomisation and concealment allocation.

Primary outcomes

It is important to emphasise that this review still remains underpowered to detect clinically important differences in serious neonatal morbidity.

Any perinatal mortality after randomisation (16 studies, 10,225 babies)

The difference in perinatal mortality between the two groups was statistically significant (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.52 to 0.98, 16 studies, 10,225 babies, 1.2% versus 1.7%, number needed to treat to treat (NNT) 203, 95% CI

103 to 4352, [Analysis 1.1](#)). A sensitivity analysis including only the three studies of high quality (low risk of bias for sequence generation and concealment allocation) ([Haley 1997](#); [Hofmeyr 1991](#); [Nienhuis 1997](#)) showed no statistically significant difference, though, clearly, the numbers are small and it lacks the power of the overall analysis (RR 0.61, 95% CI 0.24 to 1.53, three studies, 1197 babies).

There is no evidence that the treatment effect varies between subgroups as CIs overlap ([Analysis 1.1](#)) although the risk ratio for the singleton subgroup was somewhat lower compared with the others (RR = 0.59 compared with 0.88, 0.86 and 0.68). There is significant evidence of funnel plot asymmetry ('small-study effects' $P = 0.057$ using [Harbord 2006](#)) indicating publication bias ([Figure 2](#)). This is of concern given the borderline significance of the pooled meta-analysis result.

Figure 2. Funnel plot of comparison: I Doppler ultrasound versus no Doppler ultrasound, outcome: I.I Any perinatal death after randomisation.

It is also important to note that we did not adjust for the non-independence of twins because of the lack of reported inter-correlation coefficients (ICC).

Serious neonatal morbidity (three studies, 1098 babies)

Only three studies reported relevant neonatal morbidity data ([Newnham 1991](#); [Norman 1992](#); [Tyrrell 1990](#)) showing no significant differences in serious perinatal morbidity between women having Doppler ultrasound and those monitored by standard

methods (Analysis 1.2). The heterogeneity was high ($\text{Tau}^2 = 3.84$, $\text{Chi}^2 P = 0.04$, $I^2 = 76\%$) and the numbers of babies with serious morbidity too small to be able to say anything with any degree of certainty. We have therefore, on the advice from our statistician, decided not to pool the data for this outcome.

Secondary outcomes

The difference in perinatal deaths remained significant when the analysis focused just on potentially preventable perinatal deaths (RR 0.67, 95% CI 0.46 to 0.98, 16 studies, 10,225 babies, Analysis 1.5).

The data for stillbirths (Analysis 1.3), neonatal deaths (Analysis 1.4) and low Apgar score (Analysis 1.7) are consistent with the overall picture showing fewer adverse outcomes in the Doppler group, but these did not reach statistical significance.

The reduction in caesarean sections with the use of Doppler ultrasound (Analysis 1.8; Analysis 1.9; Analysis 1.10) was statistically significant (RR 0.90, 95% CI 0.84 to 0.97, 14 studies, 7918 women, Analysis 1.8), though the upper limit of the confidence

interval was close to one. When caesarean sections were reported as either elective and emergency, the reduction in caesareans appeared to be confined to the emergency procedures. This is something that will be explored in a meta-regression in future updates if more data become available.

There was also some evidence of publication bias in the funnel plots (Figure 3; Figure 4; Figure 5). The Harbord test (Harbord 2006) for all caesarean sections was non-significant ($P = 0.12$) but visually there does appear to be asymmetry indicating there may be some small studies missing. This is of concern because the pooled meta-analysis result is only borderline significant. With elective caesarean sections, there was evidence of asymmetry ($P = 0.1$) and the visual assessment indicating the 'missing' studies are those below a relative risk of one, so the pooled result is likely to be even closer to the null. For emergency caesarean sections, there was significant evidence of asymmetry ($P = 0.09$), again this being a small-study effect. There is also heterogeneity which can contribute to funnel plot asymmetry, so overall we should be cautious about the significance of the pooled result.

Figure 3. Funnel plot of comparison: I Doppler ultrasound versus no Doppler ultrasound, outcome: I.8 Caesarean section (elective and emergency).

Figure 4. Funnel plot of comparison: I Doppler ultrasound versus no Doppler ultrasound, outcome: I.9 Cesarean section - elective.

Figure 5. Funnel plot of comparison: I Doppler ultrasound versus no Doppler ultrasound, outcome: 1.10 Cesarean section - emergency.

Caesarean section results for subgroups based on the populations (singletons, multiples, not specified) were consistent with overall effect in terms of the direction and size. However, the heterogeneity in the subgroup of emergency caesarean section was high and, therefore, random-effects were used for pooling (average RR 0.81, 95% CI 0.67 to 0.98) ([Analysis 1.10](#)). This analysis provides evidence that the average relative risk across studies is significantly less than one, indicating a reduction in emergency caesarean section. However, we also calculated the 95% prediction interval for the underlying effect in any future studies (PI = 0.49 to 1.35); this indicates that the underlying risk ratio may be greater than one in an individual study due to the between-study heterogeneity.

Overall, there were no significant differences identified in spontaneous vaginal births and operative vaginal births for women having the Doppler ultrasound compared with women not having the Doppler ultrasound ([Analysis 1.11](#); [Analysis 1.12](#)).

There was, however, a significant average reduction in induction of labour for women with the Doppler intervention (average RR 0.89, 95% CI 0.80 to 0.99, 10 studies, 5633 women, random-effects [$T^2 = 0.01$, $\text{Chi}^2 P = 0.08$, $I^2 = 41\%$], prediction interval 0.68 to 1.16, [Analysis 1.13](#)). Although the average effect across studies is statistically significant, the prediction interval suggests that, due to the between-study heterogeneity, we cannot rule out

that the underlying effect in a future study may actually increase induction of labour. There may be some clinical heterogeneity around the assessment of induction of labour due to the varying methods and timings of this intervention.

There was no difference identified overall in intubation or ventilation (average RR 1.42, 95% CI 0.87 to 2.30, six studies, 3136 babies, [Analysis 1.16](#)). Again, random-effects were used because of high heterogeneity ($T^2 = 0.14$, $\text{Chi}^2 P = 0.09$, $I^2 = 47\%$) and a wide prediction interval was estimated due to the large heterogeneity and small number of studies in the meta-analysis (PI 0.41 to 4.94, [Analysis 1.16](#)).

There was evidence of a difference between subgroups (interaction test for inverse variance analysis gives $\text{Chi}^2 = 8.67$, $\text{df} = 2$ ($P = 0.01$)) suggesting that there may be an effect in singletons but not in multiple pregnancies. The data are limited because there is only one trial in multiples and one with singleton and multiples combined. Further studies are needed to confirm if there is a difference here or not.

Overall, there was a small but significant increase in gestational age for babies exposed to Doppler ultrasound (average mean difference (MD) 0.21, 95% CI -0.02 to 0.43, eight studies, 4066 babies, random-effects [$T^2 = 0.04$, $\text{Chi}^2 P = 0.11$, $I^2 = 40\%$], [Analysis](#)

1.28). However, the prediction interval suggests that, due to between study heterogeneity, we cannot rule out that a future study may show a decrease in gestational age. This finding may, therefore, have little clinical significance.

There was a significant reduction in the length of infant hospital stay in singleton pregnancies that had Doppler intervention (standardised MD (SMD) -0.28, 95% CI -0.40 to -0.16, three studies, 1076 babies, [Analysis 1.30](#)).

We have also included reported data for all other pre-specified secondary outcomes when available, none of which conclusively showed clinically important differences between groups.

Non-prespecified outcomes

For completeness, we have also included the graphs for eight clinically relevant outcomes that were not pre-specified in our protocol ([Analysis 1.31](#); [Analysis 1.32](#); [Analysis 1.33](#); [Analysis 1.34](#); [Analysis 1.35](#); [Analysis 1.36](#); [Analysis 1.37](#); [Analysis 1.38](#)).

2) Doppler ultrasound versus no Doppler ultrasound (all subgroups)

Six studies reported primary outcomes by subgroups. Five studies assessed women with suspected SGA/IUGR ([Almstrom 1992](#); [Haley 1997](#); [Neales 1994](#); [Nienhuis 1997](#); [Pattinson 1994](#)), one study assessed women with hypertension/pre-eclampsia ([Pattinson 1994](#)) and one study assessed women with a previous pregnancy loss ([Norman 1992](#)). Studies only assessed perinatal mortality and none assessed serious neonatal morbidity. Findings are reported in [Analysis 2.1](#).

3) Doppler ultrasound as an alternative to CTG monitoring (four studies, 2834 women)

Four trials have been included in this comparison ([Almstrom 1992](#); [Haley 1997](#); [Hofmeyr 1991](#); [Williams 2003](#)). Unfortunately, this analysis has much less power for assessing main clinical outcomes than the main comparison which included also 12 studies where additional methods of fetal monitoring were used in both groups.

In terms of quality, two of the four studies were judged to be of good quality ([Haley 1997](#); [Hofmeyr 1991](#)) whilst the rest were classified as 'unclear' because of the lack of information on randomisation and the allocation process.

Primary outcomes

Overall, there was no significant difference identified in perinatal mortality (RR 0.45, 95% CI 0.17 to 1.15, four studies, 2813 babies, [Analysis 3.1](#)). Only two studies were judged to have adequate sequence generation and allocation concealment ([Haley 1997](#); [Hofmeyr 1991](#)) and using only these in a sensitivity analysis similarly showed no significant difference identified in perinatal

mortality (RR 0.58, 95% CI 0.20 to 1.73, two studies, 1047 babies).

There is no evidence that the treatment effect varies between subgroups as confidence intervals overlap.

Unfortunately, none of the studies provided the data on serious perinatal morbidity.

Secondary outcomes

Although, as above, there were fewer deaths in the Doppler groups, those differences did not reach statistical significance for stillbirths (RR 0.48, 95% CI 0.14 to 1.71, four studies, 2813 babies, [Analysis 3.3](#)), neonatal death (RR 0.52, 95% CI 0.16 to 1.72, three studies, 1473 babies, [Analysis 3.4](#)) and potentially preventable deaths (RR 0.38, 95% CI 0.12 to 1.18, four studies, 2813 babies, [Analysis 3.5](#)). The same is true for all other secondary outcomes with the exception of caesarean section rate and length of hospital stay for neonates.

Overall rates of caesarean section, when both elective and emergency caesareans were combined, showed a trend towards fewer caesareans in the Doppler group that did not reach statistical significance (RR 0.89, 95% CI 0.79 to 1.01, four studies, 2813 babies, [Analysis 3.8](#)). Interestingly, the results from three studies that reported emergency and elective caesareans separately showed significantly fewer emergency caesareans (RR 0.66, 95% CI 0.52 to 0.84, three studies, 1473 women, [Analysis 3.10](#)) and more elective caesareans (RR 1.53, 95% CI 1.12 to 2.09, three studies, 1473 women, [Analysis 3.9](#)) in the Doppler group. There are too few studies to explore this differential effect in a formal meta-regression, but lack of heterogeneity between these subgroups suggest that the effect of the Doppler studies on the type of caesareans is real.

There was a significant reduction in the length of infant hospital stay with Doppler ultrasound compared with CTG (SMD -0.25, 95% CI -0.41 to -0.08, two studies, 576 babies, [Analysis 3.30](#)). The two studies that reported this outcome included just singleton pregnancies. However, the number of babies involved was too small to be able to say anything with any degree of certainty.

Non-prespecified outcomes

For completeness, we have also included the graphs for eight clinically relevant outcomes that were not pre-specified in our protocol ([Analysis 3.31](#); [Analysis 3.32](#); [Analysis 3.33](#); [Analysis 3.34](#); [Analysis 3.35](#); [Analysis 3.36](#); [Analysis 3.37](#); [Analysis 3.38](#)).

4) Doppler ultrasound as an alternative to CTG monitoring (all subgroups)

Three studies reported primary outcomes by subgroups. Two studies assessed women with suspected SGA/IUGR ([Almstrom 1992](#); [Haley 1997](#)) and one study assessed women with hypertension/pre-eclampsia ([Pattinson 1994](#)). Studies only assessed perinatal

mortality and none assessed serious neonatal morbidity. Findings are reported in [Analysis 4.1](#); Analysis 4.2.

Subgroup analysis

There are insufficient data in the subgroup analyses to say whether Doppler ultrasound has differential effect depending on the indication, e.g. IUGR, hypertension or previous pregnancy loss. There were no data at all for diabetes and prolonged pregnancies (see [Analysis 5.1](#) through to Analysis 14.2).

DISCUSSION

The first meta-analysis showing that Doppler studies of the umbilical artery, when used in singleton high-risk pregnancies, results in the reduction in perinatal deaths without increase in obstetric interventions was published in 1995 ([Alfirevic 1995](#)). This Cochrane review update confirms these results, although formal quality assessment of the included studies revealed very few studies of high quality by today's standards. An international agreement on how best to report clinical trials is relatively recent ([CONSORT 2001](#)) and most studies simply did not report information on random sequence generation and allocation blinding that is nowadays considered essential for quality assessment. This makes formal quality assessment of older studies very imprecise resulting in most them being labelled as 'quality unclear'.

The other criticism of the current evidence is lack of a hitherto agreed intervention(s) that should follow an abnormal Doppler finding. Doppler ultrasound is a screening test and of itself cannot influence clinically important outcomes. It is the clinical decisions influenced by Doppler findings that may or may not change the outcome. The evidence from this review suggests that better timing of caesarean sections may be the 'cause' of reduced perinatal mortality. Overall decrease in caesarean sections appears to be confined to emergency procedures which lead us to believe that clinicians with no access to Doppler studies are more often faced with a seriously compromised baby in labour.

It is difficult to say to what extent this review constitutes the 'definitive' evidence of benefit (and absence of harm) for Doppler ultrasound. Some may argue that this meta-analysis is an ideal example of the epidemiological evidence that should trigger a definitive, high-quality large multi-centre clinical trial with an agreed treatment protocol that follows an abnormal Doppler finding in the umbilical artery. Most clinicians feel that a window of opportunity for such a trial is long gone, at least in singleton pregnancies with suspected 'placental insufficiency'. However, it is quite possible that for some 'high-risk' groups, Doppler of the umbilical artery does not offer any protection (e.g. post-term pregnancy, uncomplicated dichorionic pregnancy). Large enough clinical trials of

umbilical artery Doppler in these groups of women are unlikely to be funded as clinical attention focuses on more sophisticated use of Doppler ultrasound. It is hoped that clinical trials evaluating such techniques (e.g. Doppler studies of the fetal ductus venosus) will be of high quality with adequate power to detect important differences in neonatal morbidity.

AUTHORS' CONCLUSIONS

Implications for practice

Doppler studies of the umbilical artery should be incorporated in the protocols for fetal monitoring in high-risk pregnancies thought to be at risk of placental insufficiency. The clear definition of suspected placental insufficiency, frequency of Doppler studies and timing of delivery in the presence of abnormal Doppler studies remains elusive. Women with hypertensive disorders and small-for-date fetuses are obvious candidates whilst the role of umbilical artery Doppler in other risk groups like post-term, diabetes and uncomplicated dichorionic twin pregnancy is still debatable.

Use of more sophisticated Doppler tests such as assessment of blood flow in the middle cerebral artery and ductus venosus have not been subjected to the rigorous evaluation in clinical trials so far and, therefore, cannot be recommended in routine clinical practice.

Implications for research

As discussed, a case could be made for a larger trial of Doppler ultrasound than has been mounted hitherto, particularly in risk groups where the risk of fetal growth restriction caused by impaired placental blood flow is relatively low. Observational studies suggest that fetal vessels other than the umbilical artery may be better markers of fetal well-being, fetal ductus venosus in particular. It is hoped that future clinical studies evaluating possible added benefit of these tests will comply with the most recent CONSORT statement (www.consort-statement.org) and use clinical outcomes from this Cochrane review as the minimum data set.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Almstrom 1992

Methods	2-arm prospective randomised controlled trial - randomised block design; individual women	
Participants	Singleton pregnancies with suspected IUGR at 31 completed weeks of pregnancy. IUGR if fetal weight < 2 SD below the mean at 31 weeks N = 427 women.	
Interventions	Intervention: Doppler of umbilical artery only every 2 weeks till birth unless: <ul style="list-style-type: none">• fetal weight 28% to 33% below mean then every week;• fetal weight > 34% below the mean then twice a week and admission to hospital. Comparison: CTG (NST).	
Outcomes	Primary: GA at delivery, frequency of caesarean section, frequency of operative delivery for fetal distress, CS, vacuum, forceps, length of stay at NICU Secondary: number of fetal monitoring occasions, duration of antenatal hospital stay, frequency of labour induction, birthweight, frequency of small for dates infants, Apgar score at 1 min and 5 min, need for respiratory support	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised block design. No information about how the randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Sealed numbered envelopes according to a randomisation block design This may mean separate randomisation schedules for the 4 different hospitals. No mention of whether the envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible

Almstrom 1992 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No women were lost to follow-up. 3 women declined to take part in the trial. 1 woman in the CTG group had to be excluded from data analysis since all her records were mislaid before evaluation All women seemed to get their allocated Doppler or CTG, so this is an ITT analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes have been described in results section but we have not assessed the trial protocol
Other bias	High risk	The study was not stopped earlier. Baseline imbalance: <ul style="list-style-type: none"> significantly more operations (elective CS) due to breech presentation and suspected fetopelvic disproportion in the Doppler group; the proportion of smokers was higher in the Doppler group than in the CTG group. Differential diagnosis: Almstrom 1995 concluded that obstetricians may have been influenced by the knowledge of a normal umbilical Doppler examination when assessing the CTG in labour. This may contribute bias to the finding of fewer emergency CS for fetal distress in the Doppler group than in the CTG group

Biljan 1992

Methods	Randomised controlled study.
Participants	Women with high-risk singleton pregnancies. N = 674 women randomised.
Interventions	Intervention: Doppler of umbilical artery revealed. N = 338. Comparison: no Doppler. N = 336.
Outcomes	Elective births; GA at birth; birthweight; Apgar scores, admissions to NICU, length of time in NICU, number of babies ventilated, length of ventilation, perinatal mortality
Notes	The information comes only from the 2 conference abstracts and personal communication (ZA). Sadly, Dr Biljan has died, so further detailed information on the study is not available. The information on the number of women randomised to each group was obtained from previous published version of this systematic review (Alfirevic 1995), and data on 'potentially preventable perineal deaths' was calculated from data in a previous

	version of this Cochrane review (Neilson 1996).	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...were randomised..."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided in the conference abstract to assess this
Selective reporting (reporting bias)	High risk	Only gave data for the significant findings and reported the non-significant findings just as lower but not statistically significant
Other bias	Unclear risk	Insufficient information provided in the conference abstract to assess this

Burke 1992

Methods	Prospective randomised controlled trial, individual women, 2 trial arms
Participants	Women with high-risk pregnancies (suspected IUGR, hypertensive disorders, previous baby < 2.5 kg, antepartum haemorrhage, previous perinatal death, diminished fetal movements, post maturity, diabetes and others) N = 476 women.
Interventions	Intervention: Doppler of umbilical artery and fetal biometry and BPP scoring Comparison: fetal biometry and BPP scoring.
Outcomes	Primary outcomes: induction of labour, elective and emergency CS, preterm delivery and perinatal loss
Notes	
<i>Risk of bias</i>	

Burke 1992 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by a random number sequence but it is unclear whether this was made by a third independent person
Allocation concealment (selection bias)	Unclear risk	Sealed numbered envelopes but there is no information whether the envelopes were opaque and whether there was an ordered numbered sequence
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation. Reported as ITT.
Selective reporting (reporting bias)	Unclear risk	All outcomes have been described in result section but we have not assessed the trial protocol
Other bias	Low risk	The study was not stopped early. Baseline imbalance: "Doppler examinations were not carried out in the control group unless specifically requested by the consultant in charge of patients" - 2 women in control group had a Doppler and were not excluded

de Rochambeau 1992

Methods	2-arm randomised controlled trial of individual women.
Participants	Women with singleton post-term pregnancies (40 +3 weeks to 42 +3 weeks) N = 107 women.
Interventions	Intervention: Doppler ultrasound of umbilical artery. Comparison: no Doppler ultrasound, and standard care (FHR).
Outcomes	CS, RDS and post maturity.
Notes	Paper in French with English abstract, paper was translated. Most of the data are missing

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women "...were randomly divided...". No information on how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> • none reported. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> • there appears to be none. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> • probably.
Selective reporting (reporting bias)	Unclear risk	There is no list of pre-specified outcomes as far as we can ascertain and we have not assessed the trial protocol
Other bias	Unclear risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> • no. Describe any baseline in balance: <ul style="list-style-type: none"> • no information provided. Describe any differential diagnosis: <ul style="list-style-type: none"> • unclear.

Giles 2003

Methods	Multi-centred randomised controlled trial - block randomisation, block of 20 Individual women, 2-trial arm.
Participants	Women with twin pregnancies (monochorionic and dichorionic) at 25 weeks. 2 viable apparently normally formed fetuses seen on ultrasound scan Exclusions: fetal anomalies; polyhydramnios/oligohydramnios; demise of 1 twin before

	25 weeks Significance of chorionicity not realised at time randomisation began so no attempt was made to assess chorionicity N = 539 women.	
Interventions	Intervention: Doppler and biometry ultrasound. <ul style="list-style-type: none">• Doppler + biometry at 25, 30 and 35 weeks;• “the clinicians were advised to undertake interventions if there was an abnormal umbilical artery Doppler study (> 95th centile systolic diastolic ratio) or abnormal ultrasound biometry indicating discordant growth. The suggested intervention was intensive surveillance by obstetrics caregivers...if other indicators of fetal well-being (lack of serial growth, decreased amniotic fluid or abnormal fetal monitoring) were abnormal, the early delivery was advised after 25 weeks;• “An abnormality of Doppler waveforms themselves was not considered an indication for immediate delivery unless there was absence of diastolic flow velocity at > 32 weeks of gestation”. Comparison: biometry ultrasound. <ul style="list-style-type: none">• Biometry only at 25, 30 and 35 weeks.	
Outcomes	Maternal: antenatal admission, presence of hypertension, gestation at delivery, indication for delivery and mode of delivery Fetal: ultrasound biometry measurements, umbilical artery doppler systolic diastolic ratios and the occurrence of fetal death and causative factors Neonatal: birthweight, Apgar scores, admission to NICU, admission to special care nursery, requirements for ventilation and occurrence of neonatal death (up to 28 days of life)	
Notes		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“...opaque sealed envelopes containing the randomisation code the envelope being opened by an observer remote from patient care”
Allocation concealment (selection bias)	Low risk	“...opaque sealed envelopes containing the randomisation code the envelope being opened by an observer remote from patient care”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible

Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> 539 women were randomised in Doppler Assessment in multiple pregnancy (DAMP) study: Doppler 268 and control 271. 13 were lost to follow-up after randomisation at 25 weeks and were not included in the results. This left 526 women with complete follow-up 262 in Doppler and 264 in no Doppler. Describe any exclusion of participants after randomisation: was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> 7 women in the no Doppler group had Doppler.
Selective reporting (reporting bias)	Unclear risk	There seems to be no evidence of selective reporting bias but we have not assessed the trial protocol
Other bias	Low risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> not stopped early but PNM on which power calculation was much lower than expected. Power calc on 85.7/1000 and in reality 11/1000 so study significantly underpowered - needed 3300 per arm. Describe any baseline in balance: <ul style="list-style-type: none"> no imbalances.

Haley 1997

Methods	2-arm randomised controlled trial with stratified block randomisation producing 4 groups: Caucasian primiparous and multiparous women, and Asian primiparous and multiparous women. Randomised in blocks of 8 using table of random numbers. However, the results are not reported by any of these subgroups - only Doppler vs CTG overall Randomisation was of individual women.
Participants	Women with singleton fetuses with ultrasound examination showing the abdominal circumference < 2 SD of the mean for the gestational age fetal heart rate on charts recommended by British Medical Ultrasound Society. There was no gestational age constraint although all women were > 26 weeks' gestation N = 150 women.

Interventions	Intervention: Doppler of umbilical artery and no CTG. Comparison: CTG.	
Outcomes	Primary: duration of hospital antenatal admission, induction of labour rates Secondary: number of investigations (CTG or Doppler), number of outpatient visits to hospital, emergency CS rate, length of stay on the NICU, birthweight, and 1 min and 5 min Apgar score All women were sent a questionnaire asking their views on the process of their care	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 8 using a table of random number.
Allocation concealment (selection bias)	Low risk	"...randomisation only possible by telephone sequentially numbered sealed opaque envelopes..."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of participants at follow-up. No exclusion after the randomisation. ITT analysis.
Selective reporting (reporting bias)	Unclear risk	We have not assessed the trial protocol. Also, despite the stratified randomisation to look at ethnicity and parity, the results are not reported by any of these subgroups, only Doppler vs CTG overall
Other bias	Low risk	Study went to completion. Baseline in balance: more women had no live-in support at home in the CTG group Differential diagnosis: "...there was not a rigid protocol except that clinicians usually felt that a CTG record gave reassurance for 48-72 hours and a Doppler examination for a week or more ..."

Hofmeyr 1991

Methods	2-arm RCT - but with additional evaluation by the non-allocated technique Randomisation was of individual women.
Participants	Women undergoing evaluation of fetal well-being in the high-risk obstetric unit. 867 women randomised N = 897 women.
Interventions	Intervention: Doppler ultrasound of umbilical artery. Comparison: computerised CTG.
Outcomes	Number and duration of tests; perinatal outcomes. “Our objective was to determine whether the experimental policy of Doppler study followed when necessary by FHR testing would take less time than routine FHR testing alone”
Notes	We contacted the authors to ask for clarification of the phrase, “computer generated algorithm based on the hospital number”. They kindly responded with an explanation: “allocation was done automatically by a computer programme. Although the algorithm made use of the woman’s hospital number, it was impossible for the midwife performing the fetal assessment to predict to which group the women would be allocated. The ‘algorithm’ was simply a mathematical sequence which was applied to the woman’s hospital number to generate an allocation”

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“...computer generated algorithm based on the hospital number...”. We sought clarification from the authors who kindly responded: “allocation was done automatically by a computer programme.”
Allocation concealment (selection bias)	Low risk	Not described in the paper but we wrote for clarification from the authors who kindly responded: “although the algorithm made use of the woman’s hospital number, it was impossible for the midwife performing the fetal assessment to predict to which group the women would be allocated. The ‘algorithm’ was simply a mathematical sequence which was applied to the woman’s hospital number to generate an allocation”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible

Hofmeyr 1991 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> • none-apparent. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> • none apparent. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> • it would appear so.
Selective reporting (reporting bias)	Unclear risk	There is no list of pre-specified outcomes from protocol, and we have not assessed the trial protocol
Other bias	High risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> • not stopped early as far as can ascertain. Describe any baseline in balance: <ul style="list-style-type: none"> • imbalance in numbers in each group 439 Doppler vs 459 FHR; • unspecified number of women in CTG group had also Doppler evaluation - assessment by the alternate non allocated method was required on 1241 (66%) of 1869 occasions in which the allocated method was Doppler, and 804 (39%) of 2069 occasions when the allocated method was FHR testing.

Johnstone 1993

Methods	2-arm RCT. Randomisation by Zelen method - only those randomised to Doppler were invited to participate in the trial. Those allocated to CTG were being given normal care so their permission was regarded as not required Randomisation was of individual women.
Participants	Women with pregnancies identified clinically as being at increased risk. N = 2289 out of the 8018 women giving birth at the hospital during the time of the study All women attending the hospital were randomised (2289). There were 8018 women giving birth in the hospital over this time period. Doppler or CTG or BPP given to pregnant women where there was concern by medical staff about antenatal fetal well-being by random allocation. Women were admitted to the trial if there was a wish for

	Doppler studies or a referral for AN fetal monitoring (CTG or BPP). So, all women meeting these criteria were randomised regardless of risk N = 2289 women.	
Interventions	Intervention: Doppler ultrasound of umbilical artery (and other monitoring) Comparison: no Doppler - but other monitoring used (CTG/BPP)	
Outcomes	Fetal mortality and morbidity; obstetric interventions; use of other tests of fetal monitoring; impact on obstetric decision making; health and personal costs; women's satisfaction (to be presented in a separate report)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just described as randomised.
Allocation concealment (selection bias)	Low risk	“Sequentially numbered opaque sealed envelopes were attached by stapling to the case notes of all women attending this hospital. Randomisation was carried out by opening the envelope for every woman who met the criteria described above.”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none">all women seemed to have data collected. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none">of the 1114 women allocated to Doppler, 24 did not have Doppler assessment (2%);3 women got “Doppler“ though they were randomised to “no Doppler“;uneven, but numbers are small relative to the size of the study. Was the analysis ITT? If not have the data

Johnstone 1993 (Continued)

		<p>been able to be re-included?</p> <ul style="list-style-type: none"> • “data analysis was on an ITT basis”.
Selective reporting (reporting bias)	Unclear risk	They seem to report on their pre-specified outcomes but we have not assessed the trial protocol.
Other bias	Low risk	<p>If the study was stopped early, explain the reasons:</p> <ul style="list-style-type: none"> • no. <p>Describe any baseline in balance:</p> <ul style="list-style-type: none"> • none reported in the text. <p>Describe any differential diagnosis:</p> <ul style="list-style-type: none"> • seems okay. <p>Receiving the other intervention:</p> <ul style="list-style-type: none"> • 24 women allocated to Doppler did not have it performed; • 3 women in No Doppler had Doppler.

Neales 1994

Methods	2-arm randomised controlled study of individual women.
Participants	<p>Women of 24 weeks or greater gestation with a singleton pregnancy, and ultrasonic evidence of IUGR (abdominal circumference < on or below 5th centile for gestational age).</p> <p>N = 467 women.</p>
Interventions	<p>Intervention: Doppler ultrasound of umbilical artery revealed, weekly or more often if indicated. Documented in notes. Discussed with registrar</p> <p>Comparison: Doppler US weekly but recorded in separate file and not disclosed to clinicians</p>
Outcomes	<p>Obstetric management: gestation at birth, time from enrolment to birth, mode of birth/ onset of labour, fetal distress in labour</p> <p>Neonatal outcome: perinatal mortality, birthweight, admission to NICU, neonatal outcome</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information other than 'randomised'.

Neales 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	Sealed envelopes but there is no information as to whether the envelopes were opaque and whether they were distributed in a sequential order
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> no withdrawals reported. Describe any exclusion of participants after randomisation: no exclusion: <ul style="list-style-type: none"> no withdrawals reported. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> ITT as far as able to assess. Not specifically stated as such.
Selective reporting (reporting bias)	High risk	Not all outcomes available and we have not assessed the trial protocol
Other bias	Unclear risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> not stopped early for benefit, but underpowered due to 'cannot do a large enough study'.

Newnham 1991

Methods	Randomised controlled trial - 2-arm RCT, stratified for twin pregnancies Randomisation was of individual women.
Participants	Women with high-risk pregnancies, singletons and twins. That was - those disorders of pregnancy in which an increased risk of retarded fetal growth or impaired fetal well-being were considered likely N = 505 women.
Interventions	Intervention: Doppler of umbilical and utero-placental (within the placental bed) artery <ul style="list-style-type: none"> N = 254, including 21 twins. Performed immediately after randomisation and then frequency by clinical judgement.

	<ul style="list-style-type: none">• The ratio of peak systolic (S) to least diastolic (D) Doppler shift frequency was calculated from waveforms obtained from an umbilical artery and from a maternal uteroplacental artery within the placental bed. These ratios were not adjusted to standard fetal or maternal heart rates”. Comparison: No Doppler. <ul style="list-style-type: none">• N = 251, including 19 twins.	
Outcomes	Primary: duration of neonatal stay in hospital. Secondary: number and type of fetal heart monitoring studies, obstetric interventions, frequency of fetal distress, birthweight, Apgar score, and need for NICU	
Notes		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just described as random.
Allocation concealment (selection bias)	Low risk	Numbered opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of neonatal outcomes were indeed blind to Doppler results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none">• no loss reported. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none">• none described. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none">• apparently yes.
Selective reporting (reporting bias)	Unclear risk	Reported outcomes were the same as those pre-specified but we have not assessed the trial protocol
Other bias	Low risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none">• no. Describe any baseline in balance:

		<ul style="list-style-type: none"> groups comparable for maternal age, height, parity, smoking and GA. No 'P' values given but looks alright. Describe any differential diagnosis: <ul style="list-style-type: none"> seems alright.
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Nienhuis 1997

Methods	Randomised controlled study - stratified randomisation and block randomisation Stratification by gestational age (< 32 weeks and > 32 weeks) and smoking (regardless of number smoked) Randomisation by individual women, 2-trial arms.
Participants	Women with clinically suspected IUGR of > 2 weeks diagnosed by fundal height measurements at the outpatient clinic. Singleton pregnancies Exclusions: multiple pregnancies, uncertain GA, non-Caucasian origin, maternal or fetal conditional requiring immediate hospitalisation or intervention N = 161 women.
Interventions	Intervention: Doppler ultrasound of umbilical artery revealed: <ul style="list-style-type: none"> done weekly until birth; maintaining outpatient management while the Doppler was in the normal range, in a setting whereby hospitalisation was the management of choice for significant IUGR was suspected. Comparison: Doppler ultrasound of umbilical artery concealed: <ul style="list-style-type: none"> the PIs were not calculated until after birth and the results were concealed from the clinicians in charge; standard clinical management for suspected IUGR.
Outcomes	Effect on costs in terms of hospitalisation, perinatal outcome, neurological development and postnatal catch-up growth, onset and mode of birth, birthweight, and GA at birth
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<ul style="list-style-type: none"> Randomised numbers from a published table of random number from a person not involved in patient management. Although study stated "...even number allocated the participant to the intervention group....uneven numbers were allocated to the control group" (Nienhuis 1995). A block size of 10 was used.

Allocation concealment (selection bias)	Low risk	<ul style="list-style-type: none"> • “A randomisation number was requested over the telephone from an independent person not involved in patient management”. • After the stratification the next number of one of the 4 randomisation lists was read.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of neonatal outcomes were indeed blind to Doppler results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Describe any loss of participants to follow-up at each data collection point:</p> <ul style="list-style-type: none"> • 11 women refused to participate to the study. <p>Describe any exclusion of participants after randomisation:</p> <ul style="list-style-type: none"> • 8 cases were excluded (4 in intervention group and 4 in control group) because of congenital defects. Was the analysis ITT? If not have the data been able to be re-included? • not for some outcomes - not able to re-include; • authors took out protocol violation and re-evaluated because they said: “14 participants were admitted during pregnancy despite a normal Doppler. Suspected IUGR was the sole reason and they should not have been admitted. The authors recalculated excluding these 14 and this is inappropriate as it is likely to reflect real life.
Selective reporting (reporting bias)	Unclear risk	All the outcomes has been reported but we have not assessed the trial protocol
Other bias	High risk	<p>If the study was stopped early, explain the reasons:</p> <ul style="list-style-type: none"> • not reported as stopping early. <p>Describe any baseline in balance:</p> <ul style="list-style-type: none"> • slight difference in primipara: Doppler 34/74 (46%) and control 43/76

		(57%) but reported as NS; <ul style="list-style-type: none"> • 58.1% boys in intervention group and 36.8% boys in control group; • 4.1% breech in intervention group and 18.4% breech in control group; • in the analysis the possible influence of the skewed distribution of sex was reduced by using sex-specific growth reference.
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Nimrod 1992

Methods	Randomised controlled trial - 2-arm trial randomising individual women
Participants	Pregnant women seen at the 'Fetal Assessment Unit' over 40 weeks' gestation
Interventions	Intervention: pulsed Doppler revealed. Fetal aorta and umbilical artery assessed. BPP and NST also undertaken Comparison: pulsed Doppler concealed. BPP and NST were reported
Outcomes	CS; gestation at birth; meconium in amniotic fluid; need for phototherapy
Notes	Conference abstract available, but no full publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.
Selective reporting (reporting bias)	Unclear risk	Very limited data in the conference abstract. We have not assessed the trial protocol

Nimrod 1992 (Continued)

Other bias	Unclear risk	No information available on which to judge this aspect.
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Norman 1992

Methods	Randomised controlled trial. Individual women randomised in 2 arms
Participants	Women with high-risk pregnancies with recurrent pregnancy loss (2 or more mid trimester or early third trimester losses which resulted in IUFD, stillbirth or neonatal death) at least 24 weeks' pregnant. 54 women randomised N = 54 women.
Interventions	Intervention: Doppler velocimetry of umbilical artery revealed Comparison: Doppler velocimetry of umbilical artery concealed
Outcomes	Maternal intervention, hospital stay, induction of labour, CS, perinatal mortality and morbidity
Notes	A conference poster (incomplete data).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women were randomly allocated.
Allocation concealment (selection bias)	Unclear risk	Sealed envelope, but no mention of how there were distributed no whether they were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> 1 woman lost to follow-up, but no explanation. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> no information. Was the analysis ITT? If not have the data been able to be re-included?

		<ul style="list-style-type: none"> no information.
Selective reporting (reporting bias)	Unclear risk	No information in the poster to enable this to be assessed. Also we have not assessed the trial protocol
Other bias	Low risk	<p>If the study was stopped early, explain the reasons:</p> <ul style="list-style-type: none"> was not stopped early. <p>Describe any baseline in balance:</p> <ul style="list-style-type: none"> "...both groups were comparable at study entry as regards maternal age, number of previous losses and GA". <p>Describe any differential diagnosis:</p> <ul style="list-style-type: none"> seems fine.

Ott 1998

Methods	2-arm randomised controlled trial of individual women.
Participants	Women referred to the perinatal laboratory so high-risk pregnancies (risk of UPI; fetal risk; postdates; maternal diabetes; PROM/PTL; fluid abnormalities) N = 715 women.
Interventions	Intervention: fetal and umbilical Doppler + modified BPP. Comparison: no Doppler but modified BPP.
Outcomes	Primary outcome: neonatal morbidity rate (admission to NICU, length of stay in NICU, significant neonatal morbidity) Secondary outcome: GA at delivery, neonatal weight, CS for fetal distress
Notes	The outcome of 'significant neonatal morbidity' assessed in this study included central nervous system complications, sepsis, acidosis/asphyxia, cardiomyopathy, anaemia, metabolic but excluded RDS. Anaemia and metabolic outcomes were not defined. We considered this outcome to be sufficiently different from the reviews primary outcome of 'serious neonatal morbidity - composite outcome including hypoxic ischaemic encephalopathy, IVH, BPD, NEC' that we have not included these data in the meta-analysis. This study found no significant difference in 'significant neonatal complications' between the Doppler group (8%) and the no Doppler group (6.6%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random number allocation system."
Allocation concealment (selection bias)	Unclear risk	No information provided.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> • 20.5% patients refused to participate in the study; • 50/715 patients (7.0%) withdrew from the study - delivered at another institution or were lost to follow-up; • 37 (11.7%) women in control arm had Doppler US at physician's request. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> • see above. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> • no, not ITT. It was not reported how many women were randomised to each group, only given how many analysed in each group and this had to be calculated from the information on reasons for testing in Table 2.
Selective reporting (reporting bias)	Unclear risk	Although the pre-specified outcomes in the paper were reported on we were not able to assess the protocol so are not sure re outcome reporting bias. They only reporting on CS for fetal distress, and not on all CS.
Other bias	Low risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> • no, not stopped early. Describe any baseline in balance: <ul style="list-style-type: none"> • seems that the groups were balanced. Describe any differential diagnosis: <ul style="list-style-type: none"> • 37 (11.7%) women in control arm had Doppler US at physician's request.

Pattinson 1994

Methods	Randomised controlled trial - block randomisation of individual women: <ul style="list-style-type: none">● 2-arm RCT but with 3 subgroups: group 1. women with fetuses with AEDV; group 2: women with hypertension but fetuses with EDV and group 3: women with fetuses suspected of being SGA but with EDV present;● 3 groups were created based on clinical picture and Doppler results;● if the woman was hypertensive and fetus had EDV and was suspected of being small then she went to HT group.● each subset was managed differently;● balanced block randomisation in blocks of 10 for AEDV and 20 for other groups. There were equal numbers of women in each groups; <ul style="list-style-type: none">● data analysed at completion of each block;● in each group Doppler revealed and Doppler concealed.	
Participants	Women > 28 weeks’ pregnant with hypertension and/or suspected SGA fetuses were referred for Doppler US. 212 women with singleton pregnancies N = 212 women.	
Interventions	Intervention: Doppler velocimetry of umbilical artery revealed: <ul style="list-style-type: none">● other tests available, e.g. sonar and AN FHR. Comparison: Doppler velocimetry of umbilical artery concealed: <ul style="list-style-type: none">● other test available, e.g. sonar and AN FHR.	
Outcomes	Perinatal mortality and morbidity, antenatal hospitalisation, maternal intervention, admission to the NICU and hospitalisation until discharge from the neonatal wards	
Notes		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“...randomisation was performed by the person doing the Doppler velocity”
Allocation concealment (selection bias)	Unclear risk	“.....opaque sealed envelopes.....”, but no mention of numbered and sequentially ordered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none">● none were lost.

		Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> not apparent. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> probably.
Selective reporting (reporting bias)	Unclear risk	All the outcomes have been reported but we have not assessed the trial protocol
Other bias	High risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> in the group of AEDF (20 women) there were 6 perinatal deaths in control group and 1 perinatal death in study group. The trial was stopped at this point because significantly more fetuses had died in the control group. Describe any differential diagnosis: <ul style="list-style-type: none"> if AEDV detected then Doppler repeated following day. In control group Doppler repeated weekly if the woman was in hospital and fortnightly if the woman was an outpatient; in the AEDV, we might have biased the outcome because the clinicians was aware we were specifically interested in the outcome and so more care might have been taken; women in the control group were managed by consultants who may have infertility or gynaecology base for their speciality where women with problems identified were managed with a specific management plan. So may not see a difference in a hospital where all high-risk pregnancies are managed by clinicians who are subspecialist in perinatal medicine.

Trudinger 1987

Methods	2-arm randomised controlled trial of Individual women.
Participants	Women with high fetal risk (singletons). More than 28 weeks' gestation N = 300 women.

Interventions	Intervention: Doppler of umbilical artery revealed: <ul style="list-style-type: none">• full access to other methods of fetal assessment, e.g. fetal movements chart, CTG, ultrasound measurements and imaging, maternal estrogens, placental lactogens. Comparison: Doppler of umbilical artery concealed: <ul style="list-style-type: none">• full access to other methods of fetal assessment e.g. fetal movements chart, CTG, ultrasound measurements and imaging, maternal estrogens, placental lactogens.	
Outcomes	Perinatal mortality, CS, induction of labour, etc.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random number though no information on how they were generated and by whom
Allocation concealment (selection bias)	Unclear risk	“Each patient was asked to draw an envelope containing a random number and those with even numbers were allocated to the Doppler report available group”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none">• 11 women gave birth at other hospitals (6 Doppler and 5 controls) - left Doppler with 127 women and control with 162 women. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none">• available case analysis.
Selective reporting (reporting bias)	Unclear risk	No outcome listed in methods section and we have not assessed the trial protocol.
Other bias	Low risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none">• not stopped. Describe any baseline in balance:

		<ul style="list-style-type: none"> • fine. Describe any differential diagnosis: <ul style="list-style-type: none"> • seems ok.
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Tyrrell 1990

Methods	Randomised controlled trial - pragmatic 2-arm trial.
Participants	<p>Women with high-risk singleton pregnancies.</p> <p>Specifically, 500 pregnant women at high risk of growth retardation or stillbirth. IUGR clinically suspected or by US scan, previous SGA baby, previous antepartum haemorrhage, hypertension</p> <p>Exclusions: women with diabetes, twin pregnancies.</p> <p>N = 500 women.</p>
Interventions	<p>Intervention: routine use of Doppler and BPP testing + other tests:</p> <ul style="list-style-type: none"> • Doppler of umbilical and uteroplacental arteries; • testing at 28 weeks' gestation, or at the time of presentation if risk factors appeared later than this. Thereafter, they had weekly Doppler and Fetal biophysical assessment for 3 weeks, followed by fortnightly examinations until delivery. <p>Comparison: no Doppler and no biophysical assessment but other tests only:</p> <ul style="list-style-type: none"> • "clinicians responsible for the care of women in the selectively investigated arm could only obtain Doppler and biophysical assessment on special request, and this happened in only 12 pregnancies".
Outcomes	Total number of days of antenatal admission, rate of induction of labour (by any method), mode of birth (elective CS and emergency CS), 1 and 5 min Apgar, birthweight, admission to NICU
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<ul style="list-style-type: none"> • "...random number sequence..." though it is not clear how this was generated; • "...the randomisation was performed by the 2 ultrasonographers involved in the study neither of whom knew anything about the patients or was involved in their clinical management..."
Allocation concealment (selection bias)	Unclear risk	<ul style="list-style-type: none"> • "...sealed, sequentially numbered envelopes..." though it is not clear whether these were opaque.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none"> “...the data on duration of antenatal stay and induction of labour were obtained retrospectively, and the case notes could not be traced in 15% of the women”. Describe any exclusion of participants after randomisation: <ul style="list-style-type: none"> no exclusion. Was the analysis ITT? If not have the data been able to be re-included? <ul style="list-style-type: none"> 12 women in “no Doppler” group had Doppler and BPP at specific request of obstetrician. These seems to be assessed in the group to which women were randomised, so appears to be ITT.
Selective reporting (reporting bias)	Unclear risk	Not all outcomes have been reported, emergency CS just reported in the text. We have not assessed the trial protocol
Other bias	Unclear risk	If the study was stopped early, explain the reasons: <ul style="list-style-type: none"> not reported; the registered study aimed for 28000 over 7 years, but this was probably impractical. Describe any baseline in balance: <ul style="list-style-type: none"> “clinicians responsible for the care of women in the selectively investigated arm could only obtain Doppler and biophysical assessment on special request, and this happened in only 12 pregnancies”. Describe any differential diagnosis: <ul style="list-style-type: none"> seems alright.

Williams 2003

Methods	Randomised controlled study - block randomisation (block of 4 and 6) Individual women.	
Participants	Women with high-risk pregnancies - singletons (IUGR 7%, hypertension 10%, diabetes 11%, prolonged pregnancy 43%, decreased fetal movements 22%). GA > 32 weeks N = 1360 women.	
Interventions	Intervention: umbilical artery Doppler: <ul style="list-style-type: none">if Doppler normal then women seen twice a week; if equivocal then amniotic fluid index done; if abnormal then proceeded to induction/delivery within 24 hours. Comparison: electronic FHR with NST: <ul style="list-style-type: none">twice a week; Kulbi score (5 components). If equivocal (Kulbi = 6) identified then assessment of amniotic fluid volume; if abnormal (Kulbi = 4) identified then induction/delivery within 24 hours.	
Outcomes	Primary outcome: incidence of CS for fetal distress in labour (non reassuring FHR) Secondary outcome: total CS, Apgar score 1 and 5 min, the incidence of stillbirth, the presence of meconium, and the incidence of transfer to the NICU with severe neonatal morbidity	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table with a variable block size of 4 and 6.
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered opaque envelopes although no information as to whether they were sealed “...envelopes were kept in a locked drawer that was accessible only to the unit clerk. The envelopes was opened by the nurse/sonographer in the presence of the patient”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding women and/or staff in these trials was not generally feasible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Describe any loss of participants to follow-up at each data collection point: <ul style="list-style-type: none">no final outcome data were available for 16 women (10 in NST group and 6 in Doppler group).

		<p>Describe any exclusion of participants after randomisation:</p> <ul style="list-style-type: none"> • 4 women were assigned in error and did not have the identified high-risk condition - removed from further analysis - 1356 women in study. <p>Was the analysis ITT?</p> <ul style="list-style-type: none"> • “once assigned randomly to particular group, the patient remained in that group for any subsequent assessment that took place in that pregnancy”.
Selective reporting (reporting bias)	Unclear risk	All the outcomes have been reported but we have not assessed the trial protocol
Other bias	Low risk	<p>If the study was stopped early, explain the reasons:</p> <ul style="list-style-type: none"> • study not stopped early for benefit. <p>Describe any baseline in balance:</p> <ul style="list-style-type: none"> • this seems fine. <p>Describe any differential diagnosis:</p> <ul style="list-style-type: none"> • this seems alright.

AEDF: absent end diastolic flow
 AEDV: absent end diastolic velocity
 AN: antenatal
 BPD: bronchopulmonary dysplasia
 BPP: biophysical profile
 CS: caesarean section
 CTG: cardiotocography
 EDV: end diastolic velocities
 FHR: fetal heart rate
 GA: gestational age
 ITT: intention-to-treat
 IUFD: intrauterine fetal death
 IUGR: intrauterine growth retardation
 IVH: intraventricular haemorrhage
 min: minute
 NEC: necrotising enterocolitis
 NICU: neonatal intensive care unit
 NS: not significant
 NST: non-stress test
 PTL: preterm labour
 PROM: preterm rupture of membranes
 RCT: randomised controlled trial
 RDS: respiratory distress syndrome
 SD: standard deviation

SGA: small-for-gestational age
 US: ultrasound
 vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Davies 1992	Participants are an “unselected population”.
Gonsoulin 1991	Full report not available.
Mason 1993	Participants are “low-risk primigravid women”.
McCowan 1996	Conference abstract only but outcomes were comparing women with normal and abnormal Doppler ultrasound readings, so not a randomised comparison
McParland 1988	This study has never been reported in full although it has been partly reported in a review article (McParland 1988) and a full manuscript has been given to the review authors by Dr Pearce, who has been accused of publishing reports of trials whose veracity cannot be confirmed (BJOG 1995). Consequently, the Doppler trial data are not now thought by the review authors to be sufficiently reliable to be retained within this review.
Newnham 1993	Participants are an “unselected population”.
Omtzigt 1994	Participants are a “non-selected University Hospital population”
Pearce 1992	Dr Pearce has been accused of publishing reports of trials whose veracity cannot be confirmed (BJOG 1995). Consequently, the Doppler trial data are not now thought by the reviewers to be sufficiently reliable to be retained within this review.
Schneider 1992	Participants are an “unselected pregnant population”.
Whittle 1994	Participants are an “unselected population”.

Characteristics of ongoing studies *[ordered by study ID]*

Lees 2005

Trial name or title	Trial of umbilical and fetal flow in Europe (TRUFFLE): a multicentre randomised study
Methods	RCT - multicentre (20 centres), stratified by gestational age at enrolment
Participants	Women with IUGR diagnosed by ultrasound at 26-32 weeks' gestation

Lees 2005 (Continued)

Interventions	Intervention 1: delivery based on early ductus venosus changes (pulsatility index > 95th centile Intervention 2: delivery based on late ductus venosus changes (a-wave reaches the baseline, i.e. 0 mc/s) Control: current standard care: timing of delivery based on CTG criteria for delivery, namely short-term variation below preset cut-offs based on gestation
Outcomes	Primary: survival without neurological impairment at 2 years Secondary: long-term outcomes at 2 years corrected for prematurity: frequency of severe disability; respiratory outcomes; weight; length; head circumference; blood pressure; survival analysis
Starting date	2005, expected end date June 2009.
Contact information	Christoph Lees, Rosie Maternity Hospital, Addenbrookes NHS Trust, Cambridge, CB2 2QQ, UK Email: christoph.lees@addenbrookes.nhs.uk
Notes	

CTG: cardiotocography

IUGR: intrauterine growth restriction

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Doppler ultrasound versus no Doppler ultrasound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation	16	10225	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.98]
1.1 Singleton pregnancy	9	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.01]
1.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.41]
1.3 Singleton plus multiple pregnancies	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.53]
1.4 Not specified whether singleton or multiple pregnancies	4	1638	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.36, 1.30]
2 Serious neonatal morbidity	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Singleton pregnancy	1	500	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.99]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	1	545	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.31, 28.14]
2.4 Not specified whether singleton or multiple pregnancies	1	53	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Stillbirth	15	9560	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.04]
3.1 Singleton pregnancy	8	3996	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.31, 1.19]
3.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 4.00]
3.3 Singleton plus multiple pregnancy	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.40, 3.56]
3.4 Not specified whether singleton or multiple pregnancies	4	1638	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.19, 1.22]
4 Neonatal death	13	8167	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.24]
4.1 Singleton pregnancy	7	2656	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.53]
4.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.29, 3.46]
4.3 Singleton plus multiple pregnancies	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.38, 1.50]
4.4 Not specified whether singleton or multiple pregnancies	3	1585	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.40, 2.53]
5 Any potentially preventable perinatal death*	16	10225	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.46, 0.98]
5.1 Singleton pregnancy	9	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.30, 1.13]
5.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.41]
5.3 Singleton plus multiple pregnancies	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.38, 1.73]
5.4 Not specified whether singleton or multiple pregnancies	4	1638	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.21]
6 Fetal acidosis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

6.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Apgar < 7 at 5 minutes	7	6321	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.24]
7.1 Singleton pregnancy	4	2555	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.09]
7.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Singleton plus multiple pregnancies	2	2869	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.78, 1.90]
7.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.36, 2.39]
8 Caesarean section (elective and emergency)	14	7918	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
8.1 Singleton pregnancy	7	2929	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.95]
8.2 Multiple pregnancy	1	526	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.19]
8.3 Singleton plus multiple pregnancies	2	2794	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
8.4 Not specified whether singleton or multiple pregnancies	4	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]
9 Caesarean section - elective	11	6627	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.93, 1.22]
9.1 Singleton pregnancy	6	1934	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.90, 1.38]
9.2 Multiple pregnancy	1	526	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.47]
9.3 Singleton plus multiple pregnancies	2	2794	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.14]
9.4 Not specified whether singleton or multiple pregnancies	2	1373	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.96, 1.78]
10 Caesarean section - emergency	10	6175	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.98]
10.1 Singleton pregnancy	5	1482	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.43, 0.78]
10.2 Multiple pregnancy	1	526	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.23]
10.3 Singleton plus multiple pregnancies	2	2794	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.88, 1.29]
10.4 Not specified whether singleton or multiple pregnancies	2	1373	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.02]
11 Spontaneous vaginal birth	5	2504	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.10]
11.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.96, 1.18]
11.2 Multiple pregnancy	1	526	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.19]
11.3 Singleton plus multiple pregnancies	1	505	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.11]
11.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]
12 Operative vaginal birth	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.14]
12.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.22]
12.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

12.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.25]
13 Induction of labour	10	5633	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.99]
13.1 Singleton pregnancy	5	1784	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.64, 0.97]
13.2 Multiple pregnancy	1	526	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.80, 1.50]
13.3 Singleton plus multiple pregnancies	2	2794	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.05]
13.4 Not specified whether singleton or multiple pregnancies	2	529	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.23]
14 Oxytocin augmentation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Neonatal resuscitation required	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Infant requiring intubation/ventilation	6	3136	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.87, 2.30]
16.1 Singleton pregnancy	4	1539	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.40, 5.96]
16.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.25]
16.3 Singleton plus multiple pregnancies	1	545	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.79, 1.98]
16.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Neonatal fitting/seizures	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
17.1 Singleton pregnancy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
17.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Preterm labour	2	626	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.72, 1.75]
18.1 Singleton pregnancy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.51, 2.07]
18.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Singleton plus multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

18.4 Not specified whether singleton or multiple pregnancies	1	476	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.66, 2.11]
19 Infant respiratory distress syndrome (RDS)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.07, 16.48]
19.1 Singleton pregnancy	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.07, 16.48]
19.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Meconium aspiration	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Neonatal admission to SCBU and/or NICU	12	9334	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.03]
21.1 Singleton pregnancy	8	4511	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.80, 1.06]
21.2 Multiple pregnancy	1	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.88, 1.05]
21.3 Singleton plus multiple pregnancies	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
21.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.73, 1.37]
22 Hypoxic ischaemic encephalopathy	2	1045	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.01, 33.07]
22.1 Singleton pregnancy	1	500	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.64]
22.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22.3 Singleton plus multiple pregnancies	1	545	Risk Ratio (M-H, Random, 95% CI)	4.91 [0.24, 101.79]
22.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23 Intraventricular haemorrhage	4	2008	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.47, 4.30]
23.1 Singleton pregnancy	3	1463	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.38, 4.16]
23.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.3 Singleton plus multiple pregnancies	1	545	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 71.99]
23.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Bronchopulmonary dysplasia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

24.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Necrotising enterocolitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Single plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Long-term infant neurodevelopmental outcome	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Singleton plus multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Women's views of their care	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.2 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.4 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Gestational age at birth	8	4066	Mean Difference (IV, Random, 95% CI)	0.21 [-0.02, 0.43]
28.1 Singleton pregnancy	3	1043	Mean Difference (IV, Random, 95% CI)	0.54 [-0.00, 1.09]
28.2 Multiple pregnancy	1	1052	Mean Difference (IV, Random, 95% CI)	0.10 [-0.24, 0.44]
28.3 Singleton plus multiple pregnancies	1	545	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.81, 0.41]
28.4 Not specified whether singleton or multiple pregnancies	3	1426	Mean Difference (IV, Random, 95% CI)	0.11 [-0.16, 0.38]
29 Birth weight	7	3887	Mean Difference (IV, Fixed, 95% CI)	31.33 [-8.70, 71.37]
29.1 Singleton pregnancy	3	1916	Mean Difference (IV, Fixed, 95% CI)	49.34 [-0.62, 99.31]
29.2 Multiple pregnancy	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.3 Singleton plus multiple pregnancies	1	545	Mean Difference (IV, Fixed, 95% CI)	-48.0 [-192.49, 96.49]
29.4 Not specified whether singleton or multiple pregnancies	3	1426	Mean Difference (IV, Fixed, 95% CI)	11.89 [-63.58, 87.36]
30 Length of infant hospital stay	3	1076	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.40, -0.16]
30.1 Singleton pregnancy	3	1076	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.40, -0.16]
30.2 Multiple pregnancy	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.3 Singleton plus multiple pregnancies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.4 Not specified whether singleton or multiple pregnancies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

31 Birth < 34 weeks (not prespecified)	2	976	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.62, 6.69]
31.1 Singleton pregnancy	1	500	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.40, 3.42]
31.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.4 Not specified whether singleton or multiple pregnancies	1	476	Risk Ratio (M-H, Random, 95% CI)	3.90 [1.11, 13.65]
32 Antenatal admissions (not prespecified)	2	893	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.88]
32.1 Singleton pregnancy	2	893	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.88]
32.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Phototherapy for neonatal jaundice (not prespecified)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.87]
33.1 Singleton pregnancy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.87]
33.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Abnormal neurological development at 9months (not pre-specified)	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.45]
34.1 Singleton pregnancy	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.45]
34.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35 Hospitalisation for IUGR neonatal (not prespecified)	1	142	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.75, 1.41]
35.1 Singleton pregnancy	1	142	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.75, 1.41]
35.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Fetal distress in labour (not prespecified)	1	289	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.10, 1.22]
36.1 Singleton pregnancy	1	289	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.10, 1.22]
36.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

36.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 Birth weight < 5 percentile (not prespecified)	1	289	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.51, 2.64]
37.1 Singleton pregnancy	1	289	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.51, 2.64]
37.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38 Periventricular leucomalacia (not prespecified)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.00]
38.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.3 Singleton plus multiple pregnancies	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.00]
38.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 Antenatal hospital stay	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.39, 1.19]
39.1 Singleton pregnancy	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.39, 1.19]
39.2 Multiple pregnancy	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
39.3 Singleton plus multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
39.4 Not specified whether singleton or multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Doppler ultrasound versus no Doppler ultrasound (all subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 SGA/IUGR	5	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.35]
1.2 Hypertension/pre-eclampsia	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
1.3 Diabetes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Prolonged pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Previous pregnancy loss	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.17]
2 Serious neonatal morbidity	1	53	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 SGA/IUGR	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Hypertension/pre-eclampsia	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

2.3 Diabetes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Prolonged pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Previous pregnancy loss	1	53	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Doppler ultrasound alone versus CTG alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.17, 1.15]
1.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.68]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.16, 1.73]
2 Serious neonatal morbidity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Stillbirth	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.14, 1.71]
3.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.05, 1.70]
3.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.15, 7.41]
4 Neonatal death	3	1473	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.16, 1.72]
4.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.15, 7.10]
4.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.07, 1.72]
5 Any potentially preventable perinatal death*	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.12, 1.18]
5.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.08, 2.11]
5.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

5.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.07, 1.72]
6 Fetal acidosis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Apgar < 7 at 5 minutes	3	2663	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.37]
7.1 Singleton pregnancy	2	1766	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.49, 1.43]
7.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.36, 2.39]
8 Caesarean section (elective and emergency)	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.79, 1.01]
8.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.02]
8.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.14]
9 Caesarean section - elective	3	1473	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.12, 2.09]
9.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.07, 2.67]
9.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.91, 2.15]
10 Caesarean section - emergency	3	1473	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.52, 0.84]
10.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.36, 0.83]
10.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.98]
11 Spontaneous vaginal birth	2	1323	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.15]
11.1 Singleton pregnancy	1	426	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.91, 1.19]
11.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]

12 Operative vaginal birth	3	2663	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.17]
12.1 Singleton pregnancy	2	1766	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]
12.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.25]
13 Induction of labour	2	576	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.40]
13.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.40]
13.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Oxytocin augmentation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Neonatal resuscitation required	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Infant requiring intubation/ventilation	2	576	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.08]
16.1 Singleton pregnancy	2	576	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.08]
16.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Neonatal fitting/seizures	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
17.1 Singleton pregnancy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
17.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Preterm labour	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

18.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Infant respiratory distress syndrome	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Meconium aspiration	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Neonatal admission to SCBU and/or NICU	4	2813	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.03]
21.1 Singleton pregnancy	3	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.99]
21.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.4 Not specified whether singleton or multiple pregnancies	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.73, 1.37]
22 Hypoxic ischaemic encephalopathy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Intraventricular haemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Bronchopulmonary dysplasia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

24.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Necrotising enterocolitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Long term infant neurodevelopmental outcome	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Women's views of their care	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Gestational age at birth	3	1473	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.00, 0.47]
28.1 Singleton pregnancy	2	576	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.06, 0.59]
28.2 Multiple pregnancy	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.3 Singleton plus multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.4 Not specified whether singleton or multiple pregnancies	1	897	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.15, 0.55]
29 Birth weight	4	2813	Mean Difference (IV, Fixed, 95% CI)	38.41 [-6.14, 82.97]
29.1 Singleton pregnancy	3	1916	Mean Difference (IV, Fixed, 95% CI)	49.34 [-0.62, 99.31]
29.2 Multiple pregnancy	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.3 Singleton plus multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.4 Not specified whether singleton or multiple pregnancies	1	897	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-102.42, 94.42]
30 Length of infant hospital stay	2	576	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.41, -0.08]
30.1 Singleton pregnancy	2	576	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.41, -0.08]
30.2 Multiple pregnancy	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

30.3 Singleton plus multiple pregnancies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.4 Not specified whether singleton or multiple pregnancies	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Birth < 34 weeks (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Antenatal admissions (not pre-specified)	1	426	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.55, 0.90]
32.1 Singleton pregnancy	1	426	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.55, 0.90]
32.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Phototherapy for neonatal jaundice (not pre-specified)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.87]
33.1 Singleton pregnancy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.87]
33.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Abnormal neurological development at 9months (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35 Hospitalisation for IUGR neonatal (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

36 Fetal distress in labour (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 Birth weight < 5 percentile (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38 Periventricular leucomalacia (not pre-specified)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 Antenatal hospital stay	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.39, 1.19]
39.1 Singleton pregnancy	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.39, 1.19]
39.2 Multiple pregnancy	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
39.3 Singleton plus multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
39.4 Not specified whether singleton or multiple pregnancies	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Doppler ultrasound alone versus CTG alone (all subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 SGA/IUGR	2	572	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.09]
1.2 Hypertension/pre-eclampsia	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
1.3 Diabetes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Prolonged pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Previous pregnancy loss	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2 Serious neonatal morbidity	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 SGA/IUGR	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Hypertension/pre-eclampsia	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Diabetes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Prolonged pregnancy	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Previous pregnancy loss	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Doppler ultrasound versus no Doppler ultrasound - SGA/IUGR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (SGA/IUGR)	5	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.35]
1.1 Singleton pregnancy	4	1189	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.28]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	1	103	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.13, 73.36]
2 Serious neonatal morbidity (SGA/IUGR)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Doppler ultrasound alone versus CTG - SGA/IUGR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (SGA/IUGR)	2	572	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.09]
1.1 Singleton pregnancy	2	572	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.09]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2 Serious neonatal morbidity (SGA/IUGR)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Doppler ultrasound versus no Doppler ultrasound - in hypertension/pre-eclampsia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (hypertension/pre-eclampsia)	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
2 Serious neonatal morbidity (hypertension/pre-eclampsia)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. Doppler ultrasound versus CTG - in hypertension/pre-eclampsia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (hypertension/pre-eclampsia)	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

1.4 Not specified whether singleton or multiple pregnancies	1	89	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.42, 30.73]
2 Serious neonatal morbidity (hypertension/pre-eclampsia)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 9. Doppler ultrasound versus no Doppler ultrasound - in diabetes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (in diabetes)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity (in diabetes)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 10. Doppler ultrasound versus CTG - in diabetes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (in diabetes)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity (in diabetes)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 11. Doppler ultrasound versus no Doppler ultrasound - in prolonged pregnancies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (in prolonged pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity (in prolonged pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 12. Doppler ultrasound versus CTG - in prolonged pregnancies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (in prolonged pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity (in prolonged pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 13. Doppler ultrasound versus no Doppler ultrasound - previous pregnancy loss

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (previous pregnancy loss)	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.17]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.17]
2 Serious neonatal morbidity (previous pregnancy loss)	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.4 Not specified whether singleton or multiple pregnancies	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
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Comparison 14. Doppler ultrasound versus CTG - previous pregnancy loss

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any perinatal death after randomisation (previous pregnancy loss)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity (previous pregnancy loss)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Singleton pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Multiple pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Singleton plus multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Not specified whether singleton or multiple pregnancies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 1 Any perinatal death after randomisation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 1 Any perinatal death after randomisation

(Continued ...)

Analysis 1.2. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 2 Serious neonatal morbidity.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 2 Serious neonatal morbidity

Analysis 1.3. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 3 Stillbirth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 3 Stillbirth

(Continued ...)

Analysis 1.4. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 4 Neonatal death.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 4 Neonatal death

(Continued ...)

Analysis 1.5. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 5 Any potentially preventable perinatal death*.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 5 Any potentially preventable perinatal death*

(Continued ...)

Analysis 1.7. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 7 Apgar < 7 at 5 minutes.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 7 Apgar < 7 at 5 minutes

Analysis 1.8. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 8 Caesarean section (elective and emergency).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 8 Caesarean section (elective and emergency)

(Continued ...)

Analysis 1.9. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 9 Caesarean section - elective.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 9 Caesarean section - elective

(Continued ...)

Analysis 1.10. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 10 Caesarean section - emergency.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 10 Caesarean section - emergency

(Continued ...)

Analysis 1.11. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 11 Spontaneous vaginal birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 11 Spontaneous vaginal birth

(Continued ...)

Analysis 1.12. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 12 Operative vaginal birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 12 Operative vaginal birth

Analysis 1.13. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 13 Induction of labour.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 13 Induction of labour

(Continued ...)

Analysis 1.16. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 16 Infant requiring intubation/ventilation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 16 Infant requiring intubation/ventilation

(Continued ...)

Analysis 1.17. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 17 Neonatal fitting/seizures.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 17 Neonatal fitting/seizures

Analysis 1.18. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 18 Preterm labour.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 18 Preterm labour

Analysis 1.19. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 19 Infant respiratory distress syndrome (RDS).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 19 Infant respiratory distress syndrome (RDS)

Analysis 1.21. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 21 Neonatal admission to SCBU and/or NICU.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 21 Neonatal admission to SCBU and/or NICU

(Continued ...)

Analysis 1.22. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 22 Hypoxic ischaemic encephalopathy.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 22 Hypoxic ischaemic encephalopathy

(Continued ...)

Analysis 1.23. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 23 Intraventricular haemorrhage.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 23 Intraventricular haemorrhage

Analysis 1.28. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 28 Gestational age at birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 28 Gestational age at birth

Analysis 1.29. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 29 Birth weight.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 29 Birth weight

Analysis 1.30. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 30 Length of infant hospital stay.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 30 Length of infant hospital stay

Analysis 1.31. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 31 Birth < 34 weeks (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 31 Birth < 34 weeks (not prespecified)

Analysis 1.32. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 32 Antenatal admissions (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 32 Antenatal admissions (not prespecified)

Analysis 1.33. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 33 Phototherapy for neonatal jaundice (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 33 Phototherapy for neonatal jaundice (not prespecified)

Analysis 1.34. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 34 Abnormal neurological development at 9months (not pre-specified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 34 Abnormal neurological development at 9months (not pre-specified)

Analysis 1.35. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 35 Hospitalisation for IUGR neonatal (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 35 Hospitalisation for IUGR neonatal (not prespecified)

Analysis 1.36. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 36 Fetal distress in labour (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 36 Fetal distress in labour (not prespecified)

Analysis 1.37. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 37 Birth weight < 5 percentile (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 37 Birth weight < 5 percentile (not prespecified)

Analysis 1.38. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 38 Periventricular leucomalacia (not prespecified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 38 Periventricular leucomalacia (not prespecified)

Analysis 1.39. Comparison 1 Doppler ultrasound versus no Doppler ultrasound, Outcome 39 Antenatal hospital stay.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 1 Doppler ultrasound versus no Doppler ultrasound

Outcome: 39 Antenatal hospital stay

Analysis 2.1. Comparison 2 Doppler ultrasound versus no Doppler ultrasound (all subgroups), Outcome 1 Any perinatal death after randomisation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 2 Doppler ultrasound versus no Doppler ultrasound (all subgroups)

Outcome: 1 Any perinatal death after randomisation

Analysis 2.2. Comparison 2 Doppler ultrasound versus no Doppler ultrasound (all subgroups), Outcome 2 Serious neonatal morbidity.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 2 Doppler ultrasound versus no Doppler ultrasound (all subgroups)

Outcome: 2 Serious neonatal morbidity

Study or subgroup	Doppler US n/N	No Doppler US n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 SGA/IUGR					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Hypertension/pre-eclampsia					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Diabetes					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Prolonged pregnancy					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Previous pregnancy loss					
Norman 1992	0/26	0/27			Not estimable
Subtotal (95% CI)	26	27			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	26	27			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi ² = 0.0, df = 1 (P = 0.0), I ² = 0.0%					

0.01 0.1 1 10 100
Favours Doppler Favours no Doppler

Analysis 3.1. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 1 Any perinatal death after randomisation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 1 Any perinatal death after randomisation

Analysis 3.3. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 3 Stillbirth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 3 Stillbirth

Analysis 3.4. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 4 Neonatal death.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 4 Neonatal death

Analysis 3.5. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 5 Any potentially preventable perinatal death*.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 5 Any potentially preventable perinatal death*

Analysis 3.7. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 7 Apgar < 7 at 5 minutes.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 7 Apgar < 7 at 5 minutes

Analysis 3.8. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 8 Caesarean section (elective and emergency).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 8 Caesarean section (elective and emergency)

Analysis 3.9. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 9 Caesarean section - elective.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 9 Caesarean section - elective

Analysis 3.10. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 10 Caesarean section - emergency.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 10 Caesarean section - emergency

Analysis 3.11. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 11 Spontaneous vaginal birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 11 Spontaneous vaginal birth

Analysis 3.12. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 12 Operative vaginal birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 12 Operative vaginal birth

Analysis 3.13. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 13 Induction of labour.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 13 Induction of labour

Analysis 3.16. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 16 Infant requiring intubation/ventilation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 16 Infant requiring intubation/ventilation

Analysis 3.17. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 17 Neonatal fitting/seizures.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 17 Neonatal fitting/seizures

Analysis 3.21. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 21 Neonatal admission to SCBU and/or NICU.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 21 Neonatal admission to SCBU and/or NICU

Analysis 3.28. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 28 Gestational age at birth.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 28 Gestational age at birth

Analysis 3.29. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 29 Birth weight.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 29 Birth weight

Analysis 3.30. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 30 Length of infant hospital stay.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 30 Length of infant hospital stay

Analysis 3.32. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 32 Antenatal admissions (not pre-specified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 32 Antenatal admissions (not pre-specified)

Analysis 3.33. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 33 Phototherapy for neonatal jaundice (not pre-specified).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 33 Phototherapy for neonatal jaundice (not pre-specified)

Analysis 3.39. Comparison 3 Doppler ultrasound alone versus CTG alone, Outcome 39 Antenatal hospital stay.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 3 Doppler ultrasound alone versus CTG alone

Outcome: 39 Antenatal hospital stay

Analysis 4.1. Comparison 4 Doppler ultrasound alone versus CTG alone (all subgroups), Outcome 1 Any perinatal death after randomisation.

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 4 Doppler ultrasound alone versus CTG alone (all subgroups)

Outcome: 1 Any perinatal death after randomisation

Analysis 5.1. Comparison 5 Doppler ultrasound versus no Doppler ultrasound - SGA/IUGR, Outcome 1 Any perinatal death after randomisation (SGA/IUGR).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 5 Doppler ultrasound versus no Doppler ultrasound - SGA/IUGR

Outcome: 1 Any perinatal death after randomisation (SGA/IUGR)

Analysis 6.1. Comparison 6 Doppler ultrasound alone versus CTG - SGA/IUGR, Outcome 1 Any perinatal death after randomisation (SGA/IUGR).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 6 Doppler ultrasound alone versus CTG - SGA/IUGR

Outcome: 1 Any perinatal death after randomisation (SGA/IUGR)

Analysis 7.1. Comparison 7 Doppler ultrasound versus no Doppler ultrasound - in hypertension/pre-eclampsia, Outcome 1 Any perinatal death after randomisation (hypertension/pre-eclampsia).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 7 Doppler ultrasound versus no Doppler ultrasound - in hypertension/pre-eclampsia

Outcome: 1 Any perinatal death after randomisation (hypertension/pre-eclampsia)

Analysis 8.1. Comparison 8 Doppler ultrasound versus CTG - in hypertension/pre-eclampsia, Outcome 1 Any perinatal death after randomisation (hypertension/pre-eclampsia).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 8 Doppler ultrasound versus CTG - in hypertension/pre-eclampsia

Outcome: 1 Any perinatal death after randomisation (hypertension/pre-eclampsia)

Analysis 13.1. Comparison 13 Doppler ultrasound versus no Doppler ultrasound - previous pregnancy loss, Outcome 1 Any perinatal death after randomisation (previous pregnancy loss).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 13 Doppler ultrasound versus no Doppler ultrasound - previous pregnancy loss

Outcome: 1 Any perinatal death after randomisation (previous pregnancy loss)

Analysis 13.2. Comparison 13 Doppler ultrasound versus no Doppler ultrasound - previous pregnancy loss, Outcome 2 Serious neonatal morbidity (previous pregnancy loss).

Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies

Comparison: 13 Doppler ultrasound versus no Doppler ultrasound - previous pregnancy loss

Outcome: 2 Serious neonatal morbidity (previous pregnancy loss)

Study or subgroup	Doppler US n/N	No Doppler US n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Singleton pregnancy					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Multiple pregnancy					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Singleton plus multiple pregnancies					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Not specified whether singleton or multiple pregnancies					
Norman 1992	0/26	0/27			Not estimable
Subtotal (95% CI)	26	27			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	26	27			Not estimable
Total events: 0 (Doppler US), 0 (No Doppler US)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\text{Chi}^2 = 0.0$, $\text{df} = 1$ ($P = 0.0$), $I^2 = 0.0\%$					

0.01 0.1 1 10 100
Favours Doppler Favours no Doppler

APPENDICES

Appendix I. Methods used in previous version of the review

Data collection and analysis

The methodology for data collection and analysis was based on the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008).

Selection of studies

Two review authors (G Gyte and T Stampalija) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion, or if required we consulted a third author.

Data extraction and management

We designed a form to extract data. Two review authors extracted the data using the agreed form. We resolved discrepancies through discussion, or if required we consulted a third author. Data were entered into Review Manager software (RevMan 2008), and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement through discussion, or by involving a third review author.

1) Sequence generation (checking for possible selection bias)

We have described, for each included study, the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We have assessed the methods as:

- adequate (any truly random process, e.g. random number table; computer random-number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

2) Allocation concealment (checking for possible selection bias)

We have described, for each included study, the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during, recruitment.

We have assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear.

3) Blinding (checking for possible performance bias)

We have described, for each included study, all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We have also provided any information relating to whether the intended blinding was effective. Where blinding was not possible, we have assessed whether the lack of blinding was likely to have introduced bias. We have assessed blinding separately for different outcomes or classes of outcomes.

We have assessed the methods as:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We have described, for each included study, the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported, the numbers (compared with the total randomised participants), reasons for attrition/exclusion where reported, and any re-inclusions in analyses which we undertook.

We have discussed whether missing data greater than 20% might impact on outcomes acknowledging that with long-term follow-up complete data are difficult to attain.

5) Selective reporting bias

We have described, for each included study, how the possibility of selective outcome reporting bias was examined by us and what we found.

We have assessed the methods as:

- adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

6) Other sources of bias

We have described, for each included study, any important concerns we have about other possible sources of bias.

We have assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

7) Overall risk of bias

We have made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings.

Measures of treatment effect

Where there were multiple pregnancies, we have used the number of women who were randomised as the denominator for maternal outcomes, and the number of babies of women who were randomised as the denominator for neonatal outcomes.

We have also used as the denominator, the number of babies of women who were randomised even though some babies could not have attained the outcome, for example, if there was a stillbirth then this baby would not have been able to attain the outcome of 'admission to special care baby unit'.

There was insufficient information about multiple pregnancies to enable us to deal with the non-independence of these data and so these data have been analysed as individual data.

Dichotomous data

For dichotomous data, we have presented the results as summary risk ratio (RR) with 95% confidence intervals.

Continuous data

For continuous data, we have used the mean difference (MD) if outcomes were measured in the same way between trials. We have used the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

If there had been several time points for assessment of an outcome, we would have performed separate analyses. In studies specifically of multiple pregnancies there were issues of non-independence, but we were unable to use the cluster-trial methods because the necessary information was not available in the studies.

Dealing with missing data

For included studies, we have noted levels of attrition. We considered that there was insufficient information and data for us to undertake sensitivity analyses for missing data.

For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis: i.e. we have attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised, minus any participants whose outcomes were known to be missing (available case analysis). For competing outcomes, for example, where there is a stillbirth the baby would not be eligible for 'admission to neonatal intensive care unit', we have kept as the denominator for the primary analyses, the number randomised (rather than the number eligible for the outcome).

Assessment of heterogeneity

We have assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We have regarded heterogeneity as substantial if τ^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identified substantial heterogeneity, we explored the causes of it by pre-specified subgroup analysis. Where random-effects were used because of heterogeneity, we have reported the average relative risk, average mean difference or average standard mean difference. Our interpretations take into account that for outcomes with less than 10 studies it is difficult to assess subgroup effects with adequate power.

Assessment of reporting biases

If there were 10 or more studies in a meta-analysis we have investigated reporting biases (such as publication bias) using funnel plots. We have assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes we have used the test proposed by [Egger 1997](#), and for dichotomous outcomes we have used the tests proposed by [Harbord 2006](#). If asymmetry was detected by any of these tests or was suggested by a visual assessment, we have tried to explain this.

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. We did not find any missing data of sufficient magnitude to impact on outcomes. Had we done so, we would have explored this by a Sensitivity analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software ([RevMan 2008](#)). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects analysis to produce an overall summary, if this was considered clinically meaningful. If an average treatment effect across trials was not clinically meaningful we did not combine heterogeneous trials.

If we used random-effects analyses, the results were presented as the average treatment effect and its 95% confidence interval, the 95% prediction interval, and the estimates of τ^2 , χ^2 , P value and I^2 . The 95% prediction interval provides a 95% interval for the predicted underlying treatment effect in a future study ([Higgins 2009](#)).

We sought to perform meta-analysis for each occasion where multiple trials were identified that examined the same intervention, and the trials' populations and methods were judged sufficiently similar to make meta-analysis clinically meaningful.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following *a priori* subgroup analyses on all outcomes rather than undertaking separate reviews on singleton and multiple pregnancies:

1. singleton pregnancies versus multiple pregnancies;
2. monochorionic twins versus dichorionic twins.

We planned to carry out the following additional *a priori* subgroup analyses on the primary outcomes only and have only done this where we have sufficient data available:

1. where the fetus was suspected small-for-gestational age;
2. where the woman had hypertension or pre-eclampsia;
3. where the women had diabetes;
4. prolonged pregnancy;
5. where there had been previous pregnancy loss.

For fixed-effect meta-analyses, we conducted planned subgroup analyses classifying whole trials by interaction tests as described by [Deeks 2001](#). For random-effects meta-analyses, we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We have undertaken sensitivity analysis to explore the effect of trial quality for important outcomes in the review where there were sufficient high-quality data.

Appendix 2. Methods to be used in future updates

Selection of studies

Two review authors will independently assess for inclusion all potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. We will enter data into Review Manager software ([RevMan 2012](#)) and check data entry for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement through discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as a summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials will not be considered eligible for inclusion.

Multiple pregnancies

Trials of multiple pregnancies are eligible for inclusion. Wherever possible, analyses will be adjusted for clustering to take into account the non-independence of babies from the same pregnancy (Gates 2004). Treating babies from multiple pregnancies as if they are independent, when they are more likely to have similar outcomes than babies from different pregnancies, will overestimate the sample size and give confidence intervals that are too narrow. Each woman can be considered a cluster in multiple pregnancy, with the number of individuals in the cluster being equal to the number of fetuses in her pregnancy. Analysis using cluster trial methods allows calculation of relative risk and adjustment of confidence intervals. Usually this will mean that the confidence intervals get wider. Although this may make little difference to the conclusion of a trial, it avoids misleading results in those trials where the difference may be substantial. We plan to adjust for clustering in the analyses, wherever possible, and to use the inverse variance method for adjusted analyses, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either the τ^2 is greater than zero, or there is a low P-value (< 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2012](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We will carry out the following *a priori* subgroup analyses on all outcomes rather than undertaking separate reviews on singleton and multiple pregnancies:

1. singleton pregnancies versus multiple pregnancies;
2. monochorionic twins versus dichorionic twins.

We plan to carry out the following additional *a priori* subgroup analyses on the primary outcomes:

1. where the fetus was suspected small-for-gestational age;
2. where the woman had hypertension or pre-eclampsia;
3. where the women had diabetes;
4. prolonged pregnancy;
5. where there had been previous pregnancy loss.

We will assess subgroup differences by interaction tests available within RevMan ([RevMan 2012](#)). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to carry out sensitivity analyses to explore the effect of trial quality assessed by adequate labelled sequence generation and adequate allocation concealment, with poor-quality studies (unclear or high risk of bias) being excluded from the analyses in order to assess whether this makes any difference to the overall result.

WHAT'S NEW

Last assessed as up-to-date: 30 September 2013.

Date	Event	Description
30 September 2013	New search has been performed	Search updated. Methods updated.
30 September 2013	New citation required but conclusions have not changed	No new trials identified.

CONTRIBUTIONS OF AUTHORS

T Stampalija (TS) drafted the background section with Z Alfirevic (ZA) and G Gyte (GG) providing comments and suggestions. GG drafted the methodology section, with ZA and TS providing comments and suggestions. TS and GG undertook the data extraction, TS input the data into RevMan ([RevMan 2012](#)) and GG checked the data entry. ZA drafted the discussion and conclusions, and TS and GG checked these.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The University of Liverpool, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcome of 'any perinatal death after randomisation excluding malformations' was changed to 'any potentially preventable perinatal death', which was defined as 'perinatal death excluding chromosomal abnormalities, termination of pregnancies, birth before fetal viability (less than 500 g) and fetal death before use of the intervention'.

The methods have been updated to the current Cochrane Pregnancy and Childbirth Group standard text, see [Appendix 2](#).

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy, High-Risk; *Ultrasonography, Prenatal; Cesarean Section [utilization]; Fetal Monitoring [*methods]; Labor, Induced [utilization]; Perinatal Mortality; Randomized Controlled Trials as Topic; Umbilical Cord [blood supply; *diagnostic imaging]

MeSH check words

Female; Humans; Pregnancy