Variation in outcome reporting in randomised controlled trials of interventions for the prevention and treatment of fetal growth restriction

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Running Head: Variation in outcome reporting in FGR

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ABSTRACT

Background: Fetal growth restriction (FGR) contributes to stillbirth, prematurity, neonatal and infant mortality and morbidity. Although FGR is well known to be associated with adverse outcomes for the mother and offspring, effective interventions for the prevention of FGR are yet to be established. The majority of pregnancies complicated by FGR are not detected antenatally and there are limited effective interventions for established FGR. Trials reporting interventions for the prevention and treatment of FGR may be limited by heterogeneity in the underlying pathophysiology. Systematic evaluation of available trials is hampered by the variation in the outcomes measured and reported.

Methods: We conducted a systematic review of randomised controlled trials investigating therapies for the prevention and treatment of FGR up to August 2018. We searched Medline, EMBASE and the Cochrane Central Register of Controlled Trials and systematically assessed studies, extracted and categorised data on which outcomes were reported in the included studies.

Results: The search identified 2609 citations of which 153 were selected for full text review and 72 were included in the final analysis. There were 44 trials relating to the prevention of FGR and 24 trials of interventions for the treatment of FGR. We identified 238 outcomes across the included studies. The most commonly reported were birthweight (88.2%), gestational age at birth (72.1%) and small for gestational age babies (67.6%). Few studies reported on any measure of neonatal morbidity (27.9%) and adverse effects of the interventions were reported in only 17.6% of trials.

Conclusion: Significant variation in outcome reporting exists across trials of therapies for both prevention and treatment of FGR. The clinical applicability of future research would be enhanced by the development of a core outcome set for use in future trials.

BACKGROUND

The failure of a fetus to reach its growth potential can be attributed to many different pathological processes – infection, placental dysfunction and maternal disease or malnutrition. Although there are inconsistencies in classification and diagnosis, between quarter and half of all stillbirths are associated with fetal growth restriction (FGR) and a significant proportion of babies suffering birth asphyxia are similarly growth restricted.[1–3] Apart from the risks of perinatal morbidity and mortality,[4,5] there is a long term impact on childhood neurological development, metabolic and cardiovascular disorders; [6,7] thought to be at least in part due to epigenetic changes induced by the pathological intra-uterine environment in addition to the direct pathological effects of altered blood flow and intra-uterine malnutrition. Despite the clinical implications of FGR, the majority of affected infants are not detected antenatally,[8] and as yet, no therapeutic interventions have been demonstrated to reverse or ameliorate the effects of FGR.

Research in FGR has focused firstly on improving antenatal detection; and then on determining the optimal timing of delivery of these infants to balance the risks of intrauterine demise and iatrogenic preterm delivery. Studies investigating interventions for the prevention and treatment of FGR have reported a wide variety of outcomes,[6] and have not always included outcomes that relate to harm from the interventions.[9] Heterogeneity in outcomes and outcome measures across studies limits the synthesis of findings across studies and the rarity of outcomes including stillbirth and neonatal death leads to many studies being underpowered to answer the clinical question of interest. The extent of heterogeneity of outcomes reported in FGR intervention studies has not been formally assessed.

The aim of this study was to conduct a systematic evaluation of outcomes reported in randomised controlled trials (RCT) evaluating the effects of interventions for the prevention or treatment of FGR to identify and categorise the variation in outcome reporting.

METHODS

The protocol for this systematic review was registered on PROSPERO (International Prospective Register of Systematic Reviews), registration number: CRD42018074910. We followed the reporting guidelines for meta-analyses and systematic reviews of randomised controlled trials, as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] We searched Cochrane Central Register of Controlled Trials, EMBASE, and Medline from inception to August 2018 for randomised controlled trials evaluating any potential intervention for prevention or treatment of FGR (Supplementary Table 1). Medical Subject Headings (MeSH) including FGR, fetal therapies, prenatal care and pregnancy complications were used. Additional records were identified by hand searching. The search was restricted to the English language. We included randomised controlled trials of interventions for the prevention or treatment of fetal growth restriction as either the primary or secondary outcome. Cohort and case-control studies, case series and reports and systematic reviews were excluded. We accepted the authors' definitions of fetal growth restriction.

At least two researchers (HK, LS or RT) independently reviewed each potentially relevant record based on title and abstract. Full texts were retrieved for each potentially relevant citation and two authors independently reviewed the full text of each selected study to assess eligibility for inclusion. Discrepancies between the authors were resolved by discussion.

Using a standardised data extraction form, at least two researchers (FGS, LS and RT) reviewed each included study and independently extracted trial characteristics including participants, funding sources, country of study, definition of FGR, interventions, and outcomes. The methodological quality of the included studies was assessed in duplicate with the JADAD score which awards 2 points for adequate randomisation, 2 for adequate blinding and 1 for follow up of all randomised patients.[11]

A comprehensive inventory of all outcomes was developed and initially organised into four broad categories: fetal outcomes, maternal outcomes, neonatal outcomes and childhood outcomes.

RESULTS

The literature search identified 2605 citations and an additional 4 records were identified through hand searches. Of these, 2434 abstracts were excluded and 153 papers were selected for full text review. Eighty-one papers were excluded after full text review, the majority as non-randomised studies or duplicates of already included studies (Supplementary Table 2). Seventy-two reports from 68 trials met the inclusion criteria. Five papers reporting outcomes from the DIGITAT trial and 2 papers from the TRUFFLE trial were included. Forty-three trials reported on potential interventions for the prevention of FGR and 23 reported on interventions for the treatment of pregnancies affected by FGR. One further paper included two separate trials addressing both points.(12) In total, 44 trials (45062 participants) reporting interventions for prevention of FGR and 24 trials (3357 participants) evaluating antenatal treatments of FGR were included (Figure 1: PRISMA flow chart).

All included studies were randomised controlled trials. The interventions evaluated for the prevention of FGR included aspirin (9), diet or exercise advice (3), nutritional supplementation (18), psychosocial interventions (5), low molecular weight heparin (LMWH) (2), hospital admission (1), intravenous immunoglobulins (1) and management of maternal medical conditions (such as hypertension, heroin addiction and periodontal disease - 5). The interventions evaluated for the treatment of FGR included aspirin (4), L-arginine (4), fetal nutrition (1), fish oil/Omega 3 (2), plasma volume expansion (1), hospital admission (2), intensive antenatal monitoring (4), nitric oxide donors (1), heparin (2), sildenafil (1), dydrogesterone (1) and maternal hyperoxygenation (1). Table 1 outlines the characteristics of the included studies. Twenty-two studies compared the intervention to placebo, 23 to an alternative treatment and 23 to routine care only. Forty-six studies were in high resource settings (determined by the human development index (HDI) of the study location) and 18 were in low resource settings with the remainder including both high resource and low resource settings. Studies of prevention included more participants (median 870, IQR 219-1297) than studies of treatment (median 69, IQR 49-138). Fifty-seven trials declared funding sources, one reported no funding and 10 made no declaration. Nine included studies received a JADAD score of 5, and the mean score was 3.06.

The included studies reported 238 outcomes (Table 2). These were maternal (44.1%), fetal (11.8%), neonatal and infant (37.4%) and relating to resource usage (6.7%). The most commonly reported outcomes were birthweight (88.2%), gestational age at delivery (72.1%), small for gestational age (SGA) (67.6%), stillbirth (60.3%) and mode of delivery (55.9%) (Table 2). Where mortality outcomes were reported, they were not always defined clearly. Of those studies reporting stillbirth, perinatal or neonatal death, only 20%, 17% and 32% gave the temporal definitions of these terms, respectively. Where stillbirth was defined, the term was used heterogeneously to include either all fetal loss or intrauterine demise after 20, 22, 24 and 28 weeks. Early and late neonatal deaths were reported separately in three studies although there was no temporal definition given in the majority of the studies reporting neonatal death.

Of the 105 maternal outcomes reported, these were frequently related to an underlying or co-morbid medical conditions (32/105 outcomes, 30.5%), and only rarely to potential adverse effects of the intervention (5/105 outcomes, reported in 12/68 (17.6%) of included trials). The most commonly reported maternal outcomes were mode of delivery (reported in 38/68 trials, 55.9%) and development of hypertensive disorders of pregnancy (HDP) and their complications. Many included trials (19/68 studies, 27.9%) theorised that a reduction in FGR would be brought about by the intervention reducing the incidence and/or severity of HDP. One trial reported maternal self-reported outcomes of anxiety and pain at 6 months postpartum,[13] but no other studies evaluated long term maternal outcomes.

Fetal outcomes other than stillbirth and miscarriage were infrequently reported in prevention trials (9/44, 20.5%), which tended to have a larger sample size and focus on outcomes measured at birth. Ultrasound measurements (Doppler, biometry and liquor assessments) were the most commonly reported fetal outcomes (15/28 fetal outcomes) and were assessed in 13/24 (54.2%) treatment trials and 7/44 (15.9%) prevention trials. Investigators considered Doppler assessment of the umbilical, uterine and middle cerebral arteries, ductus venosus and the thoracic aorta and fetal biometry. Additional fetal testing via fetal blood sampling through the umbilical cord or scalp in labour was reported in two studies.

When considering the perinatal outcomes, birthweight and gestational age at delivery were reported consistently across most trials (88.2% and 72.1%, respectively for birthweight and gestational age) although the presentation varied. Neonatal intensive care unit admission (36/68 trials, 52.9%), APGAR scores (29/68 trials, 42.6%) and umbilical cord blood gas analysis (10/68 trials, 14.7%) were commonly reported as outcomes relating to fetal status at birth. Other measures of fetal hypoxia reported included the need for neonatal resuscitation, birth trauma and birth asphyxia. Investigators more frequently reported neonatal death (28 trials) than perinatal mortality (23 trials).

Many studies did not report on neonatal morbidity beyond 28 days of life. Only 19 (27.9%) of the included trials reported on any neonatal morbidity outcome, and trials of treatment interventions were more likely to report on neonatal morbidity than prevention trials. 6 prevention trials (13.6%) and 13 treatment trials (54.2%) reported any neonatal morbidity outcomes. The most frequently reported items included intraventricular haemorrhage (IVH) and other neurological morbidity, respiratory compromise (including respiratory distress syndrome, bronchopulmonary dysplasia, chronic lung disease, need for ventilation, continuous positive airway pressure and oxygen) and sepsis. Four trials used a score (MAIN [Morbidity assessment index for newborns], CRIB [clinical risk index for babies] or the Prechtl neonatal neurological exam score) to quantify the neonatal overall or neurological morbidity. Three studies [14–16] reported a composite outcome for neonatal morbidity including neurological, respiratory and GI morbidity with two additionally including retinopathy of prematurity or sepsis. One study reported the composite of perinatal death and neonatal morbidity.[14] Treatment studies were more likely to report neonatal morbidity and both prevention and treatment studies published after 2000 were more likely to report neonatal morbidity outcomes. Seven percent of prevention trials published before 2000 compared to 33.3% prevention trials published after 2000 and 42.8% v 58.8% treatment trials before and after 2000 respectively reported any neonatal morbidity outcome. Only five trials reported on longer-term follow-up (up to two years) of included infants and only three assessed motor, behavioural and cognitive development.

Figure 2 illustrates the variation in outcome reporting across the 30 largest prevention trials and the 24 included treatment trials.

DISCUSSION

Summary of the main findings

We have identified a wide range and significant variation in maternal and offspring outcomes reported in trials evaluating the effects of interventions for the prevention and treatment of FGR. Most reported birthweight, gestational age at delivery and small for gestational age (SGA) babies whereas only approximately half reported stillbirth, mode of delivery, admission to NICU and preterm delivery. Only a quarter of trials reported important neonatal morbidity outcomes, including respiratory distress syndrome, necrotising enterocolitis and neurological complications. Three studies addressed the problem of low incidence of important perinatal outcomes using a composite outcome, but in each case the composite differed enough between trials to preclude direct comparison. Few trials reported outcomes related to potential harm from the interventions considered.

Strengths and limitations

This study provides a comprehensive overview of outcomes evaluated by investigators. It is, however, difficult to speculate why specific outcome are selected; they are likely to reflect areas of clinical or research interest of the individuals involved in study design; this in turn may be influenced by medical, societal, cultural and governmental importance given to such interventions. When considering novel interventions for the prevention and treatment of FGR, most trials were not industry-funded. We have included trials from high and low resource settings and from a diverse range of international centres, which ensures inclusion of the maximum range of outcomes. The identification of trials and data extraction were systematically conducted by two reviewers and in line with the recommendations of the COMET initiative guidelines[17] to maintain the highest standards of research quality.

None of the included trials reported inclusion of patient or family representatives in the choice of outcomes measured and reported. It is possible that additional outcomes would be identified as important or given greater weight by stakeholders other than clinicians. Exploring this point would require additional qualitative research. Furthermore, interventions for prevention or

treatment of FGR are often directed at maternal medical conditions associated with FGR, and maternal outcomes related to these conditions (hypertension, thrombosis and infections) are therefore frequently reported in the included trials, but might not be key outcomes in the study of FGR in other contexts. Equally, trials reporting FGR as a secondary outcome may have been less likely to have been identified from the targeted literature search but the key outcome of interest in this review is fetal growth restriction, and broadening the search would have increased the number of outcomes not directly related to fetal growth restriction and irrelevant to the development of a core outcome set. The key maternal condition most closely associated with FGR is pre-eclampsia, and variation in outcome reporting in pre-eclampsia trials was investigated in depth by the iHOPE collaboration.[18–20] The majority of outcomes identified in the included studies were also identified in our review, and of those not specified in the trials included in this study, most were maternal outcomes relating to the complications of severe pre-eclampsia e.g maternal cardiac failure. These are clearly important end points for trials investigating pre-eclampsia, but are not likely to be relevant to trials in FGR. Although there is a pathophysiological overlap between pre-eclampsia and fetal growth restriction, these are two separate disorders and the outcomes likely to be important to researchers, patients and stakeholders are not and should not be identical.

Clinical and research implication of the findings

As described previously in studies investigating outcome reporting in other obstetric conditions including pre-eclampsia[18] and twin-to-twin transfusion syndrome, we have demonstrated significant variation in outcome reporting in trials of interventions for FGR. With the creation of national and international initiatives aimed at reducing stillbirths and perinatal mortality [21] and improving child health, addressing FGR is now a key clinical priority. Interventions to prevent or treat FGR have the potential to improve fetal, neonatal and child health and must be evaluated in the context of potential harms and benefits to the mother and baby. There is a clear need for robust investigation of new interventions for prevention and treatment of FGR, but the observed variation in outcome reporting is a factor limiting the comparison of studies on FGR, and thus their clinical applicability.

Identification of high value interventions for the prediction and treatment of FGR might be improved by the development of a Core Outcome Set (COS). A COS is the minimum set of outcomes that authors should report in all trials evaluating the effects of interventions for a given condition/field. Core outcome sets are developed with the idea to reduce waste in research by selecting those outcomes that are most relevant to all stakeholders and applicable in most research settings. The use of a COS would reduce variation in outcome reporting and promote the routine collection of such data. Standardised reporting of outcomes would increase generalizability, allow for meaningful pooled analysis and be of greater relevance to clinicians and stakeholders. Development of core outcome sets within women's health is recommended by the 'The CoRe Outcomes in Women's and Newborn health (CROWN) initiative (www.crown-initiativeorg), which seeks to harmonise outcome reporting in women's health research. It is important to add that a COS is not the only requirement for optimal comparability of studies. As demonstrated in this review, if outcomes are measured with different definitions comparability is also compromised. Standardization of 'how' to measure these outcomes is also vital. The findings of this review can be taken forward to form the basis of the development of a COS via discussion with clinical and patient stakeholders. The outcomes identified as frequently reported by researchers in this review should form the starting point for a Delphi process to establish consensus on the key outcomes to be included in a COS for fetal growth restriction, with attention given subsequently to standardizing measurement and definition of these core outcomes. The involvement of researchers in this process and the leadership of major journals in committing to the CROWN initiative is key to ensure uptake of the core outcome set in future studies and ultimately our ability as a research community to prevent and treat fetal growth restriction.

Conclusion

Significant variation exists in outcome reporting in randomised controlled trials investigating interventions for the prevention and treatment of FGR. FGR is a key target area for improving fetal and neonatal health. Identification of key outcomes, and a move to standardised reporting

is urgently needed to facilitate high quality investigation of novel interventions and minimise research waste.

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Figure Legends

Figure 1. PRISMA flow chart

Figure 2a. Maternal, fetal, neonatal, and childhood outcomes reporting across the largest thirty prevention studies.

Figure 2b. Maternal, fetal, neonatal, and childhood outcomes reporting across the treatment studies.

Author	Year	Country	JADAD score	Participants	Definition of FGR	Intervention	Primary outcome
Ashorn[22]	2015	Malawi	4	1391	BW <10th centile	Lipid based nutrition supplements	BW and length
Ali, Alobaid [23]	2018	Saudi Arabia	3	179	Not defined	Vitamin D (4000 units)	Pre-eclampsia
Bar[24]	1997	Israel	5	87	not defined	Aspirin (60 mg)	fetal circulation parameters
Binder [25]	2008	Czech Republic	1	117	BW <10th centile	Substitution therapy in heroin addicted women	Pregnancy and perinatal outcomes, neonatal abstinence
Bhutta[26]	2009	Pakistan	3	2378	not defined	Multiple micronutrients	maternal health and birth outcomes
Branch[27]	2000	USA	5	16	BW<10th centile	Intravenous immunoglobulin	obstetric and neonatal outcomes
Brown[28]	1998	Australia	2	220	BW <3rd and <10th centile	Management of hypertension using Korotkoff 5	No. of episodes of severe HTN, no. of women with severe HTN or adverse fetal outcomes
Chan[29]	2009	Hong Kong	4	1164	BW <10th centile	Ferrous sulphate	risk of GDM
Crowther[30]	1992	Zimbabwe	3	218	not defined	Hospital admission	development of severe HTN, proteinuria, BW, NNU admission and length of stay
Cruickshank[31]	1992	UK	3	114	BW <10th centile	Labetalol	BW <10th centile
Donovan[32]	1977	UK	1	1202	not defined	Smoking cessation	FGR

ECPPA[33]	1996	Brazil	4	1009	BW<3rd centile	Aspirin (60 mg)	Pre-eclampsia
Fawzi[34]	1998	Tanzania	4	1075	BW <2500g	Multivitamin supplementation	Progression of HIV-1 and birth outcomes
Goffinet[35]	2001	France	3	3317	BW <3rd and <10th centile	Aspirin after screening (100mg)	FGR and Pre-eclampsia
Groom[15]	2017	Multinational	3	156	BW <5th centile	Low molecular weight heparin	Pre-eclampsia and SGA
Harrington[36]	2000	UK	3	946	BW <3rd and <10th centile	Aspirin after screening (100mg SR)	GA at delivery, development of pre-eclampsia, APH or SGA
Hossain[37]	2014	Pakistan	1	193	BW <2500g	Vitamin D	not specified
Janmohamed[38]	2016	Cambodia	3	547	BW <10th centile	Dietary supplementation	BW and length
Kokanali[39]	2014	Turkey	1	295	BW <10th centile	Dietary advice	Maternal and perinatal morbidity
Kumwenda[40]	2002	Malawi	5	697	BW <2500g	Vitamin A	Birth outcomes
Kupka[41]	2008	Tanzania	4	913	BW <10th centile	Selenium	Maternal HIV disease progression, pregnancy outcomes and maternal and child survival
Lagendijk [42]	2018	Netherlands	3	5296	BW <10th centile	Triaged antenatal care	Preterm birth or SGA
Levine[43]	1997	USA	4	4589	BW <10th centile	Calcium	Pre-eclampsia and SGA

Metcoff [44]	1985	USA	2	471	BW <3150g	Food supplementation	Birthweight
Moses[45]	2014	Australia	3	691	BW <10th centile	Low GI diet	Fetal growth centile and PI
Newnham[46]	2009	Australia	3	1082	BW <10th centile	Periodontal disease management	PTB, FGR and pre-eclampsia
Olsen[12]	2000	Europe	4	280	BW <10th centile	Fish oil	Recurrence of FGR
Onwude[47]	1995	UK	5	233	BW <3rd and <10th centile	Fish oil	PE, PIH and asymmetric growth restriction
Parazzini[48]	1993	Italy	3	1032	BW<10th centile	Aspirin (50mg)	PIH and FGR
Poston[49]	2015	UK	3	1555	BW <10th customised centile	Behavioural intervention	GDM and LGA
Rahmshani[50]	2012	India	5	93	Fetus unable to reach its required growth potential for its gestational age'	Yoga	HDP, FGR, PTB, GDM, miscarriage, IUD and congenital anomalies
Ramakrishnan[51]	2003	Mexico	4	873	BW <10th centile	Multiple micronutrients	Birth size
Rodger[52]	2014	Multinational	3	289	BW<10th centile	LMWH	Major VTE, severe PE, SGA, pregnancy loss
Tolnik [53]	2017	UK	5	1776	BW <5th centile	Aspirin (150mg after screening)	Preterm pre-eclampsia

Roth [54]	2018	Bangladesh	5	1300	BW <10th centile	Vitamin D	Infant length-for-age Z score at 1 year
[illegible]ga-Riz [55]	2006	USA	5	867	BW <10th centile	Ferrous sulphate	Anaemia
Stanescu[56]	2018	Romania	3	150	EFW <10th centile	Aspirin (150mg)	FGR
[illegible]eketee[57]	1996	Malawi	0	1766	BW<2500g and >37 weeks	Mefloquine	LBW
Subramanian[58]	2012	USA	3	1025	not defined	Targeted antenatal care	not specified
Sureau[59]	1991	France	2	478	not defined	Aspirin and dipyridamole	FGR, IUD, abruption
Toe[60]	2015	Burkina Faso	2	1296	BW<10th centile	Lipid based nutrition supplements	BW, birth length, IUGR and PTB
Vainio[61]	2002	Finland	3	86	IUGR defined as BW <10th centile	Aspirin (0.5mg/kg)	PIH, PE, FGR, duration of pregnancy and BW
Villar[62]	1992	Multinational	2	2235	BW<10th centile	Psychosocial support	FGR
Villar[63]	2009	Multinational	3	1365	BW<10th centile	Vitamins C and E	PE, LBW, SGA, perinatal death

Table 1a. Characteristics of included prevention trials

BW: birthweight, HTN: hypertension, GDM: gestational diabetes, NNU: neonatal unit, FGR: fetal growth restriction, SGA: small for gestational age, GA: gestational age, APH: antepartum haemorrhage, PI: pulsatility index, PTB: preterm birth, PE: pre-eclampsia, PIH: pregnancy induced hypertension, LGA: large for gestational age, IUD: intrauterine demise, HDP: hypertensive disorders of pregnancy, VTE: venous thromboembolism, LBW: low birth weight, IUGR: intra-uterine growth restriction

Author	Year	Country	JADAD score	Participants	Definition of FGR	Intervention	Primary outcome
Ali Abbas[64]	2017	Egypt	3	60	AC <2SD below mean and HC:AC ratio increased	Aspirin	Change in EFW
A. Amin[65]	2017	Egypt	3	80	AC <2SD below mean and HC:AC ratio increased	Omega 3	Change in EFW
Almstrom[66]	1992	Sweden	3	426	EFW <2SD below mean	Umbilical artery Doppler monitoring	GA at delivery, mode of delivery and NICU LoS
Battaglia [67]	1992	Italy	2	38	AC <10th centile	Hyperoxygenation	Not specified
DIGITAT [13,68–71]	2011	Nether-lands	4	650	AC<10th or EFW<10th +/- reduced growth velocity	Induction of labour	Composite: death before discharge, APGAR 5<7, cord arterial pH <7.05, NICU admission)
Cabero[72]	1988	Spain	1	98	> 2 weeks discrepancy between menstrual and ultrasound dates	Hospital admission	Not specified

Di Iorio[73]	2002	Italy	2	20	BPD<10th centile and AC<5th centile and reduced growth velocity	Glyceryl tri-nitrate	Serum NO metabolites, AM levels and fetoplacental Dopplers
Ganzevoort[74]	2005	Netherlands	3	216	EFW <10th centile or AC <5th centile	Plasma volume expansion	Neurological score
Hansen [75]	2018	Denmark	3	53	EFW <2.3rd centile	Low molecular weight heparin	BW, fetal growth rate
TRUFFLE [16,76]	2013	Multinational	3	503	AC<10th centile and UA PI >95th centile	Monitoring with DV	Composite: fetal or postnatal death, bronchopulmonary dysplasia, severe cerebral germinal matrix haemorrhage, cPVL, proven sepsis or NEC)
McCowan[77]	1999	Australia	4	65	AC<10th centile and UA PI >95th centile	Aspirin	BW
Lonincx[78]	1997	Netherlands	3	150	not defined	Hospital admission	Neurological score
Newnham[79]	1995	Australia	4	51	AC<10th centile and UA PI >95th centile	Aspirin (100mg)	BW
Olsen[12]	2000	Europe	4	280	not defined	Fish oil	BW
Sharp [14]	2018	UK	5	135	EFW or AC <10th centile	Sildenafil	Time to delivery

					and AREDF in the umbilical artery		
Sieroszewski[80]	2004	Poland	1	108	EFW<10th centile	L-arginine	Change in EFW
Singh[81]	2015	India	1	60	EFW <10th centile	L-arginine	Neonatal outcomes
Tchirikov[82]	2017	Germany	3	14	EFW<5th centile and UA PI >95th centile	Intraumbilical fetal nutrition	Feasibility of intervention
Trudinger[83]	1988	Australia	4	46	UA S/D ratio >95th centile	Aspirin (150mg)	GA at delivery, BW and perinatal morbidity
Van den Hove [84]	2006	Netherlands	3	33	AC <10th centile or reduced growth velocity	Induction of labour	Obstetric intervention and neonatal outcomes
Winer[85]	2009	France	4	43	AC<3rd centile with abnormal uterine Doppler	L-arginine	BW and neonatal morbidity
Xiao[86]	2005	China	1	66	HC:AC ratio <10th centile	L-arginine	Maternal NO_2/NO_3 levels and BW
Yu [87]	2010	China	1	73	SFH<10th centile or HC:AC ratio <10th centile or FL <10th centile or abnormal UA Doppler	LMWH	Not specified
Zarean [88]	2018	Iran	4	89	EFW <10th centile	Dydrogesterone	Fetal weight, MCA and uterine artery RI

Table 1b. Characteristics of included treatment trials

EFW: estimated fetal weight, BW: birthweight, BPD: biparietal diameter, SD: standard deviation, S/D: systolic/diastolic, DV: ductus venosus, LMWH: low molecular weight heparin, cPVL: cystic periventricular leukomalacia, NEC: necrotising enterocolitis, NICU: neonatal intensive care unit, GA: gestational age, AC: abdominal circumference, HC: head circumference, PI: pulsatility index, SFH: symphysiofundal height, FL: femur length, UA: umbilical artery, LoS: length of stay, AM: adrenomedullin, NO: nitric oxide.

Outcome	Prevention studies (44)	Treatment studies (24)	Total number of times reported
Mortality outcomes			
Stillbirth	28 (63.6%)	13 (54.2%)	41
Neonatal death	18 (40.9%)	10 (41.7%)	28
Perinatal mortality	15 (34.1%)	8 (33.3%)	23
Miscarriage	22 (50.0%)	1 (4.2%)	23
Maternal death	8 (6.8%)	2 (8.3%)	10
Infant death	4 (9.1%)	2 (8.3%)	6
Abortion	1 (2.3%)	0	1
Late termination of pregnancy	1 (2.3%)	0	1
Fetal outcomes			
Ultrasound measurements			
Umbilical Doppler	2 (4.6%)	12 (50.0%)	14
Uterine Doppler	1 (2.3%)	5 (20.8%)	6
Estimated fetal weight	0	5 (20.8%)	5
Middle cerebral artery Doppler	0	5 (20.8%)	5
Fetal growth velocity	0	4 (16.7%)	4
Suspected FGR	4 (9.1%)	0	4
Oligohydramnios	3 (6.8%)	0	3
Aortic Doppler	1 (2.3%)	1 (4.2%)	2
Cerebroplacental ratio	0	2 (8.3%)	2

Abdominal circumference (fetal)	0	1 (4.2%)	1
Biparietal diameter	1 (2.3%)	0	1
Ductus venosus	0	1 (4.2%)	1
Femur length	1 (2.3%)	0	1
Humerus length	1 (2.3%)	0	1
Polyhydramnios	1 (2.3%)	0	1
Fetal morbidity			
Delivery for suspected fetal compromise	3 (6.8%)	4 (16.7%)	7
Abnormal fetal heart monitoring in labour	1 (2.3%)	0	1
Scalp pH in labour	1 (2.3%)	0	1
Meconium in amniotic fluid	1 (2.3%)	0	1
Intrauterine cardiac complications	1 (2.3%)	0	1
Intrauterine renal complications	1 (2.3%)	0	1
Intrauterine respiratory complications	1 (2.3%)	0	1
Intrauterine neurological complications	1 (2.3%)	0	1
Fetal blood testing	0	1 (4.2%)	1
Maternal outcomes			
Mode of delivery	24 (54.6%)	14 (58.33%)	38
Preterm delivery	34 (77%)	1 (4.2%)	35
Onset of labour	12 (27.3%)	5 (20.8%)	17
Post term delivery	3 (6.8%)	1 (4.2%)	4

Delivery for maternal indication	0	3 (12.5%)	3
PPROM	2 (4.6%)	0	2
Pyrexia in labour	1 (2.3%)	0	1
Retained placenta	1 (2.3%)	0	1
Epidural use	1 (2.3%)	0	1
Duration of labour	1 (2.3%)	0	1
Threatened preterm labour	1 (2.3%)	0	1
Hypertensive morbidity			
Pre-eclampsia	22 (50.0%)	4 (16.7%)	26
Pregnancy induced hypertension	10 (22.7%)	3 (12.5%)	13
Eclampsia	5 (11.4%)	3 (12.5%)	8
Proteinuria	3 (6.8%)	0	3
HELLP	2 (4.6%)	2 (8.3%)	4
Severe hypertension	2 (4.6%)	0	2
Need for antihypertensives	2 (4.6%)	0	2
Pulmonary oedema	0	2 (8.3%)	2
Renal failure	2 (4.6%)	0	2
Oedema	1 (2.3%)	0	1
Headache	1 (2.3%)	0	1
Neurological features of pre-eclampsia	1 (2.3%)	0	1
Cerebral haemorrhage or thrombosis	1 (2.3%)	0	1
DIC	1 (2.3%)	0	1
Use of anticonvulsants	1 (2.3%)	0	1

Pre-term pre-eclampsia	1 (2.3%)	0	1
Liver haematoma	0	1 (4.2%)	1
Encephalopathy	0	1 (4.2%)	1
Bleeding and thrombosis			
Abruption	10 (22.7%)	3 (12.5%)	13
Postpartum haemorrhage	7 (15.9%)	1 (4.2%)	8
Bleeding (any)	5 (11.4%)	1 (4.2%)	6
Thromboembolism	2 (4.6%)	2 (8.3%)	4
Antepartum haemorrhage	3 (6.8%)	0	3
Thrombocytopenia	2 (4.6%)	0	2
Need for transfusion	1 (2.3%)	0	1
Use of anticoagulants	1 (2.3%)	0	1
Retroplacental bleeding	0	1 (4.2%)	1
Placental infarct	0	1 (4.2%)	1
Other morbidity			
Anaemia	3 (6.8%)	1 (4.2%)	4
Gestational diabetes	4 (9.1%)	0	4
Heparin induced thrombocytopenia	3 (6.8%)	0	3
Sepsis	1 (2.3%)	1 (4.2%)	2
Osteopenic fracture	2 (4.6%)	0	2
Urolithiasis	2 (4.6%)	0	2
Adverse drug reactions	1 (2.3%)	0	1
ICU admission	1 (2.3%)	0	1
Febrile episodes	1 (2.3%)	0	1

Backache	1 (2.3%)	0	1
Vomiting	1 (2.3%)	0	1
Cough	1 (2.3%)	0	1
General weakness	1 (2.3%)	0	1
Abdominal Pain	1 (2.3%)	0	1
Use of beta-mimetics	1 (2.3%)	0	1
Maternal accident	1 (2.3%)	0	1
Sexually transmitted disease in pregnancy	1 (2.3%)	0	1
Iron depletion	1 (2.3%)	0	1
Iron deficiency	1 (2.3%)	0	1
Insulin resistance	1 (2.3%)	0	1
Maternal amino acids	1 (2.3%)	0	1
Maternal nutrients	1 (2.3%)	0	1
Maternal anthropometry			
Maternal weight gain	5 (11.4%)	0	5
Upper arm circumference	3 (6.8%)	0	3
Mid-thigh circumference	2 (4.6%)	0	2
Skinfold thicknesses	2 (4.6%)	0	2
Physical activity scores	1 (2.3%)	0	1
Wrist circumference	1 (2.3%)	0	1
Bone mineral density	1 (2.3%)	0	1
Fundal height	1 (2.3%)	0	1
Other maternal anthropometry	1 (2.3%)	0	1

Laboratory tests			
Maternal haemoglobin	3 (6.8%)	1 (4.2%)	4
Nitric oxide	0	4 (16.7%)	4
Serum 25 OHD	3 (6.8%)	0	3
Elevated aspartate transaminase	2 (4.6%)	0	2
Vitamin A	2 (4.6%)	0	2
Ferritin	2 (4.6%)	0	2
2 hour glucose OGTT	2 (4.6%)	0	2
CD3,4 and 8 cell counts	2 (4.6%)	0	2
Platelet count	0	1 (4.2%)	1
LDL cholesterol	1 (2.3%)	0	1
HDL cholesterol	1 (2.3%)	0	1
VLDL cholesterol	1 (2.3%)	0	1
Fasting glucose	1 (2.3%)	0	1
Fasting plasma insulin	1 (2.3%)	0	1
sEng	1 (2.3%)	0	1
PlGF	1 (2.3%)	0	1
sVCAM-1	1 (2.3%)	0	1
ET-1	1 (2.3%)	0	1
HIV viral load	1 (2.3%)	0	1
Serum sFlt-1	1 (2.3%)	0	1
Fasting triglycerides	1 (2.3%)	0	1
Adrenomedullin	0	1 (4.2%)	1
Blood viscosity	0	1 (4.2%)	1

Plasma viscosity	0	1 (4.2%)	1
Erythrocyte aggregation index	0	1 (4.2%)	1
Blood yield stress	0	1 (4.2%)	1
Zinc	1 (2.3%)	0	1
Calcium	1 (2.3%)	0	1
Urinary calcium:creatinine ratio	1 (2.3%)	0	1
Intact parathyroid hormone plasma concentration	1 (2.3%)	0	1
C3-epi-25(OH)D	1 (2.3%)	0	1
Long term outcomes			
Pain after delivery	0	1 (4.2%)	1
General health after delivery	0	1 (4.2%)	1
Anxiety and depression after delivery	0	1 (4.2%)	1
Perinatal outcomes			
Birthweight	38 (86.4%)	22 (91.7%)	60
GA at delivery	32 (72.7%)	17 (70.8%)	49
SGA	36 (81.8%)	10 (41.7%)	46
Admission to NICU	20 (45.5%)	16 (66.7%)	36
APGAR score	13 (29.6%)	16 (66.7%)	29
LBW	21 (47.7%)	1 (4.2%)	22
Newborn length	10 (22.7%)	2 (8.3%)	12
Umbilical blood acid-base values	4 (9.1%)	6 (25%)	10
Head circumference	8 (18.2%)	2 (8.3%)	10

Hypoglycaemia	2 (4.6%)	3 (12.5%)	5
Placental weight	4 (9.1%)	1 (4.2%)	5
Macrosomia	3 (6.8%)	1 (4.2%)	4
Congenital abnormalities	4 (9.1%)	0	4
Ponderal index	2 (4.6%)	1 (4.2%)	3
Newborn stunting	3 (6.8%)	0	3
Neonatal resuscitation	2 (4.6%)	1 (4.2%)	3
Neonatal skinfold thickness	1 (2.3%)	1 (4.2%)	2
Newborn arm circumference	2 (4.6%)	0	2
Birth asphyxia	0	2 (8.3%)	2
LGA	2 (4.6%)	0	2
Birth weight ratio	0	2 (8.3%)	2
Unexpected SGA	1 (2.3%)	0	1
Length for gestational age	1 (2.3%)	0	1
Weight for gestational age	1 (2.3%)	0	1
Placental hypoplasia	0	1 (4.2%)	1
Severe placental changes	1 (2.3%)	0	1
Crown rump length	1 (2.3%)	0	1
Birth trauma	1 (2.3%)	0	1
Chest circumference	0	1 (4.2%)	1
Abdominal circumference	0	1 (4.2%)	1
Neonatal morbidity			
IVH	6 (13.6%)	6 (25%)	12
Ventilation	4 (9.1%)	6 (25%)	10

Sepsis	4 (9.1%)	5 (20.8%)	9
NEC	3 (6.8%)	6 (25%)	9
Oxygen use	2 (4.6%)	6 (25%)	8
RDS	2 (4.6%)	4 (16.7%)	6
cPVL	1 (2.3%)	3 (12.5%)	4
Exchange transfusion	1 (2.3%)	2 (8.3%)	3
Phototherapy	1 (2.3%)	2 (8.3%)	3
Jaundice	1 (2.3%)	2 (8.3%)	3
Retinopathy of prematurity	2 (4.6%)	1 (4.2%)	3
Pulmonary hypertension	1 (2.3%)	1 (4.2%)	2
Chronic lung disease	1 (2.3%)	1 (4.2%)	2
Hypothermia	0	2 (8.3%)	2
Bronchopulmonary dysplasia	0	2 (8.3%)	2
Parenteral nutrition	0	2 (8.3%)	2
Neurological exam score	0	2 (8.3%)	2
Neonatal hypocalcaemia	1 (2.3%)	0	1
Haematocrit	1 (2.3%)	0	1
Polycythaemia	1 (2.3%)	0	1
Thrombocytopenia	0	1 (4.2%)	1
Hyponatraemia	0	1 (4.2%)	1
Any cerebral haemorrhage	0	1 (4.2%)	1
Contriction of the ductus arteriosus	1 (2.3%)	0	1
Surfactant use	0	1 (4.2%)	1
Neonatal 25(OH)D	1 (2.3%)	0	1

Neonatal anaemia	1 (2.3%)	0	1
Pulmonary haemorrhage	1 (2.3%)	0	1
Cerebral germinal matrix haemorrhage	0	1 (4.2%)	1
Intubation	1 (2.3%)	0	1
CPAP	1 (2.3%)	0	1
Suction	1 (2.3%)	0	1
Discharged on oxygen	1 (2.3%)	0	1
Metabolic diseases	1 (2.3%)	0	1
Hydrocephalus	1 (2.3%)	0	1
Meningomyelocoele	1 (2.3%)	0	1
MAIN score	0	1 (4.2%)	1
Chromosomal abnormalities	0	1 (4.2%)	1
Persistent ductus arteriosus	0	1 (4.2%)	1
CRIB score	0	1 (4.2%)	1
Apnoea	0	1 (4.2%)	1
Finnegan score	1 (2.3%)	0	1
Neonatal haemoglobin	1 (2.3%)	0	1
Infant outcomes			
Development quotient	0	2 (8.3%)	2
Gastrointestinal disease	1 (2.3%)	0	1
Nutritional complications	1 (2.3%)	0	1
Diarrhoea	1 (2.3%)	0	1
Dehydration	1 (2.3%)	0	1

Motor impairment	0	1 (4.2%)	1
Respiratory infections	1 (2.3%)	0	1
Behavioural disorder	0	1 (4.2%)	1
Neurological disability	1 (2.3%)	0	1
Infant 25(OH)D	1 (2.3%)	0	1
Hearing loss	0	1 (4.2%)	1
Visual loss	0	1 (4.2%)	1
Cerebral palsy	0	1 (4.2%)	1
Resource use			
Length of stay in NICU	6 (13.6%)	10 (41.6%)	16
Hospital admission	8 (18.2%)	5 (20.8%)	13
Number of CTGs	1 (2.3%)	2 (8.3%)	3
Number of ultrasounds	1 (2.3%)	1 (4.2%)	2
Number of blood tests	0	1 (4.2%)	1
Number of consultations	1 (2.3%)	0	1
Number of blood pressure measurements	0	1 (4.2%)	1
Place of birth	1 (2.3%)	0	1
Referral to diabetic antenatal services	1 (2.3%)	0	1
Frequency of child hospital visits	1 (2.3%)	0	1
Antenatal sick time for pregnancy related reasons	1 (2.3%)	0	1
Average duration of fetal surveillance	0	1 (4.2%)	1

Total cost of care	0	1 (4.2%)	1
Clinical encounters	1 (2.3%)	0	1
Referral to non-obstetric care	1 (2.3%)	0	1
Referral to preventive medicine services	1 (2.3%)	0	1

Table 2: All outcomes reported in included prevention and treatment trials

SGA: small for gestational age, GA: gestational age, LGA: large for gestational age, LBW: low birth weight, cPVL: cystic periventricular leukomalacia, RDS: respiratory distress syndrome, FGR: fetal growth restriction, PPROM: preterm prelabour rupture of membranes, HELLP: haemolysis, elevated liver enzymes and low platelets, DIC: disseminated intravascular coagulation, NICU: neonatal intensive care unit, NEC: necrotising enterocolitis, ICU: intensive care unit, OGTT: oral glucose tolerance test, IVH: intraventricular haemorrhage, LDL: low density lipoprotein, HDL: high density lipoprotein, VLDL: very low density lipoprotein, sENG: soluble endoglin, PlGF: placental growth factor, ET-1:endothelin-1, sVCAM-1: soluble vascular cell adhesion molecule -1, sFlt-1: soluble fms-like tyrosine kinase -1, CPAP: continuous positive airway pressure, MAIN : morbidity assessment index for newborns, CRIB: clinical risk index for babies, HIV: human immunodeficiency virus, CTG: cardiotocograph.

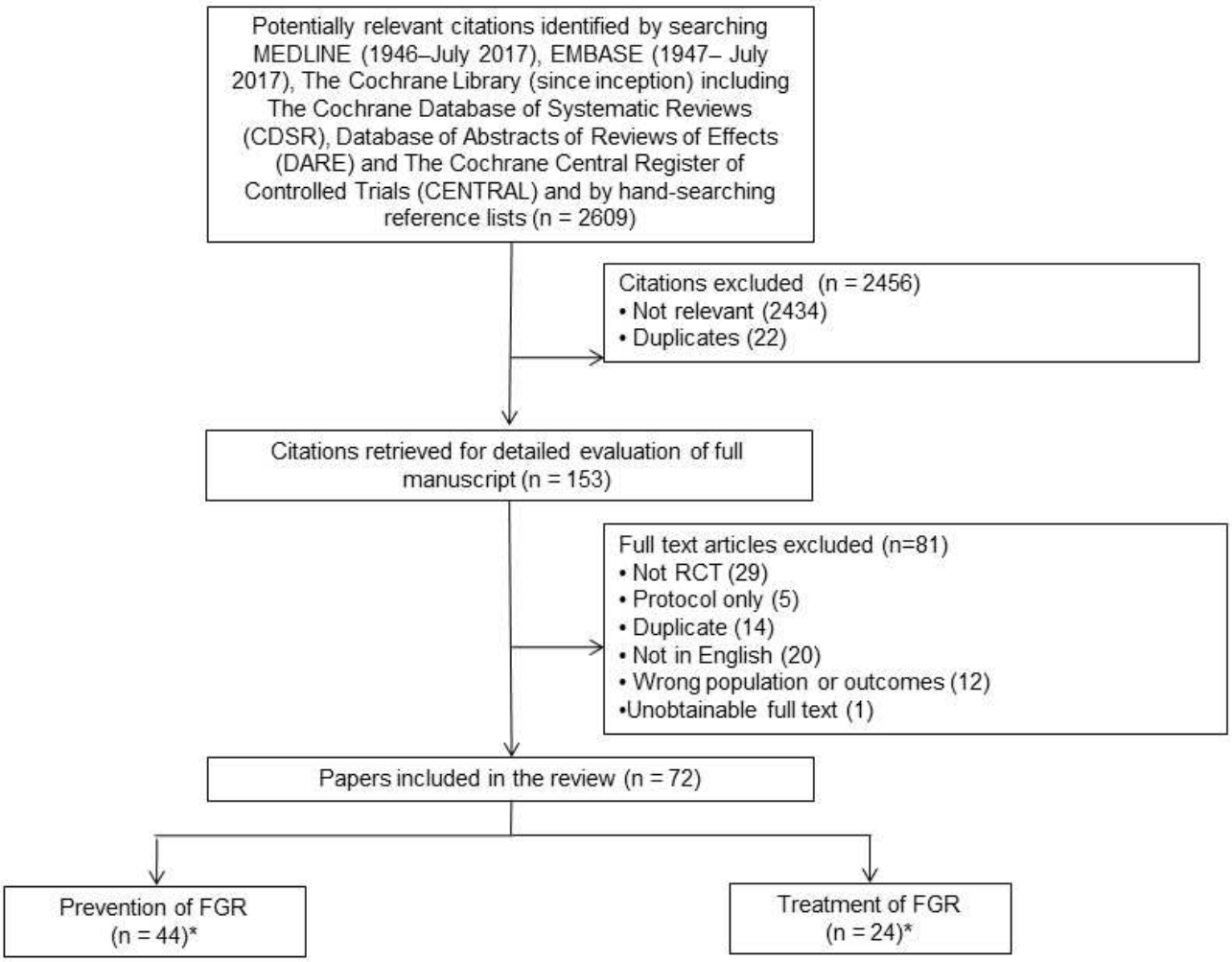
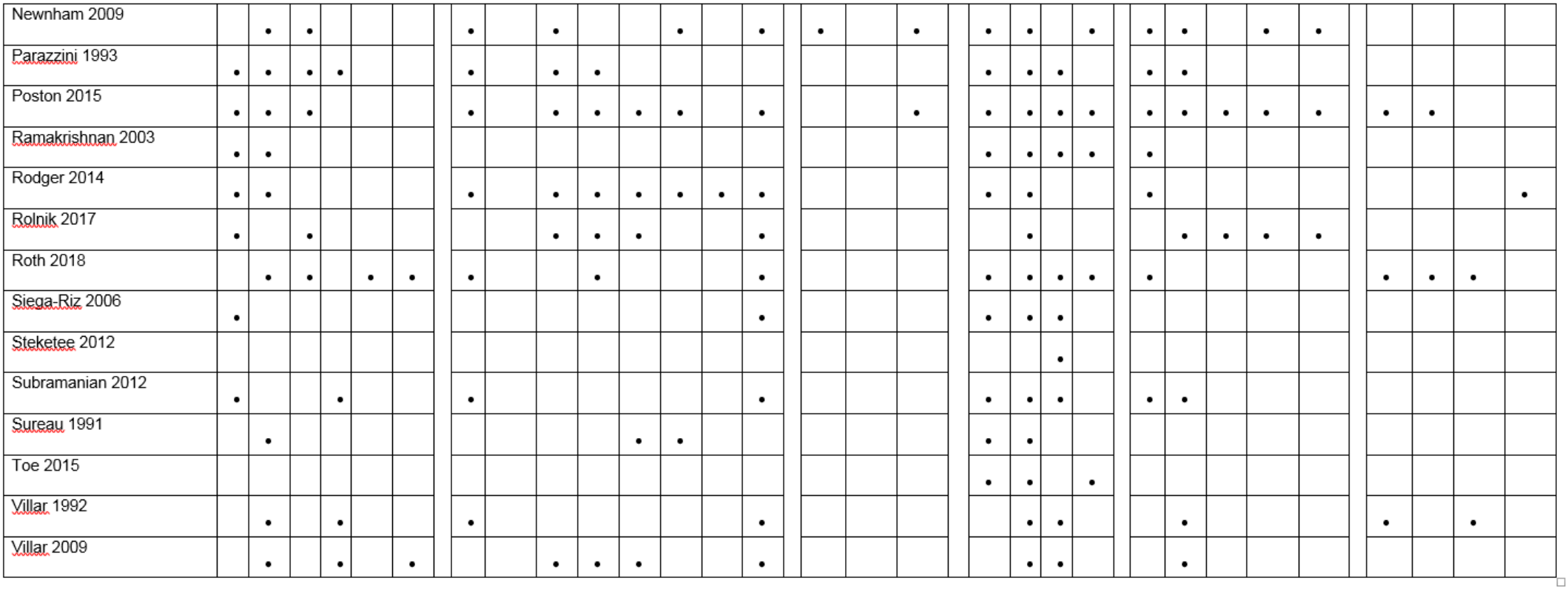


Figure 1 Flow chart illustrating identification of studies included in this systematic review. *number of included trials (some trials reported over >1 citation).

Included studies	Mortality outcomes						Maternal outcomes								Fetal outcomes			Offspring size				Neonatal outcomes					Long term and resource usage outcomes			
	Miscarriage	Stillbirth	Neonatal death	Perinatal death	Infant death	Maternal death	Mode of delivery	Other delivery related outcomes	Pre-eclampsia	Other hypertensive morbidity	Abruption	Other maternal bleeding	Thrombosis	Other maternal morbidity	Umbilical artery Doppler	Fetal growth	Other fetal morbidity	Birthweight	SGA	LBW	Other size measures	GA at delivery	Neonatal condition at birth	Neurological morbidity	Respiratory morbidity	Other neonatal morbidity	Hospital admission	Other resource usage	Long term infant outcomes	Long term maternal outcomes
Ashorn 2015	•	•	•		•	•												•	•	•	•	•	•				•			
Bhutta 2009	•	•	•				•			•				•				•		•	•	•								
Chan 2009							•							•				•	•			•	•			•				
Donovan 1996				•														•		•	•									
ECPPA 1996	•	•	•			•	•		•	•	•	•						•	•			•		•		•				
Fawzi 1998	•	•												•				•	•	•	•	•								
Goffinet 2001	•	•	•	•			•		•	•		•				•	•	•	•			•	•				•	•	—	
Harrington 2000	•			•			•		•	•	•	•						•	•			•	•							
Kupka 2008	•	•	•	•	•	•								•				•	•	•	•	•								
Janmohamed 2016	•	•		•										•				•	•		•							•		
Kokanali 2014	•						•		•									•	•		•		•			•				
Kumwenda 2002	•	•	•		•									•				•			•								•	
Kupka 2008	•	•	•	•	•	•								•				•	•	•	•	•								
Lagendijk 2018				•		•		•						•		•			•				•					•		
Levine 1997	•	•	•		•		•		•	•	•			•				•	•	•		•	•							
Metcoff 1985	•	•												•		•		•		•		•								
Moses 2014														•				•	•		•	•								



Newnham 2009		•	•				•		•			•		•	•		•		•	•		•		•	•		•	•					
Parazzini 1993	•	•	•	•			•		•	•									•	•	•			•	•								
Poston 2015	•	•	•				•		•	•	•	•		•			•		•	•	•	•		•	•	•	•	•	•	•			
Ramakrishnan 2003	•	•																	•	•	•	•		•									
Rodger 2014	•	•					•		•	•	•	•	•	•					•	•				•									•
Rolnik 2017	•		•						•	•	•			•						•					•	•	•	•					
Roth 2018		•	•		•	•	•			•				•					•	•	•	•		•						•	•	•	
Siega-Riz 2006	•													•					•	•	•												
Steketee 2012																					•												
Subramanian 2012	•			•			•							•					•	•	•			•	•								
Sureau 1991		•									•	•							•	•													
Toe 2015																			•	•		•											
Villar 1992		•		•			•							•						•	•				•					•		•	
Villar 2009		•		•		•			•	•	•			•						•	•				•								

Figure 2a. Maternal, fetal, neonatal, and childhood outcomes reporting across the largest thirty prevention studies.

	Mortality outcomes						Maternal outcomes								Fetal outcomes			Offspring size				Neonatal outcomes					Long term and resource usage outcomes			
Included studies	Miscarriage	Stillbirth	Neonatal death	Perinatal death	Infant death	Maternal death	Mode of delivery	Other delivery related outcomes	Pre-eclampsia	Other hypertensive morbidity	Abruption	Other maternal bleeding	Thrombosis	Other maternal morbidity	Umbilical artery Doppler	Fetal growth	Other fetal morbidity	Birthweight	SGA	LBW	Other size measures	GA at delivery	Neonatal condition at birth	Neurological morbidity	Respiratory morbidity	Other neonatal morbidity	Hospital admission	Other resource usage	Long term infant outcomes	Long term maternal outcomes
Ali, Abbas 2017							•								•	•		•				•	•							
Ali, Amin 2017							•								•	•		•				•	•							
Almstrom 1992		•	•	•			•											•				•	•		•	•	•	•		
Battaglia 1992							•	•	•						•		•	•	•				•				•			
Cabero 1988		•	•	•			•											•	•				•							
Di Iorio 2002														•	•			•				•	•							
DIGITAT		•	•	•		•	•	•	•	•	•	•	•					•	•			•	•	•	•	•	•		•	•
Ganzevoort 2005		•	•	•		•	•			•	•		•	•				•	•			•	•	•	•	•				
Hansen 2018		•		•					•	•	•	•		•	•			•	•	•		•	•	•	•	•				
McCowan 1999		•		•			•		•	•	•				•			•	•		•	•	•							
Moninckx 1997		•		•			•											•	•			•	•		•	•	•	•		
Newnham 1995															•			•	•		•	•	•							
Olsen 2000	•	•	•											•				•	•	•	•	•	•	•		•	•			
Sharp 2018		•	•				•		•			•		•	•		•	•	•	•		•	•	•	•	•	•	•		
Sieroszewski 2004															•	•	•	•	•											
Singh 2015		•	•				•							•	•			•				•	•	•	•	•				
Tchirikov 2017		•	•													•		•				•	•	•	•	•				

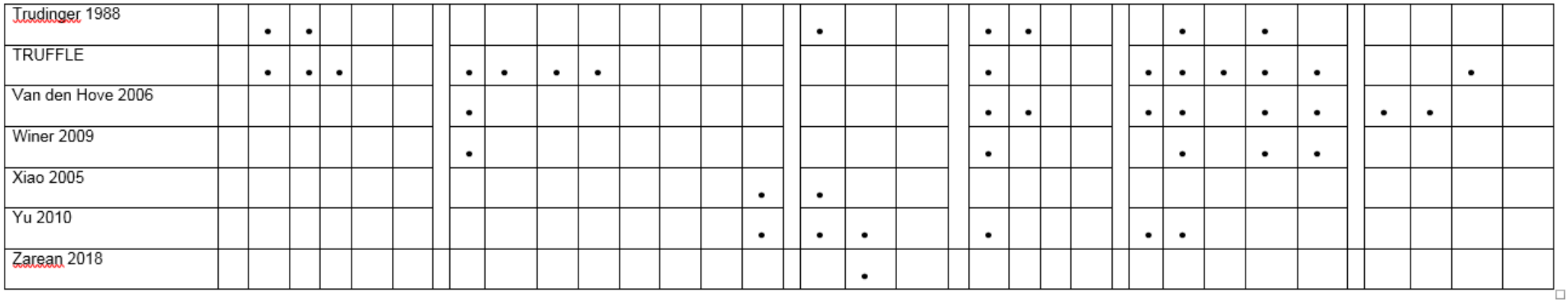


Figure 2b. Maternal, fetal, neonatal, and childhood outcomes reporting across the treatment studies.