Ultrasound Obstet Gynecol 2019; **53**: 598–608
Published online 2 April 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20189

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

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KEYWORDS: aspirin; core outcome set; fetal growth restriction; randomized controlled trial; research waste

ABSTRACT

Objective *Although fetal growth restriction (FGR) is well known to be associated with adverse outcomes for the mother and offspring, effective interventions for the management of FGR are yet to be established. Trials reporting interventions for the prevention and treatment of FGR may be limited by heterogeneity in the underlying pathophysiology. The aim of this study was to conduct a systematic review of outcomes reported in randomized controlled trials (RCTs) assessing interventions for the prevention or treatment of FGR, in order to identify and categorize the variation in outcome reporting.*

Methods *MEDLINE, EMBASE and The Cochrane Library were searched from inception until August 2018 for RCTs investigating therapies for the prevention and treatment of FGR. Studies were assessed systematically and data on outcomes that were reported in the included studies were extracted and categorized. The methodological quality of the included studies was assessed using the Jadad score.*

Results *The search identified 2609 citations, of which 153 were selected for full-text review and 72 studies (68 trials) were included in the final analysis. There were 44 trials relating to the prevention of FGR and 24 trials investigating interventions for the treatment of FGR. The mean Jadad score of all studies was 3.07, and only nine of them received a score of 5. We identified 238 outcomes across the included studies. The most commonly reported were birth weight (88.2%), gestational age at birth (72.1%) and small-for-gestational age (67.6%). Few studies reported on any measure of neonatal morbidity (27.9%), while adverse effects of the interventions were reported in only 17.6% of trials.*

Conclusions *There is significant variation in outcome reporting across RCTs of therapies for the 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. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The failure of a fetus to reach its growth potential can be attributed to many different pathological processes such as infection, placental dysfunction or maternal disease or malnutrition. Although there are inconsistencies in classification and diagnosis, between one-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 risk of perinatal morbidity

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Accepted: 22 November 2018

and mortality[4,5], there is a long-term impact of growth restriction on childhood neurological development and metabolic and cardiovascular disorders[6,7], which is thought to be, at least in part, due to epigenetic changes induced by the pathological intrauterine environment in addition to the direct pathological effects of altered blood flow and intrauterine malnutrition. Despite the clinical implications of FGR, the majority of affected infants are not detected antenatally[3], and, as yet, no therapeutic interventions have been demonstrated to reverse or ameliorate the effects of FGR.

Research on FGR has focused primarily on improving antenatal detection and then on determining the optimal timing of delivery in order 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[8]. Heterogeneity in outcomes and outcome measures reported across studies hinders the synthesis of findings, while the rarity of outcomes such as 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 randomized controlled trials (RCTs) assessing the effects of interventions for the prevention or treatment of FGR in order to identify and categorize the variation in outcome reporting.

METHODS

The protocol for this systematic review was registered on PROSPERO (registration number: CRD42018074910). We followed the reporting guidelines for meta-analyses and systematic reviews of RCTs, as outlined by the PRISMA statement[9]. EMBASE, MEDLINE and The Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to August 2018 for RCTs evaluating any potential intervention for the prevention or treatment of FGR (Table S1). Medical Subject Headings (MeSH) including FGR, fetal therapies, prenatal care and pregnancy complications were used, and additional records were identified by manually searching reference lists; the search was restricted to the English language. We included RCTs in which interventions for the prevention or treatment of FGR were either the primary or secondary outcome. Cohort and case–control studies, case series, case reports and systematic reviews were excluded. We accepted the authors' definition of FGR.

At least two researchers (H.K., L.S. or R.T.) independently reviewed each potentially relevant record based on the 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 its eligibility for inclusion. Discrepancies between the authors were resolved by discussion.

Using a standardized data extraction form, at least two researchers (F.S., L.S. or R.T.) reviewed each included study and independently extracted trial characteristics including number of participants, funding sources, country of study, definition of FGR, intervention evaluated and outcomes. The methodological quality of the included studies was assessed by each of the two reviewers independently using the Jadad score, which awards 2 points for adequate randomization, 2 for adequate blinding and 1 for follow-up of all randomized patients[10]. Discordant scores were resolved by consensus.

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

RESULTS

A total of 2605 citations were identified through the literature search and an additional four records by manual searching. After exclusion of 2456 abstracts, 153 papers were selected for full-text review. Of these, 81 papers were excluded, the majority because they were a non-randomized study, were not in English or were a duplicate of an already included study (Table S2). Seventy-two reports from 68 trials met the inclusion criteria and were included in the systematic review (Figure 1). Forty-four trials reported on potential interventions for the prevention of FGR[11–54] and 24 (29 studies) reported on interventions for the treatment of pregnancies affected by FGR[30,55–82]. Five papers reporting outcomes from the DIGITAT trial[78–82] and two from the TRUFFLE trial[60,61] were included. One paper included two separate trials addressing both points[30]. In total, 44 trials (45 062 participants) reporting interventions for the prevention of FGR and 24 trials (3357 participants) evaluating antenatal treatments for FGR were included (Figure 1).

All included studies were RCTs. The interventions evaluated for the prevention of FGR included administration of aspirin ($n = 9$), diet or exercise advice ($n = 3$), nutritional supplementation ($n = 18$), psychosocial intervention ($n = 5$), low-molecular-weight heparin ($n = 2$), hospital admission ($n = 1$), intravenous immunoglobulin ($n = 1$) and management of maternal medical conditions such as hypertension, heroin addiction and periodontal disease ($n = 5$). The interventions evaluated for the treatment of FGR included aspirin ($n = 4$), L-arginine ($n = 4$), fetal nutrition ($n = 1$), fish oil/omega-3 ($n = 2$), plasma volume expansion ($n = 1$), hospital admission ($n = 2$), intensive antenatal monitoring ($n = 2$), induction of labor ($n = 2$), nitric oxide donors ($n = 1$), low-molecular-weight heparin ($n = 2$), sildenafil ($n = 1$), dydrogesterone ($n = 1$) and maternal hyperoxygenation ($n = 1$). The characteristics of the included studies evaluating interventions for the

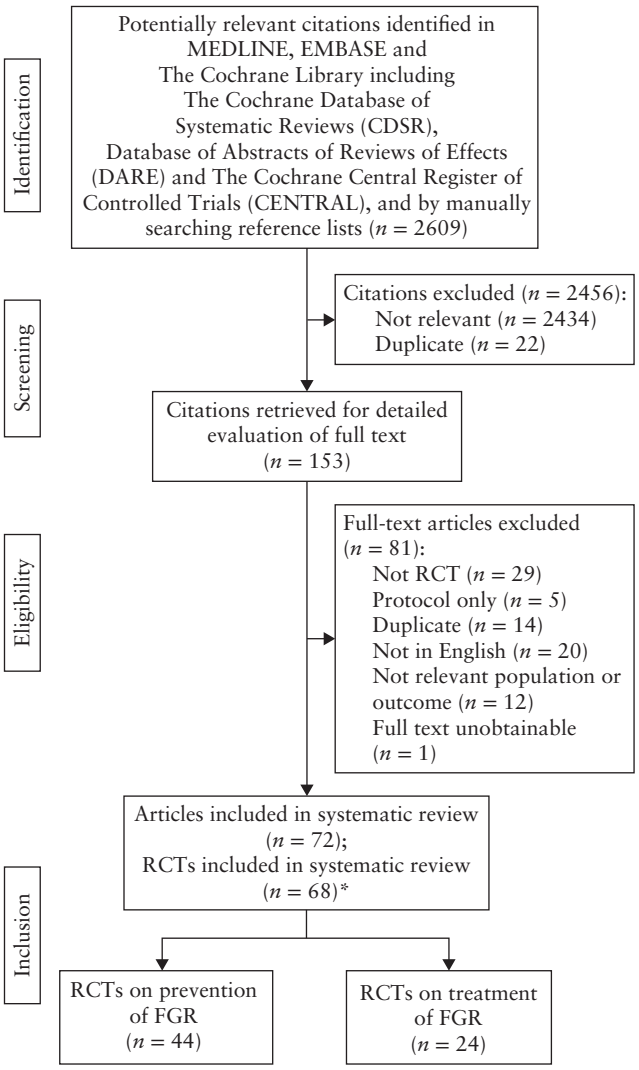


Figure 1 Flowchart illustrating selection and inclusion in this systematic review of randomized controlled trials (RCTs) evaluating potential interventions for prevention or treatment of fetal growth restriction (FGR). *Some articles reported on outcomes from same trial.

prevention and treatment of FGR are outlined in Tables 1 and 2, respectively. Twenty-two studies compared the intervention with placebo, 23 with an alternative treatment and 23 with routine care only. Forty-six studies were performed in high-resource settings (determined by the human development index of the study location) and 18 in low-resource settings, with the remainder including both high- and low-resource settings. Studies evaluating the prevention of FGR included more participants (median, 870 (interquartile range (IQR), 219–1297)) than did studies investigating 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, while the mean Jadad score of all studies was 3.07 (Table S3).

The included studies reported on 238 outcomes (Table S4). These were maternal (44.1%), fetal (11.8%), neonatal or infant (37.4%) and relating to resource usage (6.7%). The most commonly reported outcomes were birth weight (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 S4). When mortality outcomes were reported, they were not always defined clearly. Of those studies reporting stillbirth, perinatal or neonatal death, only 20%, 17% and 32%, respectively, provided the temporal definitions of these terms. When 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 comorbid medical condition (32/105 (30.5%) outcomes), and only rarely to potential adverse effects of the intervention (5/105 outcomes, reported in 12/68 (17.6%) of the included trials). The most commonly reported maternal outcomes were mode of delivery (38/68 (55.9%) trials) and the development of hypertensive disorders of pregnancy (HDP) and their complications. Nineteen (27.9%) of the included trials theorized 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[80], 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 amniotic fluid assessments) were the most commonly reported fetal outcomes (15/28 (53.6%) 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 fetal middle cerebral arteries, ductus venosus and the thoracic aorta, and fetal biometry. Additional fetal testing via fetal blood sampling in the umbilical cord or scalp in labor was reported in two studies.

When considering perinatal outcomes, birth weight and gestational age at delivery were reported consistently across most trials (in 88.2% and 72.1% of trials, respectively), although the presentation varied. Admission to the neonatal intensive care unit (NICU) (36/68 (52.9%)), Apgar score (29/68 (42.6%)) and umbilical cord blood-gas analysis (10/68 (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 postpartum. 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 were prevention trials. Six (13.6%) prevention trials and 13

Table 1 Characteristics of randomized controlled trials investigating interventions for prevention of fetal growth restriction (FGR), included in systematic review

Study	*Country*	*Jadad score*	*Participants* (n)	*Definition of FGR*	*Intervention*	*Primary outcome*
Ashorn (2015)[11]	Malawi	4	1391	BW < 10th centile	Lipid-based nutrition supplementation	BW and length
Ali (2018)[12]	Saudi Arabia	3	179	ND	Vitamin D (4000 units)	PE
Bar (1997)[23]	Israel	5	87	ND	Aspirin (60 mg)	Fetal circulation parameters
Binder (2008)[34]	Czech Republic	1	117	BW < 10th centile	Substitution therapy in heroin-addicted women	Pregnancy and perinatal outcomes, NAS
Bhutta (2009)[45]	Pakistan	3	2378	ND	Multiple micronutrients	Maternal health and birth outcomes
Branch (2000)[50]	USA	5	16	BW < 10th centile	Intravenous immunoglobulin	Obstetric and neonatal outcomes
Brown (1998)[51]	Australia	2	220	BW < 3rd and < 10th centiles	Management of hypertension using Korotkoff Phase V	Number of episodes of severe HTN, number of women with severe HTN or adverse fetal outcomes
Chan (2009)[52]	Hong Kong	4	1164	BW < 10th centile	Ferrous sulfate	Risk of GDM
Crowther (1992)[53]	Zimbabwe	3	218	ND	Hospital admission	Development of severe HTN, proteinuria, BW, NICU admission and LoS
Cruickshank (1992)[54]	UK	3	114	BW < 10th centile	Labetalol	BW < 10th centile
Donovan (1977)[13]	UK	1	1202	ND	Smoking cessation	FGR
ECPPA (1996)[14]	Brazil	4	1009	BW < 3rd centile	Aspirin (60 mg)	PE
Fawzi (1998)[15]	Tanzania	4	1075	BW < 2500 g	Multivitamin supplementation	Progression of HIV-1, birth outcomes
Goffinet (2001)[16]	France	3	3317	BW < 3rd and < 10th centiles	Aspirin after screening (100 mg)	FGR, PE
Groom (2017)[17]	Multinational	3	156	BW < 5th centile	LMWH	PE, SGA
Harrington (2000)[18]	UK	3	946	BW < 3rd and < 10th centiles	Aspirin after screening (100 mg SR)	GA at delivery, development of PE, APH or SGA
Hossain (2014)[19]	Pakistan	1	193	BW < 2500 g	Vitamin D	Not specified
Janmohamed (2016)[20]	Cambodia	3	547	BW < 10th centile	Dietary supplementation	BW and length
Kokanali (2014)[21]	Turkey	1	295	BW < 10th centile	Dietary advice	Maternal and perinatal morbidity
Kumwenda (2002)[22]	Malawi	5	697	BW < 2500 g	Vitamin A	Birth outcome
Kupka (2008)[24]	Tanzania	4	913	BW < 10th centile	Selenium	Maternal HIV disease progression, pregnancy outcome, maternal and child survival
Lagendijk (2018)[25]	Netherlands	3	5296	BW < 10th centile	Triaged antenatal care	PTB, SGA
Levine (1997)[26]	USA	4	4589	BW < 10th centile	Calcium	PE, SGA
Metcoff (1985)[27]	USA	2	471	BW < 3150 g	Food supplementation	BW
Moses (2014)[28]	Australia	3	691	BW < 10th centile	Low GI diet	Fetal growth centile and PI
Newnham (2009)[29]	Australia	3	1082	BW < 10th centile	Periodontal disease management	PTB, FGR, PE
Olsen (2000)[30]	Europe	4	280	BW < 10th centile	Fish oil	Recurrence of FGR
Onwude (1995)[31]	UK	5	233	BW < 3rd and < 10th centiles	Fish oil	PE, PIH, asymmetric growth restriction
Parazzini (1993)[32]	Italy	3	1032	BW < 10th centile	Aspirin (50 mg)	PIH, FGR
Poston (2015)[33]	UK	3	1555	BW < 10th customized centile	Behavioral intervention	GDM, LGA
Rakhshani (2012)[35]	India	5	93	Fetus unable to reach required growth potential for GA	Yoga	HDP, FGR, PTB, GDM, miscarriage, IUD, congenital anomalies

Continued over.

Table 1 *Continued*

Study	Country	Jadad score	Participants (n)	Definition of FGR	Intervention	Primary outcome
Ramakrishnan (2003)[36]	Mexico	4	873	BW < 10th centile	Multiple micronutrients	BW and length
Rodger (2014)[37]	Multinational	3	289	BW < 10th centile	LMWH	Major VTE, severe PE, SGA, pregnancy loss
Rolnik (2017)[38]	UK	5	1776	BW < 5th centile	Aspirin (150 mg after screening)	Preterm PE
Roth (2018)[39]	Bangladesh	5	1300	BW < 10th centile	Vitamin D	Infant length-for-age *Z*-score at 1 year
Siega-Riz (2006)[40]	USA	5	867	BW < 10th centile	Ferrous sulfate	Anemia
Stanescu (2018)[41]	Romania	3	150	EFW < 10th centile	Aspirin (150 mg)	FGR
Steketee (1996)[42]	Malawi	0	1766	BW < 2500 g and > 37 weeks	Mefloquine	Low BW
Subramanian (2012)[43]	USA	3	1025	ND	Targeted antenatal care	Not specified
Sureau (1991)[44]	France	2	478	ND	Aspirin and dipyridamole	FGR, IUD, abruption
Toe (2015)[46]	Burkina Faso	2	1296	BW < 10th centile	Lipid-based nutrition supplements	BW, birth length, FGR, PTB
Vainio (2002)[47]	Finland	3	86	BW < 10th centile	Aspirin (0.5 mg/kg)	PIH, PE, FGR, duration of pregnancy, BW
Villar (1992)[48]	Multinational	2	2235	BW < 10th centile	Psychosocial support	FGR
Villar (2009)[49]	Multinational	3	1365	BW < 10th centile	Vitamins C and E	PE, low BW, SGA, perinatal death

Only first author of each study is given. APH, antepartum hemorrhage; BW, birth weight; EFW, estimated fetal weight; GA, gestational age; GDM, gestational diabetes mellitus; GI, glycemic index; HDP, hypertensive disorders of pregnancy; HIV, human immunodeficiency virus; HTN, hypertension; IUD, intrauterine demise; LGA, large-for-gestational age; LMWH, low-molecular-weight heparin; LoS, length of stay; NAS, neonatal abstinence syndrome; ND, not defined; NICU, neonatal intensive care unit; PE, pre-eclampsia; PI, pulsatility index; PIH, pregnancy-induced hypertension; PTB, preterm birth; SGA, small-for-gestational age; SR, slow release; VTE, venous thromboembolism.

(54.2%) treatment trials reported any neonatal morbidity outcomes. The most frequently reported items included intraventricular hemorrhage and other neurological morbidity, respiratory compromise (including respiratory distress syndrome, bronchopulmonary dysplasia, chronic lung disease and need for ventilation, continuous positive airway pressure and oxygen), necrotizing enterocolitis 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[17,61,65] reported a composite outcome for neonatal morbidity, including neurological, respiratory and gastrointestinal morbidity, with two additionally including retinopathy of prematurity or sepsis. One study[61] reported the composite of perinatal death and neonatal morbidity. Treatment studies were more likely to report neonatal morbidity, while 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 with 33.3% published after 2000 reported any neonatal morbidity outcome, while the respective rate for treatments trials was 42.8% *vs* 58.8%. Only five trials reported on longer-term follow-up (up to 2 years) of included infants and only three assessed motor, behavioral and cognitive development.

The variation in outcome reporting across the 30 largest prevention trials and the 24 included treatment trials is illustrated in Figures 2 and 3, respectively.

DISCUSSION

Summary of main findings

We have identified a wide range of, 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 birth weight, gestational age at delivery and SGA whereas only approximately half reported stillbirth, mode of delivery, admission to the NICU and preterm delivery. Only a quarter of trials reported important neonatal morbidity outcomes, including respiratory distress syndrome, necrotizing 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 sufficiently 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 assessing interventions for the prevention or treatment of FGR. It is, however, difficult to speculate why specific outcomes were selected in each study; they are likely to reflect areas of clinical or research interest of the individuals involved in the study design, which, in turn, may be influenced by the medical, societal, cultural or governmental importance given to such interventions. When considering

Table 2 Characteristics of randomized controlled trials investigating interventions for treatment of fetal growth restriction (FGR), included in systematic review

Study	*Country*	*Jadad score*	*Participants (n)*	*Definition of FGR*	*Intervention*	*Primary outcome*
Ali (2018)[55]	Egypt	3	60	AC < 2 SD below mean and HC:AC ratio increased	Aspirin	Change in EFW
Ali (2017)[66]	Egypt	3	80	AC < 2 SD below mean and HC:AC ratio increased	Omega 3	Change in EFW
Almström (1992)[76]	Sweden	3	426	EFW < 2 SD below mean	UA Doppler monitoring	GA at delivery, mode of delivery, NICU LoS
Battaglia (1994)[77]	Italy	2	38	AC < 10th centile	Hyperoxygenation	Not specified
Cabero (1988)[56]	Spain	1	98	> 2-week discrepancy between menstrual and ultrasound dates	Hospital admission	Not specified
Di Iorio (2002)[57]	Italy	2	20	BPD < 10th centile and AC < 5th centile and reduced growth velocity	Glyceryl trinitrate	Serum NO metabolites, AM levels, fetoplacental Dopplers
DIGITAT (2010–2013)[78–82]	Netherlands	4	650	AC < 10th or EFW < 10th with or without reduced growth velocity	Induction of labor	Composite of death before discharge, 5-min Apgar score < 7, cord arterial pH < 7.05, NICU admission
Ganzevoort (2005)[58]	Netherlands	3	216	EFW < 10th centile or AC < 5th centile	Plasma volume expansion	Neurological score
Hansen (2018)[59]	Denmark	3	53	EFW < 2.3rd centile	LMWH	BW, fetal growth rate
McCowan (1999)[62]	Australia	4	65	AC < 10th centile and UA-PI > 95th centile	Aspirin	BW
Monincx (1997)[63]	Netherlands	3	150	ND	Hospital admission	Neurological score
Newnham (1995)[64]	Australia	4	51	AC < 10th centile and UA-PI > 95th centile	Aspirin (100 mg)	BW
Olsen (2000)[30]	Europe	4	280	ND	Fish oil	BW
Sharp (2018)[65]	UK	5	135	EFW or AC < 10th centile and AREDF in UA	Sildenafil	Time to delivery
Sieroszewski (2004)[67]	Poland	1	108	EFW < 10th centile	L-arginine	Change in EFW
Singh (2015)[68]	India	1	60	EFW < 10th centile	L-arginine	Neonatal outcome
Tchirikov (2017)[69]	Germany	3	14	EFW < 5th centile and UA-PI > 95th centile	Intraumbilical fetal nutrition	Feasibility of intervention
Trudinger (1988)[70]	Australia	4	46	UA S/D ratio > 95th centile	Aspirin (150 mg)	GA at delivery, BW, perinatal morbidity
TRUFFLE (2013[61], 2017[60])	Multinational	3	503	AC < 10th centile and UA-PI > 95th centile	DV Doppler monitoring	Composite of fetal or postnatal death, bronchopulmonary dysplasia, severe cerebral germinal matrix hemorrhage, cPVL, proven sepsis or NEC
van den Hove (2006)[71]	Netherlands	3	33	AC < 10th centile or reduced growth velocity	Induction of labor	Obstetric intervention, neonatal outcome
Winer (2009)[72]	France	4	43	AC < 3rd centile with abnormal UtA Doppler	L-arginine	BW, neonatal morbidity

Continued over.

Table 2 *Continued*

Study	*Country*	*Jadad score*	*Participants (n)*	*Definition of FGR*	*Intervention*	*Primary outcome*
Xiao (2005)[73]	China	1	66	HC:AC ratio < 10th centile	L-arginine	Maternal NO_2/NO_3 levels, BW
Yu (2010)[74]	China	1	73	SFH < 10th centile or HC:AC ratio < 10th centile or FL < 10th centile or abnormal UA Doppler	LMWH	Not specified
Zarean (2018)[75]	Iran	4	89	EFW < 10th centile	Dydrogesterone	Fetal weight, MCA- and UtA-RI

Only first author of each study is given. AC, abdominal circumference; AM, adrenomedullin; AREDF, absent or reversed end-diastolic flow; BPD, biparietal diameter; BW, birth weight; cPVL, cystic periventricular leukomalacia; DV, ductus venosus; EFW, estimated fetal weight; FL, femur length; GA, gestational age; HC, head circumference; LMWH, low-molecular-weight heparin; LoS, length of stay; MCA, middle cerebral artery; ND, not defined; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NO, nitric oxide; NO_2, nitrite; NO_3, nitrate; PI, pulsatility index; RI, resistance index; S/D, systolic/diastolic; SFH, symphysiofundal height; UA, umbilical artery; UtA, uterine artery.

novel interventions for the prevention and treatment of FGR, most trials were not funded by industry. The included trials were from both high- and low-resource settings and from a diverse range of international centers, 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 to maintain the highest standards of research quality[83].

None of the included trials reported the 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 the 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 infection) are therefore reported frequently 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 we performed, but the key outcome of interest in this review was FGR, and broadening the search would have increased the number of outcomes not related directly to FGR and irrelevant to the development of a core outcome set (COS). 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[84–86]. 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, such as maternal cardiac failure. These are clearly important endpoints for trials investigating pre-eclampsia, but are not likely to be relevant to trials on FGR. Although there is a pathophysiological overlap between pre-eclampsia and FGR, 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 implications

As described previously in studies investigating outcome reporting in other obstetric conditions including pre-eclampsia[86] and twin-to-twin transfusion syndrome[87], we have demonstrated significant variation in outcome reporting in trials of interventions for FGR. With the establishment of national and international initiatives aimed at reducing stillbirths and perinatal mortality[88] 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 should be evaluated in the context of potential harm and benefits to the mother and baby. There is a clear need for robust investigation of new interventions for the 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.

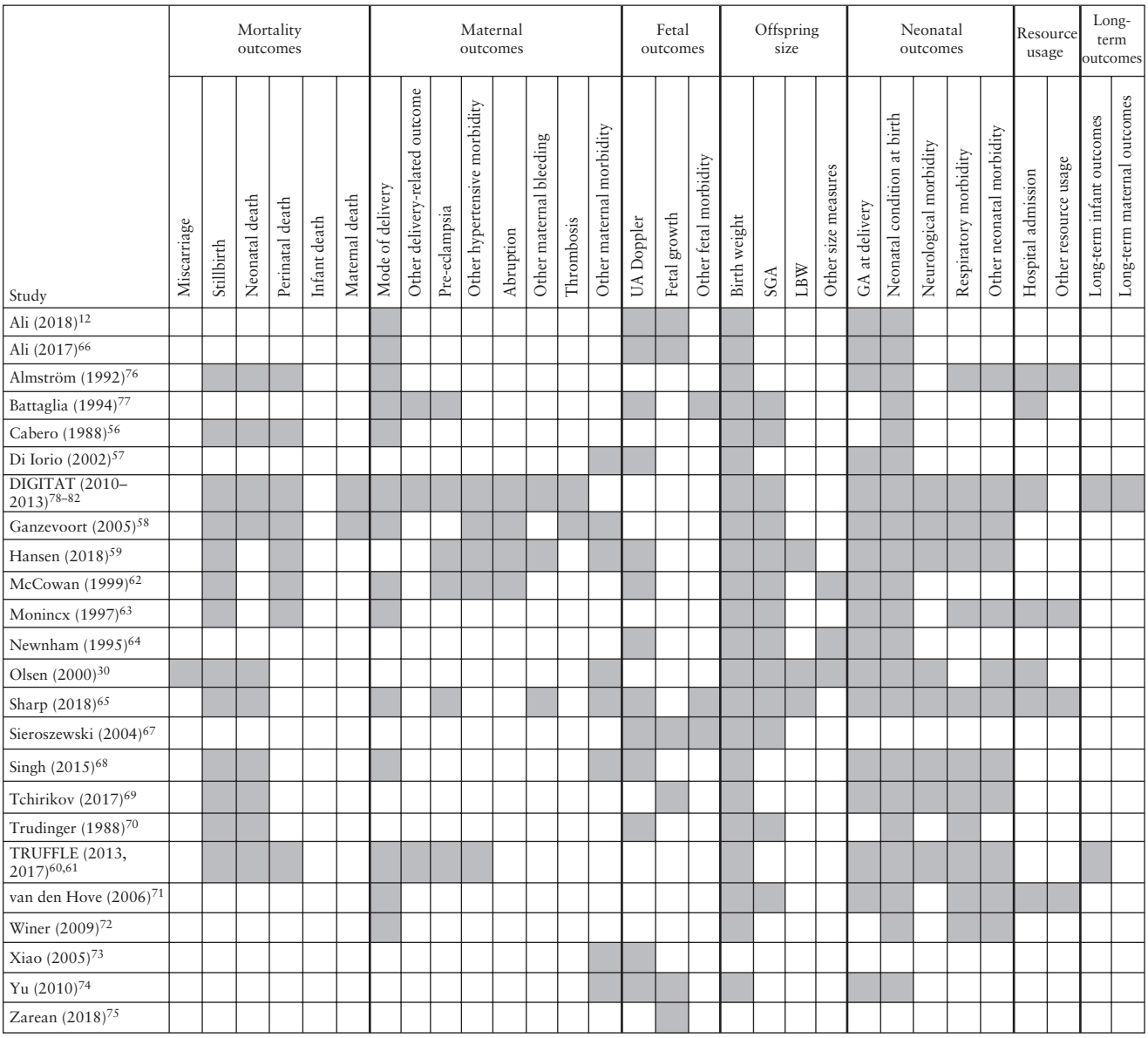
Identification of high-value interventions for the prediction and treatment of FGR might be improved by the development of a COS, which is the minimum set of outcomes that authors should report on in all trials evaluating the effects of interventions for a given condition/field. COSs are developed with the idea of reducing waste in research by selecting those outcomes that are most relevant to all stakeholders and are applicable in most research settings. The use of a COS would reduce variation in outcome reporting and promote the routine collection of such data. Standardized reporting of outcomes would increase generalizability, allow for meaningful pooled analysis and be of greater

relevance to clinicians and stakeholders. Development of COSs within women's health is recommended by 'The CoRe Outcomes in Women's and Newborn health (CROWN) initiative' (www.crown-initiative.org), which seeks to harmonize 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 shown 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 could 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 FGR, with attention given subsequently to standardizing the definition and measurement of these core outcomes. The involvement of researchers in this process and the leadership of major journals in committing to the CROWN initiative are key to ensure uptake of the COS in future studies, and ultimately

	Mortality outcomes						Maternal outcomes								Fetal outcomes			Offspring size				Neonatal outcomes					Resource usage		Long-term outcomes	
Study	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	UA Doppler	Fetal growth	Other fetal morbidity	Birth weight	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)[11]	■	■	■		■	■												■	■	■	■	■	■				■			
Bhutta (2009)[45]	■	■	■				■			■				■				■		■	■	■								
Chan (2009)[52]							■							■				■	■			■	■			■				
Donovan (1977)[13]				■														■		■	■									
ECPPA (1996)[14]	■	■	■			■	■		■	■	■	■						■	■			■		■		■				
Fawzi (1998)[15]	■	■												■				■	■	■	■	■								
Goffinet (2001)[16]	■	■	■	■			■		■	■		■				■	■	■	■			■	■				■	■		
Harrington (2000)[18]	■			■			■		■	■	■	■						■	■			■	■							
Janmohamed (2016)[20]	■	■		■										■				■	■		■							■		
Kokanali (2014)[21]	■						■		■									■	■		■		■			■				
Kumwenda (2002)[22]	■	■	■		■									■				■			■								■	
Kupka (2008)[24]	■	■	■	■	■	■								■				■	■	■	■	■								
Lagendijk (2018)[25]				■		■		■						■		■			■				■					■		
Levine (1997)[26]	■	■	■		■		■		■	■	■			■				■	■	■		■	■							
Metcoff (1985)[27]	■	■												■		■		■		■		■								
Moses (2014)[28]														■				■	■		■	■								
Newnham (2009)[29]		■	■				■		■			■		■	■		■	■	■		■	■	■		■	■				
Parazzini (1993)[32]	■	■	■	■			■		■	■				■				■	■	■		■	■							
Poston (2015)[33]	■	■	■				■		■	■	■	■		■			■	■	■		■	■	■	■	■	■	■	■		
Ramakrishnan (2003)[36]	■	■																■	■	■	■	■								
Rodger (2014)[37]	■	■					■		■	■	■	■	■	■				■	■			■								■
Rolnik (2017)[38]	■		■						■	■	■			■					■				■	■	■	■				
Roth (2018)[39]		■	■		■	■	■			■				■				■	■	■	■	■					■	■	■	
Siega-Riz (2006)[40]	■													■				■	■	■										
Steketee (1996)[42]																				■										
Subramanian (2012)[43]	■			■			■							■				■	■	■		■	■							
Sureau (1991)[44]		■									■	■						■	■											
Toe (2015)[46]																		■	■		■									
Villar (1992)[48]		■		■			■							■					■	■			■				■		■	
Villar (2009)[49]		■		■		■			■	■	■			■					■	■			■							

Only first author of each study is given. GA, gestational age; LBW, low birth weight; SGA, small-for-gestational age; UA, umbilical artery.

Figure 2 Reporting of maternal, fetal, neonatal and childhood outcomes in 30 largest randomized controlled trials investigating interventions for prevention of fetal growth restriction included in review.



Only first author of each study is given. GA, gestational age; LBW, low birth weight; SGA, small-for-gestational age; UA, umbilical artery.

Figure 3 Reporting of maternal, fetal, neonatal and childhood outcomes in 24 randomized controlled trials investigating interventions for treatment of fetal growth restriction included in review.

our ability as a research community to prevent and treat FGR.

Conclusions

Significant variation exists in outcome reporting in RCTs 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 standardized reporting, are urgently needed to facilitate high-quality investigation of novel interventions and minimize research waste.

ACKNOWLEDGMENTS

This study received funding from the Health Research Board Mother and Baby Clinical Trials Network Ireland (HRB-M&B-CTNI).

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy

Table S2 Excluded studies and reason for exclusion

Table S3 Jadad score of randomized controlled trials included in this systematic review

Table S4 All outcomes reported in randomized controlled trials included in this systematic review, according to whether they investigated intervention for prevention or treatment of fetal growth restriction (FGR)

