Addressing the variation in outcome reporting in high risk twin studies: The key to reducing research waste and improving clinical care

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The recent investigation of variation in outcome reporting in studies of twin-to-twin transfusion syndrome has highlighted the problem of variable and inconsistently defined outcome reporting in studies of twin-to-twin transfusion syndrome (TTTS).(1) Similar heterogeneity in outcome reporting has been identified across women's and newborn health including pre-eclampsia, childbirth trauma and endometriosis.(2–8) However, there is a need for a more focused effort to improve the quality of research studies on complications of multiple pregnancy. As these complicated pregnancies are uncommon, multicentre observational studies and large international trials hold the key to developing future insights

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into the efficacy and safety of potential interventions. Meta-analyses can be frustrated by variable outcome reporting and definitions, precluding rapid resolution of important clinical questions. Where the patient population is scarce, studies are pragmatically challenging to perform and yet clinical significance is high, the drive to standardise outcome reporting is only more important. Although research waste is increasingly recognised to be prevalent,(9) it is nowhere more ethically unacceptable than in research involving the willing participation of dedicated mothers keen to contribute to better care for their babies and others yet to come. Women carrying high risk multiple pregnancies and fearing for the lives of their babies have an urgent need for sound evidence on which their antenatal management can be based, and every investigation reported must be able to contribute effectively to the picture. (10)

TTTS is the most widely studied complication of monochorionic twin pregnancies and women and babies worldwide have benefited from the introduction of fetoscopic laser treatment. Despite over 20 years of investigation, the TTTS review found only 6 randomised controlled trials to evaluate. The evidence relating to the optimal surgical approach, prognostic factors before and after laser, the use of laser in stage 1 TTTS, triplet pregnancy or TTTS co-existent with selective fetal growth restriction (sFGR) remains scarce. Other similarly important clinical questions including the use of rescue cerclage in twin pregnancies, use of fetoscopic interventions for sFGR or twin anaemia polycythaemia sequence (TAPS) have yet to be addressed.

We welcome the planned development of a core outcome set (COS) for studies of interventions for TTTS.(11) However, we question whether these core outcomes will be generalisable to other interventions in multiple pregnancy or if different outcomes will be of greater importance to clinicians and families in the setting of other complications of multiple pregnancy. For example, a key condition to consider is sFGR, which complicates between 10 to 15% of monochorionic twin pregnancies (12,13) and for which a consensus definition

has recently been developed.(14) The Gratacos classification stratifies pregnancies affected by sFGR according to the umbilical artery doppler patterns and is well correlated with perinatal outcomes.(15) Available interventions for sFGR include expectant management with delivery in the event of fetal compromise, cord occlusion of the compromised twin, and fetoscopic laser ablation of the communicating placental vessels, but the optimal management has not been determined. (*Townsend 2018, submitted and at first revision)* With clear definition, classification and genuine uncertainty about optimal management, the time has come to design and carry out studies that will determine the management of sFGR for the future. Harmonising the collection and reporting of outcomes and outcome measures across future studies on sFGR is an important stage in developing efficient research infrastructure, and the outcomes of interest in these studies might differ from those identified as relevant for TTTS.(16)

We have investigated variation in outcome reporting across studies of intervention for sFGR according to the methodology reported in the linked systematic review of outcome reporting in TTTS and guided by the Cochrane Collaboration handbook, COMET initiative handbook, and other core outcome sets in development.(17-24) Using a comprehensive search strategy, Medline, Embase, Cinahl, Clinicaltrials.gov and the Cochrane Library databases were searched electronically (Supplementary Table 1). Thirty-nine studies were included, 21 retrospective cohort studies, 13 prospective cohort-studies, three non-comparative studies, one case-control study, and one cross-sectional study.(13,25–61) (Table 1) Fetal, neonatal, and perinatal mortality were commonly reported across the included studies. Over half of included studies reported live birth, stillbirth and neonatal mortality although most did not report mortality by smaller or larger twin status. A quarter of studies reported fetal parameters as study outcomes: 21% (8 studies) evaluated included umbilical artery dopplers, 10% (4 studies) fetal neurological morbidity and one study (3%) hypertrophic cardiomyopathy. Pregnancy outcomes including preterm delivery, mode of delivery and premature preterm rupture of membranes were reported in around a third of included

studies, but maternal, procedure related and childhood outcomes were infrequently reported. Although neonatal morbidity was relatively frequently reported, there was inconsistency in the choice of morbidity outcomes. The most commonly reported were intraventricular haemorrhage, respiratory distress syndrome and necrotising enterocolitis, but a wide range of others were included. Figure 1 illustrates maternal, fetal, neonatal, and childhood outcomes reporting across the largest 20 studies, Table 2 lists the frequency of outcome reporting across the included studies.

Outcomes identified through a systematic review of published studies largely reflect outcomes healthcare professionals and researchers have considered important to collect, measure and report. The balance of outcomes reported in the included papers primarily focused on perinatal survival and neonatal morbidity outcomes with relatively infrequent reporting of maternal, procedural and childhood outcomes. There are, however, important differences in the pattern of outcome reporting between these studies and those identified in the review of TTTS studies, particularly relating to the fetal outcomes. The review of TTTS studies identified frequently reported fetal outcomes including recurrence of TTTS or development of TAPS. These outcomes are not relevant to sFGR and were not identified in any of the included sFGR studies. In sFGR the fetal doppler findings are typically used to identify disease progression and plan timing of delivery. The umbilical and middle cerebral arteries and ductus venosus Doppler findings were relatively frequently reported as outcomes after intervention for sFGR, whereas these parameters were not reported as outcomes in any of the studies investigating TTTS.

Furthermore, 69% (27 studies) of papers investigating sFGR reported intra-uterine death (IUD) as an outcome in contrast to only 31% (31 studies) of TTTS studies included in the earlier review. The most frequently reported neonatal morbidity outcomes were intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) in both TTTS and sFGR studies. IVH was reported in 51% (20 studies) of sFGR and 16% (16 studies) of TTTS

and PVL in 46% (18 studies) of sFGR and 17% (17 studies) of TTTS papers. We conclude that where neonatal morbidity is reported in either TTTS or sFGR the conditions of greatest interest to investigators are neurological, but it is noteworthy that substantially more sFGR studies report neurological outcomes. In view of the fact that the management of sFGR aims at preventing IUD of the smaller twin and subsequent mortality or neurological morbidity in surviving co-twins, the relative importance of these outcomes may differ between sFGR and TTTS. Fetoscopic intervention for sFGR is of particular interest because, although associated with a high risk of IUD, it may be able to protect the larger twin from the consequences of the co-twin demise without requiring cord occlusion and still afford the smaller twin a chance of survival. Consistent reporting of IUD and neurological morbidity is clearly essential to determining the clinical utility of interventions for sFGR.

Fetoscopy in sFGR is known to be more technically challenging than in TTTS, principally due to the absence of polyhydramnios which limits the visibility and access to the placental anastamoses. It is particularly disappointing then to find that there is poor reporting in both TTTS and sFGR studies of procedural complications and maternal outcomes in studies reporting the use of fetoscopy. Since this intervention is increasingly being offered to mothers, it is important to be able to assess the risk of maternal and procedural complications and it is possible that these complications might differ in frequency following fetoscopy for sFGR compared to fetoscopy for TTTS. Inadequate safety reporting is a common theme in studies of outcome reporting, but in order to fully evaluate the balance of risks and benefits it is key that potential harms as well as benefits of each intervention are reported. (5)

The outcomes identified through these reviews of TTTS and sFGR have been shown to be important to researchers but may not hold the same relevance to other stakeholders, including women with a twin pregnancy complicated by sFGR. In particular, morbidity outcomes other than neurological complications may be important to parents. Moreover,

long term outcomes are likely to be more important to them than short term morbidity. A small minority of published studies in both TTTS and sFGR have collected and reported childhood outcomes, including long-term neurodevelopmental outcomes. The duration of follow up will be a key consideration in planning future studies, balancing feasibility with identifying important outcomes. With near total variation in the reported length of follow up and definition of outcomes, expert consensus and stakeholder consultation is needed to agree the optimal follow up and outcomes to be assessed. It is likely that outcomes important to parents and other stakeholders in TTTS will be comparable to those in sFGR, but their perspective deserves to be as thoroughly investigated as that of clinical researchers.

Selective FGR in MCDA twin pregnancies is an uncommon condition with key differences to TTTS and other pathologies of monochorionic pregnancies that affect the key outcomes in these studies. A research agenda will need to be developed to prioritise unanswered research questions which can be addressed within internationally collaborative observational studies and large international trials. A core outcome set should be developed to assist in planning future research, either in addition to a core outcome set for TTTS or as a separate component within a larger core outcome set for studies in complicated monochorionic pregnancies.

In planning future studies in TTTS and sFGR we have the opportunity to consider outcomes beyond survival that are clinically relevant and important to parents. We also have the duty to ensure that robust, clearly defined outcomes covering both benefits and risks of intervention are reported across all studies, minimising research waste and setting standards for high quality evidence generation and synthesis across the field of high risk obstetrics.

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Figure legend:

Figure 1. Maternal, fetal, neonatal and childhood outcomes reporting across the largest twenty studies.

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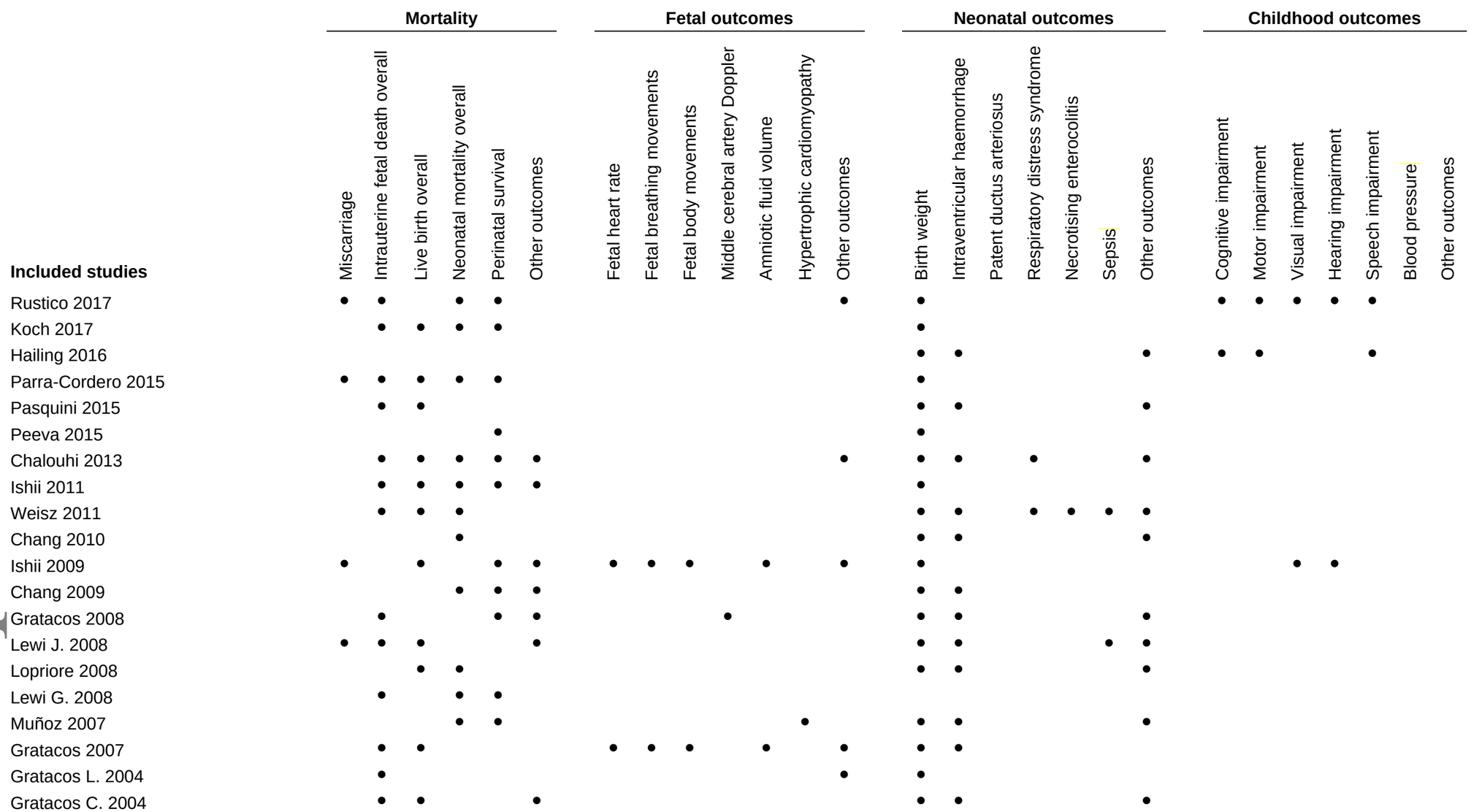

Table 1. Characteristics of included studies.

Author Year	Study design	Maternal participants (n)	Offspring Participants (n)	Intervention 1	Intervention 2	Selective Fetal Growth Restriction definition
Rustico 2017	Retrospective cohort study	140	217	Expectancy	Cord occlusion	Estimated fetal weight <10th centile in one twin OR estimated fetal weight discrepancy >25%
Koch 2017	Retrospective cohort study	25	44	Expectancy	Laser	Estimated fetal weight <10th percentile in one twin
Wang 2017	Non comparative study	4	3	Cord Occlusion		Not specified
Panciatici 2017	Prospective cohort study	2	2	Cord Occlusion		Not specified
Parra-Cordero 2015	Non comparative study	90	87	Cord Occlusion		Estimated fetal weight <10th centile OR abdominal circumference <10th centile WITH an inter-twin discordance ≥25%
Peng 2016	Retrospective cohort study	16	NS	Cord occlusion		Estimated fetal weight <2nd centile in one twin
Halling 2016	Cross-sectional study	24	48	Expectancy		Birthweight discordance ≥20%
Ishii 2015	Non comparative study	10	13	Laser		Estimated fetal weight of smaller twin <-1.5SD
Pasquini 2015	Retrospective cohort study	42	77	Expectancy		Abdominal circumference of smaller twin ≤10th centile for gestational age
Peeva 2015	Retrospective cohort study	142	NS	Laser		< 22 weeks: abdominal circumference <5th centile; ≥ 22 weeks: estimated fetal weight <5th centile AND Estimated fetal weight difference ≥ 25%
Yinon 2015	Retrospective cohort study	23	20	Cord Occlusion		Estimated fetal weight <10th centile in one twin AND estimated fetal weight discordance ≥25%
Zuckerwise 2014	Retrospective cohort study	16	NS	Expectancy		Estimated fetal weight discordance >20%
Machado 2014	Retrospective cohort study	18	33	Expectancy		Estimated fetal weight <10th centile in one twin
Has 2014	Retrospective cohort study	12	11	Cord Occlusion		Estimated fetal weight <10th centile in one twin AND inter-twin estimated fetal weight discordance ≥25%
Chalouhi 2013	Retrospective cohort study	45	44	Laser	Cord Occlusion	Estimated fetal weight <5th centile AND estimated fetal weight discordance > 25% AND absent/reverse end-diastolic flow in Umbilical Artery Doppler
Visentin 2013	Prospective cohort study	14	28	Expectancy		Estimated fetal weight <10th centile in one twin
Gao 2012	Case-control study	38	NS	Expectancy		Birthweight <10th centile + inter-twin Estimated fetal weight discordance >20%
Bebbington 2012	Retrospective cohort study	24	NS	Cord Occlusion		Estimated fetal weight <10th centile in one twin AND intertwin weight difference of >25%
Lanna 2012	Retrospective cohort study	30	28	Cord Occlusion		Not specified
Ishii 2011	Retrospective cohort study	101	152	Expectancy		Estimated fetal weight <10th centile in one twin
Weisz 2011	Prospective cohort study	37	74	Expectancy		Estimated fetal weight <10th centile in one twin
Smith 2010	Retrospective cohort study	Unclear	Unclear	Expectancy		Birthweight discordance >25%
Chang 2010	Prospective cohort study	27	54	Expectancy		Estimated fetal weight <10th centile in one twin
Machado 2009	Retrospective cohort study	12	24	Expectancy		Birthweight discordance ≥20%
Chang 2009	Prospective cohort study	24	48	Expectancy		Estimated fetal weight <10th centile in one twin
Ishii 2009	Retrospective cohort study	63	104	Expectancy		Estimated fetal weight <10th centile in one twin
Gratacos 2008	Retrospective cohort study	49	76	Expectancy	Laser	Estimated fetal weight <10th centile in one twin
Lewi, Jani 2008	Prospective cohort study	29	53	Expectancy	Cord Occlusion	Birthweight discordance >25%
Lopriore 2008	Retrospective cohort study	50	94	Expectancy		Estimated fetal weight <10th centile in one twin
Lewi, Gucciardo 2008	Prospective cohort study	28	50	Expectancy	Cord Occlusion	16 weeks: difference in abdominal circumference ≥90th centile 20-26 weeks: estimated fetal weight discordance >20%
Kennelly 2007	Retrospective cohort study	22	40	Expectancy		Abdominal circumference <5th percentile AND absent/reverse end-diastolic flow in Umbilical Artery Doppler
Muñoz-Abellana 2007	Prospective cohort study	80	135	Expectancy	Cord Occlusion	Estimated fetal weight <10th centile in one twin
Acosta-Rojas 2007	Prospective cohort study	9	16	Expectancy		Estimated fetal weight <10th centile AND inter-twin growth discordance >25%
Gratacos 2007	Prospective cohort study	134	105	Expectancy	Cord Occlusion	Estimated fetal weight <10th centile in one twin
Halvorsen 2006	Retrospective cohort study	13	26	Expectancy		Birthweight <-2 SD in one twin
Adegbite 2005	Retrospective cohort study	15	30	Expectancy		Birthweight discordance >20% with normal amniotic fluid in the larger twin OR abdominal circumference <5th centile with abnormal umbilical artery Doppler waveform in the smaller twin
Gratacos, Lewi 2004	Prospective cohort study	40	73	Expectancy		Estimated fetal weight <5th centile AND inter-twin growth discordance >25%
Gratacos, Carreras 2004	Prospective cohort study	42	75	Expectancy		Estimated fetal weight <5th centile AND inter-twin growth discordance >25%
Quintero 2001 *	Prospective cohort study	30	41	Expectancy	Laser	Estimated fetal weight <10th percentile; AND absent/reverse end-diastolic flow in Umbilical Artery after January 2000

* Third comparison: Cord Occlusion

Table 2. Variation in outcome reporting across research studies on selective fetal growth restriction.

	Studies, *n*
Fetal, neonatal, and perinatal mortality	
Miscarriage	6
Termination of pregnancy	10
Intrauterine fetal death overall	27
Intrauterine fetal death reported per twin	21
Double intrauterine fetal loss	13
Live birth overall	22
Live birth per twin	10
Neonatal mortality overall	26
Neonatal mortality per twin	9
Perinatal mortality	8
Perinatal mortality per twin	8
Perinatal survival	19
Fetal outcomes	
Middle Cerebral Artery Doppler	4
Ductus Venosus Doppler	5
Umbilical Artery Doppler	8
Neurological morbidity in the surviving twin following cord occlusion	4
Other fetal outcomes	7
Pregnancy and childbirth outcomes	
Premature preterm rupture of membranes	11
Mode of delivery	12
Gestational age at delivery	39
Preterm delivery	14
Procedure to delivery time interval	3
Other pregnancy and childbirth outcomes	8
Procedure related outcomes	
Membrane septostomy	3
Intrauterine infections	5
Other procedure related outcomes	7
Neonatal outcomes	
Birth weight	35
Apgar score	7
Inter-twin birth weight discordance	14
Intraventricular haemorrhage	20
Periventricular leukomalacia	18
Retinopathy of prematurity	2
Hypertrophic cardiomyopathy	2
Respiratory distress syndrome	8
Intubation and mechanical ventilation	3
Necrotising enterocolitis	8
Sepsis	6
Neonatal intensive care unit admission	6
Other neonatal outcomes	12
Childhood outcomes	
Cognitive impairment	6
Motor impairment	6
Visual impairment	3
Hearing impairment	3
Behavioural disorders	4
Blood pressure	1
Other childhood outcomes	1