Definition, management and prognosis in severe early-onset fetal growth restriction

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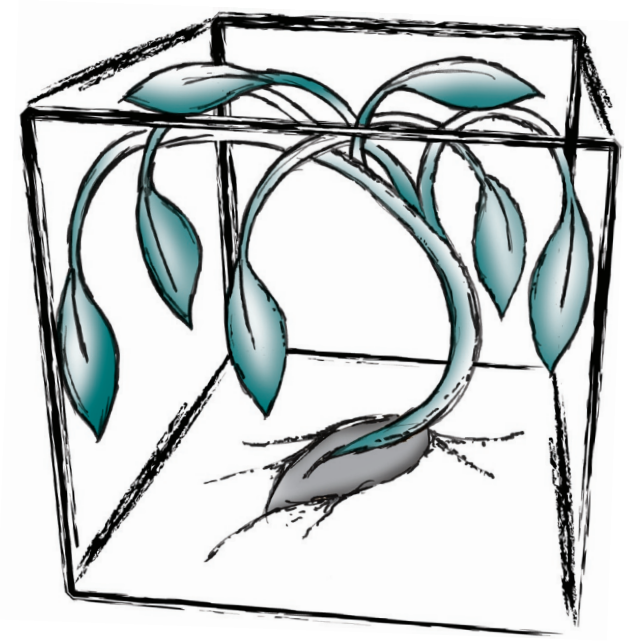

Anouk Pels

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Definition, management and prognosis in severe early-onset fetal growth restriction

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in het openbaar te verdedigen in de Aula der Universiteit
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door Anouk Pels

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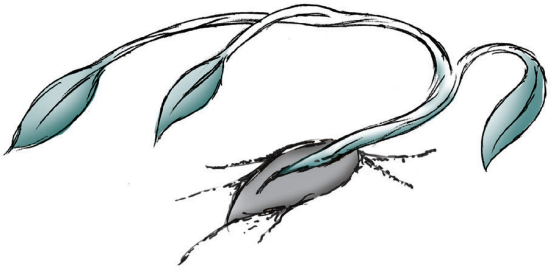
Chapter 1

Introduction



Introduction

General introduction

In prenatal care fetal growth is monitored by estimating fetal size by physical examination of fundal height or by measurement of several fetal biometric characteristics by ultrasound. The importance of this is that very small or large babies have higher mortality and morbidity rates than infants of normal size. Estimated fetal weight is compared with growth charts specific for particular gestational age and sex(1) and a baby is diagnosed as small for gestational age (SGA) if the weight is below the limit of 10th percentile.

The differential diagnosis of SGA includes incorrect dating of the gestational age, a constitutionally small baby, congenital abnormalities including chromosomal abnormalities, congenital infections, maternal smoking, drug use or placental dysfunction(2). The latter is usually classified as fetal growth restriction (FGR), and the term describes the process in which a fetus does not reach its intrinsic full growth potential because the placental insufficiency causes the placenta not to meet the fetal requirements.

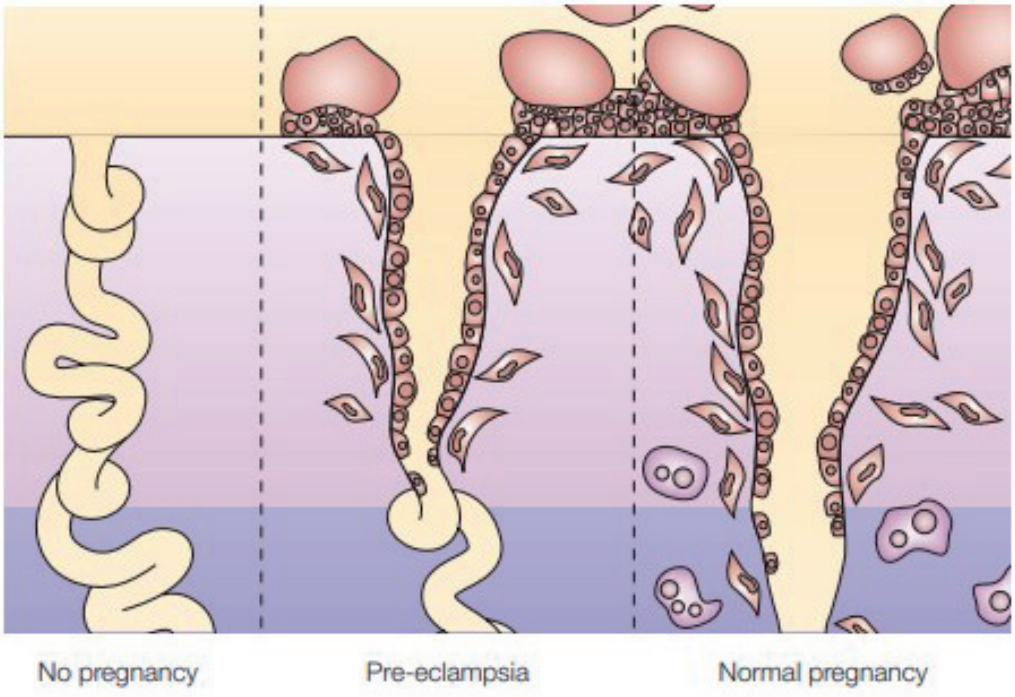
FGR before 32 weeks of gestation is classified as 'early-onset' FGR and after 32 weeks of gestation it is classified as 'late onset' FGR(3). Early-onset FGR complicates approximately 0.4% of pregnancies in The Netherlands(4), and is the most extreme form with high rates of perinatal mortality and neonatal morbidity. Late-onset FGR occurs in approximately 10% of pregnancies and overlaps partly with SGA. The incidence of severe adverse perinatal outcomes is low, but on a population level the consequences are significant and for each individual consequences can be dramatic, since stillbirths amount to 200 per annum in the Netherlands. Placental function is thus the cornerstone of fetal survival.

The placenta is a complex organ that forms the connecting system between the maternal and fetal circulation in which transfer of oxygen and metabolites takes place. In the first trimester the extra villous trophoblast invades the myometrium as well as the vasculature of the uterine wall. The trophoblast replaces the endothelial lining and the musculoelastic tissue in the spiral arteries, the arteries of the uterus. Since this process impairs the ability to contract, a high flow low resistance circulation develops(5).

Placental dysfunction in the second trimester (early-onset FGR) is thought to arise from inadequate remodeling of the spiral arteries in the first trimester. Early-onset FGR has a high co-incidence with the hypertensive disorders of pregnancy, in the literature varying from 15 to 50%(6-9). The proposed mechanism is that in the overall state of oxidative stress and fluctuating oxygen concentrations analogous to hypoxia-reperfusion within the placental environment(5, 10) a release of signal molecules from the placenta activates the maternal endothelium in the systemic vasculature.

Depending on the extent of the inadequacy of the trophoblast invasion the fetus shows impaired growth earlier or later in gestation, when the placental dysfunction puts a limit on the necessary exchange. In this process the scarcities from the placental dysfunction

leads to the fetus using compensation mechanisms that maintain fetal homeostasis as long as possible. Among these adaptations are hemodynamic redistribution resulting in asymmetrical growth, brain sparing and oligohydramnios. When the dysfunction progressively worsens, compensation mechanisms fail and the fetus decompensates and dies if there is no medical intervention(11, 12).



Placentation (trophoblast invasion and remodeling of maternal spiral arteries) in normal pregnancies and in pregnancies complicated by preeclampsia and/or severe early-onset FGR(13).

At present, no treatment or therapy is proven to be effective in improving the placental function and the growth of an FGR fetus(10). The only accepted intervention is to optimally time the birth with the highest possible gestational age and weight, and before acidemia and fetal death occur. In early-onset FGR, in contrast with late-onset FGR, delivery is usually by cesarean section because the fragile fetal condition does not allow the challenges of uterine contractions. Early iatrogenic birth carries risks of prematurity in which the neonate needs to be supported in its vital functions for which it requires care in a neonatal intensive care unit (NICU) and is at risk for short-term mortality and morbidity, such as intra-ventricular haemorrhage (IVH)(14-16), periventricular leukomalacia (PVL)(17, 18), bronchopulmonary dysplasia (BPD)(19-23), necrotizing enterocolitis (NEC)(24, 25), retinopathy of prematurity (ROP)(26, 27) and sepsis. These morbidities could cause long-term physical and neurosensory health problems. Long-term neurodevelopmental impairment occurs more frequently in children born after FGR than in the

general population and is mostly related to the severity of FGR and neonatal morbidity(28, 29). Also, more social and attention problems are reported(30).

Expectant management has the advantage of decreasing the degree of prematurity and the risks of concurrent neonatal morbidity, but carries the risks of stillbirth or episodes of fetal hypoxia, but also confers maternal risk in pregnant women with concomitant pre-eclampsia such as eclampsia, lung edema, stroke, myocardial ischaemia, placental abruption, and acute kidney injury(31). Obstetricians, together with neonatologists in prenatal consultation, often try to weigh maternal and fetal perinatal risks in order to determine the optimal moment for delivering the fetus, aiming at minimizing fetal and maternal adverse consequences.

Optimal timing of birth is challenging and based on an estimation of the placental function by Doppler measurements and the fetal condition by cardiotocography (CTG)(7, 32). The difficulty in monitoring the fetal condition by visual assessment of the CTG, is the high inter- and intra-observer variability and the relatively low predictive value of an abnormal CTG for neonatal acidemia, morbidity and mortality(33). Computerized assessment of CTG (cCTG) is a variably implemented technique in which the short-term variation (STV) is software calculated. STV serves as a marker for autonomic dysfunction and as such it is related to fetal hypoxia(34). How this predictive value should be applied and if its application has better outcomes than visual CTG assessment remains to be investigated. Complementary value can be found in the use of Doppler ultrasound measurements that offer an opportunity to estimate the worsening of the placental function and the extent of fetal compensation mechanisms, such as absent end-diastolic flow (AEDF) of the umbilical artery. Doppler ultrasound can also be used to identify when the fetal circulation decompensates such as when the Doppler ultrasound measurements of the ductus venosus show abnormalities (negative or absent A-wave). Performing a cesarean section or induction of labour when any of the above events occur is an accepted management strategy. However, trials that investigated these different techniques as criteria for delivering the fetus, are scarce and show variable effects(7, 35).

Apart from timing of delivery, to date, no therapy or pharmacological agent has been found to be effective in improving placental function in cases of severe, early-onset FGR. Since in FGR the defective remodeling have caused the spiral arteries to retain their vasoconstrictive potential, a pharmacological agent causing vasodilation in the uterine artery and the feto-maternal circulation, could be hypothesized to promote fetal growth and delay the moment of fetal compromise. If so, the fetus could be delivered at a higher gestational age and with a higher birthweight resulting in significant reduction of perinatal compromise. L-arginine is an agent that has been investigated with this purpose, but the number of patients included in appropriate trials is too small to draw definitive conclusions(36). Phosphodiesterase 5 inhibitors, among which sildenafil, have also been suggested to improve fetal growth and maternal blood pressure regulation during FGR and pre-eclampsia(8, 9, 37-41). To date, large randomized clinical trials are still needed to confirm or reject the therapeutic effect on (long-term) healthy survival.

The objectives of the thesis
The objective of this thesis is to provide an overview of different aspects of early-onset FGR: prognosis, monitoring and treatment.

Aspects of management of pregnancies complicated by FGR this thesis focuses on:
1. Short term variation of the computerized cardiotocography
2. Blood pressure target of antihypertensive treatment in maternal hypertension
3. The phosphodiesterase 5 inhibitor sildenafil

To reflect on these subjects:

Part 1 of the thesis focuses on the definition and prognosis of FGR.

Chapter 2 describes the definition of FGR in the existing literature over time by summarizing the used definitions in the years 1994, 2004 and 2014.

Chapter 3 consists of a systematic review on the reported fetal and neonatal mortality and short- and long-term morbidity in cohorts of women with early FGR.

Chapter 4 reports the neurodevelopmental outcomes at five years of age in a cohort of children born after severe early-onset FGR, participating in the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study.

Part 2 of the thesis focuses on the management of severe early-onset FGR.

Chapter 5 studies the prognostic accuracy of STV of the fetal heart rate on the CTG in pregnancies complicated by FGR.

Chapter 6 consists of a secondary analysis of the Control of Hypertension In Pregnancy Study (CHIPS) focusing on the influence of gestational age at commencing antihypertensive treatment on fetal growth.

Chapter 7 describes the protocol of the Sildenafil TheRapy in Dismal prognosis Early onset fetal growth Restriction (STRIDER) trials, evaluating the effect of the phosphodiesterase 5 inhibitor sildenafil compared with placebo for treating FGR.

Chapter 8 consists of the detailed statistical analysis plan for the Dutch STRIDER trial.

Chapter 9 reports the results of the Dutch STRIDER trial.

Chapter 10 describes the methods of data validation within the Dutch STRIDER trial on the outcome pulmonary hypertension.

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Part 1

Definition and prognosis of severe early-onset fetal growth restriction

Part 1

Chapter 2

Temporal variation in definition of fetal growth restriction in the literature

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A Pels
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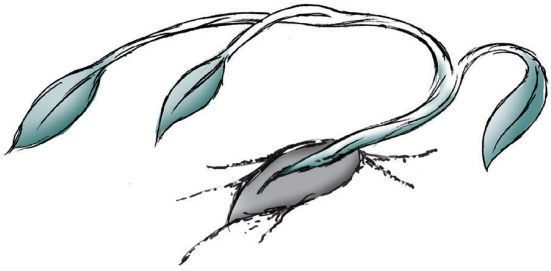
Ultrasound in Obstetrics & Gynecology
2019 May; 53(5): 569-570



Fetal growth restriction (FGR) is a major obstetric problem contributing significantly to perinatal morbidity and mortality(1,2). The adverse intrauterine environment associated with FGR also has an impact on long-term health outcomes, such as neurological and cognitive impairment, and cardiovascular and endocrine diseases(3). Although its impact is acknowledged universally, FGR is defined poorly. In many studies, the term FGR is used for fetuses that are in fact small-for-gestational age (SGA). Birth weight, estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile is often used as a cut-off to define FGR(4,5). However, SGA and FGR are principally different. SGA is the statistical deviation of fetal size from a reference, and may describe a healthy fetus at the lower end of the normal growth range. FGR is a pathological condition in which the fetus does not reach its intrinsic growth potential.

Fetal size at a certain gestational age can reflect past growth, but it does not provide any information about fetal growth velocity and placental function over time. As fetal growth is a dynamic process, it can be evaluated adequately only through sequential measurements. Detection of growth restriction by observation of reduced or declining growth velocity is difficult because it may take weeks before it is apparent on ultrasound measurements. Another way to gain insight into placental function is by evaluating functional parameters, such as Doppler measurements and placental biomarkers. The combination of Doppler measurements and fetal biometry has higher sensitivity in detecting FGR than do biometric measurements alone(6–10). Moreover, serum markers for placental function have been identified to be associated with placental pathology(11–14). Based on these new insights, contemporary research is focused increasingly on the combination of functional parameters and biometric measurements to identify fetuses at risk for growth restriction and define FGR.

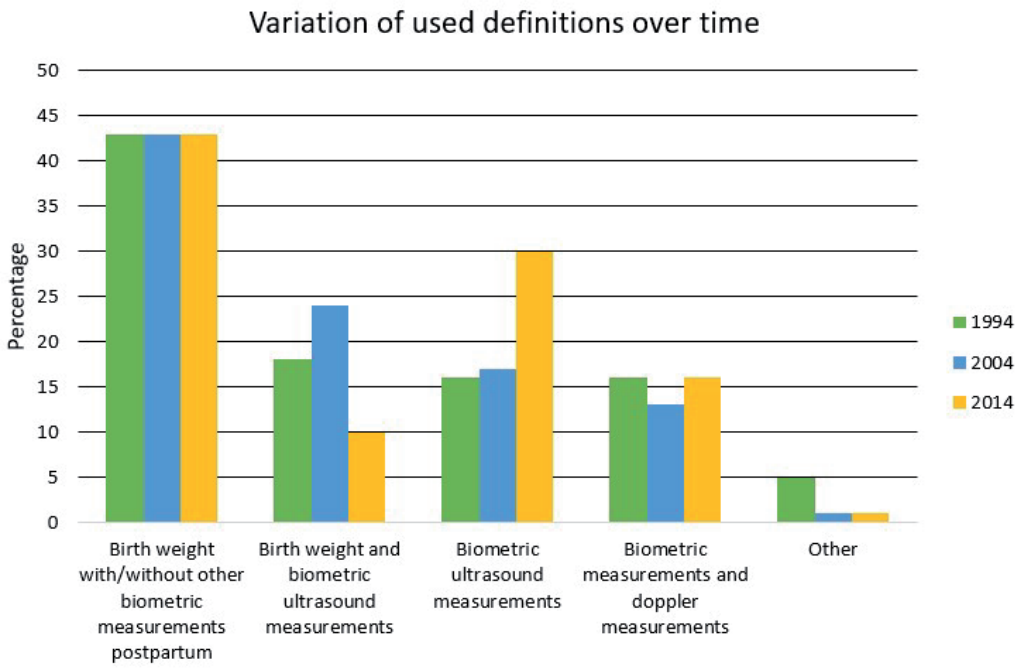
We aimed to describe different definitions of FGR used in the literature and how these changed over the past two decades, between 1994 and 2014, before a consensus-based definition for early and late FGR was established through a Delphi procedure(15).

We reviewed the definition of FGR used in all studies with focus on FGR published in the years 1994, 2004 and 2014. Animal studies, reviews, editorials, case reports and unpublished studies were excluded. We also excluded studies that focused on neonatal growth or SGA when the term was not used synonymously with FGR. Only records available in English were included. The literature search yielded 118 records published in 1994, 191 records in 2004 and 307 records in 2014. After screening the title, abstract and (if necessary) the full text, 56, 75 and 115 records published in 1994, 2004 and 2014, respectively, met the inclusion criteria (Appendix S1). In total, 28 (11%) records were excluded because no definition for FGR was reported, even though the articles were dedicated specifically to FGR.

A total of 31, 33 and 44 different definitions of FGR were identified in articles published in 1994, 2004 and 2014, respectively (Tables S1–S3). The majority of the studies published in any of the 3 years used birth weight < 10th percentile to define FGR, indicating that

growth restriction was identified only after birth (Figure 1). Diagnosis of FGR postpartum precludes the opportunity to reduce the effects of this pathological condition by frequent fetal monitoring and/or planned timing of delivery. The proportion of studies that used FGR definitions based on antenatal parameters increased with time. The definition of FGR was based on antepartum findings alone in 47% of studies published in 2014, vs in 34% and 30% of studies published in 1994 and 2004, respectively (Figure 1). This reflects the improved ability to determine accurately fetal size using ultrasound and the increased availability of other ultrasound parameters that assess reduced fetal growth.

Figure 1: Variation of used definitions over time



In addition to the variability in the definition of FGR, different reference growth charts were also used between the studies to define FGR. In all three publication years, the most commonly used charts were local population-based growth charts (30%, 39% and 43% of studies published in 1994, 2004 and 2014, respectively), defined as hospital-, country- or area-based. Approximately a quarter of all included studies did not describe which reference chart they used. In all definitions of FGR, abnormal growth was based on cut-offs beyond a certain percentile of the reference growth charts. However, since different growth charts are based on different reference populations, a fetus of a certain size might be considered growth-restricted on one chart but normal on another.

The findings of our review point out the major heterogeneity and weaknesses in definitions of FGR used over the past two decades. The lack of a uniform definition of one of the major and most common obstetric problems hampers adequate interpretation from a clinical perspective as well as data synthesis from a research perspective.

The terms FGR and SGA are frequently used interchangeably, despite the fact that they are not synonymous and reflect different patient populations with different perinatal risks. Using the definition of SGA to define FGR, up to 72% of fetuses would have normal perinatal outcome(16). This reflects the lack of a gold standard for the definition of FGR, which poses a difficulty in pinpointing an exact definition for this condition. For this reason, researchers resort to a definition that is exact yet faulty. In the absence of a gold standard, SGA may be a sensible surrogate population to study, as almost half of SGA fetuses are thought to be growth-restricted. The lower the cut-off for size the higher is the risk for FGR and adverse outcome(17). However, it should be taken into account that study results and effects are diluted by healthy fetuses(18). This hampers correlation studies for etiologic factors and intervention studies of FGR.

A Delphi procedure was conducted in 2015 among recognized FGR experts and consensus was reached, based on contemporary knowledge, on definitions for early and late FGR due to placental insufficiency(15). These included not only size parameters but also functional parameters that reflect placental function. Although less than exact, these definitions probably narrow down more accurately the patient group of interest. If new and stronger markers for FGR become available, it may become opportune to repeat such a procedure in due time to decide if the evidence is strong enough to add the variable to the definition.

The present literature analysis highlights the importance of a uniform definition of FGR in order to allow comparison of different study cohorts and implementation of findings in clinical practice. Henri Ford was exemplary in thinking of the benefits of standardization as the best that we know today but which is to be improved tomorrow(19). We propose that researchers adopt the contemporary definition of FGR established by the Delphi consensus(15).

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Supplementary information

Table S1: Identified definitions of fetal growth restriction in 1994

All definitions reported 1994	no.
BW <p10(1-19)	19
BW <p3(20)	1
BW <2500gr(21, 22)	2
EFW <p10(23)	1
EFW <p3(24)	1
AC <p5(25-27)	3
AC <p10(28)	1
BW <p10 + birth length <p10(29)	1
BW <p10 + AC <p10(30)	1
BW <p10 + crossing centiles AC + increase in HC/AC ratio >2SD(31, 32)	2
BW <p3 + EFW <p3(33, 34)	2
BW not stated + EFW <p3(35)	1
BW <p3 + birth length <p3(36)	1
BW <p10 + FGR <0,85(37)	1
BW <p10 + EFW <p10 + AC <p5(38)	1
EFW<p10 + AC <p10(39, 40)	2
AC <p10 + crossing centiles AC(41)	1
FGR <0,85(42)	1
BW <p10 + BPD <p10 + FL <p10(43)	1
BW <p10 + AC <p10 + BPD <p10(44)	1
AC <p5 + UA PI >p95 + a. Uterina >p95(45)	1
BW <p5 + AC <p5 + AEDF UA(46)	1
BW <p5 + AC <p5 + AEDF UA + unilateral notch a. Uterina(47, 48)	2
BW <p5 + AC <p5 + AEDF UA + unilateral notch a. Uterina + oligohydramnios(49)	1
BW + EFW -1,5SD, UA+1SD, MCA -1SD (50)	1
BW + UA abnormal, both not stated(51)	1
EFW <p10 + ratio UA/MCA >p95(52)	1
AC <p5 + abnormal UA not stated + normal HC & FL(53)	1
BW <p5 or BW <p10 + oligohydramnios + UA systole/diastole ratio >4 + crossing centiles EFW(54)	1
Lubchenco score(55)	1
Ponderal index and subscapilar skinfold measurement(56)	1

BW = birth weight; EFW = estimated fetal weight; AC = abdominal circumference; HC = head circumference; BPD = biparietal diameter; FL = femur length; UA = umbilical artery; PI = pulsality index, AEDF = absent end diastolic flow; a. Uterina = uterine arteries; MCA = pulsatility index of middle cerebral artery

Table S2: Identified definitions of fetal growth restriction in 2004

All definitions reported 2004	no.
BW <p10(57-77)	21
EFW <p10(78-83)	6
BW <p10 + EFW <p10(84-86)	3
BW <p5(87-90)	4
EFW <p5(91)	1
BW <p5 + EFW <p5(92)	1
AC <p5(93-95)	3
BW <p10 +AC <p10(96-101)	6
BW <p3(102-105)	4
BW <p5 +AC <p5(106)	1
BW <p10 + EFW <p10 + UA PI >p95(107)	1
BW <p10 + UA PI >p90 + a. Uterina >p90(108)	1
AC <p5 + crossing centiles AC(109)	1
BW <p10 + crossing centiles AC(110)	1
BW <p10 + AC<p10 + crossing centiles EFW >=40% (111)	1
BW <p5 + obstetric documentation of FGR(112, 113)	2
BW <p10 + birth length <p10(114, 115)	2
AC <p3(116)	1
EFW <p3 + crossing centiles EFW(117)	1
AC <p3 + UA PI >p95 + a. Uterina RI >p95(118)	1
EFW <p5 + UA RI >p90(119)	1
EFW <p5 + oligohydramnios + abnormal UA(120)	1
FGR <0,85(121)	1
EFW <p10 + oligohydramnios + asymmetrical growth(122)	1
BW <p10 + EFW <p10 + UA RI >p95(123)	1
BW <p5 + EFW <p5 + crossing centiles EFW(124)	1
BW <p10 + AC <p10 + UA PI >p95 + crossing centiles AC + Caesarean for fetal distress + NICU admission for neonatal morbidity(125)	1
BW <p3 + EFW <p5(126)	1
Abnormal BW + EFW + AEDF aortic blood flow (127)	1
Abnormal BW + EFW + aortic blood flow (cut-offs not stated)(128)	1
BW <p10 + AC <p10 + abnormal UA (cut-off not stated) + crossing centiles AC(129)	1
BW <p10 + fundal height <p3(130)	1
BW <p10 + crossing centiles EFW + clinical evidence of inappropriate growth(131)	1

BW = birth weight; EFW = estimated fetal weight; AC = abdominal circumference; UA = umbilical artery; PI= pulsality index, RI = resistance index; FGR= fetal growth ratio, AEDF = absent end-diastolic flow; NICU = neonatal intensive care unit

Table S3: Identified definitions of fetal growth restriction in 2014

All definitions reported 2014	no.
BW <p10(132-164)	33
EFW <p10(165-183)	19
AC <p10(184)	1
BW <p5(185-189)	5
EFW <p5(190, 191)	2
BW <p3(192-195)	4
BW + EFW <p10(196-201)	6
EFW + AC <p10(202, 203)	2
EFW + AC <p5(204)	1
BW <p10 + UA >p95(205)	1
EFW <p10 + UA >p95(206-208)	3
AC <p5 + crossing centiles AC(209, 210)	2
BW + EFW <p10 + UA PI <p95(211, 212)	2
FGR <0,85(213)	1
BW + EFW <p10 UA >p95(214, 215)	2
BW <p10 + crossing centiles EFW(216, 217)	2
EFW <p10 + AC <p5(218)	1
EFW <p10 + oligohydramnios or UA PI >p95(219)	1
EFW <p5 + asymmetrical growth(220)	1
BW <p10 + abnormal UA and a. Uterina (cut-offs not stated)(221)	1
BW <p3 + AEDF UA(222)	1
BW abnormal + AEDF UA(223)	1
BW <p10 + abnormal UA (cut-off not stated)(224, 225)	2
BW + EFW <p10 + oligohydramnios + crossing centiles EFW + HC/AC >p95(226)	1
Presence of catch-up growth(227)	1
BW <2500gr(228)	1
BW <p3 + a. Uterina >p95 + MCA PI <p5(229)	1
EFW + AC <p5 + oligohydramnios + UA PI >p95(230)	1
BW <70% of expected BW(231)	1
EFW <p10 + asymmetrical growth(232)	1
BW <p3, <p5, <p10 and <2500gram, UA normal(233)	1
EFW + AC <p10 and crossing centiles of EFW + AC(234)	1
EFW <p10 + a. Uterina RI >p95 + CPR <p5(235)	1
Crossing centiles EFW(236)	1
BW <p10 + HC <p2,5(237)	1
BW + EFW + AC <p10(238)	1
EFW + AC <p10 and crossing centiles of EFW(239)	1
AC <p3 + oligohydramnios and abnormal UA (cut-off not stated)(240)	1
BW + EFW <p10 and skin-fold thickness + Ponderal index <p5(241)	1
BW <p10 + abnormal EFW + AC (cut-offs not stated)(242)	1
BW + EFW <p10 + REDF UA + abnormal DV (cut-off not stated)(243)	1

All definitions reported 2014	no.
EFW <p10 + AC <p5 + crossing centiles AC + HC/AC >p90(244)	1
BW <p3 + brain/liver weight ratio >4(245)	1
BW <p3 + FGR <0,85(246)	1

BW = birth weight; EFW = estimated fetal weight; AC = abdominal circumference; HC = head circumference; UA = umbilical artery; PI = pulsatility index; AEDF = absent end diastolic flow; a. Uterina = uterine arteries; RI = resistance index; MCA = middle cerebral artery; CPR = cerebroplacental ratio; REDF = reversed end-diastolic flow; DV = ductus venosus, FGR = fetal growth ratio

Figure S1: Flowchart on record selection

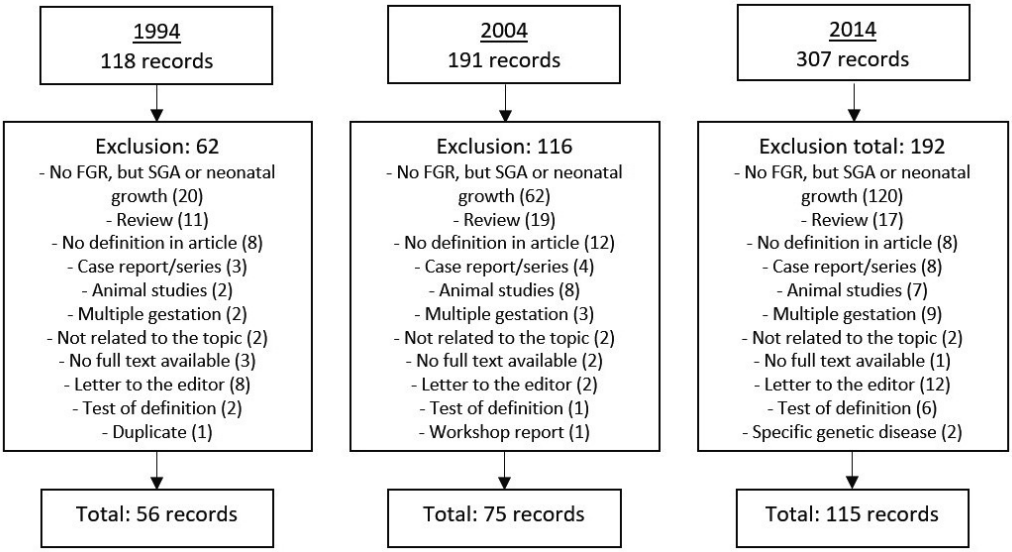


Figure S2: Variation in used definitions in 1994

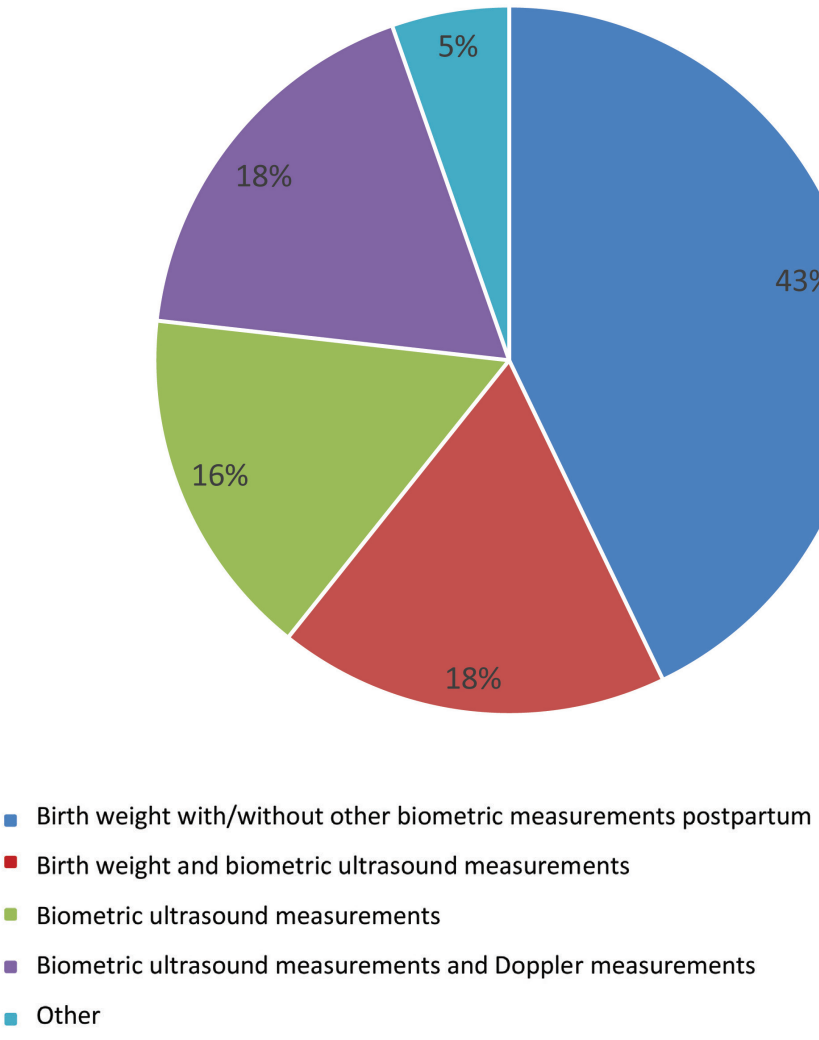


Figure S3: Variation in used definitions in 2004

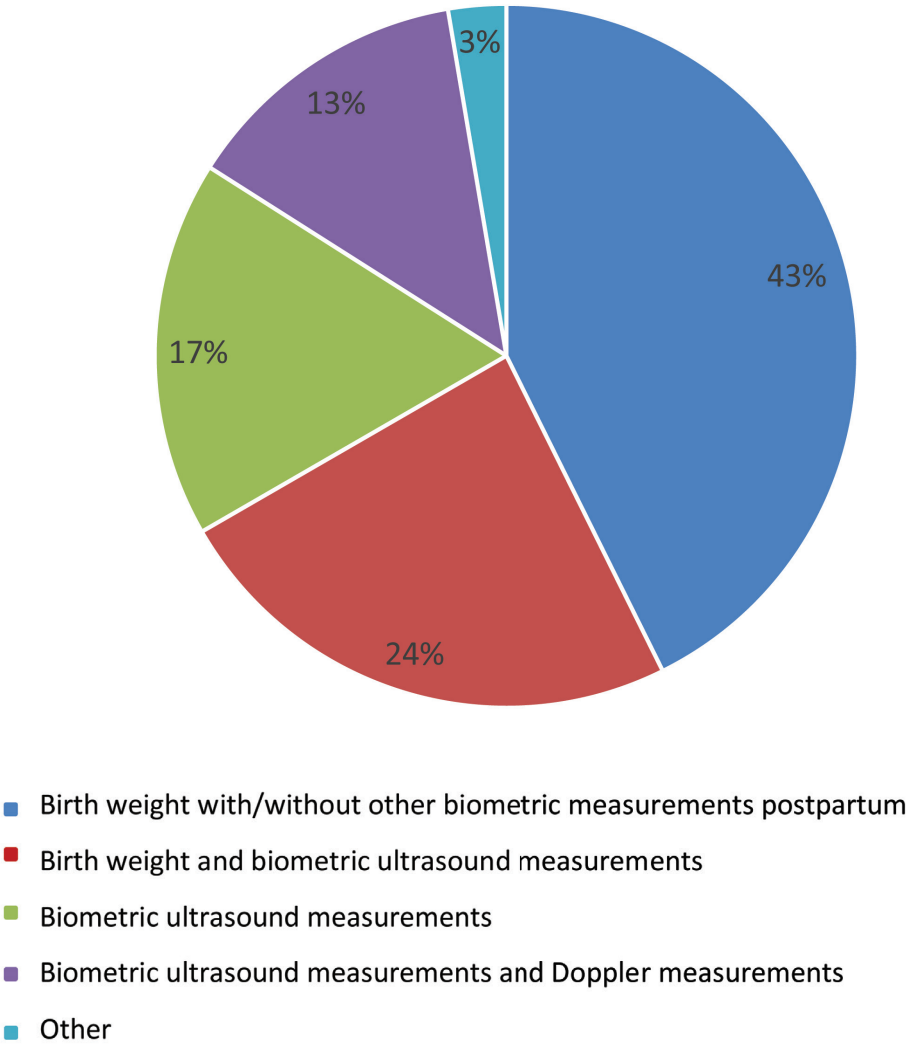


Figure S4: Variation in used definitions in 2014

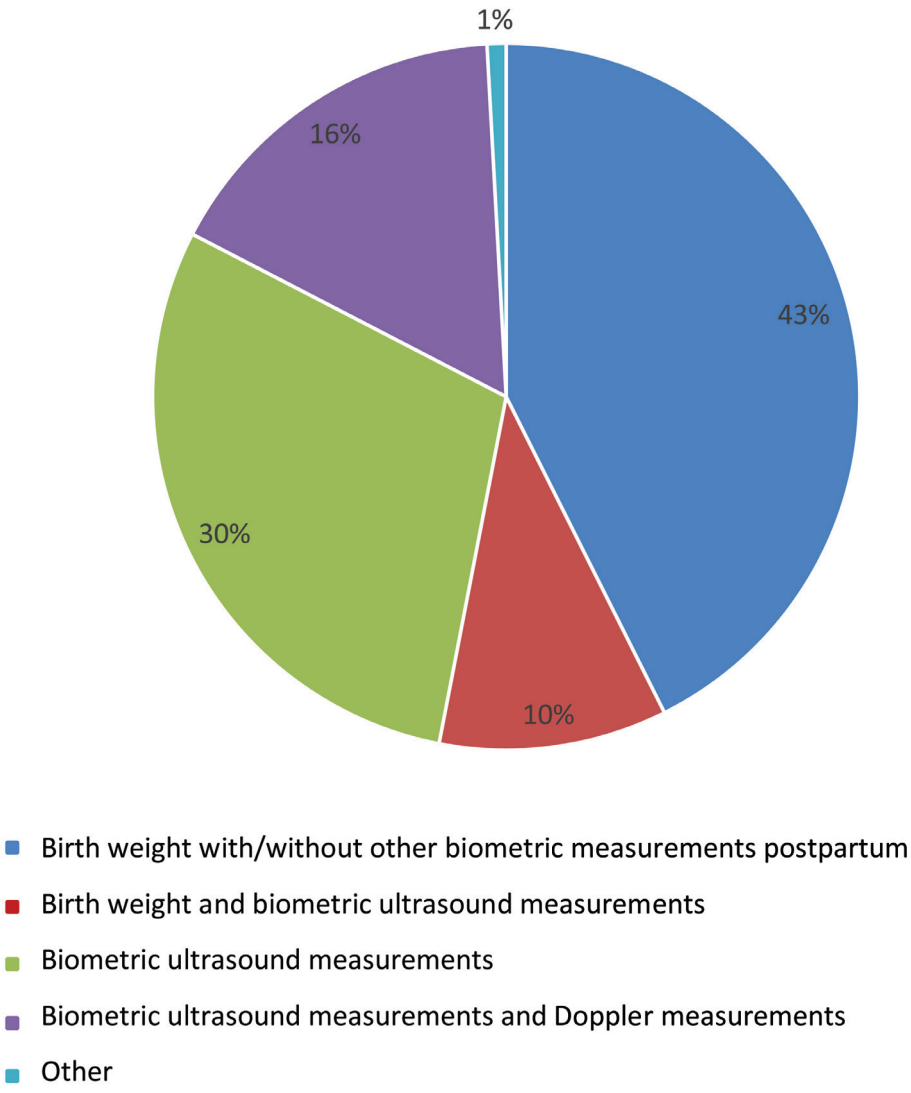


Figure S5: Growth formulas used in 1994

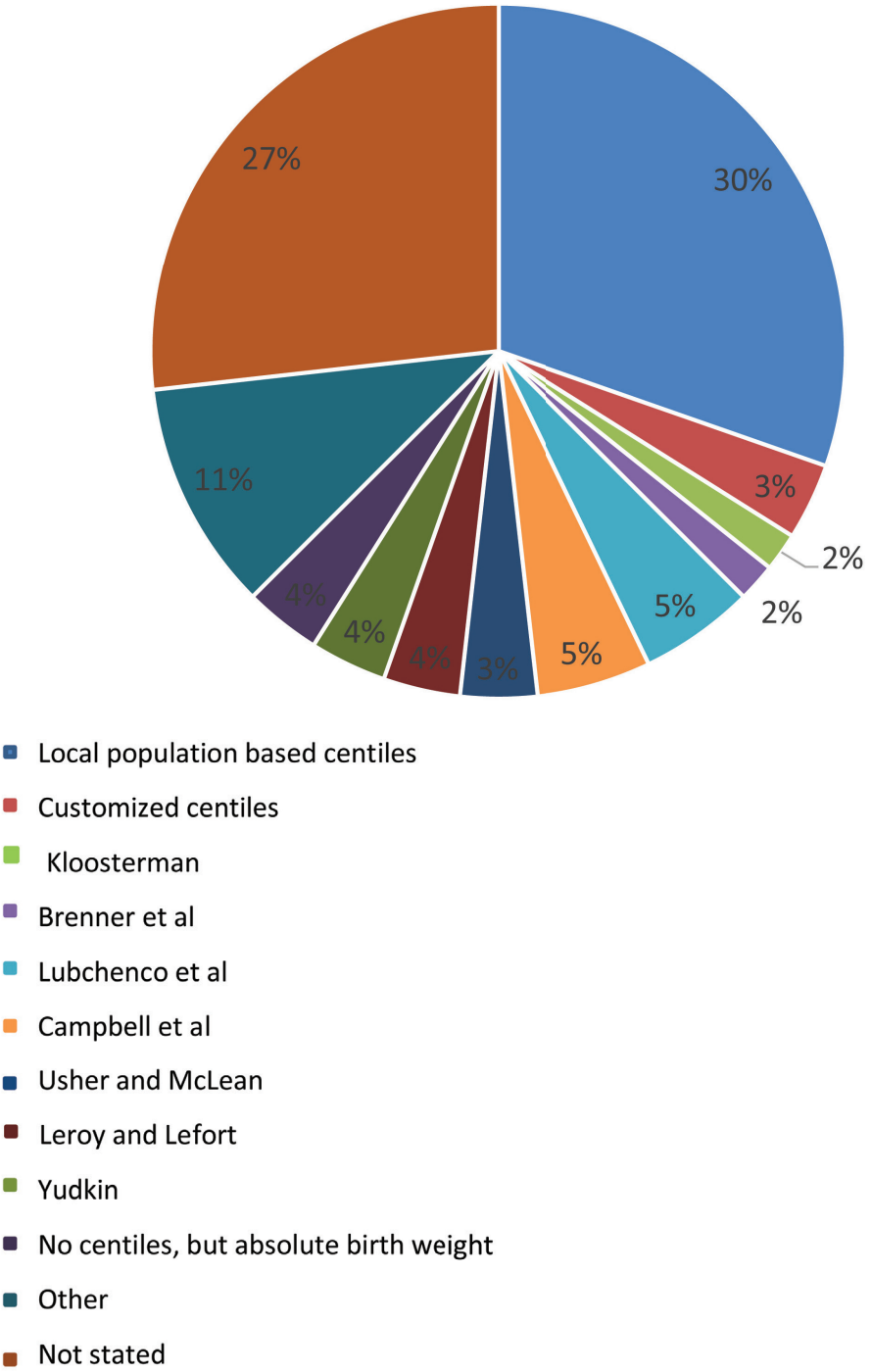


Figure S6: Growth formulas used in 2004

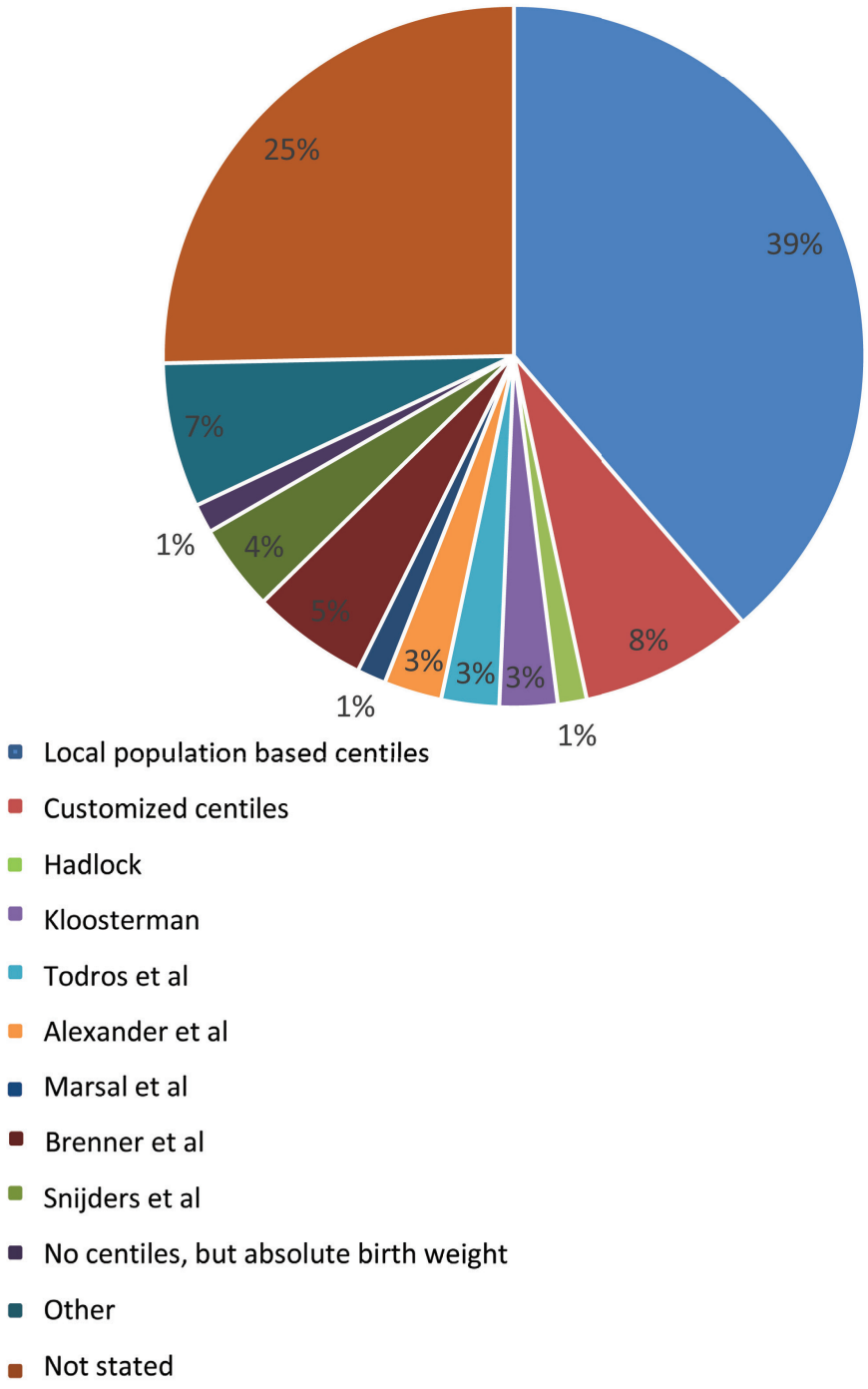
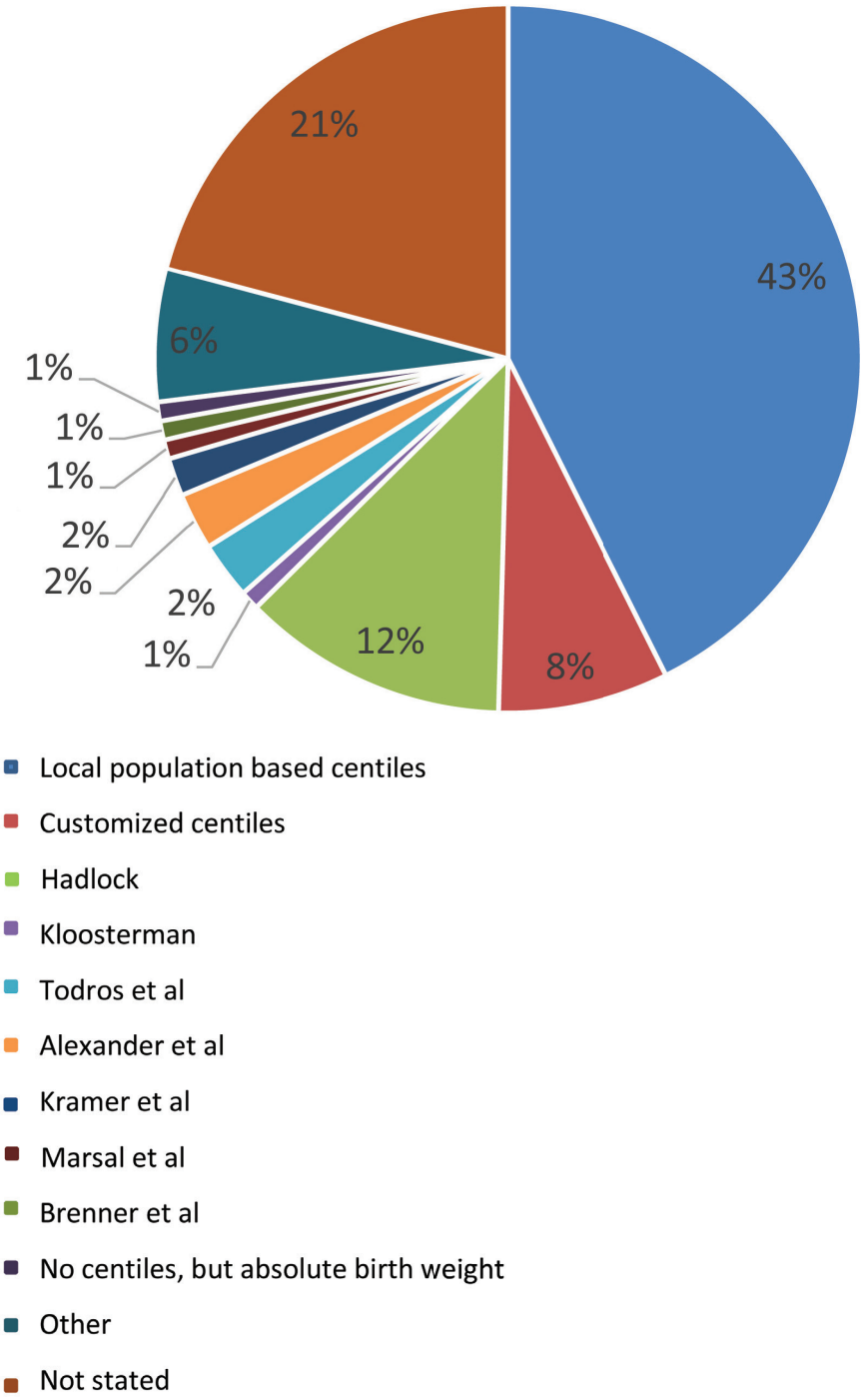


Figure S7: Growth formulas used in 2014



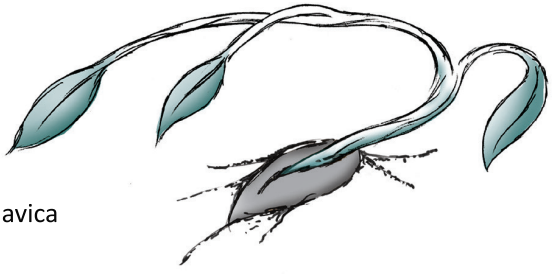
Appendix S1: Articles included in systematic review of definition of fetal growth restriction

Please find the list of articles included in the systematic review in the supporting information online.

Chapter 3

Early-onset fetal growth restriction: a systematic review on mortality and morbidity

A Pels
IM Beune
AG van Wassenaer-Leemhuis
J Limpens
W Ganzevoort



Acta Obstetricia et Gynecologica Scandinavica
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Abstract

Introduction:
Severe early-onset fetal growth restriction is an obstetric condition with significant risks of perinatal mortality, major and minor neonatal morbidity, and long-term health sequelae. The prognosis of a fetus is influenced by the extent of prematurity and fetal weight. Clinical care is individually adjusted. In literature, survival rates described vary and studies often only include live-born neonates with missing rates of antenatal death. This systematic review aims to summarize the literature on mortality and morbidity.

Material and methods:
A broad literature search was conducted in OVID MEDLINE from 2000 to 26 April 2019 to identify studies on fetal growth restriction and perinatal death. Studies were excluded when all included children were born before 2000 because (neonatal) health care has considerably improved since this period. Studies were included that described fetal growth restriction diagnosed before 32 weeks of gestation and antenatal mortality and neonatal mortality and/or morbidity as outcome. Quality of evidence was rated with the GRADE instrument.

Results:
Of the 2604 publications identified, 25 studies, reporting 2895 pregnancies, were included in the systematic review. Overall risk of bias in most studies was judged as low. The quality of evidence was generally rated as very low to moderate, except for 3 large well-designed randomized controlled trials. When combining all data on mortality, in 355 of 2895 pregnancies (12%) the fetus died antenatally, 192 died in the neonatal period (8% of live-born neonates) and 2347 (81% of all pregnancies) children survived. Of the neonatal morbidities recorded, respiratory distress syndrome (34% of the live-born neonates), retinopathy of prematurity (13%) and sepsis (30%) were most common. Of 476 children that underwent neurodevelopmental assessment, 58 (12% of surviving children, 9% of all pregnancies) suffered from cognitive impairment and/or cerebral palsy.

Conclusions:
When combining the data of 25 included studies, survival in fetal growth restriction pregnancies, diagnosed before 32 weeks of gestation was 81%. Neurodevelopmental impairment was assessed in a minority of surviving children. Individual prognostic counseling on the basis of these results is hampered by differences in patient and pregnancy characteristics within the included patient groups.

Introduction

Severe early-onset fetal growth restriction (FGR) with placental insufficiency as its mechanism(1) is an obstetric condition that is mostly managed in tertiary-care hospitals. By consensus FGR is defined as onset before 32 weeks of gestation, a fetal abdominal circumference or estimated fetal weight (EFW) below the 3rd centile or absent end-diastolic flow in the umbilical artery, or abdominal circumference or EFW below the 10th centile combined with a pulsatility index of the uterine artery above the 95th centile and/or pulsatility index of the umbilical artery above the 95th centile(2). This patient group needs high amounts of care and has a high likelihood of iatrogenic premature delivery, both for fetal and for secondary maternal indications such as the development of the maternal syndrome of preeclampsia(3). As these FGR children usually are born very preterm, the condition carries significant risks of neonatal mortality, major and minor morbidity, and long-term health sequelae(4, 5). These risks are not only strongly related to gestational age, but also to the extent of growth restriction. Reported survival rates vary(3).

Counseling patients with severe early-onset FGR about perinatal prognosis is difficult due to the uncertain influence of different prognostic variables of the condition. Furthermore, the widespread variability of existing data on survival and long-term prognosis of the fetus proves decision-making in this patient group even more difficult.

Overview of total mortality is often lacking in literature on this subject. For example many studies describe the prognosis of live-born neonates after FGR and do not take antenatal death into account. From an obstetric perspective, long-term outcomes can only be interpreted optimally if they are presented together with the proportions of antenatal and neonatal death(6). The aim of this systematic review is to describe the chances of overall (antenatal and neonatal) survival and long-term morbidity and neurodevelopment based on the total number of fetuses at first FGR diagnosis in order to inform patients and obstetricians in their counseling and decision-making.

Material and methods

Data sources

An information specialist (JL) performed a broad search in OVID MEDLINE from 2000 to 27 April 2019. The search consisted of controlled terms, including MeSH terms, and text words for FGR and antenatal/perinatal mortality or neurodevelopment in infants with demonstrated FGR, combined with search filters to retrieve primary and secondary studies (the latter only as a check). We searched from 2000 onwards because neonatal health care has changed fundamentally in the current millennium. No further restrictions were applied. The complete search strategy is shown in the Supplementary Material (Table S1). The retrieved records were imported and de-duplicated in ENDNOTE X7. The included studies were screened for additional relevant cited or citing references.

Main outcomes measures
Six important research questions were identified:

1. What is, in severe early-onset FGR, the chance of intra-uterine death?
2. What is, in live-born neonates after severe early-onset FGR, the chance of neonatal death?
3. What is, in surviving children after severe early-onset FGR, the chance of neurodevelopmental impairment (NDI) at or before 5 years of age in long-term follow-up?
4. What is, in surviving children after severe early-onset FGR, the mean cognitive score at or before 5 years of age?
5. What is, in surviving children after severe early-onset FGR, the mean motor score at or before 5 years of age?
6. What is, in surviving children after severe early-onset FGR, the chance of cerebral palsy at or before 5 years of age?

Eligibility criteria
Records covering singleton pregnancies diagnosed with FGR, as defined by trialists, diagnosed before 32 weeks of gestation, were included when the antenatal and perinatal data on mortality were reported. If a study included patients diagnosed with FGR before and after 32 weeks of gestation (for example between 24 and 38 weeks of gestation) the study was only included if data on the subgroup below 32 weeks of gestation was reported separately in the publication. Because of the progress of quality of obstetric and neonatal care, only patient groups (partially) born in or after the year 2000 were included. Furthermore, only records published in English and with an available full text were included.

Records were excluded if they only described neonates born after FGR, evaluating the postnatal data, without describing the antenatal and perinatal mortality.

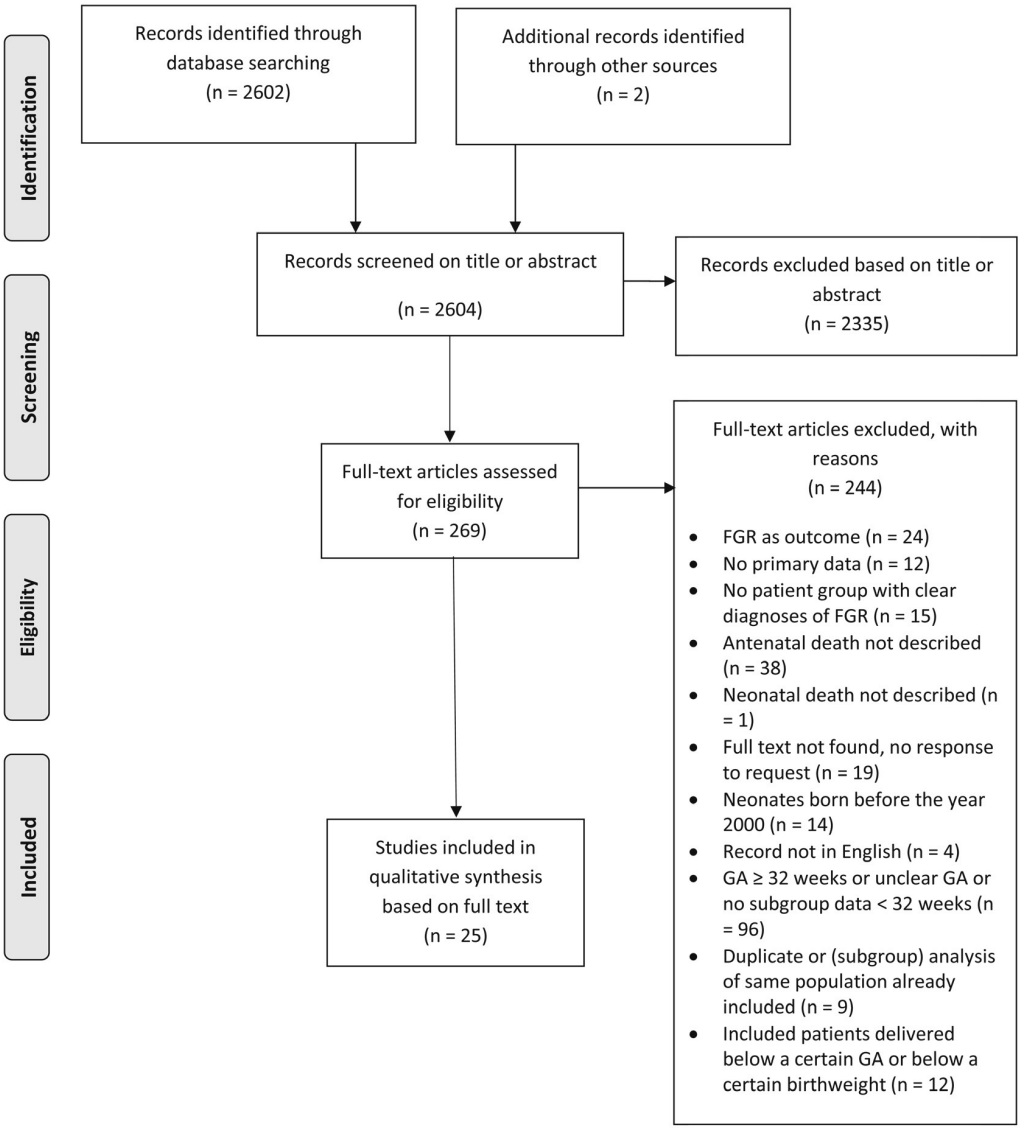
Data collection
Titles and abstracts of all search results were independently screened by 2 researchers (AP and IMB). Discrepancies were resolved by discussion with a third researcher (WG). The full text of potentially eligible studies was assessed. Relevant data were extracted from the full text by 2 researchers independently (AP and IMB) and compared for purpose of completeness and correctness.

The quality of the evidence was rated by using the GRADE instrument(7).

Results

The literature search identified 2602 unique records, and 2 additional records were identified through reference and citation checks. After title and abstract screening, 269 full-text records were assessed for eligibility; 25 studies comprising 2895 patients were included in the systematic review (Figure 1).

Figure 1: flowchart article selection



General characteristics of the studies

Table 1 summarizes the characteristics of the included studies. The number of included pregnancies varied from 8 to 503. FGR was defined differently among the included studies; some studies focused on the EFW or abdominal circumference only, whereas other studies included Doppler measurements as well (Table 1).

Table 1: Characteristics of included studies

	Study design	Number of patients	Definition of FGR	Gestational age at diagnosis FGR (wk + d) (mean ± SD or median (IQR))	EFW at diagnosis FGR (g) (mean ± SD or median (IQR))	Preeclampsia or HELLP at diagnosis FGR
Ali, 2017(8)	Clinically retrospectively registered, open, parallel, randomized controlled trial	80	AC < 10th percentile with increased HC:AC ratio	Group 1 (n=34) mean 30 ± 0.5; Group 2 (n=34) mean 30 ± 0.3	Group 1 (n=34) mean 1202 ± 72; Group 2 (n=34) mean 1209 ± 48	0 %
Ali, 2018(9)	Clinically registered, open, parallel, randomized clinical trial	60	AC or birthweight < 10th centile	Group 1 (n=30) mean 30 ± 0.5; Group 2 (n=30) mean 30 ± 0.4	Group 1 (n=30) mean 1193 ± 51; Group 2 (n=30) mean 1216 ± 63	0 %
Aoki, 2014(10)	Retrospective cohort study	17	<5th percentile (not defined what needs to be <5th percentile)	Median 25.4 (22.6-27.7)	Median 513 (260-741)	17 / 17 = 100%
Baschat, 2001(11)	Prospective cohort study	44	AC <5th percentile and umbilical artery Doppler PI more than 2 SD above the gestational mean by local reference values	Median 25+1 (range 16+4-31+6)	Not described	Not described
Belghiti, 2011(12)	Retrospective cohort study	10 FGR patients with reported outcomes	<5th percentile (not defined what needs to be <5th percentile)	25+0 - 25+6	Not described for subgroup FGR	10 / 10 = 100%
Fox, 2008(13)	Retrospective case-control study	252	EFW < 25th percentile	21.0 ± 1.0	Not described	Not described
Fujisaki, 2016(14)	Prospective, one-arm, interventional pilot study	14	EFW ≤ 5th percentile	Median 25+3 (22+6 – 25+5)	Mean 418 ±160	0 %
Groom, 2019(15)	Triple-blind, placebo-controlled, parallel, phase II-III trial randomized at the participant level	122	At 22+0 – 27+6 weeks of gestation: AC ≤ 3rd centile At 28+0 – 29+6 weeks of gestation: EFW < 700 g	Group 1 (n = 63): Mean 24.5 ± 1.7 Group 2 (n = 59): Mean 24.8 ± 1.7	Group 1 (n = 63): Mean 479.3 ± 148.1 Group 2 (n = 59): Mean 495.7 ± 170.2	16 / 122 = 13.1%
Hasegawa, 2015(16)	Retrospective cohort study	26	<5th percentile (not defined what needs to be <5th percentile)	Group 1 (n=17) median 25.3 (21.4-29.9) Group 2 (n=9) median 25.3 (20.4-28.1)	Not described	Not described

	Study design	Number of patients	Definition of FGR	Gestational age at diagnosis FGR (wk + d) (mean ± SD or median (IQR))	EFW at diagnosis FGR (g) (mean ± SD or median (IQR))	Preeclampsia or HELLP at diagnosis FGR
Herraiz, 2017(17)	Observational prospective cohort study	74	EFW < 3rd centile or EFW < 10th centile + abnormal fetal Doppler	Group 1 (n=37): 27.0 ± 2.8. Group 2 (n=36): 27.9 ± 2.0	Not described	36 / 74 = 48.6%
Kubo, 2017(18)	Open label, phase 1 clinical trial	8 (< 32 weeks)	EFW ≤ to -1,5 SD on ultrasonography from the Japanese standard table	Median 28+4 (26+0 – 30+5)	Median 967 (708 – 1164)	Not described
Lawin-O'Brien, 2016(19)	Multicenter retrospective study of databases	245	AC ≤ 3d percentile for gestational age, AC calculated according to UK recommended standard and Altman and Chitty chart	Median 23+4 weeks (range 22+0 - 25+6)	Median 353 gram (range 166-677)	81 / 245 = 33%
Lees, 2015(20)	Prospective multicenter non-blinded management trial	503	AC below 10th percentile according to local standards and abnormal umbilical artery Doppler PI above 95th percentile based on local standards, irrespective of the presence of absent or reversed EDF	Mean 29+0 ± 11	Mean 881 ± 217 gram	195 / 503 = 38.8%
Maged, 2018(21)	Prospective non-randomized study	50	EFW < 10^{th} percentile or AC < 10^{th} percentile with abnormal umbilical artery Doppler indices	Group 1 (n = 25): Mean 27.4 ± 1.6 Group 2 (n = 25): Mean 28.1 ± 1.5	Not described	Not described
Petersen, 2009(22)	Retrospective cohort study	33 patients, with 36 pregnancies	EFW <10th percentile for GA and at least two of the following: normal karyotype, notched uterine artery Doppler waveforms in the second trimester, placental histology changes consistent with uteroplacental insufficiency	Median 24 (range 18-29)	Median 364 gram (range 167-496)	Not described
Rizzo, 2008(23)	Cohort study (unclear whether prospective or retrospective)	31	EFW < 10th percentile for population standard confirmed at birth	Median 26.1 weeks (range 22.6-29.1)	Not described	0 / 31 = 0%
Savchev, 2014(24)	Retrospective analysis of a prospective cohort	211 subgroup < 32 weeks	EFW <10th percentile	Mean 28.1 ± 4.0 weeks	Mean 1061 ± 494 gram	74 / 211 = 35.1%

	Study design	Number of patients	Definition of FGR	Gestational age at diagnosis FGR (wk + d) (mean ± SD or median (IQR))	EFW at diagnosis FGR (g) (mean ± SD or median (IQR))	Preeclampsia or HELLP at diagnosis FGR
Sharp, 2018(25)	Randomised placebo controlled trial	135	AC or EFW < 10th percentile and absent or reversed EDF in the umbilical artery	Group 1 (n = 70): Median 25.1 (24.0 – 27.5) Group 2 (n = 65): Median 25.6 (24.1 – 27.4)	Group 1 (n = 70): Median 451 (352 – 613). Group 2 (n = 65): Median 436 (326 – 594)	24 / 135 = 17.8%
Simonazzi, 2013(26)	Retrospective cohort study	16	EFW and/or AC <5th centile	Median 22+3 (range 20+0 to 23+3)	Median 324 gram (range 248-509)	Not described
Story, 2015(27)	Retrospective cohort study	20	EFW <3rd centile	Median 21+4 (range 18+2 - 24+0)	Not described	Not described
Takahashi, 2014(28)	Prospective cohort study	18	< 1.5 SD Japanese standard	Median 23.0 (range 18-25)	Not described	0 / 18 = 0%
Temming, 2017(29)	Retrospective cohort study	355	EFW < 10th percentile using Warsof growth curves before 20+0 wk of gestation and Hadlock growth curves from 20+0 wk onward	Mean 19.5 ± 0.9	Not described	Not described
Von Dadelszen, 2011(30)	Case-control study	27	AC <5th percentile	Group 1 (n=17) median 21+1 (19+5 - 23+2) Group 2 (n=10) median 22+4 (21+1 - 23+4)	Not described	Not described
Yildirim, 2008(31)	Retrospective cohort study	300	EFW <10th percentile	Group 1 (n= 137) median 30.8 (CI 30.3-31.3) weeks Group 2 (n=163) 30.1 (CI 29.6-30.6) weeks	Not described	184 / 300 = 61.3%
Zhang-Rutledge, 2018(32)	Retrospective cohort study	254	EFW ≤ 10th percentile	Group 1 (n = 91): Average 21+5 Group 2 (n = 163): Average 21+3	Not described	Not described

AC = abdominal circumference; EDF = end-diastolic flow; EFW = estimated fetal weight; FGR = fetal growth restriction; GA = gestational age; HC = head circumference; IQR = interquartile range; PI = pulsatility index; SD = standard deviation

Table S2A,B (see Supplementary material) shows the judgement of risk of bias of the individual studies. Two (8, 9) of the 5(8, 9, 15, 20, 25) included randomized controlled trials (RCT) were judged as 'unknown' risk of bias. This judgement was mostly based on the fact that these studies were retrospectively registered and not blinded, and that some of the baseline criteria and outcomes were not reported for pregnancies that involved neonatal death. The other RCTs and the observational studies included were generally judged as 'low' risk of bias.

Synthesis of the results

The results on mortality are summarized in Table 2. When combining all data on mortality, of 2895 pregnancies, 355 (12.3%; range 0%-53%) ended in an antenatal death. Of 2540 live-born children, 1 child was lost to follow-up. In all, 192 (7.6% of 2539 and 6.6% of the total of 2895 pregnancies; range 0%-71%) neonatal deaths occurred, and 2347 (81%; range 14%-100%) of pregnancies survived.

A subset of the studies report neonatal morbidity (see Supplementary Material, Table S3). When combining the data, 34% of the live-born neonates experienced respiratory distress syndrome (2 studies, range 34%-36%), 9.1% had bronchopulmonary dysplasia (4 studies, range 4%-19%), 4.3% had intraventricular hemorrhage (10 studies, range 0%-25%), 5.6% had necrotizing enterocolitis (9 studies, range 0%-22%), 2.6% had persistent pulmonary hypertension of the newborn (2 studies, range 1.9%-9.1%), 12.5% had retinopathy of prematurity (4 studies, range 2%-29%) and 30% had sepsis (4 studies, range 25%-64%). One study used a composite outcome for severe neonatal morbidity(26) and 1 study used a composite for respiratory distress syndrome and chronic lung disease(10).

The ages at which the neurodevelopmental outcome was assessed, the types of tests used for the assessment and the definition of NDI differed between studies. Therefore, not all studies could be included in the evidence table. From the 476 children (402 from 1 larger study, the remainder from 6 small studies) who underwent neurodevelopmental assessment (Table 3), 58 children (12%; 0%-27%) suffered from cognitive impairment and/or cerebral palsy. Overall, cerebral palsy rates in the 7 studies were low: varying from 1% to 10%. NDI was diagnosed in 50 children (11% of surviving children assessed). Eight per cent of 629 pregnancies resulted in a surviving infant with NDI. Only Lees et al(20), reporting 10% NDI among the assessed children, included all important domains in the definition of NDI (Bayley III score, cerebral palsy, hearing loss and visual loss).

Table 4 and 5 present the quality of evidence for our research questions on the mortality and the long-term neurodevelopment, respectively. Our fourth and fifth research question were not addressed in any of the included studies.

Table 2: Outcome data on mortality

	No of patients in final analysis	GA at delivery (wk + d) (mean ± SD or median (IQR))	Birthweight (g) (mean ± SD or median (IQR))	Antenatal death	Live born	Neonatal death	Survival at discharge
Ali, 2017(8)	73 7 / 80 lost to follow-up	Group 1 (n=34) mean 36 ± 0.9. Group 2 (n=34) mean 36 ± 0.7	Group 1 (n=34) mean 2022 ± 25 Group 2 (n=34) mean 2324 ± 19	0 / 73 = 0%	73 / 73 = 100%	5 / 73 = 6.8%	68 / 73 = 93.2%
Ali, 2018(9)	55 5 / 60 lost to follow up	Group 1 (n=25) mean 36.8 ± 0.8 Group 2 (n=20) mean 34.8 ± 0.6 (among surviving babies)	Group 1 (n= 25) mean 1854 ± 262 Group 2 (n=20) mean 1694 ± 169 (among surviving babies)	0 / 55 = 0%	55 / 55 = 100%	10 / 55 = 18.2%	45 / 55 = 81.8%
Aoki, 2014(10)	17	Median 27.3 (23.7-29.3) weeks	Median 568 (300-764)	1 / 17 = 5.9%	16 / 17 = 94.1%	2 / 16 = 12.5%	14 / 17 = 82.4%
Baschat, 2001(11)	44	Median 29+6 (range 26+4- 37+6) for live birth. Median 26+6 (range 25+1-28) for stillbirth	Median 725 (range 420-2260)	10 / 44 = 22.7%	34 / 44 = 77.3%	1 / 34 = 2.9%	33 / 44 = 75.0%
Belghiti, 2011(12)	10 with reported outcome	Median 26+2 (25+6 – 26+6)	Median 507 (429-553)	1 / 10 = 10.0%	9 / 10 = 90.0%	6 / 9 = 66.7%, of which 4 intra-partum death	3 / 10 = 30.0%
Fox, 2008(13)	252	Mean 39.2 ± 2.4	Mean 2999 ± 682	4 / 252 (1.6%)	248 / 252 (98.4%)	2 / 248 =0.8%	246 / 252 = 97.6%
Fujisaki, 2016(14)	14	Median 29+0 (26+6 – 35+3)	Median 604 (437-1340)	2 / 14 = 14.3%	12 / 14 = 85.7%	1 / 12 = 8.3%	11 / 14 = 78.6%
Groom, 2019(15)	122	1 (n = 63): Mean 31+5 ± 4+4 Group 2 (n = 59): Mean 31+2 ± 4+4	Group 1 (n = 63): 1233 ± 774 Group 2 (n = 59): 1184 ± 823	19 / 122 = 15.6%	103 / 122 = 84.4%	9 / 103 = 8.7%	94 / 122 = 77.0%
Hasegawa, 2015(16)	26	Group 1 (n=17) median 28.7 (24.7-31.7). Group 2 (n=9) median 28.5 (26.1-32.4)	Group 1 (n=18) median 695 (424-1016); group 2 (n=8) median 568 (426-654)	1/ 26 = 3.8%	25 / 26 = 96.2%	1 / 25 = 4%	24 / 26 = 92.3%
Herraiz, 2017(17)	73 1 / 74 lost to FU	Group 1 (FGR) mean 30.1 ± 3.2 Group 2 (FGR+PE) mean 29.4 ± 2.5	Group 1 (FGR): mean 994 ± 419 Group 2 (FGR+PE): 925 ± 308	4/ 73 = 5.5% (1 TOP and 3 IUFD)	69 / 73 = 94.5%	6/ 69 = 8.7%	63 / 73 = 86.3%
Kubo, 2017(18)	8	Median 37+0 (35+2 – 37+0)	Median 2157 (1553 – 2281)	0 / 8 = 0%	8 / 8 = 100%	0 / 8 = 0%	8 / 8 = 100%

	No of patients in final analysis	GA at delivery (wk + d) (mean ± SD or median (IQR))	Birthweight (g) (mean ± SD or median (IQR))	Antenatal death	Live born	Neonatal death	Survival at discharge
Lawin-O'Brien, 2016(19)	245 79 / 324 lost to FU	128 (52.2%) < 28+0 53(21.6%) 28+1 - 32+0 24 (9.8%) 32+1 - 36+0 36 (14.7%) >36+0	Survived: Median 1020 (range 435-3420) Neonatal death: median 560 (range 313-2550). Fetal death median 422 (range 155-2570). Feticide/TOP median 345 (range 220-512)	89 fetal death and 33 feticide/TOP = 122 / 245 = 49.8%	123 / 245 = 50.2%	22 / 123 = 17.9%	101 / 245 = 41.2%
Lees, 2015(20)	503 9 / 511 lost to FU	Mean 30+5 ± 16	Mean 1013 ± 321	12 / 503 = 2.4%	491 / 503 = 97.6%	27 / 490 = 5.5% (1 live-born lost to FU)	463 / 503 = 92.0%
Maged, 2018(21)	50	Group 1 (n = 25): Mean 35.3 ± 1.8 Group 2 (n = 25): Mean 34.8 ± 1.9	Group 1 (n = 25): Mean 2067 ± 352 Group 2 (n = 25): 1733 ± 361	4 / 50 = 8.0%	46 / 50 = 92.0%	4 / 46 = 8.7%	42 / 50 = 84.0%
Petersen, 2009(22)	33 patients, with 36 pregnan-cies	IUFD: Median 25 weeks (range 21-27). Live birth: Median 27 weeks (range 24-31)	IUFD: Median 308 (range 170-480) Live birth: Median 486 (320-553)	19 / 36 = 52.8%	17 / 36 = 47.2%	12 / 17 = 70.6%	5 / 36 = 13.9%
Rizzo, 2008(23)	31	Median 28.3 weeks (range 23.6-30.4)	Median 590 (range 312-915)	7 / 31 = 22.6%	24 / 31 = 77.4%	3 / 24 = 12.5%	21 / 31 = 67.7%
Savchev, 2014(24)	211	Mean 34.6 ± 8.0 weeks	Mean 1647 ± 765	9 / 211 = 4.3%	202 / 211 = 95.7%	6 / 202 = 3.0%	196 / 92.9%
Sharp, 2018(25)	135	Group 1 (n = 70): Median 28.1 (26.7 – 29.7) Group 2 (n = 65): Median 28.4 (27.3 – 30.1)	Group 1 (n = 70): Median 604 (496 – 766) Group 2 (n = 65): Median 590 (430 – 842)	43 / 135 = 31.9%	92 / 135 = 68.1%	17 / 92 = 18.5%	75 / 135 = 55.6%
Simonazzi, 2013(26)	16	Group 1 (n=4) median 34 wk (30-36) Group 2 (n=11) median 28 wk (24-30)	Group 1 (n=4) median 1598 (1100-1750) Group 2 (n=11) median 630 (408-951)	1 / 16 TOP = 6.25%	15 / 16 = 93.8%	3 / 15 = 20%	12 / 16 = 75.0%
Story, 2015(27)	20	Survived (n=12): median 32+0 (range 27+1 - 39+0) Neonatal death (n=2): 26 wk and 31+5. IUFD (n=6): median 26 (range 24+2 - 27+2)	Survived (n=12): median 980 (range 720 - 2090) Neonatal death (n=2): 620 and 1050 Fetal death (n=6): median 450 (range 424-530)	6 / 20 = 30%	14 / 20 = 70%	2 / 14 = 14.3%	12 / 20 = 60.0%

	Study design	Number of patients	Definition of FGR	Gestational age at diagnosis FGR (wk + d) (mean ± SD or median (IQR))	EFW at diagnosis FGR (g) (mean ± SD or median (IQR))	Preeclampsia or HELLP at diagnosis FGR
Sharp, 2018(25)	Randomised placebo controlled trial	135	AC or EFW < 10th percentile and absent or reversed EDF in the umbilical artery	Group 1 (n = 70): Median 25.1 (24.0 – 27.5) Group 2 (n = 65): Median 25.6 (24.1 – 27.4)	Group 1 (n = 70): Median 451 (352 – 613). Group 2 (n = 65): Median 436 (326 – 594)	24 / 135 = 17.8%
Simonazzi, 2013(26)	Retrospective cohort study	16	EFW and/or AC <5th centile	Median 22+3 (range 20+0 to 23+3)	Median 324 gram (range 248-509)	Not described
Story, 2015(27)	Retrospective cohort study	20	EFW <3rd centile	Median 21+4 (range 18+2 - 24+0)	Not described	Not described
Takahashi, 2014(28)	Prospective cohort study	18	< 1.5 SD Japanese standard	Median 23.0 (range 18-25)	Not described	0 / 18 = 0%
Temming, 2017(29)	Retrospective cohort study	355	EFW < 10th percentile using Warsof growth curves before 20+0 wk of gestation and Hadlock growth curves from 20+0 wk onward	Mean 19.5 ± 0.9	Not described	Not described
Von Dadelszen, 2011(30)	Case-control study	27	AC <5th percentile	Group 1 (n=17) median 21+1 (19+5 - 23+2) Group 2 (n=10) median 22+4 (21+1 - 23+4)	Not described	Not described
Yildirim, 2008(31)	Retrospective cohort study	300	EFW <10th percentile	Group 1 (n= 137) median 30.8 (CI 30.3-31.3) weeks Group 2 (n=163) 30.1 (CI 29.6-30.6) weeks	Not described	184 / 300 = 61.3%
Zhang-Rutledge, 2018(32)	Retrospective cohort study	254	EFW ≤ 10th percentile	Group 1 (n = 91): Average 21+5 Group 2 (n = 163): Average 21+3	Not described	Not described

FGR = fetal growth restriction; GA = gestational age; IQR = interquartile range; IUFD = intra-uterine fetal death; PE = preeclampsia; SD = standard deviation; TOP = termination of pregnancy

Table 3: Outcome data on long-term follow-up

	Number of surviving children assessed	Age at assessment	Definition of NDI	Neuro-developmental test used	Proportion of children with NDI
Aoki, 2014(10)	12 / 14 = 85.7%	Not described	"Handicapped" (not further explained)	Not described	3 / 12 = 25.0% of surviving children 3 / 17 = 17.6% of all pregnancies
Fujisaki, 2016(14)	11 / 11 = 100%	18 mo	"Mental retardation" was defined as developmental quotient of <70	Kyoto Scale of psychological Development 2001	3 / 11 = 27.3% of surviving children 3 / 14 = 21.4% of all pregnancies
Hasegawa, 2015(16)	23 / 23 = 100%	2 y (corrected)	Neurological complications were defined as cerebral palsy or mental retardation diagnosed by independent pediatric neurologists at corrected age of two years	Not described	5 / 23 = 21.7% of surviving children (1 cerebral palsy, 4 mental retardation) 5 / 26 = 19.2% of all pregnancies
Lees, 2013(33)	443 / 461 = 88%	2 y, corrected for prematurity	A cognitive Bayley III score or corrected Bayley II mental development index score of less than 85 or an estimated cognitive delay of more than 3 months, cerebral palsy, with a GMFCS of more than 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted)	Bayley III Scales of Infant and Toddler Development or corrected Bayley II	39 / 402 = 9.7% of surviving children (443 with known outcome, but 402 neurodevelopmental assessed) 39 / 502 = 7.8% of all pregnancies Cerebral palsy 6 / 402 = 1.5% of surviving children Cerebral palsy 6 / 502 = 1.2% of all pregnancies
Petersen, 2009(22)	5 / 5 = 100%	Two y of age (corrected)	Developmental delay was defined as > 1 SD below the mean	Griffiths Mental Developmental Scales	1 / 5 = 20.0% of surviving children 1 / 36 = 2.8% of all pregnancies
Simonazzi, 2013(26)	12 / 12 = 100%	Median 30 mo (24-58 mo)	Not described	Not described	0 / 12 = 0% Cerebral palsy 1 / 12 = 8.3% of surviving children Cerebral palsy 1 / 16 = 6.3% of all pregnancies
Takahashi, 2014(28)	11 / 11 = 100%	Between 2 and 13 y, median 6 y	Developmental quotient < 70	Kyoto scale of development and the Wechsler Intelligence Scale for Children III	0 / 11 = 0% Cerebral palsy 1 / 11 = 9.1% of surviving children Cerebral palsy 1 / 18 = 5.6% of all pregnancies

NDI = neurodevelopmental impairment; GMFCS = gross motor function classification system; SD = standard deviation

Table 4: Evidence table on mortality outcomes

№ of studies	Certainty assessment						Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals		
Antenatal death - RCT										
5	Randomised trials	serious[a]	serious [b]	not serious	not serious	none	74	888	⨁⨁◯◯ LOW	CRUCIAL
Antenatal death - Observational studies										
20	Observational studies	not serious	very serious [c]	serious	not serious	none	281	2007	⨁◯◯◯ VERY LOW	CRUCIAL
Neonatal death - RCT										
5	Randomised trials	serious[a]	serious [d]	not serious	not serious	none	68	813	⨁⨁◯◯ LOW	CRUCIAL
Neonatal death - Observational studies										
20	Observational studies	not serious	very serious [e]	serious [f]	not serious	none	123	1726	⨁◯◯◯ VERY LOW	CRUCIAL

FGR = fetal growth restriction; GA = gestational age; RCT = randomized controlled trial
a. Two out of five randomized controlled trials were rated as unknown risk of bias
b. Rate of antenatal death varies between 0% and 31.9%
c. Rate of antenatal death varies between 0% and 52.8%
d. Rate of neonatal death varies between 5.5 and 18.5%
e. Rate of neonatal death varies between 0% and 70.6%
f. Definitions of FGR and GA at inclusion differ

Table 5: Evidence table on neurodevelopmental outcomes

№ of studies	Certainty assessment						Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals		
Neurodevelopmental impairment at or before five years of age in long-term follow-up - RCT										
1	Randomised trials	not serious	not serious	not serious	not serious	none	39	402	⨁⨁⨁⨁ HIGH	CRUCIAL
Neurodevelopmental impairment at or before five years of age in long-term follow-up - Observational studies										
2	Observational studies	not serious	not serious	serious [a]	serious [b]	none	6	28	⨁⨁◯◯ LOW	CRUCIAL
Cerebral palsy at or before five years of age - RCT										
1	Randomised trials	not serious	not serious	not serious	not serious	none	6	402	⨁⨁⨁⨁ HIGH	IMPORTANT
Cerebral palsy at or before five years of age - Observational studies										
2	Observational studies	not serious	not serious	serious	serious [b]	none	1	28	⨁⨁◯◯ LOW	IMPORTANT

FGR = fetal growth restriction; GA = gestational age; RCT = randomized controlled trial
a. Definitions of FGR and GA at inclusion differ
b. Small sample size of one study (5 children)

Discussion

The aim of this systematic review was to collate evidence on the perinatal mortality, morbidity and long-term (neuro-)development of pregnancies complicated by early-onset FGR. Particularly in pregnancies with fetal compromise around the limits of viability, information on fetal and neonatal prognosis could offer a guide in decision-making for parents and obstetricians.

We found that antenatal mortality was about twice as high as neonatal mortality. Only a few studies reported on the number of children diagnosed with relevant neonatal morbidity, such as respiratory distress syndrome, bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn and retinopathy of prematurity. Also, a minority of the studies reported outcomes of long-term follow up. Moreover, neurodevelopmental assessments were performed on different ages and different neurodevelopmental measures were used.

The strength of this systematic review is the broad literature search and the strict inclusion criteria. We excluded studies that included all their patients before 2000, since the level of (neonatal) health care was essentially different in that period. Many studies that reported long-term follow up, did not include the antenatal and/or neonatal mortality of the sample studied(5, 34), which could create selection bias and may lead to numbers on healthy survival of early-onset severe FGR to be too optimistic. Therefore, we also predefined to exclude studies that used live birth or survival as starting criteria, since we consider it crucial to include data on all-type mortality to allow proper conclusions about prognosis from the obstetric perspective. Severity of brain damage is not only associated with FGR, but also with perinatal/neonatal management, and survival bias was therefore taken into account.

One weakness of this systematic review is the lack of consistency in the definition of FGR in the included studies. As is highlighted in Table 1, only the minority of the included studies report in detail the definition of FGR that was used. Studies basing the diagnosis of FGR only on growth parameters are especially at risk of having included small-for-gestational-age pregnancies as well, even though the risk of including small-for-gestational-age pregnancies without placental insufficiency is higher above 32 weeks of gestation compared with pregnancies below 32 weeks of gestation(35). In particular, the study of Fox et al(13) included a wide range of pregnancies based on the EFW < 25th centile. Due to the fact that these pregnancies were antenatally diagnosed as being complicated by FGR, despite the wide definition used to diagnose the FGR and the possible bias that this could cause, we decided to include the study in the systematic review. Exclusion of this study, led to an increase in the overall mortality from 18,9% to 20,4 %: in total, 351 pregnancies ended in antenatal death and 190 in neonatal death, out of 2643 pregnancies (mortalities of 13.2% and 7.2%, respectively).

The gestational age and EFW at diagnosis of FGR varied between the included studies and within some of the individual studies (with wide ranges or SD), possibly representing pregnancies with variable prognosis. The variety of definitions of FGR used and the range of gestational age and/or EFW of the included pregnancies are two of the reasons why the quality of evidence for most outcomes was rated very low, low or moderate, since the quality of evidence was downgraded due to serious indirectness(36) based on differences in study populations.

Another weakness is the lack of consistent information about hypertensive disorders of pregnancy as they share pathophysiology and often coincide. Interventions in the management of this syndrome may have caused bias in an unknown direction(37).

One large well-designed RCT(33) provides high quality of evidence on the mortality and morbidity outcomes and neurodevelopmental outcomes at 2 years of age(20). Limitations of this study are that it is a trial on patient management and some pregnancies were excluded because of fetal distress. However, the advantage of this RCT was the strict inclusion criteria of FGR and the relatively well-organized follow up with high attrition rate.

Currently, there are no specific evidence-based therapies for early-onset severe FGR. In the absence of therapeutic interventions, standard management consists of intensive maternal and fetal monitoring and counselling with timed delivery. Increased fetal surveillance is performed in the period of fetal viability, so that decisions around management and timing of delivery, usually by cesarean section, can be made(3). Informed choices depend on data on fetal and neonatal survival and morbidity. Because of the higher antenatal mortality, we hypothesize that changing thresholds for intervention to decrease antenatal mortality may result in increased postnatal mortality or increased rates of NDIs. The aim for joint obstetric and neonatal care is to improve overall survival without impairments.

Regarding the variability of prognostic profiles between patients, a systematic review of individual patient data would be useful, to be able to individualize prognostic counseling as much as possible. We excluded studies reporting on wider ranges of gestational age. This included 2 well-designed studies investigating long-term neurodevelopment(6, 38). In these studies, 10 out of 34 (29%) and 14 out of 149 (10%) children, respectively, had an abnormal IQ score, of which the latter percentage is in line with the findings of this systematic review. Together with the studies included in our analyses that reported on long-term neurodevelopment, it illustrates the need for more prospective studies starting at diagnosis of FGR and extending to early school age development of the surviving children.

Conclusion

In this systematic review based on 25 studies comprising 2895 pregnancies complicated by severe early-onset FGR, we found that the overall rates of antenatal and neonatal death was 12.3% and 6.6%, respectively. Of the 476 children included in the long-term follow-up, 12.2% of the survivors (7.9% of all pregnancies) were affected by NDI and/or cerebral palsy. Data on neurodevelopment were much less reported and mostly during toddler years, and not school age. Conclusions at an individual level are hampered by the differences in study quality and prognostic characteristics. A future analysis with individual patient data might further improve individual patient counseling. Longer follow up in prospective FGR cohorts is needed to provide data on the balance between mortality and NDI.

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Supplementary information

Table S1: Complete literature search

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to April 26, 2019
Search Strategy: 2019-04-27

#	Searches	Results
1	Fetal Growth Retardation/	15528
2	(IUGR* or FGR*).tw,kf.	7043
3	(grow* adj6 (retard* or restrict* or restrain* or poor or poorly or insuffic* or impair*)).tw,kf. and (exp pregnancy complications/ or (f?etus* or f?etal* or intra-uterine or intrauterine or in-utero or trimester* or pregnanc* or pregnant or gestat* or gravidit* or pre-nat* or prenat*).mp.)	25643
4	((extrem* or severe) adj3 ((small adj3 gestational age) or SGA or ((f?etal or f?etus*) adj2 compromis*) or ((preterm or pre-term* or prematur* or pre-matur* or immatur*) adj (f?etus* or f?etal*)))).tw,kf.	233
5	(vsga or (very adj2 ((small adj2 gestational age) or SGA or ((f?etal or f?etus*) adj2 compromis*) or ((preterm or pre-term* or prematur* or pre-matur* or immatur*) adj (f?etus* or f?etal*))))).tw,kf.	127
6	(AREDF.tw,kf. or ((end-diastolic or flow) adj2 velocity).mp.) and (Umbilical Arteries/ or Umbilical Veins/ or (DV or UA).tw. or (ductus venos* or (umbilical adj3 arter*)).tw,kf.) [DV or UA BFV]	2404
7	or/1-6 [FGR 1]	33593
8	((f?etal or f?etus*) adj2 compromis*).tw,kf.	1100
9	((preterm or pre-term* or prematur* or pre-matur* or immatur*) adj (f?etus* or f?etal*)).tw,kf.	978
10	Placental Insufficiency/	1588
11	(placent* adj3 (insufficien* or d*sfunct*)).tw,kf.	2896
12	or/8-11 [placental insufficiency, fetal compromise]	5698
13	Fetus/bs or Placental Insufficiency/dg or ((DV or ductus venos*) adj3 (flow or pulsatil*)).tw,kf. or ((ultrasonography, doppler/ or Ultrasonography, Doppler, Color/ or ultrasonography, prenatal/ or doppler.tw,kf.) and (Umbilical Arteries/ or blood flow velocity/ or (reverse flow or flow velocit* or pulsati* or PIV or umbilical arter* or ductus venosis or DV).tw,kf.))	30820
14	12 and 13 [FGR2 = PI, immature fetus as assesed by US/doppler]	677
15	7 or 14 [FGR 1-2]	33770
16	Fetal Growth Retardation/mo or Delivery, Obstetric/mo or Infant, Premature, Diseases/mo	1915
17	fetal mortality/ or perinatal mortality/	2368
18	exp fetal death/ or perinatal death/	29560
19	Live Birth/	3132
20	((surviv* or death* or mortalit*) adj6 (f?etal* or f?etus* or prenatal* or pre-natal* or antenatal* or ante-natal* or perinat* or peri-nat* or uterine or intrauterin* or pregnan*)).tw,kf.	44681
21	(stillbirth* or still-birth*).tw,kf.	11696
22	((preterm or pre-term) adj3 (surviv* or mortal* or viabilit* or death*)).tw,kf.	2266
23	(live birth* or live preterm birth*).tw,kf.	22118
24	((f?etal* or f?etus* or prenatal* or pre-natal* or antenatal* or ante-natal* or perinat* or peri-nat* or uterine or intrauterine) adj3 outcome*).tw,kf.	18301
25	or/16-24 [PERINATAL mortality]	102298
26	((neurodevelop* or neuro-develop* or neurocognit* or neuro-cognit* or ((motor or mental or cognitiv* or brain) adj2 develop*) or ((developmental or cognitiv*) adj2 (outcome* or index)) or cerebral palsy) and ((((umbilical adj2 arter*) or ductus venosus or DV or UA) and (doppler or veloci* or blood flow or pulsatility)) or end-diastolic flow or AREDF) and (newborn* or new* born* or neonat* or neo-nat* or postnat* or post-nat* or infant* or infancy or toddler* or graders or child or children or childhood or schoolchild* or school age* or schoolage* or puber* or juvenil* or youth or adolescence or adulthood or young adult* or adult life)).mp. [neurodevelopment in infants with demonstrated IUGR]	106

27	25 or 26 [PERINATAL MORTALITY OR neurodevelopment in infants with demonstrated IUGR]	102360
28	15 and 27 [FGR & PERINATAL mortality]	7431
29	(exp animals/ or (goat* or sheep or ovine or pig or pigs or monkey* or rabbit*).ti.) not humans/	4589652
30	28 not 29 [human studies on FGR and perinatal mortality]	6720
31	limit 30 to yr="2000 -Current" [human studies on FGR and perinatal mortality > 2000]	4570
32	meta-analysis/ or (meta analy* or metaanaly* or meta?analy*).tw,kf. or ((systematic* adj3 (review or literature or evidence or search*)) or ((summari* or review) adj3 evidence) or (search* adj12 (literature* or ((electronic or medical or biomedical) adj3 database*) or exhaustive)) or medline or pubmed or embase or (CENTRAL and cochrane) or "Central Register of Controlled Trials").tw. or (cochrane or clinical evidence or EBM).jw. [SR-Filter]	376132
33	31 and 32 [sec studies on FGR & PERINATAL mortality]	334
34	remove duplicates from 33 [sec studies on FGR & PERINATAL mortality >2000 -deduplicated]	323
35	(Controlled Clinical Trial/ or Randomized Controlled Trial/ or Multicenter Study/ or Observational Study/ or comparative study/ or exp cohort studies/ or case-control studies/ or registries/ or exp databases, factual/ or datasets as topic/ or exp population surveillance/ or regression analysis/ or linear models/ or logistic models/ or "Predictive Value of Tests"/ or (cohort* or case-control* or retrospective* or prospectiv* or longitudinal* or observational or epidemiologic* or descriptive or follow-up or population-based or hospital-based or consecutive or (cumulative adj3 (incidenc* or probabil*)) or registry* or registries or ((register or registers) not (Cochrane adj3 register*)) or nationwide or nation-wide or community-wide or real-life or real-world or ((national or international) adj3 (data or databas*)) or long-term trend* or (contempor* adj3 (setting* or rate* or mortalit* or surviv* or pattern* or "use" or practice* or populat* or data)) or regression or logistic or univariate or multivariate or trial or randomi*ed or randomly allocat* or double blind*).tw,kw. or (groups or subgroup*).ab. or (trends.ti. not (review/ or review.jw,ti.)) or predict*.ti.) not ((expert or current or cochrane or clinical evidence or EBM).jw. or editorial/ or books/ or (systematic* adj3 (review or literature)).ti. or ((search* adj12 (literature* or ((electronic or medical or biomedical) adj3 database*) or exhaustive or systematic)) or medline or pubmed or embase or psychinfo or (CENTRAL and cochrane) or "Central Register of Controlled Trials").tw. or (conferenc* or congress*).hw. or Case Reports/ or ((review/ or letter/ or comment/ or meta-analysis/ or (meta analy* or metaanaly* or meta?analy*).ti,ot,kf. or (systematic* adj3 (review or literature or search*)).tw,kf.) not (Controlled Clinical Trial/ or Randomized Controlled Trial/ or Multicenter Study/ or Observational Study/ or comparative study/ or exp cohort studies/ or case-control studies/ or Databases, Factual/ or medical record*.hw.)))	6667460
36	**31 and 35 [human primary studies on FGR & PERINATAL mortality >2000]**	**2603**
37	**remove duplicates from 36 [human primary studies on FGR & PERINATAL mortality >2000 - deduplicated]**	**2602**

Table S2A: Risk of bias of included randomized controlled trials

	Allocation concealment/ mode of randomisation	Blinding	Loss to follow up	Selective outcome reporting bias	Other limitations
Ali, 2017(8)	Low	Unknown	Unknown	Unknown	Unknown
Ali, 2018(9)	Low	Unknown	Unknown	Unknown	Unknown
Groom, 2019(15)	Low	Low	Low	Low	Low
Lees, 2015(20)	Low	Unknown	Low (primary analysis) / Unknown (long term follow-up)	Low	Low
Sharp, 2018(25)	Low	Low	Low	Low	Low

Table S2B: Risk of bias of included observational studies

	Development and application of appropriate eligibility criteria	Flawed measurement of both exposure and outcome	Confounding	Incomplete follow up	Other limitations
Aoki, 2014(10)	High	Low	Low	Low	Unknown
Baschat, 2001(11)	Low	Low	Low	Low	Low
Belghiti, 2011(12)	High	Low	Low	Low	Low
Fox, 2008(13)	Low	Low	Low	Unknown	Low
Fujisaki, 2016(14)	Low	Low	Low	Low	Unknown
Hasegawa, 2015(16)	Low	Unknown	Low	Low	High
Herraiz, 2017(17)	Low	Low	Unknown	Low	Low
Kubo, 2017(18)	High	High	Low	Low	High
Lawin-O'Brien, 2016(19)	Low	Unknown	Low	Unknown	Low
Maged, 2018(21)	Low	Low	Unknown	Low	Unknown
Petersen, 2009(22)	Low	Low	Low	Low	Low
Rizzo, 2008(23)	Low	Low	Low	Low	Unknown
Savchev, 2014(24)	Low	Low	Low	Low	Low
Simonazzi, 2013(26)	Low	Unknown	Low	Low	Low
Story, 2015(27)	Low	Low	Low	Low	Low
Takahashi, 2014(28)	Unknown	Low	Low	Low	Unknown
Temming, 2017(29)	Unknown	Low	Low	Low	Low
Von Dadelszen, 2011(30)	Low	Unknown	Low	Low	Low
Yildirim, 2008(31)	Low	Low	High	Unknown	Unknown
Zhang-Rutledge, 2018(32)	Unknown	Low	Low	Low	Unknown

Table S3: Outcome data on neonatal morbidity

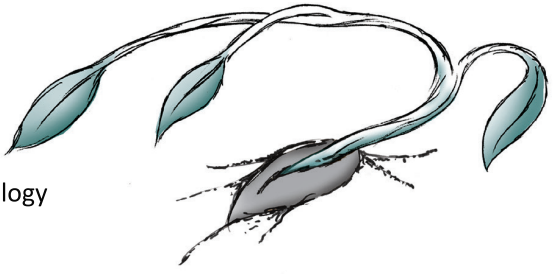
	RDS	BPD	IVH	NEC	PPHN	ROP	Sepsis
Aoki, 2014(10)	14 / 16 = 87.5%*	14 / 16 = 87.5%*	0 / 16 = 0%	0 / 16 = 0%	Not described	Not described	Not described
Groom, 2019(15)	Not described	20 / 103 = 19.4%	0 / 103 = 0% (Grade 3 or 4)	1 / 103 = 1.0% (NEC requiring surgery)	2 / 103 = 1.9%	2 / 103 = 1.9% (ROP ≥ Grade 3 requiring treatment)	Not described
Hasegawa, 2015(16)	9 / 25 = 36.0%	Not described	2 / 25 = 8%	0 / 25 = 0%	Not described	Not described	Not described
Herraiz, 2017(17)	Not described	4 / 63 = 6.3%	0 / 63 = 0%	6 / 63 = 9.5%	Not described	12 / 63 = 19.0%	27 / 63 = 42.9%
Lees, 2013(33)	Not described	49 / 490 = 10.0% (> 36 weeks)	12 / 490 = 2.4% (GMH Grade 3 or 4)	16 / 490 = 3.3% (Pneumatosis and perforation combined)	Not described	Not described	Total: 154 / 490 =31.4% Proven 87 / 490 = 18% Clinical suspected: 67 / 490 = 14%
Petersen, 2009(22)	Not described	Not described	3 / 14 = 21.4%	2 / 14 = 14.3%	Not described	4 / 14 = 28.6%	8 / 14 = 64.3%
Rizzo, 2008(23)	Not described	Not described	6 / 24 = 25.0% (grade 3 or 4)	Not described	Not described	Not described	Not described
Sharp, 2018(25)	Not described	Not described	21 / 72 = 29.2%	20 / 92 = 21.7%	Not described	16 / 92 = 17.4%	Not described
Simonazzi, 2013(26)	Composite severe neonatal morbidity (at least one of the following: BPD, NEC, PVL, IVH grade >2, ROP): 6 / 15 = 40%						
Takahasihi, 2014(28)	Not described	Not described	Not described	Not described	1 / 11 = 9.1% (of surviving children)	Not described	Not described
Temming, 2017(29)	Not described	Not described	1 / 346 (0.3%)	5 / 346 (1.4%)	Not described	Not described	Not described
Yildirim, 2008(31)	81 / 242 = 33.5%	9 / 242 = 3.7%	15 / 242 = 6.2%	28 / 242 = 11.6%	Not described	Not described	60 / 242 = 24.8%

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotising enterocolitis; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity
** Composite neonatal morbidity described as at least one of the following: RDS, chronic lung disease (CLD)*

Chapter 4

Neurodevelopmental outcomes at five years after early-onset fetal growth restriction: analyses in a Dutch subgroup participating in a European management trial

A Pels
OC Knaven
BJ Wijnberg-Williams
MJC Eijsermans
SM Mulder-de Tollenaer
CSH Aarnoudse-Moens
C Koopman-Esseboom
J van Eyck
JB Derks
W Ganzevoort
AG van Wassenaer-Leemhuis



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2019 Mar; 234: 63-70

Abstract

Objective:
The objective of this study is to explore developmental outcomes at five years after early-onset fetal growth restriction (FGR).

Study design:
Retrospective data analysis of prospective follow-up of patients of three Dutch centres, who participated in a twenty centre European randomized controlled trial on timing of delivery in early-onset FGR. Developmental outcome of very preterm infants born after extreme FGR is assessed at (corrected) age of five.

Results:
Seventy-four very preterm FGR children underwent follow-up at the age of five. Mean gestational age at birth was 30 weeks and birth weight was 910 g, 7% had a Bayley score <85 at two years. Median five years' FSIQ was 97, 16% had a FSIQ <85, and 35% had one or more IQ scores <85. Motor score ≤ 7 on movement ABC-II (M-ABC-II-NL) was seen in 38%. Absent or reversed end-diastolic flow, gestational age at delivery, birthweight and neonatal morbidity were related to an FSIQ < 85. Any abnormal IQ scale score was related to birthweight, male sex and severity of FGR, and abnormal motor score to male sex and bronchopulmonary dysplasia (BPD).

Conclusions:
Overall, median cognitive outcome at five years was within normal range, but 35% of the children had any abnormal IQ score at age five, depending on the IQ measure, and motor impairment was seen in 38% of the children. GA at delivery, birthweight, EDF prior to delivery and neonatal morbidity were the most important risk factors for cognitive outcomes.

Introduction

In fetal growth restriction (FGR) the fetus does not reach its genetic growth potential. Utero-placental insufficiency is the most common cause with possibly critical consequences for both mother and fetus(1). In early-onset placental insufficiency abnormal Doppler measurements and an asymmetrical growth are seen. A variety of definitions is found in literature, varying between an antenatal diagnosis reflecting the placental dysfunction and a postnatal diagnosis based on birthweight(2-5). The latter probably includes the fetus who is small-for-gestational-age (SGA) rather than the fetus with FGR and is less likely to identify the fetuses at risk of adverse outcomes.

Early-onset FGR, defined as below 32 weeks of gestation, is associated with an increased risk of neonatal morbidity and mortality(6-9). Of all pregnancies complicated by FGR, roughly 5-10% result in stillbirth or neonatal death(10). Delivery is indicated when signs of deteriorating of the fetal condition are noticed and the fetal condition is shortly expected to be compromised.

The Trial of Randomized Umbilical and Fetal FLow in Europe (TRUFFLE) study investigated three different monitoring and management strategies in patients with early-onset FGR. Survival without impairment in these three groups was 77-85% at two years of age. In the surviving infants of the group in which timing of delivery was based on late ductus venosus changes there was a significant reduction in neurodevelopmental impairment at the age of two years (11).

Unfortunately, cognitive and motor outcome of preterm children at two years has a low sensitivity in predicting cognitive deficit at later school age(12, 13). Formal follow-up at early school age was not part of the study protocol in the TRUFFLE study. However, in some NICU follow-up clinics in the Netherlands, children were invited for neonatal follow-up at five years of age according to a national guideline. This enabled us to evaluate these outcomes in Dutch TRUFFLE children.

The present analysis aims to investigate the neurodevelopmental outcome data of this cohort of very preterm early-onset growth restricted children at five years of age and compare them with the two years neurodevelopmental outcome data.

Material and methods

The design of the TRUFFLE study has been previously described(9, 11, 14). The original TRUFFLE study was a prospective, multicenter, unblinded management trial in twenty European tertiary-care centres. Patients included were women over 18 years of age with a singleton pregnancy at 26-32 weeks of gestation, diagnosed with FGR based on a fetal abdominal circumference <10th percentile, an umbilical artery Doppler PI >95th percentile and an estimated fetal weight (EFW) of >500 grams. Study participants were randomly allocated to three study groups in which timing of delivery was determined on different criteria (short term variation on cardiotocography, ductus venosus pulsatility index or late ductus venosus changes). Additionally, delivery could be decided when safety-net criteria required it. All parents consented to take part in the developmental follow-up as part of the TRUFFLE study and according to the local neonatal follow-up program that was considered standard care. The trial was conducted according to the principles of the Declaration of Helsinki Medical(15), Dutch legislation regarding medical research involving human subjects(16, 17) and Good Clinical Practice Guidelines (GCP)(18).

The population of this analysis comprised all surviving children of the original TRUFFLE cohort born in one of three Dutch clinics (AMC, Amsterdam; Isala, Zwolle; and UMC Utrecht). The TRUFFLE study investigated the neurodevelopmental outcomes of children in all participating countries and centres at two years of age(11). Children and their parents were contacted for a follow-up appointment at five years of age as part of standard follow-up in three centres in The Netherlands, based on criteria of gestational age and birthweight or pragmatic reasons. In AMC Amsterdam, children were invited for follow-up if they had a birthweight below 1000 g or a GA at delivery below 30 weeks. Isala Zwolle invited children with a birthweight below 1500 g or a GA at delivery below 32 weeks. In UMC Utrecht the criteria for invitation for follow-up was a GA at delivery below 28 weeks.

Baseline characteristics

Perinatal data were already reported in the original TRUFFLE study(9). Severe neonatal morbidity was defined as presence of at least one of the following: bronchopulmonary dysplasia (BPD), defined as the need for supporting oxygen at 36 weeks of postmenstrual age(19-24), severe intraventricular haemorrhage (defined as grade III or IV)(25), cystic periventricular leukomalacia, culture-proven neonatal sepsis, necrotizing enterocolitis (Bell's ≥ stage 2)(26). Birthweight ratio (BWR) was measured following Gardosi et al.(27) and defined as the ratio of birthweight to the 50th percentile weight, adjusted for maternal ethnicity, weight, length and infant sex. A BWR of 0.86 is comparable to the 10th percentile and a BWR of 0.68 to the 2.3rd percentile on a birthweight curve(27).

To investigate the influence of the parental education level on neurodevelopmental outcome, the highest completed education of mother was rated. Educational level was rated "low" when the highest completed level of education was primary school or low level secondary school ('VMBO'). Parents who graduated from middle or high level secondary school ('HAVO' or 'VWO') or low or middle level vocational education ('MBO') were

rated “middle level of education”. Parents were rated “high level of education” when they graduated from high level vocational education (‘HBO’) or university.

Neurodevelopmental assessment and outcomes

A trained psychologist and a paediatrician or pediatric physical therapist assessed the children attending the outpatient clinic. Cognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence-III-NL (WPPSI™-III-NL)(28, 29). Outcome was reported as quotient and composite score, with a mean of 100 and a standard deviation of 15. Full Scale IQ (FSIQ) was reported as well as scores on IQ scales: verbal IQ (VIQ), performance IQ (PIQ), processing speed quotient (PSQ) and general language index (ATI). A score lower than 85 (<1 SD) was considered to be abnormal. All scores were based on the age corrected for prematurity.

To establish cerebral palsy (CP), patients underwent a neurological examination. CP was classified using Surveillance of Cerebral Palsy in Europe (SCPE)(30). Severity of CP was scored using the Gross Motor Function Classification System (GMFCS)(31).

Neurodevelopmental impairment (NDI) was defined as a WPPSI-III FSIQ-score <85, CP with a GMFCS ≥1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind).

Motor impairment was assessed using the Movement Assessment Battery for Children-II-NL (M-ABC-II-NL)(32). Outcome was reported as the overall motor score and scores on the three subscales: manual dexterity, ball skills and balance skills. A total score ≤ seven points was considered to be abnormal. The total motor score of six children that underwent M-ABC-I were converted to the M-ABC-II-NL. For these six children the total, but not the subscales m-ABC-I score was converted to the second version.

Behavioural and emotional problems were assessed using the Child Behavior Checklist (CBCL)(33). A total CBCL score was considered to be borderline clinical (= mildly abnormal) in the range of 60-63 and clinical (=abnormal) when > 63 points(33).

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23. Baseline characteristics of our study group were compared to the patient population not seen at the age of five years, to detect the possibility of selection bias. Depending on the sample size, chi-square’s test or fisher’s test were used to compare frequencies of nominal variables. To compare numerical data, an unpaired t-test (in normally distributed data) or Mann-Whitney U test (in non-normally distributed data) was used.

Ethical approval

Multicentre Research Ethics Committee approved the TRUFFLE trial in September 2005 (ref: 05/Q0803/152).

Results

A total of 503 women were included in the original trial. Of these women, the three participating clinics conducting the five year follow-up, together contributed a total of 191 women (Figure 1). Ninety-nine children met the above described respective selection criteria based on which patients were invited to participate in the five year follow-up consult. Eleven children were seen at five years of age because of their participation in the two years' follow-up in TRUFFLE but without fulfilling the strict inclusion criteria for five years follow-up, following the Dutch follow-up guideline, were included as well. Our final study population consisted of 74 children.

Maternal, perinatal and environmental characteristics of children assessed during follow-up are presented in Table 1. When comparing the maternal and perinatal characteristics of the children assessed in the current follow-up study to the characteristics of the 503 infants of the original TRUFFLE cohort (11), in this cohort more women were hypertensive (82% versus 72%) and had more often preeclampsia or HELLP (62% versus 50%). The children had a slightly lower GA at delivery (29.7 versus 30.7 weeks) and a lower birthweight (910 versus 1019 gram) and slightly more severe neonatal morbidity (31% versus 25%).

Characteristics of children assessed during follow-up at the age of five years were compared to characteristics of children in the participating centres not assessed at follow-up (Table 1). In line with the applied follow-up criteria, children assessed at five years had a statistically significant lower birthweight and lower GA at birth than the children who were not assessed at the age of five. Also the assessed patient group showed a shorter interval between randomisation and delivery. Bronchopulmonary dysplasia (BPD) was more often present in this group than among the children that were not evaluated at five years of age. Of the patients evaluated at five year, five out of 74 (6,8%) had a Bayley score below 85 (and thus NDI) compared with 11 out of 89 (12.4%) in the group seen at age two but not seen at age five (p= 0.23).

The mean Bayley score at two years of age of the 74 included patients was 99.4 ±12.1 and of the 36 patients with five years' follow up indication but who were lost to follow-up, 93.3 (±15.7, p = 0.047). Perinatal outcomes did not differ between children seen and those lost to follow-up.

Figure 1: Flowchart patients TRUFFLE study

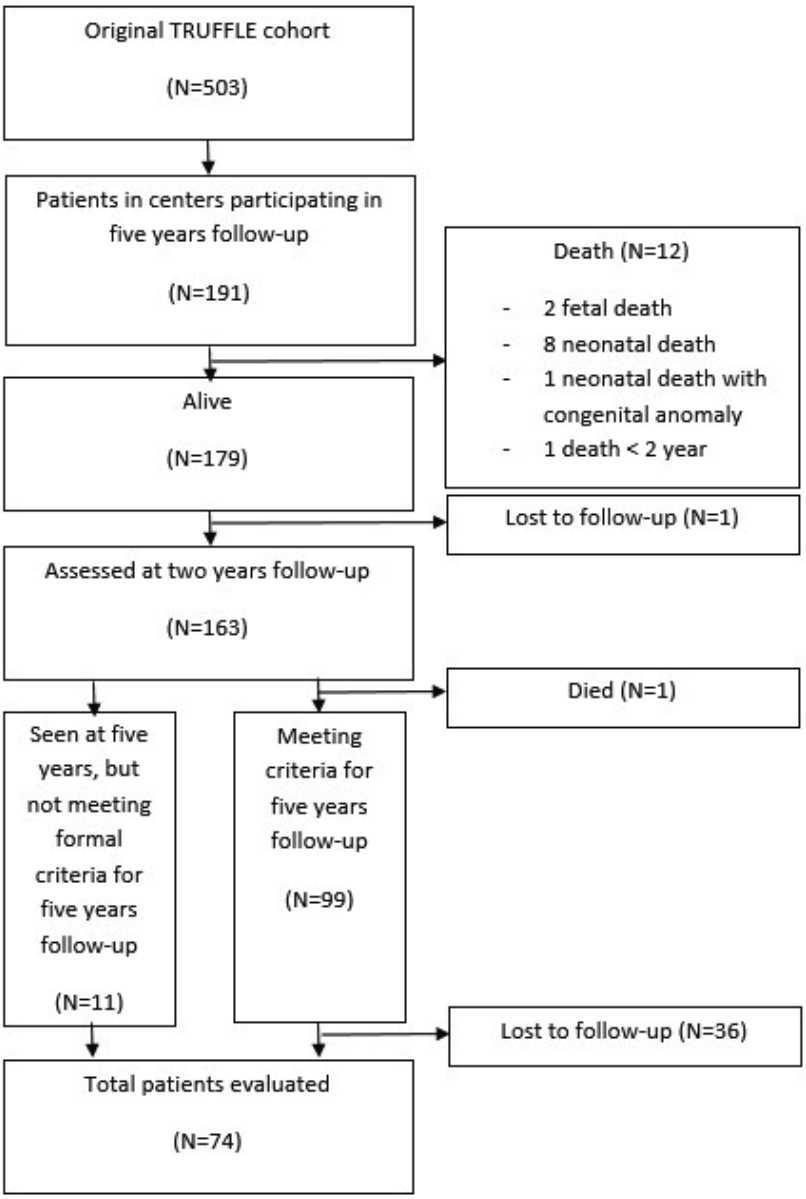

Table 1: Comparison of perinatal, maternal and neonatal characteristics of surviving TRUFFLE children in the three Dutch centers between those assessed and not assessed at age five

Variables	Children assessed at five year follow up (n=74)	Children alive and not assessed (n=105)	P-value (95% CI)
Maternal age, mean ± SD in years	29.4 ± 5.1	30.3 ± 5.9	0.300 (-0.787-2.537)
BMI, median (IQR)	23.5 (21.4-27.5)	24.2 (21.3-28.4)	0.612
Caucasian ethnicity, n (%)	58 (78.4%)	85 (81.0%)	0.672
Nulliparous, n (%)	44 (59.5%)	72 (68.6%)	0.209
Smoking during pregnancy, n (%)	10 (13.5%)	22 (21.0%)	0.201
Gestational hypertensive morbidity, n (%)	61 (82.4%)	86 (81.9%)	0.928
PE/HELLP, n (%)	46 (62.2%)	64 (61.0%)	0.870
Allocation group			0.509
CTG STV, n (%)	26 (35.1%)	33 (31.4%)	
DV p95, n (%)	20 (27.0%)	37 (35.2%)	
DV no A, n (%)	28 (37.8%)	35 (33.3%)	
Antihypertensive medication, n (%)	48 (64.9%)	67 (63.8%)	0.885
Magnesium treatment, n (%)	15 (20.3%)	22 (21.0%)	0.912
Antenatal corticosteroid, n (%)			0.055
0 courses	1 (1.4%)	0 (0%)	
1 course	70 (94.6%)	105 (100%)	
2 courses	3 (4.1%)	0 (0%)	
End diastolic flow prior to delivery			0.338
Positive	32 (43.2%)	50 (47.6%)	
Absent	36 (48.6%)	41 (39.0%)	
Reversed	6 (8.1%)	14 (13.3%)	
Interval to delivery, median (IQR) in days	4.5 (2.2-8.5)	6.9 (2.7-17.2)	0.017 *
Gestational age at delivery, mean ± SD (weeks)	29.7 ± 1.5	31.2 ± 2.0	<0.001 * (0.92-2.0)
Birthweight, mean ± SD (grams)	910 ± 194	1097 ± 280	<0.001 * (118-258)
Birthweight P50 ratio, mean ± SD	59.9 ± 9.4	60.5 ± 9.3	0.719 (-2.289-3.313)
Male sex, n (%)	34 (45.9%)	56 (53.3%)	0.330

Variables	Children assessed at five year follow up (n=74)	Children alive and not assessed (n=105)	P-value (95% CI)
Apgar score < 7 at 5 min, n (%)	4 (5.4%)	6 (5.7%)	1.000
Umbilical artery pH	n = 61	n = 90	
Median (IQR)	7.26 (7.2-7.29)	7.26 (7.21-7.30)	0.714
<7.0, n (%)	2 (3.3%)	1 (1.1%)	0.566
Severe neonatal morbidity, n (%)	23 (31.1%)	27 (25.7%)	0.431
NEC, n (%)	2 (2.7%)	2 (1.9%)	1.000
GMH ≥ grade III, n (%)	3 (4.1%)	2 (1.9%)	0.650
BPD > 36 weeks, n (%)	13 (17.6%)	6 (5.7%)	0.011 *
Proven sepsis, n (%)	9 (12.2%)	21 (20.0%)	0.167
PVL ≥ grade II, n (%)	0 (0%)	2 (1.9%)	0.512
NDI at 2 years of age[a]	5 / 74 (6.8%)	11 / 89 (12.4%)	0.231
Abnormal Bayley at 2 years of age[b], n (%)	5 / 74 (6.8%)	11 / 89 (12.4%)	0.231

SD = standard deviation; IQR = inter quartile range; CI = confidence interval; BMI = Body mass index; PE = preeclampsia; HELLP = hemolysis elevated liver enzymes low platelets; CTG = cardiotocography; STV = short term variation; DV = ductus venosus; NEC = necrotizing enterocolitis; GMH = germinal matrix cerebral haemorrhage; BPD = bronchopulmonary dysplasia; PVL = periventricular leukomalacia; NDI = neuro-developmental impairment

[a] NDI: defined as a bayley score <85, CP with a GMFCS ≥1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind)

[b] Bayley III score or corrected Bayley II mental development index score of less than 85 or an estimated cognitive delay of more than three months, cerebral palsy, with a GMFCS of more than 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted)

Table 2 presents the scores on the neurodevelopmental tests. Neurodevelopmental impairment (NDI) occurred in 11 of 73 patients (15.1%), all of whom had an FSIQ <85. Of one patient FSIQ could not be calculated, due to missing PSIQ. One or more IQ scale score <85 occurred in 26 of 74 patients (35.1%).

Motor outcomes are presented in Table 2. An abnormal M-ABC-II-NL (≤ 7) was found in 27 of 71 patients that completed the M-ABC-II-NL or M-ABC-I (38.0%). Male sex and BPD were significantly associated with abnormal M-ABC-II-NL (p=0.01) (Table 3C). On the behavioural test five (8.6%) children scored in the clinical (=abnormal) range.

Table 2: Neurodevelopmental outcome at five years of age corrected for prematurity

Developmental domain	Value N=74
Age at follow-up in months	
Calendar, median (IQR)	62 (61-65)
Corrected, median (IQR)	60 (59-62)
WPPSI-III score, median (IQR)[a]	
FSIQ	97.0 (91.0 – 107.0)
VIQ	101.0 (91.0 – 108.5)
PIQ	97.0 (88.8 – 107.0)
PSQ	94.0 (79.0 – 103.0)
WPPSI-III score < 85, n (%)[b]	
FSIQ	11 (15.1%)
VIQ	9 (12.2%)
PIQ	9 (12.2%)
PSQ	20 (27.4%)
All IQ scores normal, n (%)	48 (64.9%)
Cerebral palsy, n (%)	2 (2.7%)
Mild vision problems, n (%)	5 (6.8%)
Mild hearing problems, n (%)	1 (1.4%)
Motor development: M-ABC-II-NL n=71[c]	
Total score; median (IQR)	8.0 (6.0 – 10.0)
Manual dexterity; median (IQR)	8.0 (6.0 – 9.0)
Ball skills; median (IQR)	9.0 (6.0 – 10.0)
Balance skills; median (IQR)	9.0 (6.0 – 10.0)
Number of children with motor score ≤7[d], n (%)	27 (38.0%)
Behavior (CBCL)[e] n=58	
Total score, median (IQR)	43.0 (40.0 – 53.0)
Borderline n (%)	1 (1.7%)
Clinical score n (%)	5 (8.6%)
FSIQ<85 or M-ABC-II-NL ≤7 (or M-ABC-I < 16th percentile) or CBCL>60 or CP, n=64	34 (53.1%)

SD = standard deviation; IQR = inter quartile range; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; FSIQ = full scale intelligence quotient; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; PSQ = processing speed quotient; IQ = intelligence quotient; M-ABC-II-NL = movement assessment battery for children; CBCL = child behavior checklist; CP = cerebral palsy, defined as GMFCS ≥ 1

[a] *At age corrected for prematurity*

[b] *Of one child the PSQ (and therefore the FSIQ could not be calculated*

[c] *Six children underwent M-ABC I, for those only the total motor score is reported*

[d] *M-ABC-II-NL score ≤7 = impaired, ≥8 = normal*

[e] *CBCL score total score: 60-63 = borderline (mildly impaired), > 63 = clinical (severely impaired)*

Table 3A presents variables associated with FSIQ <85. FSIQ <85 was associated with a lower GA at delivery, a lower birthweight, absent or reversed end-diastolic flow prior to delivery and severe neonatal morbidity.

Table 3A: Analysis of factors associated with FSIQ < 85

Associated variable, n (%), mean ± SD or median (IQR)	FSIQ ≥ 85 (n = 62)	FSIQ < 85 (n = 11)	P-value
Maternal age in years	30.0 (26-33)	25.0 (24-32)	0.157
Nulliparous	35 (56.5%)	9 (81.8%)	0.182
Maternal smoking	9 (14.5%)	1 (9.1%)	>0.999
Preeclampsia/ HELLP	36 (58.1%)	9 (81.8%)	0.135
Antenatal corticosteroid treatment	61 (98.4%)	11 (100%)	>0.999
Allocation group			0.466
CTG STV	23 (37.1%)	2 (18.2%)	
DV p95	16 (25.8%)	4 (36.4%)	
DV no A	23 (37.1%)	5 (45.5%)	
End diastolic flow prior to delivery			0.020*
Positive	30 (48.4%)	2 (18.2%)	
Absent	29 (46.8%)	6 (54.5%)	
Reversed	3 (4.8%)	3 (27.3%)	
GA at delivery in weeks	29.6 (28.8-30.9)	28.9 (28.3-29.3)	0.024*
Birthweight in grams	915 (794-1043)	800 (660-920)	0.029*
Birthweight P50 ratio	58.9 (54.5-66.4)	59.3 (55.7-62.5)	0.677
Sex			0.057
Boys	25 (40.3%)	8 (72.7%)	
Girls	37 (59.7%)	3 (27.3%)	
Severe neonatal morbidity	15 (24.2%)	7 (63.6%)	0.014*
BPD	8 (12.9%)	5 (45.5%)	0.009*
NDI at 2 years of age	4 (6.5%)	0 (0%)	>0.999
Low maternal education	13 (22%)	2 (20%)	>0.999

FSIQ = full scale intelligence quotient; SD = standard deviation; IQR = interquartile range; BPD = Bronchopulmonary dysplasia; NDI = neurodevelopmental impairment = WPPSI FSIQ score <85, CP with a GMFCS ≥1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind); CTG = cardiotocography; STV = short term variation; DV = ductus venosus; GA = gestational age
**p<0.05*

Table 3B presents variables associated with any IQ scale <85. Birthweight, male sex, and birthweight ratio were associated with any IQ scale <85. A trend towards absent or reversed end-diastolic flow prior to delivery was seen. Maternal education was not associated with IQ outcomes.

Table 3B: Analysis of factors associated with any IQ scale < 85 (FSIQ, VIQ, PIQ or PSIQ)

Associated variable, n (%), mean ± SD or median (IQR)	Normal (n = 48)	Any IQ scale score <85 (n = 26)	P-value
Maternal age	30 (26-33)	27 (24-30.3)	0.059
Nulliparous	27 (56.3%)	17 (65.4%)	0.445
Maternal smoking	6 (12.5%)	4 (15.4%)	0.734
Preeclampsia/ HELLP	30 (62.5%)	18 (37.5%)	0.900
Antenatal corticosteroid treatment	47 (97.9%)	26 (100%)	>0.999
Allocation group			0.429
CTG STV	18 (37.5%)	8 (30.8%)	
DV p95	12 (25.0%)	8 (30.8%)	
DV no A	18 (37.5%)	10 (38.5%)	
End diastolic flow prior to delivery[a]			0.052
Positive	24 (50.0%)	8 (32.0%)	
Absent	23 (47.9%)	13 (52.0%)	
Reversed	1 (2.1%)	4 (16.0%)	
GA at delivery	29.5 (28.8-30.5)	29.2 (28.7-31.3)	0.973
Birthweight	930 (781-1050)	850 (735-928)	0.042*
Birthweight P50 ratio	62.3 (56.6-67.4)	56.6 (48.5-61.4)	0.003#
Sex			0.048*
Boys	18 (37.5%)	16 (61.5%)	
Girls	30 (62.5%)	10 (38.5%)	
Severe neonatal morbidity	13 (27.1%)	10 (38.5%)	0.313
BPD	7 (14.6%)	6 / 25 (24%)	0.318
NDI at 2 years of age	2 (4.2%)	3 (11.5%)	0.337
Low maternal education	10 (21.7%)	6 (25.0%)	0.758

IQ = intelligence quotient; SD = standard deviation; IQR = interquartile range; NDI = neurodevelopmental impairment = a WPPSI-III score <85, CP with a GMFCS ≥1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind); CTG = cardiotocography; STV = short term variation; DV = ductus venosus; GA = gestational age

Severe neonatal morbidity: NEC ≥ grade II, GMH ≥ grade III, BPD ≥ 36 weeks, proven sepsis or PVL ≥ grade II.

**p<0.05*

 # p<0.01

[a] *Of one patient the last EDF before delivery is missing*

Table 3C: Analysis of factors associated with a total M-ABC-II-NL ≤ 7 or M-ABC-I below 16th percentile

Associated variable, n (%), mean ± SD or median (IQR)	Normal (n = 44)	Abnormal (n = 27)	P-value
Maternal age	30 (26.5-33.5)	28 (25-31)	0.098
Nulliparous	27 (61.4%)	14 (51.9%)	0.555
Maternal smoking	6 (13.6%)	4 (14.8%)	0.692
Preeclampsia/ HELLP	31 (70.5%)	13 (29.5%)	0.114
Antenatal corticosteroid treatment	43 (97.7%)	27 (100%)	0.382
Allocation group			0.252
CTG STV	14 (31.8%)	11 (40.7%)	
DV p95	10 (22.7%)	9 (33.3%)	
DV no A	20 (45.5%)	7 (25.9%)	
End diastolic flow prior to delivery[a]			0.987
Positive	19 (43.2%)	12 (44.4%)	
Absent	22 (50.0%)	13 (48.1%)	
Reversed	3 (6.8%)	2 (7.4%)	
GA at delivery	29.6 (28.5-30.6)	29.1 (28.3-30)	0.319
Birthweight	910 (798-1023)	820 (675-965)	0.115
Birthweight P50 ratio	63.1 (57.3-68.9)	57.7 (53.4-62.1)	0.127
Sex			0.010*
Boys	14 (31.8%)	17 (63.0%)	
Girls	30 (68.2%)	10 (37.0%)	
Severe neonatal morbidity	11 (25.0%)	12 (44.4%)	0.089
BPD	4 (9.1%)	9 (33.3%)	0.010*
NDI at 2 years of age	2 (4.5%)	3 (11.1%)	0.294
Low maternal education[b]	8 (18.2%)	6 (30.0%)	0.520

m-ABC-II-NL = movement assessment battery for children; SD = standard deviation; IQR = interquartile range; NDI = neurodevelopmental impairment = WPPSI-III scale score <85, CP with a GMFCS ≥1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind); CTG = cardiotocography; STV = short term variation; DV = ductus venosus; GA = gestational age
Severe neonatal morbidity: NEC ≥ grade II, GMH ≥ grade III, BPD ≥ 36 weeks, proven sepsis, PVL ≥ grade II
** p<0.05*
[a] *Of one patient the last EDF before delivery is missing*
[b] *Of 8 patients in the normal motor score group and of 7 patients in the abnormal motor score group the maternal educational level is missing*

When combining the cognitive, motor and behavioural outcomes, there were 64 children with known outcomes of all tests. Of these children, there were 34 (53.1%) with FSIQ<85 and/or CP and/or M-ABC-II-NL ≤ 7 and/or with a CBCL score > 60. This overall outcome measure was similar for children born below and beyond 30 weeks gestational age.

Table 4 compares the neurodevelopmental outcome at two and five years of age. On a group level, outcomes remained fairly stable.

Table 4: Neurodevelopmental outcome at two and five years of age

Outcome variable	2 years	5 years
DQ/IQ (median (IQR))	100.0 (90.0 – 110.0)	97.0 (91.0 – 107.0)
Cerebral palsy, n (%)	0 / 74 (0%)	2 / 74 (2.7%)*
Mild vision problems, n (%)	2 / 72 (2.8%)	5 / 74 (6.8%)
Mild hearing problems, n (%)	0 / 73 (0%)	1 / 74 (1.4%)

DQ = developmental quotient; IQ = intelligence quotient; SD = standard deviation
The same patients were assessed at both two and five years of age
** Both children with CP had a GMFCS score of 1. One child had an one-sided hemiplegia and one child a spastic diplegia*

Comment

The outcomes of the Dutch children participating in TRUFFLE, antenatally diagnosed with FGR, born at a mean GA of 30 weeks and a mean birthweight of 910 gram, was fairly good, as illustrated by the median IQ score within normal range. The rates of children with IQ scores <85 was also comparable to the normed population. However, NDI rates increased from 6.8% at age two to 15.1% at age five. Moreover, 35% of the children had any IQ score 85, which is substantially higher than found in a control group(34). Of the studied population, about half of the children scores positive on a composite outcome measure of FSIQ<85 and/or CP and/or M-ABC-II-NL in the abnormal range and/or CBCL score > 60. M-ABC-II-NL in the abnormal range contributes most in this composite measure. Severe impairments were scarce in our study group. IQ and motor problems were related to GA, birthweight, male sex and neonatal morbidities, in particular BPD for the motor problems. Children with a FSIQ below 85 had more often reversed or absent flow prior to birth in comparison to children with a normal IQ score. GA, birthweight and male sex, and BPD are known risk factors for adverse outcomes in such patient groups. Overall rates of impairments were similar for the whole study group and those born growth restricted below 30 weeks' gestation. We hypothesize that BPD is found to be associated with long-term outcomes as being the expression of the more vulnerable children among this sample.

The strength of this study is the relatively large and homogeneous study population, and the clear antenatal diagnosis of FGR from placental insufficiency (in contrast with SGA), as much as possible with respect to the lack of consensus on the definition of FGR. Children were assessed systematically in outpatient clinics according to a standardized program, using a well validated test battery and the corrected ages to score test outcomes(35).

Limitations can be found in the restriction of the selection. Data were collected retrospectively, because the extended follow-up period was not part of the initial trial protocol. Although we studied a relatively vulnerable sample with lower GA and birthweight compared to the sample not seen at follow up, NDI at age two in our sample was lower than in the total sample. Also in the lost to follow up group, NDI at age two occurred more often than in the 74 children seen at age five. Outcome can therefore not be extrapolated to the whole TRUFFLE sample, since we cannot be certain about the direction of possible bias. Another limitation is the number of children evaluated which resulted in lack of power to figure out which of these risk factors were most related to our outcome measures in a multivariate analysis. Therefore, we decided to only show univariate relations with possible factors related to the different outcome measures.

A systematic review by Murray et al.(36) demonstrated that children with FGR, especially those who are also born preterm, have an increased risk of NDI later in childhood. In other studies investigating cognitive outcomes around five years of age in very preterm FGR or SGA children, there is a large variation in definition of FGR, primary aim, study design and type of tests used(37-46). In a systematic review performed by Levine et al.(47), 16 studies on neurodevelopmental outcomes among very preterm FGR in comparison with normally grown children were identified and 11 of these reported poorer neurodevelopmental outcome. Our cognitive results best correspond to those found by Walker et al.(43) and Schreuder et al.(40). The studies that have reported poorer cognitive outcomes in study populations comparable to our study(39, 41, 42), were limited by very small numbers of patients.

We observed impairments in processing speed in one quarter of our study group. This has previously been reported in studies in very preterm born children(48, 49). However, these studies did not focus on FGR in particular, but included all patients born below 32 weeks' gestation and all patients born below 30 weeks' gestation or below 1000 grams respectively.

The study of Korzeniewski et al.(50) compared the cognitive and behavioural outcomes at ten years of age between normally grown and growth restricted premature born fetuses. The results indicate that children with severe FGR experienced more problems on multiple domains of the cognitive and neurobehavioral development.

In the present study 35.1% of the children had any abnormal IQ scale score, which is lower than in the 46% found in the preterm and higher than the 15% in the term population in the study of Potharst et al, using the same instruments(34). Also, when comparing the

median FSIQ, VIQ, PIQ and PSIQ scores of our study group to the preterm born children(34), the scores of our group are slightly higher(34).

The current study shows a relatively high incidence of motor impairment (M-ABC score ≤ 7). Within the M-ABC-II-NL the section with the lowest score is manual dexterity with a median score of 8.0 (6.0 – 10.0). We hypothesize that processing speed problems may in part underpin these manual dexterity problems(51).

Our study cannot provide new evidence that ductus venosus measurements might improve long-term outcome as was done in the original TRUFFLE publication at age two. However, it does provide evidence of fairly low rates of severe disabilities in children participating in TRUFFLE. It is important that future management trials in FGR plan follow-up until and beyond the age of five years follow from the start. At and after the age of five, the different developmental domains can be assessed much better than at age two, when motor and mental development are more intertwined. Also, at age five and up there is much greater predictive strength towards academic achievement later on in life.

Conclusion

In general, in a neurodevelopmental follow-up study after early-onset FGR, the FSIQ of these five-year-old children was within normal limits. Nevertheless, the rate of IQ score in the abnormal range increased from 6.8% at age two to 15.1% at age five and a high rate of motor problems was seen. GA at delivery, birthweight(ratio), EDF prior to delivery and neonatal morbidity were the most important risk factors for cognitive outcomes.

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Part 2

Management of severe early-onset fetal growth restriction

Part 2

Chapter 5

The prognostic accuracy of short term variation of fetal heart rate in early-onset fetal growth restriction: a systematic review

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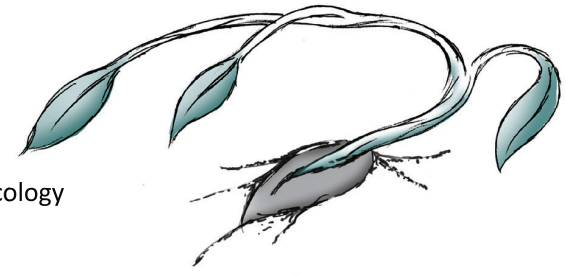

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Abstract

Objective
Cardiotocography (CTG) is an important tool for fetal surveillance in severe early-onset fetal growth restriction (FGR). Assessment of the CTG is usually performed visually (vCTG). However, it is suggested that computerized analysis of the CTG (cCTG) including short term variability (STV) could more accurately detect fetal compromise. The objective of this study was to systematically review the literature on the association between cCTG and perinatal outcome and the comparison of cCTG with vCTG.

Study design
A systematic search was performed in MEDLINE, EMBASE and Google Scholar. Studies were included that assessed prognostic accuracy of STV or compared STV to vCTG in patients with FGR. Risk of bias and concerns about applicability were assessed with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) instrument.

Results
Of the 885 records identified in the search, five cohort studies (387 patients) were included. We found no randomised studies comparing STV with visual CTG in patients with FGR. The risk of bias of all studies was generally judged as 'low'. One small study found an association of low STV with neonatal acidosis. One study observed no association of STV with long-term outcome. Composite analysis of all five studies showed a non-significant relative risk for acidosis after a low STV of 1.4 (95% CI 0.6-3.2, N=387). Further meta-analysis was hampered due to heterogeneity in outcome reporting and use of different thresholds.

Conclusion
The evidence from the included studies did not support an association of STV and short or long term outcome. However, available data are limited and heterogeneous, and influenced by management based on STV. Solid evidence from a randomized controlled trial comparing STV with vCTG including long term infant outcome is needed before STV can be used clinically for timing of delivery in patients with FGR.

Introduction

Severe early-onset fetal growth restriction (FGR) carries significant risks of neonatal mortality, morbidity, and long-term health sequelae(1-3). Fetal surveillance is of crucial importance to determine the best timing of delivery and improve perinatal outcome. Cardiotocography (CTG) is the most widespread method of fetal surveillance. The CTG is visually assessed for FHR (fetal heart rate) frequency, variability, accelerations and decelerations. A decrease of variability and absence of accelerations indicate a shortage in fetal oxygen supply and worsening of fetal condition(4, 5). Heart rate variability can also be automatically quantified by computer software. So far, it is unclear whether computerised CTG (cCTG) performs better in timing of delivery compared to visual assessment of the CTG (vCTG)(6, 7).

Evaluation of variability by vCTG conveys low intra- and inter-observer agreement, especially at early gestational age(6, 7). This may be overcome by using cCTG. Calculation of short-term variation (STV) by cCTG is hypothesized to provide a more objective and consistent parameter to assess variability. Therefore, STV may assess the fetal condition more accurately, and may be of value in the timing of delivery in early-onset FGR(8).

The mathematical formula of STV calculation has been developed by Dawes and Redman in the early 1990s(9-11). Although other indices can be calculated by computerised analysis of the cCTG, STV is the parameter that associates best with outcome(9). A systematic review of seven observational studies (including 780 patients) showed moderate prognostic accuracy of STV for acidosis(12). However, no other perinatal outcomes than acidosis were investigated and some studies included low-risk cases. Small studies have shown that in FGR fetuses the FHR was generally higher, and that STV and fetal activity were lower in unstimulated and stimulated stage(13, 14). It remains to be investigated how fetal condition in FGR should be assessed and how computerized STV analysis compares to vCTG.

We hypothesize that STV is a better predictor for fetal and neonatal outcomes than vCTG in pregnancies complicated by FGR. Therefore, we systematically reviewed the available literature on STV in order to investigate to what extent STV in cardiotocography correlates with fetal and neonatal mortality, morbidity, and acidemia. The second aim was to investigate whether STV is a better indicator of fetal and neonatal mortality and morbidity than vCTG.

Methods

This systematic review followed the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) guidelines (www.prisma-statement.org).

Search strategy
An information specialist (JL) performed a comprehensive search in OVID MEDLINE, OVID EMBASE and Google Scholar (first 150 hits via Harzing's Publish and Perish, v 6) from inception to May 30th 2018. The search included both free text and controlled terms (i.e. MeSH in MEDLINE) for the concepts 'FGR/IUGR', including conditions and complications related to FGR, and STV/cCTG. Animal studies were excluded by double negation (i.e. not (animals/ not humans/)). No other restrictions were applied. See Appendix in Supplementary material for entire search strategies. The retrieved records were imported and deduplicated in ENDNOTE X7. The included studies were screened for additional relevant cited or citing references.

Data extraction and quality assessment
Studies were included that assessed prognostic accuracy of STV in pregnant women between 26 and 32 weeks' gestation with FGR. Studies describing both vCTG and STV were included as well. FGR was defined as abdominal circumference or estimated fetal weight below the 10th percentile. The outcomes of interest were a measure of compromise of fetal or neonatal wellbeing, such as Apgar score or acidosis. Titles and abstracts of all search results were independently screened by two researchers (AP and NMC). Discrepancies were resolved by discussion. Of potentially eligible studies the full text was assessed. Relevant data were extracted from the full text by one researcher (AP) and reviewed by a second researcher (NMC).

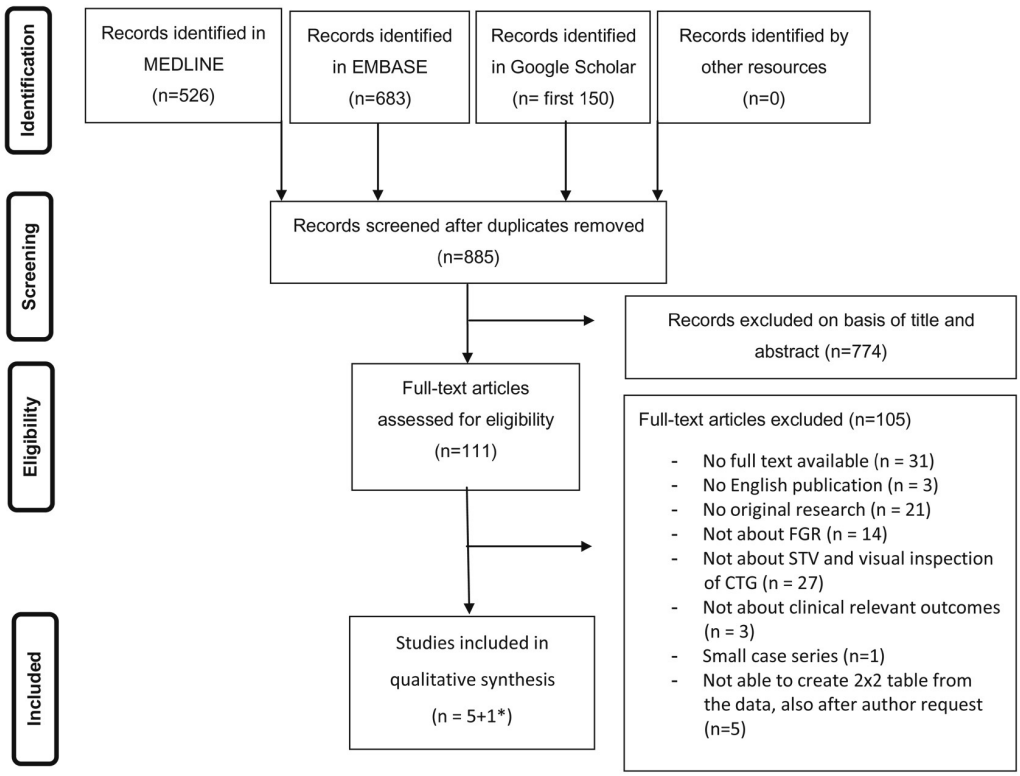
In case no two by two table could be created from the manuscript, the authors were e-mailed in order to retrieve these data. Risk of bias and concerns about applicability of the included studies were independently assessed by two researchers (AP and NMC) with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) instrument(15).

Statistical analysis
We aimed to calculate the sensitivity, specificity, positive and negative predicting value, relative risk and positive/negative likelihood ratio of the STV and the visual inspection of the CTG from the original studies. We intended to pool the data, if studies describe comparable patient populations and comparable clinical outcomes. In accordance with the Cochrane handbook(16), meta-analysis was only performed in case of low heterogeneity by using MetaXL(17). To evaluate heterogeneity the patient populations and the clinical outcomes were compared by clinical estimation of the authors. I2 was calculated to detect heterogeneity if this appeared feasible from clinical estimation(18).

Results

Of the 885 publications identified, eleven studies (comprising 3589 women) met the inclusion criteria. Nine studies lacked data to construct two-by-two tables and the corresponding authors were requested for additional data. Five of these studies were excluded because we did not get a response(19-23). Data from one study were published twice with different selection and outcome criteria and were therefore combined(24, 25). We received a new dataset, targeting our research question, from this study and from two others(26, 27). Five studies were included in the final analysis(24-29). This resulted in a total group of 387 women. Figure 1 shows the flowchart of the record selection. At the risk of bias assessment all studies were judged as generally having a low risk of bias (Table 1). No study directly compared vCTG and STV.

Figure 1: Flowchart records selection



** Data from one study were published twice with different selection and outcome criteria and were therefore combined*

Table 1: Risk of bias assessment of included studies

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Guzman, 1996	☺	☺	☺	☺	?	☺	☺
Hecher, 2001 / Bilardo, 2004	☺	☺	☺	☺	☺	☺	?
Anceschi, 2004	?	☺	☺	☺	☺	☺	☺
Lees, 2015	☺	☺	☺	☺	☺	☺	☺
Knaven 2017	☺	?	?	☺	☺	☺	?

☺Low Risk ☹High Risk ? Unclear Risk

One of the five included studies (n=38) observed a significant association of low STV with neonatal acidosis at birth(29). The other studies did not observe a significant association between STV and acidosis or other adverse short-term infant outcomes.

The only outcome measure available in all studies was 'acidosis' (Figure 2 and 3). Acidosis was defined as an umbilical pH below 7.2 in all studies. In three studies pH was measured from the umbilical artery(24, 25, 28, 29), in two it was not specified if the sample for pH was from the vein or the artery(26, 27). Table 2 summarizes the test characteristics of STV for acidosis, calculated per included study. In the annexed file a narrative description of all included studies is provided.

Although the source of umbilical pH was not defined in all studies, we performed a meta-analysis for the outcome pH <7.20, which was used in all studies as cut-off for acidosis. The pooled RR of low STV for neonatal acidosis was 1.4 (95% CI 0.6-3.2). A forest plot showed that the study by Guzman(29), which was the only study that showed a significant association of STV and acidosis, was an outlier, while the results of the remaining four studies were similar.

Two studies described the association between STV and perinatal death or neonatal morbidity, with a total of 381 patients(24, 25, 27). RR for this outcome was 1.11 (0.45-2.74)(24, 25) and 0.78 (0.59-1.04)(27). Due to the low number of studies describing this association, we decided not to pool results for this outcome.

Figure 2: Forest plot of association between low STV and fetal acidosis

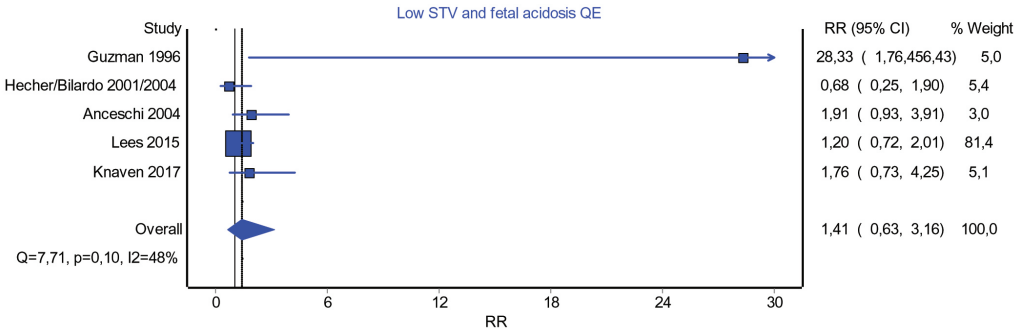
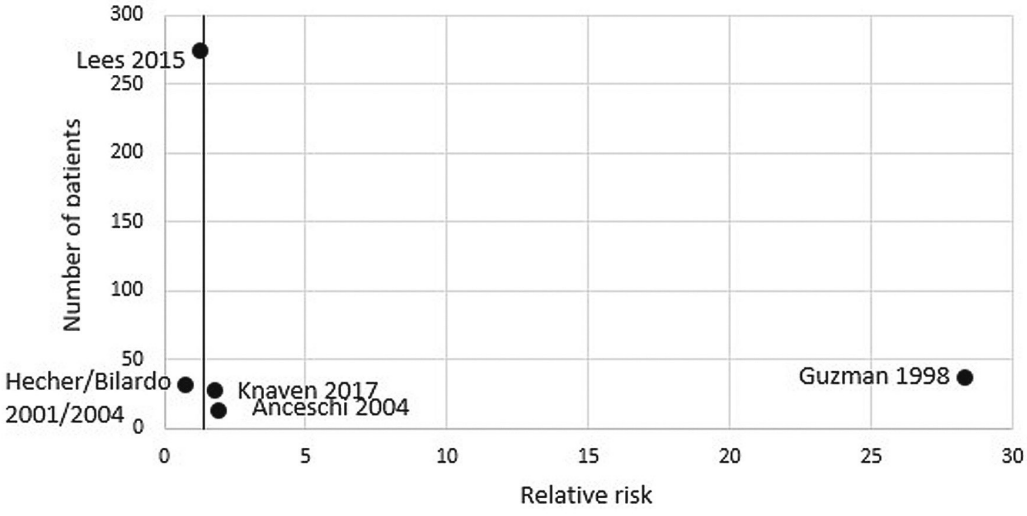


Figure 3: Association between number of included patients and relative risk for low STV and fetal acidosis



Association between number of included patients (y-axis) and relative risk of a low STV for fetal acidosis (x-axis)

Table 2: STV test characteristics

	Gestational age (weeks)	STV cutoff point (ms)	Number of patients	Outcome	Sensitivity	Specificity	Relative risk (95% confidence interval)
Guzman 1996(29)*	26-37	<3.5	38	pH <7.20	1.00	0.80	28.33 (1.76-456.43)
Hecher 2001(25) / Bilardo 2004(24)	26-32	STV <3.5 at <29 weeks or STV <4 at ≥29 weeks	32	pH <7.20	0.50	0.36	0.68 (0.25-1.90)
			41	Perinatal death or neonatal morbidity	0.54	0.50	1.11 (0.45-2.74)
Anceschi 2004(28)*	< 32	STV <3.5 at <29 weeks or STV <4 at ≥29 weeks	14	pH <7.20	0.38	1.00	1.91 (0.93-3.91)
Lees 2015(27)	26-32	STV <3.5 at <29 weeks or STV <4 at ≥29 weeks	275	pH <7.20	0.50	0.56	1.20 (0.72-2.01)
			340	Perinatal death or neonatal morbidity	0.40	0.50	0.78 (0.59-1.04)
Knaven 2017(26)	26-32	STV <3.5 at <29 weeks or STV <4 at ≥29 weeks	28	pH <7.20	0.45	0.76	1.76 (0.73-4.25)

**Studies without antenatal death*

Discussion

The results of this systematic review found no clear association between STV and short-term fetal and neonatal outcomes and it remains unclear if STV has a higher association with fetal and neonatal outcome than visual inspection of cardiotocography. No randomized controlled trials were identified that compared women with FGR who delivered based on vCTG or STV.

According to our hypothesis STV would have a better association with fetal and neonatal outcomes than the visual inspection of CTG in pregnancies complicated by FGR. Although the current systematic review does not support this hypothesis, there are theoretical considerations. First, in the studies where STV was done and possibly used in clinical management the use of STV might have led to different timing of delivery, and the incidence of adverse outcomes is influenced. Second, the advantage of STV in a cCTG is that it is reproducible, a feature that is particularly useful in research purposes, but also in clinical practice. Decisions in this type of pregnancies can be extremely challenging and the moment of delivery is crucial for the perinatal prognosis. Therefore, a quantitative assessment might be preferable and decreases the influences of inter-observer variability.

The selected studies differ in STV cut-off values and in outcome parameters. Firstly, the chosen outcomes differ between studies. Some studies used mortality as primary outcome(24, 25), others reported neurodevelopment at two years of age(27) or different morbidities as outcomes. Acidosis as a surrogate marker for neonatal outcome was used as well, however the clinical usefulness for the long-term prognosis has not been described in these studies and might therefore not be a relevant outcome to assess. Studies using death as outcome, are likely not sufficiently powered for this outcome. The definition of FGR is different in the studies and some of the studies used measurement of the umbilical artery Doppler as inclusion or exclusion criteria. This variability in STV cut-off values and outcome measures troubles comparison of the results of those studies. Another source of heterogeneity is the sample size, that ranged from 24 to 275 women. These limitations prohibit aggregation of the data of the five trials.

Interpretation of the studies investigating STV is further complicated by the use of different cut-off values to define an abnormal STV, and not all studies used the same computer program to calculate the STV. It has been suggested that STV values depend on the computer program in which they have been calculated(30). Originally, the STV is calculated by a formula developed by Dawes and Redman(31). This formula divides every minute in 16 parts of 3.75 s. The difference between consecutive pulse intervals for each interval of 3.75 s is averaged over each minute. The STV value is then calculated in milliseconds by averaging the 1-minute values over the whole reading, excluding decelerations. The Dawes and Redman analysis criteria are incorporated in a commercial system (Sonicaid Fetalcare (Huntleigh Healthcare, Cardif, UK)). In the current systematic review, four studies (24, 25, 27-29) used this software(32), Knaven(26) used FetalHrt, which was developed for research purposes following the descriptions by Dawes et al(33). It remains unclear which

cut-off value provides optimal test accuracy. We suggest this should be investigated in observational studies, prior to any randomized controlled trial and implementation in clinical practice.

This review shows that it is still unclear if STV has a stronger association with fetal and neonatal outcome than vCTG. Current literature does not show an association of vCTG with short-term infant outcome and use of STV has not been compared to vCTG yet. However, the validity of the clinical short-term endpoints that were used for these studies is questionable as these endpoints depend on many other observations or interventions apart from CTG. Solid evidence from a randomized controlled trial with long term infant outcome is needed to investigate if STV improves timing of delivery, particularly in pregnancies with early-onset FGR.

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Supplementary information

Table S1: Literature search

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy: 2018-05-30

#	Searches	Results
1	Fetal Growth Retardation/	15012
2	(IUGR or FGR).tw,kf.	6534
3	(growth adj6 (retard* or restrict* or restrain*)).tw,kf.	42564
4	(("5" or 5th) adj3 (centil* or percentil*) adj5 (circumference or cerebroplacental or weight)).tw,kf.	387
5	fetal development/ or fetal organ maturity/	8936
6	exp Infant, Low Birth Weight/ or birth weight/ or fetal weight/	64358
7	obstetric labor, premature/ or premature birth/	23203
8	(birth weight* or birthweight* or biometr*).tw,kf.	77805
9	((weight or growth or small) adj2 (infant* or newborn* or new* born* or neonat* or extrem* or f*etus* or f*etal* or baby or babies or uterine or intrauterine or birth*)).tw,kf.	96048
10	(LBW or VLBW or ELBW or SGA).tw,kf.	13815
11	((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (growth* or maturat* or high risk)).tw,kf.	22237
12	(d?strophic adj3 (f*etus* or f*etal* or baby or babies or newborn* or new* born* or infant* or uterine or intrauterine)).tw,kf.	210
13	(comprom* adj3 (f?etus* or f?etal* or growth or intrauterine or uterine)).tw,kf.	2167
14	(small adj2 (gestation* or age or date)).tw,kf.	10436
15	((born adj3 earl*) or ((prematur* or preterm or pre-matur* or pre-term) adj9 (f?etal or f?etus* or infant* or neonat* or neo-nat* or birth* or childbirth* or deliver* or labo?r or prenat* or newborn* or born))).tw,kf.	99383
16	Placental Insufficiency/	1558
17	((placenta* or uteroplacenta* or ureteroplacenta*) adj3 (insufficien* or d?sfunct* or deficien* or failure)).tw,kf.	3646
18	pregnancy, high-risk/	4491
19	(high risk pregnanc* or complicat* pregnanc*).tw,kf.	6035
20	fetal death/ or fetal mortality/ or exp pregnancy outcome/ or perinatal mortality/	73106
21	((f?etal or f?etus* or perinat* or peri-nat* or prenat* or pre-nat* or neonat* or neo-nat* or obstetric*) adj3 outcome*).tw,kf.	27783
22	((intra-uterine or intrauter* or f?etal or f?etus* or perinat* or peri-nat* or prenat* or pre-nat* or neonat* or neo-nat*) adj3 (death* or mortalit*)).tw,kf.	40757
23	exp hypertension, pregnancy-induced/	33231
24	((maternal or gravidit* or pregnan* or gestat* or pregestat* or mother) adj9 hypertens*).tw,kf.	16961
25	(preeclamp* or pre-eclamp* or eclamp* or HELLP).tw,kf.	32285
26	Apgar Score/	7313
27	apgar.tw,kf.	10774
28	(((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (wellbeing or well-being or status or condition*)) and (antepart* or ante-part* or during pregnan*)).tw,kf.	1178

29	((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (wellbeing or well-being or status or condition*)).tw,kf. not ((((labo?r or deliver*) not (preterm* or prematur* or pre-term* or prematur*)) or intrapart* or intra-part* or during birth* or childbirth*).ti. or exp Labor, Obstetric/)	6389
30	((antepart* or ante-part*) adj6 (cardiotoc*ogra* or cardio-toc*ogra* or heart rate* or f?etal heart or monitor* or cCTG or cCTGs or CTG or CTGs or FHR or FHRs or short-term varia* or STV)).tw,kf.	534
31	**or/1-30 [IUGR]**	**368923**
32	(animals/ or (goat* or sheep or ovine or pig or pigs or monkey* or rabbit*).ti.) not humans/	4451615
33	**31 not 32 [human IUGR]**	**330432**
34	((short-term or short time) adj6 (varia* or STV)).tw,kf.	3703
35	((STV or "short-and-long term") adj4 varia*).tw,kf.	394
36	(STV and (LTV or cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or cCTG or cCTGs or cCTG-s or FHRV or FHRVs)).tw,kf.	77
37	or/34-36	3971
38	(cardiotoc*ogra* or cardio-toc*ogra* or heart rate* or f?etal heart or heart monitor*).mp. or (CTG or CTGs or FHR or FHRs or bpm or bpms).tw,kf.	239642
39	**37 and 38 [I -STV]**	**1044**
40	(computer* adj9 (FHR or FHRs or heart rate*)).tw,kf.	663
41	(cCTG or cCTGs or cCTG-s).tw,kf. and (cardiotoc*ogra* or toc*ogra* or FHR or FHRs or heart rate*).mp.	35
42	(objectiv* adj2 (analy* or recording or method* or detect*) adj3 (cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or FHR or FHRs or heart rate* or f?etal heart or f?etal monitor*)).tw,kf.	38
43	((quantitat* or automat*) adj1 (cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or FHR or FHRs or heart rate* or f?etal heart or f?etal monitor*)).tw,kf.	71
44	**or/40-43 [II - cCTG1]**	**771**
45	Cardiotocography/	1855
46	(cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or cCTG or cCTGs or cCTG-s or FHRV or FHRVs).tw,kf.	5254
47	((f?etal heart rate* or FHR or FHRs) adj2 (pattern* or parameter* or analy* or recording* or monitor* or variabil* or variat* or fluctuat* or surveillan*)).tw,kf.	3030
48	or/45-47	8479
49	computing methodologies/ or automatic data processing/ or computers/ or image processing, computer-assisted/ or exp mathematical computing/ or signal processing, computer-assisted/ or Diagnosis, Computer-Assisted/ or computer simulation/ or Image Interpretation, Computer-Assisted/ or Microcomputers/	436036
50	(computer* or computing or microprocess* or micro-process* or microcomputer or microcomputers or multiparamet* or multi-paramet* or (quantif* adj3 (paramet* or variabil*))).tw,kf.	319323
51	**49 or 50**	**668945**
52	**48 and 51 [III - cCTG2]**	**900**
53	**39 or 44 or 52 [I II III STV/cCTG]**	**2235**
54	**33 and 53 [human IUGR broad + STV/cCTG I II III]**	**530**
55	**remove duplicates from 54**	**526**

Database(s): Embase Classic+Embase 1947 to 2018 May 29 Search Strategy: 2018-05-30

#	Searches	Results
1	intrauterine growth retardation/ or small for date infant/ or growth disorder/ or growth retardation/	70689
2	(IUGR or FGR).tw,kw.	10955
3	(growth adj6 (retard* or restrict* or restrain*)).tw,kw.	58621
4	(("5" or 5th) adj3 (centil* or percentil*) adj5 (circumference or cerebroplacental or weight)).tw,kw.	645
5	fetus development/ or prenatal development/ or fetus maturity/	69294
6	birth weight/ or exp low birth weight/ or fetal weight/ or prenatal growth/ or fetus growth/ or growth curve/	141162
7	biometry/	19230
8	exp "immature and premature labor"/	142562
9	(birth weight* or birthweight* or biometr*).tw,kw.	106448
10	((weight or growth or small) adj2 (infant* or newborn* or new* born* or neonat* or extrem* or f*etus* or f*etal* or baby or babies or uterine or intrauterine or birth*)).tw,kw.	132710
11	(LBW or VLBW or ELBW or SGA).tw,kw.	20302
12	((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (growth* or maturat* or high risk)).tw,kw.	31253
13	(d?strophic adj3 (f*etus* or f*etal* or baby or babies or newborn* or new* born* or infant* or uterine or intrauterine)).tw,kw.	321
14	(comprom* adj3 (f?etus* or f?etal* or growth or intrauterine or uterine)).tw,kw.	2920
15	(small adj2 (gestation* or age or date)).tw,kw.	14412
16	((born adj3 earl*) or ((prematur* or preterm or pre-matur* or pre-term) adj9 (f?etal or f?etus* or infant* or neonat* or neo-nat* or birth* or childbirth* or deliver* or labo?r or prenat* or newborn* or born))).tw,kw.	139066
17	placenta insufficiency/	3723
18	((placenta* or uteroplacenta* or ureteroplacenta*) adj3 (insufficien* or d?sfunct* or deficien* or failure)).tw,kw.	6028
19	high risk pregnancy/	10138
20	(high risk pregnanc* or complicat* pregnanc*).tw,kw.	8594
21	exp fetus death/ or fetus mortality/ or fetus outcome/ or pregnancy outcome/ or exp perinatal morbidity/ or exp perinatal mortality/ or prenatal mortality/	120597
22	((f?etal or f?etus* or perinat* or peri-nat* or prenat* or pre-nat* or neonat* or neo-nat* or obstetric*) adj3 outcome*).tw,kw.	41654
23	((intra-uterine or intrauter* or f?etal or f?etus* or perinat* or peri-nat* or prenat* or pre-nat* or neonat* or neo-nat*) adj3 (death* or mortalit*)).tw,kw.	58622
24	maternal hypertension/ or pregnancy toxemia/ or exp "eclampsia and preeclampsia"/	66387
25	((maternal or gravidit* or pregnan* or gestat* or pregestat* or mother) adj9 hypertens*).tw,kw.	26157
26	(preeclamp* or pre-eclamp* or eclamp* or HELLP).tw,kw.	49183
27	apgar score/	20822
28	apgar.tw,kw.	16946
29	(Fetal wellbeing/ or ((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (wellbeing or well-being or status or condition*)).tw,kw.) and (antepart* or ante-part* or during pregnan*).tw,kw.	1913

30	(Fetal wellbeing/ or ((f?etal or f?etus* or prenat* or pre-nat* or antenat* or ante-nat*) adj3 (wellbeing or well-being or status or condition*)).tw.) not ((((labo?r or deliver*) not (preterm* or prematur* or pre-term* or prematur*)) or intrapart* or intra-part* or during birth* or childbirth*).ti. or exp labor/)	11217
31	((antepart* or ante-part*) adj6 (cardiotoc*ogra* or cardio-toc*ogra* or heart rate* or f?etal heart or monitor* or cCTG or cCTGs or CTG or CTGs or FHR or FHRs or short-term varia* or STV)).tw,kw.	634
32	**or/1-31 [IUGR]**	**638171**
33	(animal/ or animal experiment/ or animal model/ or nonhuman/ or (goat* or sheep or ovine or pig or pigs or monkey* or rabbit*).ti.) not human/	5981416
34	**32 not 33 [IUGR - human]**	**549420**
35	((short-term or short time) adj6 (varia* or STV)).tw,kw.	4697
36	((STV or "short-and-long term") adj4 varia*).tw,kw.	508
37	(STV and (LTV or cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or cCTG or cCTGs or cCTG-s or FHRV or FHRVs)).tw,kw.	94
38	**or/35-37**	**5040**
39	(cardiotoc*ogra* or cardio-toc*ogra* or heart rate* or f?etal heart or heart monitor*).mp. or (CTG or CTGs or FHR or FHRs or bpm or bpms).tw,kw.	309764
40	**38 and 39 [I -STV]**	**1307**
41	(computer* adj9 (FHR or FHRs or heart rate*)).tw,kw.	927
42	(cCTG or cCTGs or cCTG-s).tw,kw. and (cardiotoc*ogra* or toc*ogra* or FHR or FHRs or heart rate*).mp.	36
43	(objectiv* adj2 (analy* or recording or method* or detect*) adj3 (cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or FHR or FHRs or heart rate* or f?etal heart or f?etal monitor*)).tw,kw.	50
44	((quantitat* or automat*) adj1 (cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or FHR or FHRs or heart rate* or f?etal heart or f?etal monitor*)).tw,kw.	101
45	**or/41-44 [II - cCTG1]**	**1071**
46	cardiotocography/	4313
47	(cardiotoc*ogra* or cardio-toc*ogra* or CTG or CTGs or cCTG or cCTGs or cCTG-s or FHRV or FHRVs).tw,kw.	7679
48	((f?etal heart rate* or FHR or FHRs) adj2 (pattern* or parameter* or analy* or recording* or monitor* or variabil* or variat* or fluctuat* or surveillan*)).tw,kw.	3909
49	**or/46-48**	**12647**
50	computer assisted diagnosis/ or computer analysis/ or computer program/ or computer/ or computer system/ or computer aided design/ or signal processing/ or signal detection/ or exp automation/	559307
51	(computer* or computing or microprocess* or micro-process* or microcomputer or microcomputers or multiparamet* or multi-paramet* or (quantif* adj3 (paramet* or variabil*))).tw,kw.	405036
52	**50 or 51**	**817728**
53	**49 and 52 [III - cCTG2]**	**1101**
54	**40 or 45 or 53 [I II III STV/cCTG]**	**2893**
55	**34 and 54 [IUGR broad + STV/cCTG I II III]**	**701**
56	**remove duplicates from 55**	**683**

GOOGLE SCHOLAR 2018-05-30 via Harzing's (version 6) Publish & Perish

intrauterine|"intra-uterine"|fetal|foetal "growth restriction|retardation"|IUGR "short-term variation|variability" cardiotocography|CTG|CCTG: all

first 150 hits (sorted for relevance)

S2 Narrative description of included studies

Guzman et al(29) performed a retrospective cohort study to determine the efficacy of STV for prediction of acidemia at birth at 26 to 37 weeks in 38 women with FGR. FGR was defined as suspicion of SGA on ultrasound and a birthweight at or below 10th percentile. STV was registered within 4 hours of birth by caesarean section. Indications for delivery were maternal hypertensive disorder, non-reassuring FHR tracing or arrest of fetal growth. Mean gestational age was 31.4 ± 3.1 and mean birthweight was 1152 gram ± 3 grams. Eight women had a pH below 7.20 and within this group the mean STV was 2.2 ± 0.4 ms. For the 14 women with pH 7.20 – 7.25 and for the 16 women with pH > 7.25 the STV was 4.6 ± 2.1 ms resp. 6.31 ± 1.5 ms. The relationship of umbilical artery pH with the episodes of low variation, STV, long term variation, episodes of high variation and the number of accelerations were all statistically significant. Separate analysis of deliveries at our target interval of 26 to 32 weeks was not possible, but only a minor proportion of infants was born after 32 weeks. Sensitivity, specificity and relative risk of a STV < 3.5 ms for an umbilical artery pH < 7.2 were 100%, 80% and 28.33 (1.76-456.43) respectively.

Hecher et al(25) performed an observational longitudinal prospective study of fetal monitoring parameters in women with a preterm small for gestational age fetus (abdominal circumference below fifth percentile) to describe the sequence in which these parameters became abnormal. The study included 110 women between 24 and 34 weeks gestation (of which only 93 women were analysed with at least three observations). In the subgroup with birth before 32 weeks 16 of the 17 deaths occurred: perinatal mortality was 12 of 30 (40%) if both STV and ductus venosus pulsatility index were abnormal and 4 of 30 (13%) if only one or neither was abnormal (P = 0.04). Bilardo et al (24) assessed the association of the most recent monitoring parameters before delivery and infant outcome in a subgroup of 70 women, who delivered between 26 and 33 weeks gestation, which was stated as the clinically most challenging patient population. Ductus Venosus PIV measurement was the best predictor of adverse perinatal outcome. Since for this current review we were interested in the association between STV and clinical outcome among women below 32 weeks, we requested additional data from the authors. Forty-one women delivered between 26 and 32 weeks and had an STV measurement within 24 hours of delivery. Women with an STV <3.5 ms (GA < 29 weeks) and STV <4 ms (GA ≥29 weeks) in the last 24 hours before delivery, had a relative risk of 1.11 (0.45-2.74) for perinatal death or major neonatal morbidity and a relative risk of 0.68 (0.25-1.90) for an umbilical artery pH <7.2.

Anceschi et al(28) performed an observational study to assess the association between STV within two hours of birth and oxygen metabolism in 24 women with a gestational age between 24 and 36 weeks in whom a caesarean section was performed for fetal growth restriction, defined as a birthweight below the 10th percentile. STV was significantly correlated with umbilical artery pH at birth (r=0.49;P=0.01) and pCO2 (r= -0.50; P=0.01). If we only use the results of the 14 women below 32 weeks gestation, the median gestational

age was 29 weeks and 5 days, median STV was 4.3 ms. The RR of a STV <3.5 ms (GA < 29 weeks) and STV <4 ms (GA ≥29 weeks) for neonatal acidemia was 1.91 (95% CI 0.93 to 3.91).

Lees et al(27) described the two-year follow-up of 503 women with FGR, defined as abdominal circumference below 10th percentile and a pulsatility index of the umbilical artery above 95th percentile, who were included between 26 and 32 weeks. The women in this multicentre trial were randomized between three different timing of delivery strategies: delivery based on reduced STV, based on early DV changes (cut-off at the 95th percentile; DV p95) or based on late DV changes (cut-off at absent or reversed a-wave; DV no A). The proportion of infants surviving without neuroimpairment did not differ between the CTG STV (111 [77%] of 144 infants with known outcome), DV p95 (119 [84%] of 142), and DV no A (133 [85%] of 157) groups (p trend=0·09). In July 2017 an analysis of longitudinal STV data of these patient group was published(34). A total of 149 women who delivered before 32 weeks, had consecutive CTG registration for more than three days before birth and known outcome of the two years' Bayley were included in this post-hoc analysis. In this analysis no association between the last STV before delivery and umbilical pH, Apgar scores at birth, incidence of severe neonatal morbidity or neurological impairment at the age of two years was found. Since for this current review we are interested in the association of STV with clinical outcome among women below 32 weeks, we asked for and received additional data from the authors. 340 women delivered between 26 and 32 weeks of gestation and had an STV measurement within 24 hours of delivery. Women with a low STV (STV <3.5 ms (GA < 29 weeks) and STV <4 ms (GA ≥29 weeks)) within 24 hours before delivery, had a relative risk of 0.78 (CI 0.59-1.04) for perinatal death or severe neonatal morbidity and a relative risk for the primary endpoint of the study (survival at the age of two years without neurological disability) of 0.94 (0.59 – 1.50). pH was known in 282 infants and the relative risk of a low STV for an umbilical artery pH <7.2 was 1.20 (CI 0.72-2.01).

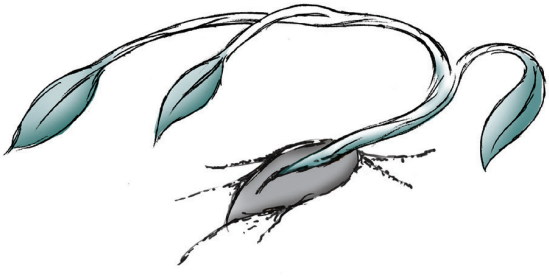
Knaven et al(26) evaluated retrospectively the CTG tracings of a cohort of 409 women who had been given corticosteroids for fetal maturation between 26 and 34 weeks of gestation, in order to assess if STV values might be influenced by corticosteroids. Of these women, 112 had FGR, defined as birthweight below tenth percentile. Since not all women in this study fulfilled the inclusion criteria for the current review, we requested the author for additional data. We received information on the 28 pregnancies with FGR delivered below 32 weeks who had an STV measurement within 24 hours before delivery. Women with a low STV (<3.5 ms before 29 weeks and 4.0 ms thereafter) in last 24 hours before delivery, had a relative risk of 1.76 (0.73-4.25) for pH <7.2.

Chapter 6

Influence of gestational age at initiation of antihypertensive therapy - Secondary analysis of CHIPS trial data

A Pels
BW Mol
J Singer
T Lee
P von Dadelszen
W Ganzevoort
E Asztalos
LA Magee

On behalf of the CHIPS Study Group



Hypertension
2018 Jun; 71(6): 1170-1177

Abstract

For hypertensive women in the CHIPS (Control of Hypertension In Pregnancy Study), we assessed whether the maternal benefits of tight control could be achieved, while minimizing any potentially negative effect on fetal growth, by delaying initiation of antihypertensive therapy until later in pregnancy.

For the 981 women with non-severe, chronic or gestational hypertension randomized to less-tight (target diastolic blood pressure 100 mmHg) or tight (target 85 mmHg) control, we used mixed effects logistic regression to examine whether the effect of less-tight (versus tight) control on major outcomes was dependent on gestational age at randomization, adjusting for baseline factors as in the primary analysis and including an interaction term between gestational age at randomization and treatment allocation. Gestational age was considered categorically (quartiles) and continuously (linear or quadratic form), and the optimal functional form selected to provide the best fit to the data based on the Akaike information criterion.

Randomization before (but not after) 24 weeks to less-tight (versus tight) control was associated with fewer babies with birth weight <10th centile ($P_{interaction}$=0.005), but more preterm birth ($P_{interaction}$=0.043), and no effect on perinatal death or high-level neonatal care >48hr ($P_{interaction}$=0.354). For the mother, less-tight (versus tight) control was associated with more severe hypertension at all gestational ages, but particularly so before 28 weeks ($P_{interaction}$=0.076).

In women with non-severe, chronic or gestational hypertension, there seems to be no gestational age at which less-tight (versus tight) control is the preferred management strategy to optimise maternal or perinatal outcomes.

Introduction

Hypertension complicates ~ 10% of pregnancies worldwide, and it is a leading cause of maternal and perinatal mortality and morbidity, in well and less-resourced settings. Hypertension may be due to chronic hypertension (~ 1% of pregnancies), gestational hypertension (~ 6%), or preeclampsia (~ 3%) that appears de novo or evolves from chronic or gestational hypertension(1). Although preeclampsia is associated with the greatest maternal and perinatal risks, those risks are also elevated in women with chronic or gestational hypertension who are twice as prevalent.

Management of pregnancy hypertension is multifaceted. Although some decisions are dependent on the hypertensive disorder (such as prevention of progression to preeclampsia among women with chronic hypertension or administration of magnesium sulphate to women with eclampsia), decisions about antihypertensive therapy are common to all hypertensive pregnant women. It has been recognised that antihypertensive for nonsevere hypertension decreases the incidence of severe hypertension and additional antihypertensive therapy(2), but the concern has been that this may be achieved at the expense of fetal growth and well-being(3, 4); the latter meta-analysis of von Dadelszen et al showed that a greater antihypertensive-induced fall in mean arterial pressure was associated with a higher proportion of small-for-gestational-age infants, based on 14 trials (slope: 0.09, SD 0.03, r2 0.48, p0.006)(3). However, the absolute decrease in birthweight was 145 gram for each 10 mmHg fall in MAP.

The CHIPS (Control of Hypertension In Pregnancy Study, ISRCTN 71416914, http://preempt.cfri.ca/CHIPS) compared the effectiveness of less-tight versus tight blood pressure (BP) control in improving pregnancy outcomes among women with non-severe, non-proteinuric chronic or gestational hypertension at 14-33 weeks of pregnancy(5). In the CHIPS trial, 987 women were randomized to less-tight control (N=497, target diastolic BP (dBP) of 100 mmHg) versus tight control (N=490, target dBP of 85 mmHg); a planned 15 mmHg difference in dBP goals aimed to achieve a 5 mmHg actual difference in dBP, which was the case; mean systolic BP (sBP) in less-tight was 138.8 ± 0.5 mmHg (versus 133.1 ± 0.3 mmHg in tight) and mean dBP in less-tight was 89.9 ± 0.3 mmHg (versus 85.3 ± 0.3 mmHg in tight). No statistically significant differences were seen in the primary perinatal outcome of perinatal death or high-level neonatal care for >48 hours (155, 31.4% versus 150, 30.7%, adjusted odds ratio (OR) 1.02 [0.77, 1.35]; p=0.89) or secondary maternal outcome of serious maternal complications, including death (18, 3.7% versus 10, 2.0%, adjusted OR 1.74 [0.79 to 3.84]; p=0.17). However, women in less-tight (versus tight) control more often developed severe maternal hypertension (200, 40.6% versus 134, 27.5%, adjusted OR 1.80 [1.34, 2.38]; p<0.001), platelet count <100 x 10^9/L (21, 4.3% versus 8, 1.6%, adjusted OR 2.63 [1.15, 6.05]; p=0.02] and elevated liver enzymes with maternal symptoms (21, 4.3% versus 9, 1.8%, adjusted OR 2.33 [1.05, 5.16]; p=0.03). In exploratory analyses, severe hypertension was associated with an excess of adverse perinatal and maternal outcomes, especially in less-tight control and even after adjustment for the co-occurrence of preeclampsia(6).

Taken together, the CHIPS results suggest that tight control might be the best clinical option, as it minimizes maternal risk without increasing perinatal risk. However, some clinicians are concerned that in tight (versus less-tight) control, there may have been an increase in birthweight <10th centile of potential clinical importance (96, 19.7% versus 79, 16.1% respectively; adjusted OR 1.28 [0.93, 1.79]; p=0.14); the lack of statistical significance may have reflected a lack of statistical power, particularly for women with chronic hypertension(7). However, what has not been highlighted is that in tight (versus less-tight) control, there was also a non-significant trend of similar magnitude towards a decrease in preterm birth (153, 31.5% versus 175, 35.6%, respectively; adjusted OR 0.85 [0.64, 1.11]; p=0.18). These surrogate outcomes for adverse perinatal outcome may have balanced each other out to result in the lack of any observed effect of tight (versus less-tight) control on the primary perinatal outcome of death or morbidity.

In this secondary, exploratory analysis, we sought to examine the relationship between gestational age at randomization and major CHIPS outcomes (including birthweight <10th centile and preterm birth) to investigate whether the maternal benefits of tight control could be achieved by delaying initiation of antihypertensive therapy until later in pregnancy, to minimize any potential negative impact of that therapy on fetal growth.

Methods

CHIPS was an open, pragmatic international multicentre trial. Women at 14+0 to 33+6 weeks gestation with non-proteinuric chronic or gestational hypertension, elevated BP (office dBP 90–105 mmHg, or 85–105 mmHg if on antihypertensives), and a live fetus were randomized (stratified by centre and hypertension type) to less-tight (100 mmHg) or tight control (85 mmHg) of blood pressure (BP). Importantly, women had to have persistently elevated BP, either on 2 consecutive outpatient visits or for 4 hours at the same visit, so many women with chronic hypertension became eligible only later in pregnancy following the mid-trimester nadir. Data of this secondary analysis will be available on request of the author.

CHIPS was approved by the Research Ethics Boards both centrally at the University of British Columbia as the coordinating center (H08-00882) and locally at all study sites. All participants gave written, informed consent. The study was designed following the principles of the Declaration of Helsinki and Guidelines for Good Clinical Practice.

The composite primary outcome was pregnancy loss or high level neonatal care (greater than normal newborn care) for >48 hr in the first 28 days of life or until primary discharge home, whichever was later. The composite secondary outcome was serious maternal complications before 6 weeks postpartum or until hospital discharge, whichever was later. Serious maternal complications included death, stroke, eclampsia, blindness, uncontrolled hypertension, the use of inotropic agents, pulmonary edema, respiratory failure, myo-

cardial ischemia or infarction, hepatic dysfunction, hepatic hematoma or rupture, renal failure, and transfusion, modelled on Delphi consensus(8). Additional major CHIPS outcomes were severe hypertension and preeclampsia for the mother, and birthweight <10th centile and preterm birth for the baby (See Table S2 for definitions).

For this secondary analysis, there were 981 women (of 987 randomized) available for analysis. Mixed effects logistic regression was used to examine the effect, by gestational age at randomization, of less-tight (versus tight) control on major outcomes: primary perinatal outcome, preterm birth, birthweight <10th centile, serious maternal complications, persistent severe maternal hypertension, and preeclampsia. An interaction term between gestational age at randomization and treatment group was included to examine treatment effect as a function of gestational age at randomization. Gestational age was considered categorically in quartiles. Adjustment was made for baseline factors as in the primary CHIPS analysis [i.e., stratification factors of hypertension type and centre (as a random effect), prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes at enrolment, and antihypertensive therapy at enrolment) and those that were different between less-tight and tight control in any gestational age quartile (i.e. ethnicity, aspirin at enrolment, perinatal mortality ratio of recruiting country and systolic BP within 1 week before randomization; Table S3). In a sensitivity analysis, we also considered gestational age at randomization continuously in either linear or quadratic form, and the optimal functional form was selected to provide the best fit to the data based on the Akaike information criterion. We conducted further subgroup analysis by hypertension type (chronic or gestational hypertension). Mixed-effects logistic regression was used for chronic hypertension, and Firth logistic regression without random effects was considered for gestational hypertension due to low outcome counts within a gestational age category or baseline factor level. A P-value <0.05 for an interaction term was considered statistically significant. SAS software, version 9.3 (SAS institute), was used for the statistical analysis.

Results

Of the 981 women in the CHIPS analysis, 493 were in less-tight and 488 in tight control. The results have been previously published(5). In brief, there were 736 (74.6%) women with chronic and 251 (25.4%) with gestational hypertension. At baseline, the less-tight and tight control groups were similar. Baseline BP was about 140/92 mmHg, but just <20% had experienced severe hypertension earlier in the index pregnancy. Just over half of women (566, 57.3%) were on antihypertensive therapy, usually (>80%) labetalol or methyldopa in equal measure, regardless of type of antihypertensive (Table S4). Few women were either smokers or had gestational diabetes (about 6% each). Importantly, ultrasonographic assessment of gestational age was performed in 907 (91.9%) women (455, 91.5% in less-tight and 452, 92.2% in tight).

Post-randomization, in the less-tight (versus tight) group, BP was higher (138.8 ± 0.5/89.9 ± 0.3mmHg versus 133.1 ± 0.5/85.3 ± 0.3mmHg, p<0.001) and fewer women took antihypertensive therapy (362, 73.4% versus 452, 92.6%, P<0.001), usually 1 drug (209, 57.7% versus 281, 62.2%) and usually labetalol (242, 66.9% versus 304, 67.3%), methyldopa (154, 42.5% versus 182, 40.3%), or nifedipine (115, 31.8% versus 136, 30.1%) (Supplementary Appendix(5)).

Perinatal outcomes

The effect of less-tight (versus tight) control on the primary perinatal outcome did not differ between the treatment groups randomized at different gestational ages ($P_{interaction}$=0.724; adjusted OR 1.01 [0.75, 1.34]); Table 1). There was, however, a significant interaction between treatment group and gestational age for birthweight <10th centile ($P_{interaction}$=0.028) and a trend toward more preterm birth; however no significant effect was seen ($P_{interaction}$=0.061). Less-tight (versus tight) control was associated with fewer babies with birthweight <10th centile at <18 weeks ($OR_{adjusted}$ 0.30 [0.14, 0.65]) with a similar, nonsignificant effect seen at 18-23 weeks ($OR_{adjusted}$ 0.63 [0.30, 1.34]), but no obvious effect at 24-29 or 30+ weeks. Less-tight (versus tight) control was associated with a nonsignificant increase in preterm birth at <18 weeks ($OR_{adjusted}$ 1.72 [0.91, 3.27]) and at 18-23 weeks ($OR_{adjusted}$ 1.73 [0.95, 3.15]), with no significant effect from 24 weeks. A similar pattern was seen for delivery at <34 weeks, but the results did not reach statistical significance ($P_{interaction}$=0.567; Table 1 overall; Table S5 for chronic and gestational hypertension subgroups).

Table 1: Major CHIPS PERINATAL outcomes in less-tight (vs. tight) control groups, according to gestational age at randomisation (N, % women)*†

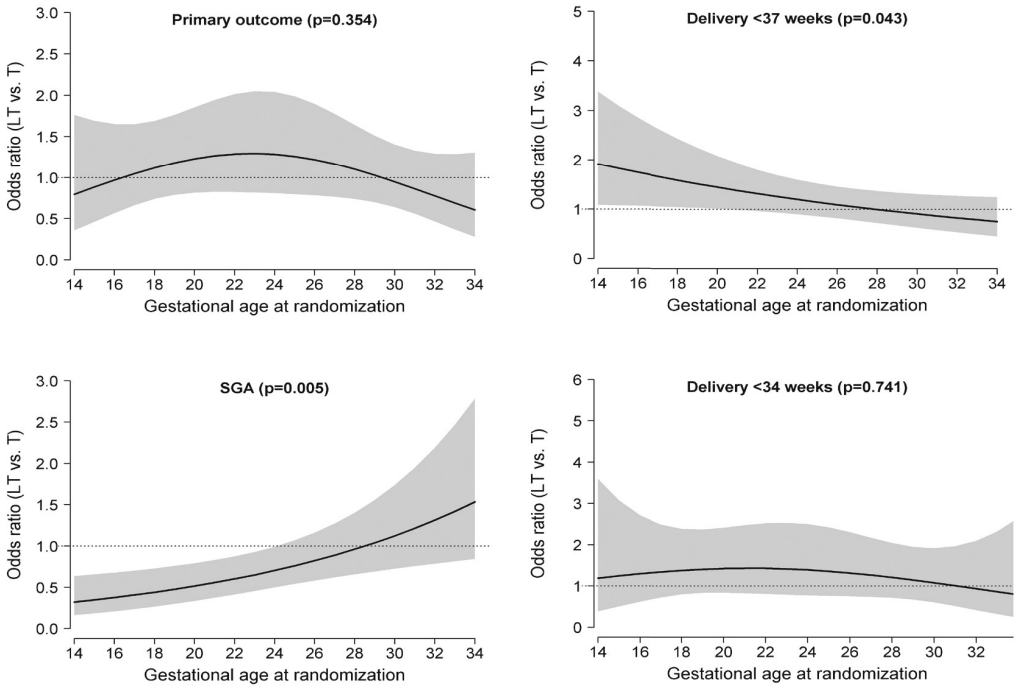
	Less tight control	Tight control	OR (95% CI)	P
Pregnancy loss or high-level neonatal care >48hr				
All women (N=981)	155/493 (50.8%)	150/488 (49.2%)	1.01 (0.75, 1.34)	0.961
According to GA at randomisation				
<18 weeks (N=226)	33/116 (28.4)	31/110 (28.2)	0.99 (0.54, 1.82)	0.971
18-23 weeks (N=238)	42/127 (33.1)	30/111 (27.0)	1.31 (0.72, 2.37)	0.380
24-29 weeks (N=251)	47/123 (38.2)	47/128 (36.7)	1.01 (0.58, 1.75)	0.977
30+ weeks (N=266)	33/127 (26.0)	42/139 (30.2)	0.81 (0.45, 1.43)	0.458
Interaction - GA and treatment				0.724
Birthweight <10th centile				
All women (N=976)	79/490 (16.1%)	96/486 (19.8%)	0.75 (0.54, 1.05)	0.098
According to GA at randomisation				
<18 weeks (N=222)	12/114 (10.5)	29/108 (26.9)	0.30 (0.14, 0.65)	0.002‡
18-23 weeks (N=237)	15/126 (11.9)	18/111 (16.2)	0.63 (0.30, 1.34)	0.229
24-29 weeks (N=251)	25/123 (20.3)	24/128 (18.8)	1.06 (0.56, 2.01)	0.852
30+ weeks (N=266)	27/127 (21.3)	25/139 (18.0)	1.20 (0.65, 2.23)	0.561
Interaction - GA and treatment				0.028‡
Delivery at <37 weeks				
All women (N=978)	175/492 (35.8%)	153/486 (31.5%)	1.16 (0.87, 1.54)	0.315
According to GA at randomisation				
<18 weeks (N=223)	35/115 (30.4)	22/108 (20.4)	1.72 (0.91, 3.27)	0.098
18-23 weeks (N=238)	48/127 (37.8)	27/111 (24.3)	1.73 (0.95, 3.15)	0.071
24-29 weeks (N=251)	43/123 (35.0)	53/128 (41.4)	0.66 (0.38, 1.14)	0.133
30+ weeks (N=266)	49/127 (38.6)	51/139 (36.7)	1.08 (0.64, 1.84)	0.765
Interaction - GA and treatment				0.061

	Less tight control	Tight control	OR (95% CI)	P
Delivery at <34 weeks				
All women (N=978)	77/492 (15.7%)	61/486 (12.6%)	1.23 (0.84, 1.81)	0.295
According to GA at randomisation				
<18 weeks (N=223)	16/115 (13.9)	12/108 (11.1)	1.26 (0.55, 2.89)	0.582
18-23 weeks (N=238)	26/127 (20.5)	13/111 (11.7)	1.86 (0.87, 3.96)	0.109
24-29 weeks (N=251)	24/123 (19.5)	25/128 (19.5)	0.90 (0.46, 1.76)	0.755
30+ weeks (N=266)	11/127 (8.7)	11/139 (7.9)	1.14 (0.46, 2.85)	0.774
Interaction - GA and treatment				0.567

CI = confidence interval; GA = gestational age; OR = Odds ratio
** Randomisation was stratified for centre and hypertension type; there was no stratification for gestational age*
† Adjustment was made for baseline factors as in the primary CHIPS analysis (i.e., stratification factors of hypertension type and centre (as a random effect), prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes at enrolment, and antihypertensive therapy at enrolment) and those that were different between 'less tight' and 'tight' control in any gestational age quartiles (ethnicity, aspirin at enrolment, PMR of recruiting country and sBP within 1 week before randomisation). An interaction term between gestational age at randomisation and treatment group was included to examine treatment effect as a function of gestational age at randomisation
‡ P values for adjusted OR (see methods) <0.05

These effects are demonstrated graphically in Figure 1 in which gestational age was treated as a continuous variable; the effects were similar in that less-tight (versus tight) at <24 weeks was associated with both a decrease in birthweight <10th centile (small for gestational age; $P_{interaction}$=0.005) and an increase in preterm birth at <37 weeks ($P_{interaction}$=0.043), with no effect on the primary outcome ($P_{interaction}$=0.354).

Figure 1: Odds ratio and 95% confidence interval for major CHIPS (Control of Hypertension in Pregnancy Study) perinatal outcomes in less-tight versus tight control groups, according to gestational age at randomization (wk)



Small-for-gestational-age (SGA) is defined as birthweight < 10th centile
The P value is shown for the interaction between treatment group and gestational age at randomization treated as a continuous variable on the relevant outcome

In CHIPS, 213 women delivered spontaneously (21.7%, 109 in less-tight and 104 in tight), 442 were induced (45.1%, 224 in less-tight and 218 in tight), and 323 had a caesarean prior to labour (32.9%, 159 in less-tight and 164 in tight)(5). The relationship between less-tight (versus tight) control at <24 weeks and an increase in preterm birth was restricted to an effect on iatrogenic (i.e., induced or elective delivery, $P_{interaction}$=0.063) and not spontaneous preterm birth ($P_{interaction}$=0.329) (Figure S1). The reasons for iatrogenic preterm birth were not systematically reported in CHIPS.

In subgroup analyses, the overall relationship between initiation of less-tight (versus tight) control at <24 weeks and perinatal outcomes was demonstrable only among women with chronic, but not gestational hypertension, whether gestational age was analysed by quartile (Table S5) or continuously (Figure S2 and S3).

Maternal outcomes

There was no demonstrable interaction between gestational age at initiation of less-tight versus tight control and serious maternal complications when gestational age was considered categorically (Table 2). However, when gestational age was considered as a continuous variable, later initiation (beyond 24 weeks) of less-tight (versus tight) control seemed to be associated with an increase in serious maternal complications (Figure 2, $P_{interaction}$=0.205); this finding appeared to be related to findings within women with gestational hypertension (Figure S3; Table 2 overall; Table S5 chronic and gestational hypertension subgroups).

Table 2: Major CHIPS MATERNAL outcomes in less-tight (vs. tight) control groups, according to gestational age at randomisation (N, % women)*†

	Less tight control	Tight control	OR (95% CI)	P
Secondary outcome (serious maternal complications)				
All women (N=981)	18/493 (3.7%)	10/488 (2.0%)	1.84 (0.83, 4.10)	0.136
According to GA at randomisation				
<18 weeks (N=226)	4/116 (3.4)	2/110 (1.8)	1.87 (0.33,10.65)	0.480
18-23 weeks (N=238)	4/127 (3.1)	3/111 (2.7)	1.14 (0.24, 5.36)	0.867
24-29 weeks (N=251)	4/123 (3.3)	4/128 (3.1)	1.07 (0.25, 4.58)	0.924
30+ weeks (N=266)	6/127 (4.7)	1/139 (0.7)	7.30 (0.85, 62.95)	0.070
Interaction - GA and treatment				*0.490*
Severe hypertension				
All women (N=981)	200/493 (40.6%)	134/488 (27.5%)	1.82 (1.36, 2.44)	<0.001‡
According to GA at randomisation				
<18 weeks (N=226)	52/116 (44.8)	26/110 (23.6)	2.49 (1.34, 4.63)	0.004‡
18-23 weeks (N=238)	51/127 (40.2)	23/111 (20.7)	2.43 (1.30, 4.55)	0.006‡
24-29 weeks (N=251)	51/123 (41.5)	45/128 (35.2)	1.35 (0.77, 2.37)	0.297
30+ weeks (N=266)	46/127 (36.2)	40/139 (28.8)	1.48 (0.85, 2.60)	0.168
Interaction - GA and treatment				*0.336*
Preeclampsia				
All women (N=979)	241/491 (49.1%)	223/488 (45.7%)	1.14 (0.87, 1.49)	0.327
According to GA at randomisation				
<18 weeks (N=226)	59/116 (50.9)	50/110 (45.5)	1.18 (0.68, 2.05)	0.564
18-23 weeks (N=237)	60/126 (47.6)	41/111 (36.9)	1.50 (0.86, 2.62)	0.153
24-29 weeks (N=251)	58/123 (47.2)	57/128 (44.5)	1.12 (0.66, 1.91)	0.673
30+ weeks (N=265)	64/126 (50.8)	75/139 (54.0)	0.90 (0.54, 1.51)	0.686
Interaction - GA and treatment				*0.621*

CI = confidence interval; GA = gestational age; OR = odds ratio

** Randomisation was stratified for centre and hypertension type; there was no stratification for gestational age*

† Adjustment was made for baseline factors as in the primary CHIPS analysis (i.e., stratification factors of hypertension type and centre (as a random effect), prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes at enrolment, and antihypertensive therapy at enrolment) and those that were different between 'less tight' and 'tight' control in any gestational age quartiles (ethnicity, aspirin at enrolment, PMR of recruiting country and sBP within 1 week before randomisation). An interaction term between gestational age at randomisation and treatment group was included to examine treatment effect as a function of gestational age at randomisation

‡ P values for adjusted OR (see methods) <0.05

Women in less-tight (versus tight) control had more severe hypertension overall ($OR_{adjusted}$ 1.82 [1.36, 2.44]) and in particular, at <18 weeks ($OR_{adjusted}$ 2.49 [1.34, 4.63]) and 18 to 23 weeks ($OR_{adjusted}$ 2.43 [1.30, 4.55]), with a nonsignificant interaction demonstrated with gestational age ($P_{interaction}$=0.336) (Table 2). However, in sensitivity analyses with gestational age as a continuous variable (Figure 2), initiation of less-tight (versus tight) control before 28 weeks seemed to be associated with more severe hypertension ($P_{interaction}$=0.076). A similar nonsignificant trend towards early initiation of less-tight (versus tight) control being associated with more preeclampsia was seen whether gestational age was considered categorically ($P_{interaction}$=0.621; Table 2) or continuous ($P_{interaction}$=0.183; Figure 2). In subgroup analyses, the relationship described between gestational age at initiation of less-tight (versus tight) control and severe hypertension or preeclampsia seemed to be similar among women with chronic or gestational hypertension (Table S5, Figure S3).

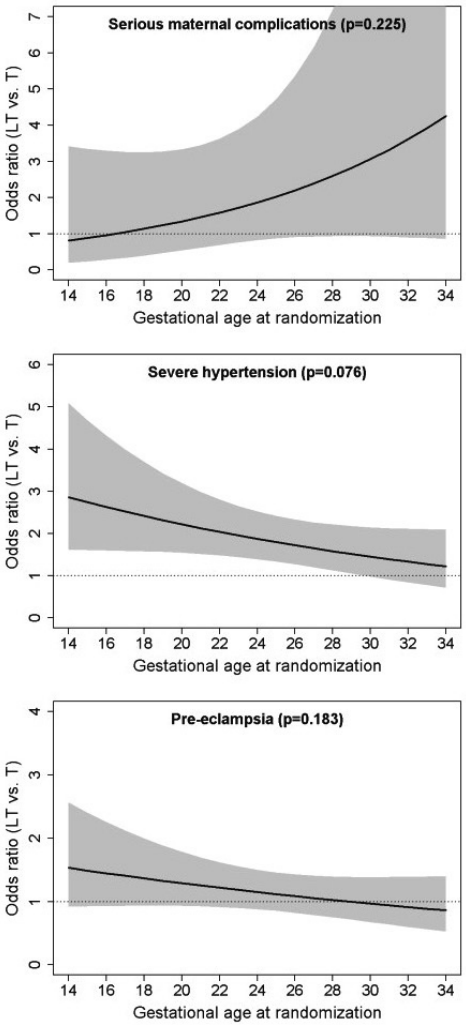


Figure 2: Odds ratio and 95% confidence intervals for major CHIPS (Control of Hypertension in Pregnancy Study) maternal outcomes in less-tight versus tight control groups, according to gestational age at randomization (wk)

The P value shown is for the interaction between treatment group and gestational age at randomization treated as a continuous variable on the relevant outcome.

Discussion

Main findings

In this secondary, exploratory analysis of the CHIPS trial of less-tight (versus tight) control of non-severe pregnancy hypertension, significant differences in outcomes were found according to the gestational age at randomization. At no gestational age at which randomization to treatment occurred overall outcomes were better if a strategy of less-tight (versus tight) BP control was pursued. This finding held true when considering women overall or for those with either chronic or gestational hypertension.

Less-tight (versus tight) control commenced before 24 weeks was associated with fewer babies born with birthweight <10th centile, but more babies born at <37 weeks; importantly, there was no overall effect on the primary outcome of pregnancy loss or high level neonatal care for >48hr. In the subgroups by type of hypertension, the findings were apparent only among women with chronic (not gestational) hypertension, among which there was no gestational age interaction; of note, by definition, women with gestational hypertension could be diagnosed only from 20 weeks.

For the mother, less-tight (versus tight) control was associated with more severe maternal hypertension at all gestational ages (as reported in the main trial publication), but this was particularly so when women were randomized before 28 weeks; a nonsignificant similar trend was seen in preeclampsia, and the effects were not obviously different by type of hypertension. Also, less-tight (versus tight) control appeared to be associated with more serious maternal complications after 28 weeks and particularly among women with gestational hypertension.

Current literature

Both small for gestational age and preterm birth are surrogates for adverse perinatal outcome(9-14). As each increases risk of perinatal mortality and morbidity, each is used commonly as a primary or secondary outcome in randomized trials, and in particular, those in pregnancy hypertension.

It has long been debated in the obstetric literature whether antihypertensive therapy in pregnancy may impair uteroplacental perfusion and through this, fetal growth and well-being. Although this concern has not been clearly documented in traditional meta-analysis of randomized trials (49 trials, 4723 women)(2), meta-regression analysis of 34 trials has suggested that lowering maternal BP (as in tight control in CHIPS) is associated with lower birthweight(3, 15). Some studies published after this meta-regression analysis confirmed this hypothesis (4, 16, 17), whereas others challenged it(2); none were able to account fully for associated maternal comorbidity or target BP. In addition, observational literature has suggested that initiation of antihypertensive therapy early in pregnancy may be a particular concern with regard to a negative impact on fetal growth(18). No demonstrable effects have been seen on preterm birth.

Although our secondary analysis of CHIPS data support these concerns and show that minimizing antihypertensive therapy through less-tight control before 24 weeks (through less-tight (versus tight) control) may have a favourable effect on fetal growth, what we have demonstrated for the first time is how a contrasting effect on preterm birth results in no impact on perinatal mortality and morbidity - the hard clinical outcomes that are the focus of our concern.

Strengths and limitations

Strengths of this study relate mainly to the quality of the trial data set on which the analyses were based, including its large size and international nature which improves generalizability. Gestational age at randomization was ascertained accurately at randomization and there was a balance between groups, including type of pregnancy hypertension (as a risk factor for fetal growth restriction) and use (and nature) of antihypertensive therapy for which the analyses were adjusted.

First, our analysis had limited statistical power to examine the relationship between gestational age and outcome because as with all trials, the sample size was based on achieving a difference between groups in the primary outcome. Power was improved by considering gestational age as a continuous variable, in addition to categorically. Also, power was particularly limited in analyses of women with gestational hypertension who made up 25.4% of the study population and by definition were not randomized before 20 weeks. Second, we used earlier gestational age at initiation of less-tight (versus tight) control as an unbiased (pre-randomization) proxy for duration of therapy - a post-randomization characteristic. Third, our results are relevant to less-tight (versus tight) control as applied in the CHIPS trial, although the antihypertensive agents used most commonly (i.e., primarily labetalol and methyldopa, and to a lesser extent, nifedipine) are those used most commonly internationally.

Perspectives

In summary, this secondary exploratory analysis of CHIPS data has shown that there is no gestational age at which less-tight (versus tight) control is the preferred clinical option, for women with chronic or gestational hypertension. Although this secondary analysis of the CHIPS trial data confirmed the hypothesis that initiating less-tight (versus tight) control at <24 weeks is associated with fewer babies with birthweight <10th centile, an effect that was counterbalanced by an increase in iatrogenic preterm birth such that there was no overall effect on perinatal death or morbidity. In addition, such early initiation of less-tight (versus tight) control was associated with a particular increase in the risk of severe hypertension. Initiation of less-tight (versus tight) control after 28 weeks may increase serious maternal complications, particularly among women with gestational hypertension. Future work should address clinicians' views about timing of delivery among women with higher BP and in particular, severe hypertension.

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Supplementary information

Table S1: CHIPS Study Group

Please find the list of participating countries and all CHIPS Study Group members in the online-only Data Supplement.

Table S2: Definitions of CHIPS outcomes

Outcome	Definition
For the baby	
Primary perinatal outcome: pregnancy loss or high level neonatal care for >48hr (until primary discharge home or 28d of life, whichever was later)	
Pregnancy loss	
• Elective termination	With reason specified, including static fetal growth
• Miscarriage	Death of a fetus <500g or <20 wks
• Ectopic pregnancy	Pregnancy outside the uterine cavity
• Stillbirth	Death of a fetus ≥500g or ≥20 wks
• Neonatal death	
High level neonatal care for >48 hr	Defined as greater-than-normal newborn care
Birthweight <10th centile	Birthweight <10th centile for gestational age and gender, according to a multiethnic reference standard [Kramer]
Delivery at <34 wk	Delivery at less than 34 weeks and 0 days of pregnancy
Delivery at <37 wk	Delivery at less than 37 weeks and 0 days of pregnancy
For the mother	
Secondary maternal outcome: one/more serious maternal complications (including death) (until primary discharge home or 6 wks postpartum, whichever was later)	
Maternal death	
Stroke	Acute neurological event with deficits lasting > 24 hr, not due to a post-ictal state
Eclampsia	Generalized convulsion in the absence of a history of epilepsy
Blindness	Either retinal or cortical, defined as loss of visual acuity in the presence of intact pupillary response to light
Uncontrolled hypertension	Need for a third parenteral antihypertensive agent (hypertension requiring administration of 3 or more different parenteral [intravenous or intramuscular] antihypertensive agents within a 12 hour period)
Inotropic support	Use of vasopressors to keep sBP > 90 mm Hg or a MAP > 70 mm Hg
Pulmonary oedema	Diagnosed clinically with one/more of oxygen saturation < 95%, diuretic treatment or x-ray confirmation
Respiratory failure	Intubation, ventilation (either by ETT or non-invasively), or need for > 50% oxygen for > 1 hr which is not due to Cesarean delivery
Myocardial ischemia or MI	By characteristic ECG changes and markers of myocardial necrosis
Hepatic dysfunction	INR>1.2 in the absence of DIC or treatment with warfarin, OR, in the presence of DIC or treatment with warfarin: either mixed hyperbilirubinemia >1.0 mg/dL (or >17 μM)or hypoglycemia <45 mg/dL (<2.5 mM) in the absence of insulin

Outcome	Definition
Hepatic hematoma or rupture	Presence of a blood collection under the hepatic capsule as confirmed by imaging or at laparotomy
Renal failure	Serum creatinine >200 μM
Transfusion	Of any blood product
Other	As detailed, with appropriate information from hospital records
Severe hypertension	sBP ≥ 160 mm Hg or dBP≥110 mm Hg
Preeclampsia	New proteinuria (≥ 2+ by urinary dipstick, ≥ 30 mg/mmol by urinary protein:creatinine ratio by spot testing, elevated urinary albumin:creatinine ratio according to local criteria, or ≥ 0.3 g/d by 24 hr urine collection) or one/more preeclampsia symptoms, signs, and/or abnormal laboratory tests
● Symptoms	Headache, visual disturbances, persistent right upper quadrant or epigastric pain, severe nausea or vomiting, chest pain, dyspnea
● Signs	In addition to severe hypertension: eclampsia, placental abruption, or pulmonary edema
● Abnormal maternal laboratory testing	Elevated aspartate or alanine aminotransferase or lactate dehydrogenase (according to local laboratory criteria) with symptoms, platelet count <100,000x10^9/L, or serum creatinine > 2.26 mg/dL (>200 μM)
Delivery at <34 wk	Delivery at less than 34 weeks and 0 days of pregnancy
Delivery at <37 wk	Delivery at less than 37 weeks and 0 days of pregnancy

dBP = diastolic blood pressure; DIC = disseminated intravascular coagulation; ETT = endotracheal tube; INR = international normalised ratio; MAP = mean arterial pressure; MI = myocardial infarction; sBP (systolic BP)

Table S3: Baseline characteristics in less-tight and tight control groups, according to gestational age at randomisation

	Randomized at <18 weeks			Randomized at 18-23 weeks			Randomized at 24-29 weeks			Randomized at 30+ weeks		
Variable	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**
Maternal age (years)			0.522			0.261			0.066			0.410
Mean (SD)	34.0 (5.4)	34.5 (5.4)		33.9 (5.6)	33.1 (5.1)		34.3 (5.7)	32.9 (6.3)		32.5 (6.0)	33.2 (6.1)	
Maternal age at EDD (years)			0.524			0.259			0.066			0.409
Mean (SD)	34.5 (5.4)	34.9 (5.4)		34.3 (5.6)	33.5 (5.1)		34.5 (5.7)	33.1 (6.3)		32.7 (6.0)	33.3 (6.1)	
Mother's self-declared ethnicity, n (%)			0.446			0.159			0.524			0.908
Caucasian	67 (57.8)	69 (62.7)		71 (55.9)	72 (64.9)		74 (60.2)	82 (64.1)		84 (66.1)	91 (65.5)	
Non-Caucasian	49 (42.2)	41 (37.3)		56 (44.1)	39 (35.1)		49 (39.8)	46 (35.9)		43 (33.9)	48 (34.5)	
Mother's self-declared ethnicity, n (%)			0.013			0.370			0.292			0.937
Caucasian	67 (57.8)	69 (62.7)		71 (55.9)	72 (64.9)		74 (60.2)	82 (64.1)		84 (66.1)	91 (65.5)	
Black	19 (16.4)	17 (15.5)		16 (12.6)	11 (9.9)		11 (8.9)	19 (14.8)		16 (12.6)	14 (10.1)	
Asian	19 (16.4)	6 (5.5)		17 (13.4)	14 (12.6)		13 (10.6)	11 (8.6)		12 (9.4)	15 (10.8)	
Hispanic	7 (6.0)	17 (15.5)		17 (13.4)	13 (11.7)		20 (16.3)	14 (10.9)		14 (11.0)	18 (12.9)	
Other	4 (3.4)	1 (0.9)		6 (4.7)	1 (0.9)		5 (4.1)	2 (1.6)		1 (0.8)	1 (0.7)	
Height (cm)			0.738			0.621			0.713			0.380
Mean (SD)	163.7 (7.1)	163.4 (7.9)		163.8 (7.2)	164.2 (6.9)		164.1 (7.5)	163.8 (7.3)		164.6 (7.6)	163.8 (6.5)	
Pre-pregnancy weight (kg)			0.988			0.929			0.650			0.164
Mean (SD)	84.5 (21.8)	84.6 (22.7)		85.7 (22.5)	85.4 (24.1)		84.2 (21.6)	82.9 (20.7)		79.1 (19.5)	82.6 (21.2)	
BMI (kg/m^2)			0.923			0.866			0.720			0.086
Median (IQR)	31.5 (7.6)	31.6 (8.0)		31.9 (7.7)	31.7 (9.0)		31.2 (7.3)	30.8 (6.8)		29.2 (6.9)	30.7 (7.3)	
BMI (kg/m^2)			0.889			0.075			0.887			0.095
Unknown	0	0		2	1		0	1		2	3	
< 25	23 (19.8)	21 (19.1)		23 (18.4)	31 (28.2)		30 (24.4)	30 (23.6)		40 (32.0)	31 (22.8)	
≥ 25	93 (80.2)	89 (80.9)		102 (81.6)	79 (71.8)		93 (75.6)	97 (76.4)		85 (68.0)	105 (77.2)	
Conceived through use of IVF ± ICSI, donor egg, and/or donor sperm			0.360			1.000			0.685			0.872
Unknown	3	5		2	1		4	0		1	1	
No	106 (93.8)	95 (90.5)		121 (96.8)	107 (97.3)		117 (98.3)	124 (96.9)		120 (95.2)	132 (95.7)	
Yes	7 (6.2)	10 (9.5)		4 (3.2)	3 (2.7)		2 (1.7)	4 (3.1)		6 (4.8)	6 (4.3)	
Nulliparous			0.697			0.215			0.335			0.440
No	87 (75.0)	80 (72.7)		82 (64.6)	80 (72.1)		84 (68.3)	80 (62.5)		79 (62.2)	80 (57.6)	
Yes	29 (25.0)	30 (27.3)		45 (35.4)	31 (27.9)		39 (31.7)	48 (37.5)		48 (37.8)	59 (42.4)	

	Randomized at <18 weeks			Randomized at 18-23 weeks			Randomized at 24-29 weeks			Randomized at 30+ weeks		
Variable	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**
Type of non-proteinuric hypertension, n (%)			-			0.925			0.934			0.487
Gestational hypertension	0 (0.0)	0 (0.0)		11 (8.7)	10 (9.0)		40 (32.5)	41 (32.0)		73 (57.5)	74 (53.2)	
Pre-existing hypertension	116 (100.0)	110 (100.0)		116 (91.3)	101 (91.0)		83 (67.5)	87 (68.0)		54 (42.5)	65 (46.8)	
Previous sBP≥160 or dBP≥110mmHg in this pregnancy			0.358			0.043			0.515			0.512
No	101 (87.1)	100 (90.9)		104 (81.9)	101 (91.0)		101 (82.1)	109 (85.2)		105 (82.7)	119 (85.6)	
Yes	15 (12.9)	10 (9.1)		23 (18.1)	10 (9.0)		22 (17.9)	19 (14.8)		22 (17.3)	20 (14.4)	
Use of antihypertensive therapy at randomization, n (%)			0.440			0.254			0.993			0.840
No	48 (41.4)	40 (36.4)		62 (48.8)	46 (41.4)		51 (41.5)	53 (41.4)		56 (44.1)	63 (45.3)	
Yes	68 (58.6)	70 (63.6)		65 (51.2)	65 (58.6)		72 (58.5)	75 (58.6)		71 (55.9)	76 (54.7)	
Type of antihypertensive therapy at randomization			0.858			0.710			0.621			0.501
Labetalol ± other antihypertensive (not methyldopa)	28 (24.1)	28 (25.5)		26 (20.5)	25 (22.5)		24 (19.5)	33 (25.8)		32 (25.2)	41 (29.5)	
Methyldopa ± other antihypertensive (not labetalol)	30 (25.9)	33 (30.0)		31 (24.4)	31 (27.9)		37 (30.1)	32 (25.0)		27 (21.3)	20 (14.4)	
Other	10 (8.6)	9 (8.2)		8 (6.3)	9 (8.1)		11 (8.9)	10 (7.8)		12 (9.4)	15 (10.8)	
None	48 (41.4)	40 (36.4)		62 (48.8)	46 (41.4)		51 (41.5)	53 (41.4)		56 (44.1)	63 (45.3)	
Currently using home BP monitoring, n (%)			0.673			0.598			0.805			0.804
No	79 (68.1)	72 (65.5)		82 (64.6)	68 (61.3)		73 (59.3)	74 (57.8)		75 (59.1)	80 (57.6)	
Yes	37 (31.9)	38 (34.5)		45 (35.4)	43 (38.7)		50 (40.7)	54 (42.2)		52 (40.9)	59 (42.4)	
In hospital at enrollment			0.677			0.688			0.449			0.717
No	114 (98.3)	107 (97.3)		123 (96.9)	109 (98.2)		110 (89.4)	118 (92.2)		115 (90.6)	124 (89.2)	
Yes	2 (1.7)	3 (2.7)		4 (3.1)	2 (1.8)		13 (10.6)	10 (7.8)		12 (9.4)	15 (10.8)	
Gestational diabetes prior to randomisation			1.000			0.421			0.868			0.400
No	111 (95.7)	106 (96.4)		125 (98.4)	107 (96.4)		115 (93.5)	119 (93.0)		110 (86.6)	125 (89.9)	
Yes	5 (4.3)	4 (3.6)		2 (1.6)	4 (3.6)		8 (6.5)	9 (7.0)		17 (13.4)	14 (10.1)	
Cigarette smoking during this pregnancy			0.852			0.398			0.504			0.163
No	109 (94.0)	104 (94.5)		118 (92.9)	106 (95.5)		116 (94.3)	118 (92.2)		115 (90.6)	132 (95.0)	
Yes	7 (6.0)	6 (5.5)		9 (7.1)	5 (4.5)		7 (5.7)	10 (7.8)		12 (9.4)	7 (5.0)	
Aspirin at enrollment			0.011			0.128			0.806			0.065
No	69 (59.5)	83 (75.5)		96 (75.6)	74 (66.7)		92 (74.8)	94 (73.4)		109 (85.8)	107 (77.0)	
Yes	47 (40.5)	27 (24.5)		31 (24.4)	37 (33.3)		31 (25.2)	34 (26.6)		18 (14.2)	32 (23.0)	

	Randomized at <18 weeks			Randomized at 18-23 weeks			Randomized at 24-29 weeks			Randomized at 30+ weeks		
Variable	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**	**Less-tight**	**Tight**	**P**
Folic acid and/or prenatal vitamin at enrollment			0.068			0.932			0.885			0.779
Unknown	0	0		0	0		0	0		1	0	
No	36 (31.0)	47 (42.7)		43 (33.9)	37 (33.3)		46 (37.4)	49 (38.3)		41 (32.5)	43 (30.9)	
Yes	80 (69.0)	63 (57.3)		84 (66.1)	74 (66.7)		77 (62.6)	79 (61.7)		85 (67.5)	96 (69.1)	
PMR of recruiting country, n (%)			0.012			0.394			0.112			0.755
Low (<10/1000 births)	107 (92.2)	89 (80.9)		106 (83.5)	97 (87.4)		94 (76.4)	108 (84.4)		106 (83.5)	114 (82.0)	
High (≥10/1000 births)	9 (7.8)	21 (19.1)		21 (16.5)	14 (12.6)		29 (23.6)	20 (15.6)		21 (16.5)	25 (18.0)	
Regions where women were recruited, n (%)			0.144			0.326			0.384			0.663
Australasia	14 (12.1)	12 (10.9)		13 (10.2)	11 (9.9)		16 (13.0)	12 (9.4)		9 (7.1)	15 (10.8)	
Middle East	5 (4.3)	3 (2.7)		1 (0.8)	5 (4.5)		3 (2.4)	2 (1.6)		3 (2.4)	3 (2.2)	
North America	28 (24.1)	23 (20.9)		43 (33.9)	35 (31.5)		36 (29.3)	41 (32.0)		43 (33.9)	52 (37.4)	
South America	8 (6.9)	20 (18.2)		20 (15.7)	12 (10.8)		27 (22.0)	19 (14.8)		19 (15.0)	22 (15.8)	
UK and Europe	61 (52.6)	52 (47.3)		50 (39.4)	48 (43.2)		41 (33.3)	54 (42.2)		53 (41.7)	47 (33.8)	
Systolic BP (mmHg) within 1 week before randomisation			0.676			0.039			0.556			0.559
Mean (SD)	140.1 (9.9)	139.6 (9.5)		141.0 (10.0)	138.2 (10.4)		140.5 (9.5)	139.8 (9.7)		140.2 (9.2)	140.9 (9.7)	
Diastolic BP (mmHg) within 1 week before randomisation			0.351			0.073			0.791			0.726
Mean (SD)	92.7 (4.8)	92.0 (6.2)		92.5 (5.3)	91.4 (4.6)		92.3 (4.6)	92.2 (4.6)		92.8 (4.6)	93.0 (5.1)	

P value was based on Chi-square test, Fisher's exact test or t-test as appropriate

Table S4: Antihypertensive therapy at randomisation, according to gestational age at randomisation* (N women, %)

	All women		Chronic hypertension		Gestational hypertension	
	Less-tight control	Tight control	Less-tight control	Tight control	Less-tight control	Tight control
Total CHIPS group						
Antihypertensives therapy	279/497 (56.1)	287/490 (58.6)	234/371 (63.1)	251/365 (68.8)	45/126 (35.7)	36/125 (28.8)
Labetalol	124 (24.9)	135 (27.6)	98 (26.4)	112 (30.7)	26 (20.6)	23 (18.4)
Methyldopa	139 (28.0)	125 (25.5)	125 (33.7)	114 (31.2)	14 (11.1)	11 (8.8)
Nifedipine	34 (6.8)	43 (8.8)	28 (7.5)	36 (9.9)	6 (4.8)	7 (5.6)
Other	16 (3.2)	14 (2.9)	12 (3.2)	13 (3.6)	4 (3.2)	1 (0.8)
According to GA at randomisation						
< 18 wk						
Antihypertensive	70/118 (59.3)	70/111 (63.1)	70/118 (59.3)	70/111 (63.1)	0/0	0/0
Labetalol	32 (27.1)	30 (27.0)	32 (27.1)	30 (27.0)	-	-
Methyldopa	34 (28.8)	35 (31.5)	34 (28.8)	35 (31.5)	-	-
Nifedipine	7 (5.9)	6 (5.4)	7 (5.9)	6 (5.4)	-	-
Other	5 (4.2)	5 (4.5)	5 (4.2)	5 (4.5)	-	-
18-23 wk						
Antihypertensive	66/128 (51.6)	66/112 (58.9)	62/116 (53.4)	65/102 (63.7)	4/12 (33.3)	1/10 (10.0)
Labetalol	31 (24.2)	27 (24.1)	29 (25.0)	26 (25.5)	2 (16.7)	1 (10.0)
Methyldopa	36 (28.1)	34 (30.4)	34 (29.3)	34 (33.3)	2 (16.7)	0 (0.0)
Nifedipine	8 (6.3)	8 (7.1)	7 (6.0)	8 (7.8)	1 (8.3)	0 (0.0)
Other	1 (0.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
24-29 wk						
Antihypertensive	72/124 (58.1)	75/128 (58.6)	58/83 (69.9)	64/87 (73.6)	14/41 (34.1)	11/41 (26.8)
Labetalol	26 (21.0)	34 (26.6)	17 (20.5)	29 (33.3)	9 (22.0)	5 (12.2)
Methyldopa	39 (31.5)	33 (25.8)	36 (43.4)	28 (32.2)	3 (7.3)	5 (12.2)
Nifedipine	9 (7.3)	13 (10.2)	8 (9.6)	11 (12.6)	1 (2.4)	2 (4.9)
Other	6 (4.8)	7 (5.5)	3 (3.6)	6 (6.9)	3 (7.3)	1 (2.4)
≥30 wk						
Antihypertensive	71/127 (55.9)	76/139 (54.7)	44/54 (81.5)	52/65 (80.0)	27/73 (37.0)	24/74 (32.4)
Labetalol	35 (27.6)	44 (31.7)	20 (37.0)	27 (41.5)	15 (20.5)	17 (23.0)
Methyldopa	30 (23.6)	23 (16.5)	21 (38.9)	17 (26.2)	9 (12.3)	6 (8.1)
Nifedipine	10 (7.9)	16 (11.5)	6 (11.1)	11 (16.9)	4 (5.5)	5 (6.8)
Other	4 (3.1)	2 (1.4)	3 (5.6)	2 (3.1)	1 (1.4)	0 (0.0)

** Randomisation was stratified by study centre and hypertension type. There was no stratification for gestational age. Categories of antihypertensive type are not mutually exclusive*

Table S5: Major CHIPS outcomes (maternal and perinatal) in less-tight (vs. tight) control groups, according to gestational age at randomisation (N, % women)*

	Chronic hypertension				Gestational hypertension			
	LT	T	OR (95% CI)	P	LT	T	OR (95% CI)	P
Pregnancy loss or high level neonatal care >48hr According to GA at randomisation								
<18 weeks	33/116 (28.4)	31/110 (28.2)	1.02 (0.54, 1.91)	0.954	-	-	-	-
18-23 weeks	39/116 (33.6)	25/101 (24.8)	1.52 (0.80, 2.90)	0.203	3/11 (27.3)	5/10 (50.0)	0.49 (0.07, 3.20)	0.453
24-29 weeks	29/83 (34.9)	29/87 (33.3)	1.06 (0.53, 2.13)	0.860	18/40 (45.0)	18/41 (43.9)	0.94 (0.37, 2.40)	0.896
30+ weeks	12/54 (22.2)	20/65 (30.8)	0.66 (0.27, 1.64)	0.376	21/73 (28.8)	22/74 (29.7)	0.85 (0.40, 1.81)	0.679
Interaction - GA and treatment				0.530				0.828
Birthweight < 10th centile According to GA at randomisation								
<18 weeks	12/114 (10.5)	29/108 (26.9)	0.30 (0.14, 0.63)	0.002	-	-	-	-
18-23 weeks	15/115 (13.0)	17/101 (16.8)	0.67 (0.31, 1.45)	0.311	0/11 (0.0)	1/10 (10.0)	0.23 (0.01, 7.14)	0.402
24-29 weeks	16/83 (19.3)	15/87 (17.2)	1.15 (0.52, 2.56)	0.726	9/40 (22.5)	9/41 (22.0)	1.06 (0.37, 3.05)	0.912
30+ weeks	8/54 (14.8)	10/65 (15.4)	1.08 (0.39, 3.03)	0.879	19/73 (26.0)	15/74 (20.3)	1.32 (0.60, 2.87)	0.489
Interaction - GA and treatment				0.072				0.610
Delivery at <37 weeks According to GA at randomisation								
<18 weeks	35/115 (30.4)	22/108 (20.4)	1.82 (0.95, 3.48)	0.072	-	-	-	-
18-23 weeks	45/116 (38.8)	23/101 (22.8)	1.95 (1.03, 3.70)	0.040	3/11 (27.3)	4/10 (40.0)	0.88 (0.13, 5.99)	0.897
24-29 weeks	23/83 (27.7)	32/87 (36.8)	0.58 (0.29, 1.17)	0.131	20/40 (50.0)	21/41 (51.2)	0.80 (0.31, 2.01)	0.629
30+ weeks	18/54 (33.3)	20/65 (30.8)	1.22 (0.53, 2.79)	0.645	31/73 (42.5)	31/74 (41.9)	0.92 (0.46, 1.85)	0.821
Interaction - GA and treatment				0.055				0.969
Delivery at <34 weeks According to GA at randomisation								
<18 weeks	16/115 (13.9)	12/108 (11.1)	1.28 (0.56, 2.94)	0.555	-	-	-	-
18-23 weeks	24/116 (20.7)	10/101 (9.9)	2.11 (0.92, 4.83)	0.078	2/11 (18.2)	3/10 (30.0)	0.98 (0.11, 8.98)	0.983
24-29 weeks	13/83 (15.7)	12/87 (13.8)	1.06 (0.44, 2.57)	0.900	11/40 (27.5)	13/41 (31.7)	0.72 (0.24, 2.16)	0.552
30+ weeks	5/54 (9.3)	3/65 (4.6)	2.30 (0.50, 10.51)	0.282	6/73 (8.2)	8/74 (10.8)	0.71 (0.23, 2.24)	0.560
Interaction - GA and treatment				0.638				0.966
Delivery at <37 weeks (spontaneous) According to GA at randomisation								
<18 weeks	9/25 (36.0)	4/24 (16.7)	5.55 (0.85, 36.40)	0.073	-	-	-	-
18-23 weeks	5/25 (20.0)	5/23 (21.7)	0.73 (0.13, 4.11)	0.719	0/2 (0.0)	0/1 (0.0)	2.50 (<0.01, >999.99)	0.786
24-29 weeks	2/18 (11.1)	1/15 (6.7)	2.01 (0.08, 51.76)	0.671	2/9 (22.2)	6/12 (50.0)	0.33 (0.04, 2.80)	0.309
30+ weeks	1/10 (10.0)	3/15 (20.0)	1.11 (0.05, 22.58)	0.944	9/20 (45.0)	5/14 (35.7)	2.19 (0.38, 12.53)	0.377
Interaction – GA and treatment				0.454				0.367

	Chronic hypertension				Gestational hypertension			
	LT	T	OR (95% CI)	P	LT	T	OR (95% CI)	P
Delivery at <37 weeks (induced/elective Caesarean without labour) According to GA at randomisation								
<18 weeks	26/90 (28.9)	18/84 (21.4)	1.65 (0.79, 3.45)	0.181	-	-	-	-
18-23 weeks	40/91 (44.0)	18/78 (23.1)	2.49 (1.21, 5.12)	0.013	3/9 (33.3)	4/9 (44.4)	0.72 (0.10, 5.37)	0.748
24-29 weeks	21/65 (32.3)	31/72 (43.1)	0.59 (0.28, 1.26)	0.174	18/31 (58.1)	15/29 (51.7)	1.02 (0.35, 3.01)	0.973
30+ weeks	17/44 (38.6)	17/50 (34.0)	1.31 (0.52, 3.28)	0.569	22/53 (41.5)	26/60 (43.3)	0.77 (0.34, 1.77)	0.539
Interaction - GA and treatment				0.054				0.911
Serious maternal complications According to GA at randomisation								
<18 weeks	4/116 (3.4)	2/110 (1.8)	2.00 (0.35, 11.46)	0.434	-	-	-	-
18-23 weeks	4/116 (3.4)	3/101 (3.0)	1.08 (0.23, 5.18)	0.919	0/11 (0.0)	0/10 (0.0)	1.14 (0.02, 70.85)	0.949
24-29 weeks	1/83 (1.2)	2/87 (2.3)	0.54 (0.05, 6.27)	0.621	3/40 (7.5)	2/41 (4.9)	1.40 (0.25, 7.69)	0.700
30+ weeks	1/54 (1.9)	1/65 (1.5)	1.17 (0.07, 20.03)	0.913	5/73 (6.8)	0/74 (0.0)	9.79 (0.89, 108.09)	0.063
Interaction - GA and treatment				0.860				0.393
Severe hypertension According to GA at randomisation								
<18 weeks	52/116 (44.8)	26/110 (23.6)	2.47 (1.33, 4.59)	0.004	-	-	-	-
18-23 weeks	48/116 (41.4)	21/101 (20.8)	2.52 (1.31, 4.85)	0.006	3/11 (27.3)	2/10 (20.0)	1.25 (0.15, 10.31)	0.837
24-29 weeks	35/83 (42.2)	31/87 (35.6)	1.30 (0.65, 2.58)	0.457	16/40 (40.0)	14/41 (34.1)	1.30 (0.49, 3.44)	0.596
30+ weeks	24/54 (44.4)	18/65 (27.7)	2.38 (1.02, 5.56)	0.044	22/73 (30.1)	22/74 (29.7)	1.03 (0.48, 2.18)	0.946
Interaction - GA and treatment				0.468				0.925
Preeclampsia According to GA at randomisation								
<18 weeks	59/116 (50.9)	50/110 (45.5)	1.19 (0.68, 2.07)	0.540	-	-	-	-
18-23 weeks	55/115 (47.8)	37/101 (36.6)	1.49 (0.83, 2.66)	0.180	5/11 (45.5)	4/10 (40.0)	1.28 (0.21, 7.82)	0.787
24-29 weeks	35/83 (42.2)	39/87 (44.8)	0.88 (0.46, 1.67)	0.693	23/40 (57.5)	18/41 (43.9)	1.88 (0.73, 4.82)	0.190
30+ weeks	27/54 (50.0)	29/65 (44.6)	1.24 (0.57, 2.70)	0.580	37/72 (51.4)	46/74 (62.2)	0.60 (0.30, 1.20)	0.150
Interaction - GA and treatment				0.696				0.145

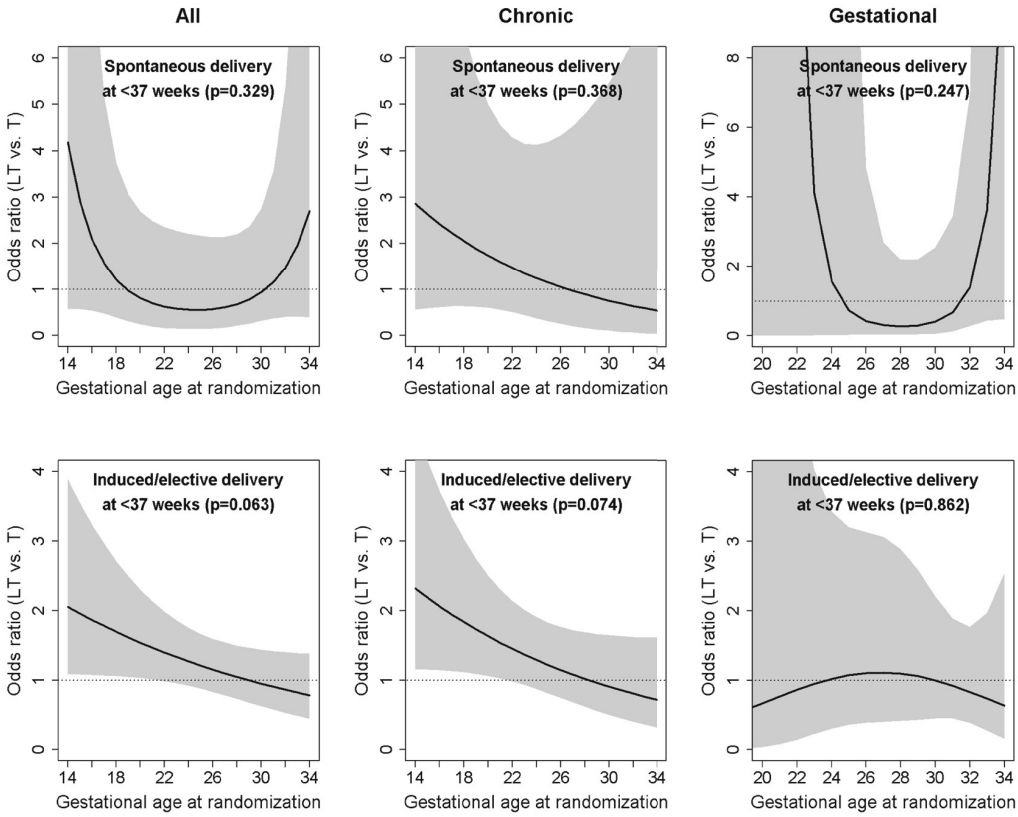
CI = confidence interval; GA = gestational age; LT = less-tight control; OR = odds ratio; T = tight control
** Randomisation was stratified for centre and hypertension type; there was no stratification for gestational age*

Table S6: Spontaneous and indicated preterm birth rates in less tight (versus tight) control, according to gestational age randomisation*

	LT control	T control	OR (95% CI)	P
Delivery at <37 weeks (spontaneous)				
All women	28/109 (25.7)	24/104 (23.1)	1.29 (0.57, 2.89)	0.541
Gestational age at randomisation				
<18 weeks	9/25 (36.0)	4/24 (16.7)	4.02 (0.76, 21.32)	0.102
18-23 weeks	5/27 (18.5)	5/24 (20.8)	0.57 (0.11, 3.03)	0.508
24-29 weeks	4/27 (14.8)	7/27 (25.9)	0.50 (0.09, 2.92)	0.442
30+ weeks	10/30 (33.3)	8/29 (27.6)	2.03 (0.44, 9.35)	0.359
Interaction between gestational age and treatment				0.239
Delivery at <37 weeks (induced/elective Caesarean without labour)				
All women	147/383 (38.4)	129/382 (33.8)	1.22 (0.89, 1.67)	0.223
Gestational age at randomisation				
<18 weeks	26/90 (28.9)	18/84 (21.4)	1.59 (0.77, 3.29)	0.208
18-23 weeks	43/100 (43.0)	22/87 (25.3)	2.07 (1.07, 4.02)	0.031
24-29 weeks	39/96 (40.6)	46/101 (45.5)	0.74 (0.40, 1.34)	0.318
30+ weeks	39/97 (40.2)	43/110 (39.1)	1.07 (0.59, 1.95)	0.812
Interaction between gestational age and treatment				0.118

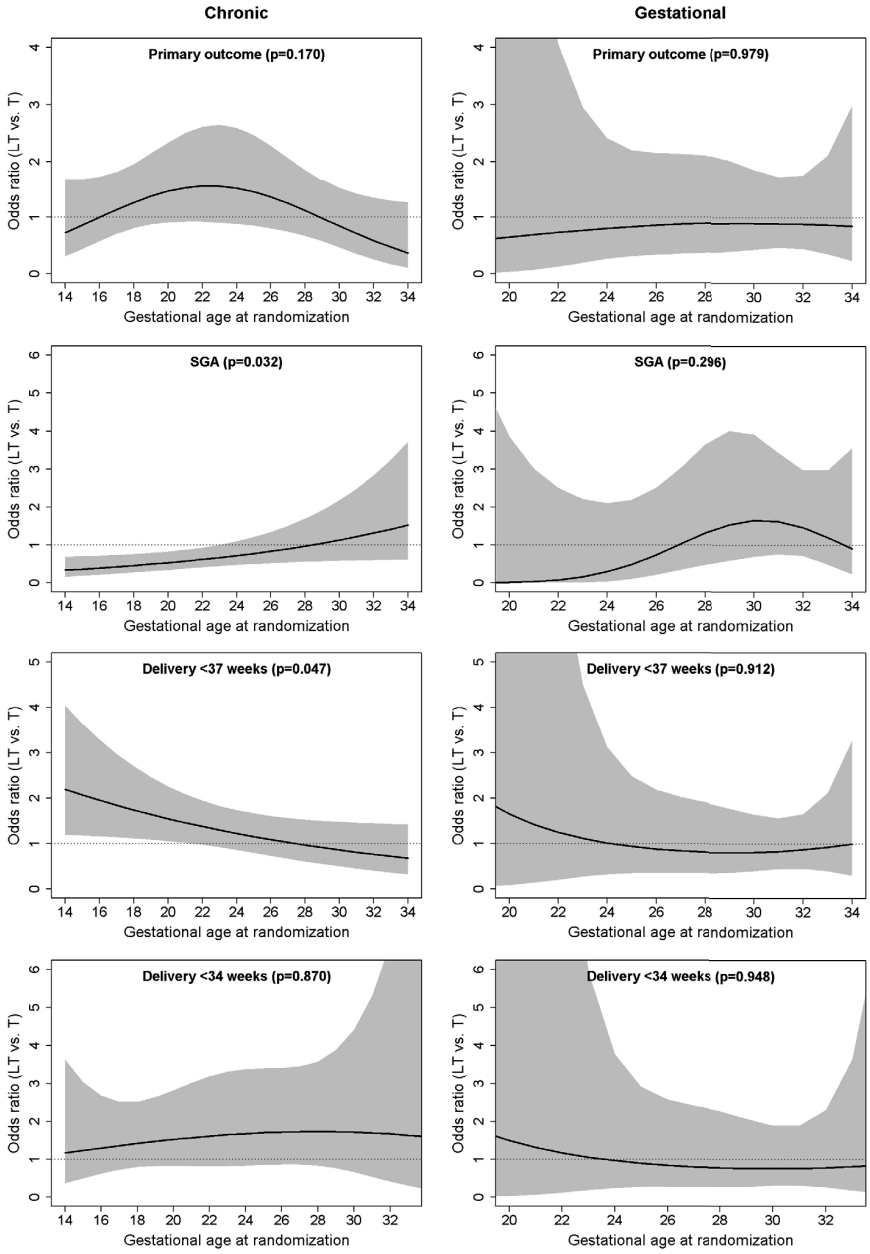
CI = confidence interval; LT = less-tight control; T = tight control
** Randomisation was stratified for centre and hypertension type. There was no stratification for gestational age*

Figure S1: Odds ratio and 95% confidence interval for spontaneous and induced/elective preterm birth in less-tight (versus tight) control, according to gestational age at randomisation (weeks)



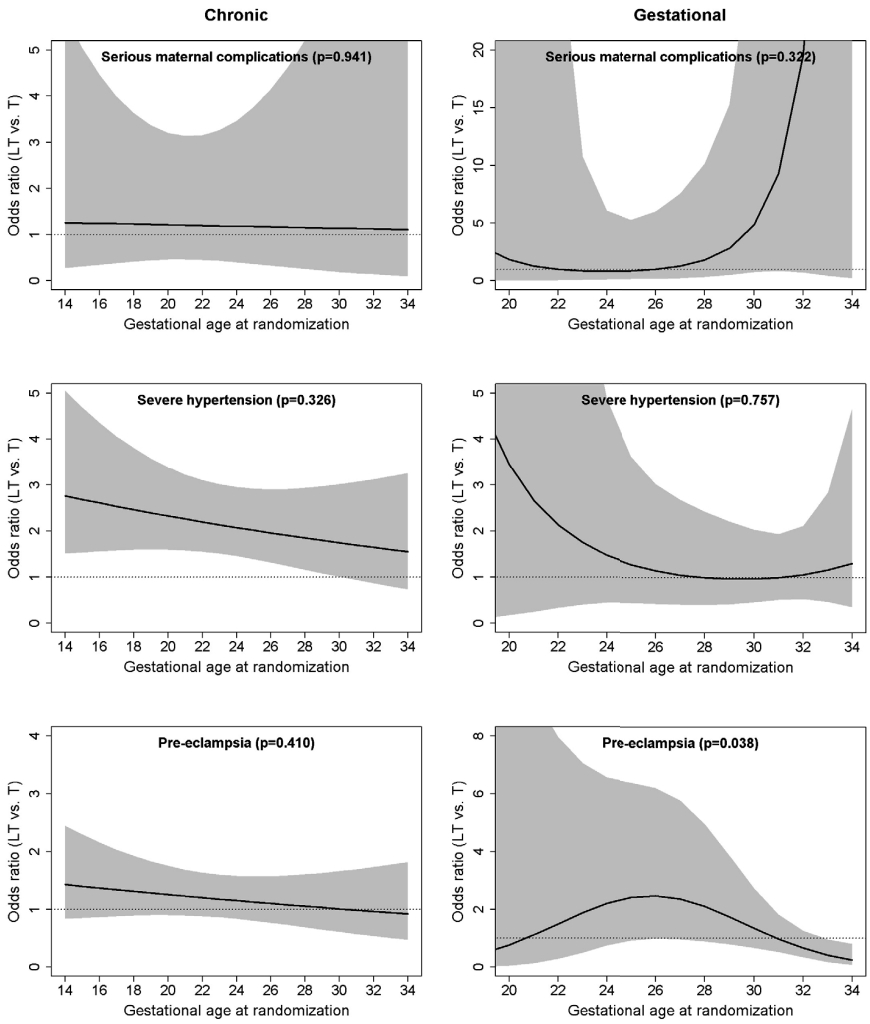
The p value shown is for the interaction between treatment group and gestational age at randomization treated as a continuous variable on the relevant outcome

Figure S2: Odds ratio and 95% confidence interval for CHIPS PERINATAL outcomes in less-tight (versus tight) control groups, according to gestational age at randomisation (weeks) in subgroups of chronic or gestational hypertension



The p value shown is for the interaction between treatment group and gestational age at randomization treated as a continuous variable on the relevant outcome

Figure S3: Odds ratio and 95% confidence interval for major CHIPS MATERNAL outcomes in less-tight (versus tight) control groups, according to gestational age at randomization (weeks) in subgroups of chronic or gestational hypertension



The p value shown is for the interaction between treatment group and gestational age at randomisation treated as a continuous variable on the relevant outcome

Chapter 7

STRIDER (Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction): an international consortium of randomised placebo-controlled trials

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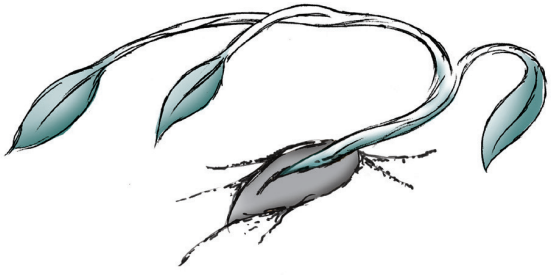

BMC Pregnancy Childbirth
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Abstract

Background

Severe, early-onset fetal growth restriction due to placental insufficiency is associated with a high risk of perinatal mortality and morbidity with long-lasting sequelae. Placental insufficiency is the result of abnormal formation and function of the placenta with inadequate remodelling of the maternal spiral arteries. There is currently no effective therapy available. Some evidence suggests sildenafil citrate may improve uteroplacental blood flow, fetal growth, and meaningful infant outcomes. The objective of the Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (STRIDER) collaboration is to evaluate the effectiveness of sildenafil versus placebo in achieving healthy perinatal survival through the conduct of randomised clinical trials and systematic review including individual patient data meta-analysis.

Methods

Five national/bi-national multicentre randomised placebo-controlled trials have been launched. Women with a singleton pregnancy between 18 and 30 weeks with severe fetal growth restriction of likely placental origin, and where the likelihood of perinatal death/severe morbidity is estimated to be significant are included. Participants will receive either sildenafil 25 mg or matching placebo tablets orally three times daily from recruitment to 32 weeks gestation.

Discussion

The STRIDER trials were conceived and designed through international collaboration. Although the individual trials have different primary outcomes for reasons of sample size and feasibility, all trials will collect a standard set of outcomes including survival without severe neonatal morbidity at time of hospital discharge. This is a summary of all the STRIDER trial protocols and provides an example of a prospectively planned international clinical research collaboration. All five individual trials will contribute to a pre-planned systematic review of the topic including individual patient data meta-analysis.

Trial registrations

New Zealand and Australia: ACTRN12612000584831. Registered 30/05/2012
Canada: NCT02442492. Registered 05/05/2015
Ireland: CT 900/572/1. Registered 15/07/2015
The Netherlands: NCT02277132. Registered 29/09/2014
United Kingdom: ISRCTN39133303. Registered 31/07/2014

Background

An estimated 0.4% of pregnancies worldwide are complicated by severe early-onset (<28 weeks gestation) fetal growth restriction (FGR) caused by placental insufficiency. This patient group utilises disproportionate amounts of obstetric care and has a high likelihood of premature birth, both for fetal and for secondary maternal indications such as the development of the maternal syndrome of pre-eclampsia. As these growth-restricted infants are usually born very preterm, they carry additional significant risks of major and minor neonatal morbidity, and long-term health sequelae if they survive. These risks are not only related to gestational age at birth, but also to the degree of FGR. Survival proportions for severely growth-restricted fetuses very remote from term (<28 weeks' gestation) vary between 7% and 33%(1-3) and less than one third of these fetuses will survive their neonatal intensive care unit (NICU) stay without significant neurodevelopmental sequelae(4).

The diagnosis of early onset FGR is often missed but even when diagnosed based on growth parameters below the normal range (<10th, <5th, or <3rd centile) with or without evidence of abnormal fetal and maternal Doppler waveforms there are currently no specific evidence-based therapies available. Non-specific interventions may include lifestyle modifications such as reducing or stopping work, stopping aerobic exercise, rest at home, and hospital admission for rest and surveillance. These interventions are used in the belief that rest will reduce the steal from the utero-placental circulation to the glutei and quadriceps muscles but are not based on any good quality evidence. In the absence of proven therapeutic interventions, standard clinical management consists of counselling, intensive monitoring, and timely delivery once a fetus has reached a viable gestation and size but often results in extreme preterm birth.

Doppler waveform analysis of pregnancies complicated by severe FGR suggests compromised utero-placental circulation and placental hypo-perfusion(5, 6). Sildenafil, a phosphodiesterase inhibitor, potentiates the action of nitric oxide thus causing vasodilatation(7). It is therefore possible that sildenafil may affect utero-placental circulation and perfusion resulting in improved gaseous and nutrient exchange and improved fetal growth and well-being. Animal and preclinical studies support this concept(8-13).

Although the number of women using sildenafil in pregnancy is low, it is increasingly used in pregnancy for maternal cardiac indications with no reports of adverse maternal or fetal effects(14-21). In a small randomised clinical trial in women with early onset pre-eclampsia, sildenafil use had no demonstrable effect on prolongation of pregnancy, but provided further reassurance on drug safety profile in pregnancy(16). Sildenafil has been used in a small cohort of women in the setting of early onset FGR. In an observational study by STRIDER collaborators in Vancouver, Canada, there was a tendency towards more live-born children with intact survival to primary discharge for women treated with sildenafil when compared to women with pregnancies at similar risk but not receiving sildenafil(17). From the limited observations to date there are no concerns of adverse

maternal, fetal, neonatal, or infant effects associated with sildenafil use in pregnancy(14-21).

On the basis of this preliminary research, some centres have already adopted treatment with sildenafil(18, 19). However, there is no clear evidence of true health benefits and, more significantly, potential harm has not yet been excluded. Use of sildenafil for other indications in clinical trials and in post-market reporting has highlighted adverse drug reactions including headache, flushing, nasal congestion, and impaired vision and, rare, serious consequences such as myocardial infarction, arrhythmias, and stroke(7). More specific to pregnancy and FGR, sildenafil's vasodilatory properties may cause a transient decrease in blood pressure with potential to adversely affect the most at risk fetuses (those with absent or reversed end diastolic flow on Doppler waveform analysis), via a reduction in critical utero-placental flow or by a direct effect on fetal vasculature. Prolonging pregnancy in FGR has the potential to shift the survival curve but will not necessarily have the same positive impact on short term outcomes and long term well-being. Well-designed, appropriately powered randomised placebo-controlled trials are required before implementation into clinical practice should be considered.

The overarching hypothesis of this collaboration of clinical trials is that sildenafil citrate compared with placebo will improve fetal growth and wellbeing, allowing prolongation of pregnancy leading to a decrease in the rate of fetal and neonatal mortality and severe morbidity.

Methods/Design

Design of the trials

Randomised placebo-controlled trials in New Zealand/Australia, Canada, Ireland, the Netherlands, and the United Kingdom including participants during 2014 to 2020. Trials are independently funded and executed and will be independently reported but all will contribute to a prospectively planned systematic review including individual patient data (IPD) meta-analysis(22). Each trial is prospectively registered: New Zealand and Australia: ACTRN12612000584831, Canada: NCT02442492, Ireland: CT 900/572/1, the Netherlands: NCT02277132 and the United Kingdom: ISRCTN39133303. Study protocols can be freely accessed URL(23-27).

Setting

Clinical trials are taking place in tertiary care centres in New Zealand/Australia, Canada, Ireland, the Netherlands, and the United Kingdom. A single trial management service hosted at the University of British Columbia, Canada, is being used by each trial and provides a randomisation service and electronic data collection system. IPD meta-analysis and systematic review will be performed by a trial and systematic review service unit in Denmark, The Copenhagen Trial Unit.

Participants
Pregnant women referred to tertiary care referral centres for evaluation and management of severe early-onset FGR at gestational ages < 30 weeks.

Inclusion and exclusion criteria
Individual trial inclusion and exclusion criteria are shown in Table 1. The differing inclusion criteria between individual trials allow for variations in feasibility, local standards, and investigator choice.

Ethics and informed consent
All trials have obtained appropriate local ethics approvals. All participating women are provided with written and verbal information regarding the trial they are going to enter and provide signed informed consent in advance of participation. Any protocol modifications once the trials are underway will be reviewed by the local Ethics Committee. Appropriate clinical trial insurance is in place for participants of each trial in the event that any participants experience harm as a consequence of participation in these trials.

Randomisation
R programming statistical software was used for generating the allocation lists. The R package blockrand function was modified to allow for varying numbers of strata. For each trial an allocation list was generated for each level of stratification variable. Each allocation list had a length of sample size + 20%. Block sizes used are specific to each individual trial.

Experimental and control interventions
Participants will receive oral sildenafil 25 mg or matching placebo tablets (Table 1) three times daily from randomisation until delivery, fetal demise, or 32 weeks gestation (whichever occurs first). Participants, researchers, dispensing pharmacists, clinicians and outcome assessors will remain unaware of treatment allocation for duration of trial. All other interventions will be provided according to local practice. Treatment code may be revealed in event of a serious adverse event where the responsible clinician deems this information to be crucial to provide on-going safe clinical care.

Sample size estimation
Assumptions for sample size estimations were made on the basis of clinical relevance, local audit, and a pilot cohort(17). Investigators for each individual trial made their own estimations, based on the choice of primary outcome and the following variables:
The New Zealand/Australian STRIDER trial has a primary outcome of fetal growth velocity determined by abdominal circumference (AC) growth velocity. Using data from the pilot cohort(17) to estimate a difference of 50% in placebo-treated versus 80% in sildenafil-treated of pregnancies with an increased post-randomisation AC growth velocity, 58 women will be randomised per group, (two-sided α of 0.05 and 90% power to detect this difference). Allowing for a 5% drop-out rate, the total sample size will be 122 women.

Three of the STRIDER trials have a primary outcome relating to the interval between

randomisation and birth. In the UK STRIDER and Irish STRIDER trials, one week (7 day) difference in mean randomisation and birth interval is considered to be clinically important. Internal audits of early-onset FGR cohorts revealed an average diagnosis-delivery interval of 20 days with standard deviation of 11 days. In order to confirm or refute that sildenafil can prolong pregnancy by one week compared with placebo, 52 women will be randomised per group in each trial (two-sided α of 0.05 and 90% power to detect this difference). Allowing for a 5% drop-out rate, the total sample size will be 112 women in each trial. Based on local pilot cohort experience, the Canadian STRIDER trial assumes a 16-day difference in mean gestational age at delivery, 189 days (placebo-treated) and 205 days (sildenafil-treated)(17). 41 women will be randomised per group (two-sided α of 0.05 and 80% power to detect this difference). Allowing for a 10% drop-out rate, the total sample size will be 90 women.

The Dutch STRIDER trial has a primary outcome of intact infant survival until hospital discharge. Assuming a 29% (placebo-treated) and 44% (sildenafil-treated) proportion of intact infant survival until hospital discharge, 161 women will be randomised per group (two-sided α of 0.05 and 80% power to detect this difference). Allowing for a 10% drop-out rate, the total sample size will be 354 women.

Outcomes

Primary outcomes of individual trials are summarised in Table 1. Individual trials have different primary outcomes but all trials collect a standard set of outcomes and apply the same definition for each outcome to ensure compatibility for future analysis.

Independent data monitoring and safety committees

All individual trials have their independent data safety monitoring committees and interim analyses of trial data are planned in some individual trial protocols. Individual trial data monitoring and safety committee charters can be freely accessed(28-32). An umbrella international data safety monitoring board has been established to provide oversight for all STRIDER trials and will review trial sequential data analysis after the completion of each trial once two trials have been completed.

Type of analyses

Independent blinded data analysis at the completion of each individual trial will occur on an intention-to-treat basis: that is, for the purpose of analysis, all women will be included in the group to which they have been randomised. Pre-planned subgroup analysis will occur within some individual trials including; assessment of the effect of low placental growth factor (PlGF) at inclusion, umbilical artery Doppler waveform analyses at inclusion (presence or absence of forward flow), and for the effect of other baseline parameters such as gestational age, estimated fetal weight, and participating centre.

Ancillary and follow-up studies
Each individual trial has ancillary studies underway. These include the effect of sildenafil on: maternal peripheral blood angiogenic factors, myometrial and placental vasculature, maternal haemodynamics, and neonatal cardiac function. Local bio-banking of placental tissue and/or umbilical cord blood is also planned in some trials.

Childhood outcome studies are proposed to assess the important longer-term outcomes of infants born to mothers participating in the STRIDER trials. This will include assessment of neurodevelopmental, cardiovascular, and metabolic outcomes. Assessment at 2-3 years of age is already funded or partially funded in the Netherlands and Ireland. Further funding applications are pending.

Recruitment status
New Zealand and Australia: Recruitment completed – data analysis in progress
Canada: Recruiting
Ireland: Not yet recruiting
The Netherlands: Recruiting
United Kingdom: Recruitment completed –primary outcome data submitted for publication

Table 1: Trial characteristics of each STRIDER trial

	Australia/ New Zealand	Canada	Ireland	The Netherlands	United Kingdom
Number of participants	122	90	112	354	112
Number of recruiting sites	12	10	6	10	18
GA (weeks)	22+0 – 29+6	18+0 – 27+6	22+0 – 29+6	20+0 – 29+6	22+0 – 29+6
Inclusion criteria	• Singleton pregnancy • Expectant management • 22+0 – 27+6 weeks: AC ≤3rd %ile • 28+0 – 29+6weeks: EFW <700g	• Singleton pregnancy • Expectant management • AC <10th %ile **AND/OR** • Reduced fetal growth (AC interval <50% of expected) with either prior severe early onset FGR with adverse perinatal outcome **OR** abnormal uterine artery waveform in index pregnancy; **OR** EFW <700g) • Serum PlGF levels < 5th %tile for GA	• Singleton pregnancy • Expectant management • EFW **OR** AC <10th centile • Absent or reversed EDF in umbilical artery	• Singleton pregnancy • Expectant management • 20+0-27+6wk: AC <3rd %ile **OR** EFW <5th %ile • 28+0-29+6wk: EFW <700g • Likely placental origin defined by a. Uterine artery notching **OR** b. Abnormal flow of umbilical artery or middle cerebral artery **OR** c. Maternal hypertensive disorder **OR** d. Low PlGF in point-of-care assessment	• Singleton pregnancy • Expectant management • EFW **OR** AC <10th centile • Absent or reversed EDF in umbilical artery
Exclusion criteria	• Known major fetal anomaly/syndrome/congenital infection deemed as likely cause for FGR • Known fetal aneuploidy • Any contra-indication to sildenafil use	• Maternal age ≤ 18 years • Known fetal aneuploidy, fetal anomaly/syndrome/congenital infection • Any contra-indication to sildenafil use • Cocaine/ crystal meth use • Pre-eclampsia or gestational hypertension	• Maternal age ≤ 18 years • Known or suspected structural or chromosomal fetal abnormality • Any contra-indication to sildenafil use • Cocaine use	• Maternal age ≤ 18 years • Known congenital malformation or infection • Any contra-indication to sildenafil use • Cocaine use • Use of cyp3A5 inhibitor	• Maternal age ≤ 16 years • Known or suspected structural or chromosomal fetal abnormality • Any contra-indication to sildenafil use • Cocaine use

		• HIV positive/ maternal heart disease • Receiving Prazosin, peripheral alpha-blockers, nitrates, vasoconstrictors			
Treatment period	Until delivery, demise or **31+6** weeks of gestation, whichever comes first	Until delivery, or **31+6** weeks of gestation, whichever comes first	Until delivery, or **31+6** weeks of gestation, whichever comes first	Until delivery, or **31+6** weeks of gestation, whichever comes first	Until delivery, or **31+6** weeks of gestation, whichever comes first
Stratification criteria	i. Umbilical artery EDF ii. GA range < 24 weeks vs ≥ 24 weeks	i. Centre	i. Centre ii. GA range (22+0 – 25+6) vs (26+0 – 29+6)	i. Centre	i. Centre ii. GA range (22+0 – 25+6) vs (26+0 – 29+6)
Primary outcome	Fetal growth velocity determined by AC growth velocity	*GA at delivery	Prolongation of pregnancy for one week as a surrogate for long term morbidity	Intact perinatal survival to term age without evidence of either severe CNS injury or non-CNS severe morbidity	Prolongation of pregnancy for one week as a surrogate for long term morbidity
Randomisation	**Centralised, computer based				
Blinding	Specifically manufactured visually matching active drug and placebo	Visually matching active drug and placebo by over encapsulation	Visually matching active drug and placebo by over encapsulation	Specifically manufactured visually matching active drug and placebo	Visually matching active drug and placebo by over encapsulation
Data management	**Centralised, computer based				

GA = Gestational age; EFW = Estimated Fetal Weight; AC = Abdominal Circumference; PlGF = Placental Growth Factor; EDF = End Diastolic Flow; HIV = Human Immunodeficiency Virus; CNS = Central Nervous System

** The first planned primary outcome for the Canadian STRIDER trial was fetal growth velocity(22). This was changed to an increase in gestational age at delivery following a funding review and assessment of feasibility*

*** Randomisation services and electronic data collection and management service (RedCap) provided to each individual trial by single co-ordinating centre at University of British Columbia, Canada*

Discussion

The STRIDER trials were conceived and designed through international collaboration. The trials are competitively funded at a national level by government funded research agencies within each country. Each individual trial protocol was developed independently by local groups of investigators but all trial designs are similar and all outcomes will be collected in all trials. Each trial will be conducted autonomously, but in close co-operation across the six countries involved. There is a central trial management service hosted at the University of British Columbia, Canada, providing a central randomisation service as well as a central electronic data collection system for each trial. The randomisation service and data collection systems have been designed collaboratively and, although each trial will use its own independent randomisation service and data collection systems these shared resources have reduced overall trial costs and will ensure data compatibility for future analysis in the prospectively planned IPD meta-analyses.

The research teams for all STRIDER trials have regular communication via e-mail, teleconferencing, face-to-face meetings, and a newsletter. Collaboration between the groups is strong with all teams committed to securing funding for long-term infant and childhood outcome studies. These data will contribute to further the systematic review and IPD meta-analysis.

The STRIDER trials are all conducted in order to reduce bias by employing central, stratified randomisation; blinding of all parties through use of matching placebos; central data management focusing on few missing data and dropouts; blinded drawing of conclusions; transparent uploading of IPD data after the trials have been published; no involvement of the pharmaceutical industries selling the product; as well as planning for systematic review of all trials including meta-analyses of individual patient data. These bias eliminating or reducing actions have all been conducted to minimize any risks of systematic errors, that is overestimation of benefits and underestimation of harms(33-40).

The STRIDER trials have all calculated their sample sizes taking into consideration a projected drop-out rate. This gives sample sizes that are inflated according to the assumed risks. We acknowledge this methodology should no longer be undertaken as there is now international consensus to analyse data with multiple imputation(41, 42). Such analyses will be used for the individual trials, however, we have not amended the sample size calculations as the projected drop-out is small in all trials.

In medicine, a single randomised clinical trial is unlikely to be able to change clinical practice(38). Therefore, the STRIDER trials have from inception been planned to be systematically reviewed together with any other randomised trials addressing the same topic(22). Furthermore, in order to better evaluate benefits and harms, the STRIDER trials are planned to be included alone or together with any other trial providing data into individual patient data meta-analyses(22). The STRIDER Consortium is presently

writing up a detailed statistical analysis plan for the systematic review and individual patient data meta-analyses.

The STRIDER Collaboration will ensure the assessment of sildenafil use for the treatment of early onset FGR occurs in a safe and timely manner and should ensure sildenafil is only introduced into clinical practice if reliable data on safety and efficacy supports its use. The extensive IPD data will also provide opportunities to broaden our knowledge of severe early onset FGR, and to explore other applications for sildenafil use if safety and efficacy are established.

Declarations

Ethics approval and consent to participate
New Zealand/Australia: New Zealand Health and Disability Ethics Committee (CEN/12/06/028/AM05), Royal Brisbane & Women's Hospital Human Research Ethics Committee (HREC/14/ORBW/178), and King Edward Memorial Hospital Ethics Committee (2014071EW).
Canada: University of British Columbia/Children's and Women's Health Centre of BC Research Ethics Board (H15-00899).
Ireland: provisional approval by Cork University Teaching Hospital Ethics Committee (ECM 5 (9) 02/02/16), full approval will be granted on confirmation of sponsorship (pending).
The Netherlands: METC AMC (NL41894.018.14).
The United Kingdom: 14.NE.0011.

All participating women are provided with written and verbal information regarding the trial they are going to enter and provide signed informed consent in advance of participation. Any protocol modifications once the trials are underway will be reviewed by the local Ethics Committee. Appropriate clinical trial insurance is in place for participants of each trial in the event that any participant experiences harm as a consequence of participation in these trials.

Consent to publish
Not applicable.

Availability of data and materials
The datasets that will be generated and/or analysed from these studies will be publicly available once all trials are complete, individual completed trial datasets will be available from the chief investigator of each trial upon reasonable request.

Competing interests
None.

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Denmark: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark.

Funders do not have any influence on study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

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Chapter 8

Detailed statistical analysis plan for the Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) randomised clinical trial on sildenafil versus placebo for pregnant women with severe early onset fetal growth restriction

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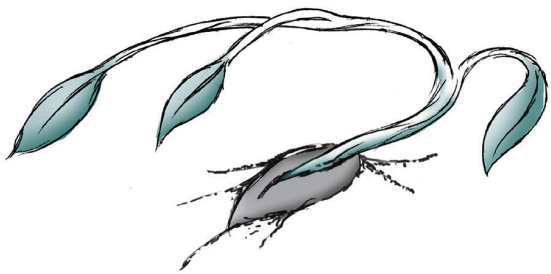

Abstract

Objective
The objective of the Dutch Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (STRIDER) randomised clinical trial is to assess the beneficial and harmful effects of sildenafil versus placebo on fetal and neonatal mortality in pregnant women with severe early-onset fetal growth restriction. The objective of this detailed statistical analysis plan is to minimise the risks of selective reporting and data-driven analysis.

Setting
The setting is 10 tertiary care hospitals and one secondary care hospital in The Netherlands.

Participants
The participants will be 360 pregnant women with severe early-onset fetal growth restriction.

Interventions
The intervention is sildenafil 25 mg or placebo orally three times a day.

Primary and secondary outcome measures
The primary outcome is a composite of death or major neonatal morbidity assessed at hospital discharge. The secondary outcomes are neurodevelopmental impairment; mean scores of the Bayley III cognitive and motor assessment; the proportion of patients experiencing either preeclampsia or haemolysis elevated liver enzymes low platelets-syndrome; pulsatility index of uterine arteries, umbilical artery, and middle cerebral artery; birthweight; and gestational age at either delivery or intra-uterine death.

Results
A detailed statistical analysis is presented, including pre-defined exploratory outcomes and planned subgroup analyses. One interim analysis after 180 patients had completed the study was planned and a strategy to minimise the risks of type I errors due to repetitive testing is presented. During review of this manuscript the interim analysis was performed by the Data Safety Monitoring Board and early stopping of the trial was recommended. Final analyses will be conducted independently by two statistically qualified persons following the present plan.

Conclusion
This pre-specified statistical analysis plan was written and submitted without knowledge of the unblinded data and updated after stopping of the trial at interim analysis.

Trial registration
ClinicalTrials.gov identifier: NCT02277132. Registered 29th of September 2014. https://clinicaltrials.gov/ct2/show/NCT02277132.
Original protocol for the study: doi:10.5281/zenodo.56148.

Background

The Dutch Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction (STRIDER) randomised clinical trial is a blinded trial that was recruiting participants recently, assessing the benefits and harms of sildenafil versus placebo in pregnant women with severe early onset fetal growth restriction (FGR) and their offspring. The primary outcome is mortality and morbidity of the children.

Fetal growth restriction is a condition in which a fetus does not reach its designated growth potential and thus is too small for gestational age (SGA), mostly defined as either estimated fetal weight or abdominal circumference determined by ultrasound below the third percentile for gestational age below the tenth percentile. However, no unanimously agreed definition has yet been adopted(1).

The predominant cause of fetal growth restriction, particularly at early onset (<32 weeks), is placental dysfunction with high resistance, low-flow, placental circulation, due to inadequate spiral artery remodelling early in pregnancy(2). Depending on the gestational age at development, the fetus has a substantial risk of mortality and morbidity(3). As the phosphodiesterase 5- (PDE5-) inhibitor sildenafil causes vasodilatation, it might improve the utero-placental circulation in fetal growth restriction resulting in improved growth and increased chances of healthy survival of the fetus(4-20).

A recent meta-analysis on sildenafil in fetal growth restriction has been published(21). This meta-analysis included only one randomised clinical trial of sildenafil in which a single administration of 50 mg sildenafil versus placebo was given to pregnant women with fetal growth restriction between 24 and 37 weeks of gestation(22). An improvement of the Doppler measurements of the umbilical artery and middle cerebral artery was seen in the sildenafil group compared with the placebo group(22). However, no patient-centred or clinically relevant outcomes (such as morbidity and mortality) were assessed and patients only received a single dose of sildenafil. The review, furthermore, described a non-randomised comparative study in which 10 women received sildenafil 25 mg three times a day compared to 17 women without sildenafil administration(23). This observational study indicated an increase in fetal abdominal circumference growth and a trend toward better survival in the sildenafil group compared to the group that was untreated(23). The review does not identify other clinical trials of sildenafil in fetal growth restriction and concludes that more randomised clinical trials are needed(21).

Besides the short-term randomised clinical trial and the observational study mentioned above, we identified one recently published clinical trial where 35 patients with fetal growth restriction were randomised to three groups, receiving either oral sildenafil, transdermal nitroglycerin, or oral placebo(24). The outcomes were non-validated surrogate outcomes(25), i.e. Doppler ultrasound measurements of the uterine arteries, umbilical artery, and middle cerebral artery were evaluated after administration of the trial interventions. Positive effects of sildenafil and nitroglycerin were seen in the pulsatility index of

the uterine artery and the umbilical artery, while no effect was seen in the placebo group(24).

A couple of randomised clinical trials on sildenafil have been conducted in women with diagnosed preeclampsia. A randomised clinical trial including 100 women with preeclampsia showed a statistically significant difference in pregnancy prolongation of 4 days in favour of the sildenafil group compared with the placebo group(26). In another randomised clinical trial, 35 patients with preeclampsia received sildenafil in increasing dose versus placebo. This trial did not find a significant difference in pregnancy prolongation after treatment with sildenafil compared with placebo(12).

Apart from sildenafil, interest has also focused on L-arginine, which is an amino-acid that interacts in the same pathway as sildenafil and theoretically could have a similar clinical effect. The aforementioned meta-analysis of Chen and colleagues included eight randomised clinical trials and one quasi-randomised study (total 576 patients) assessing L-arginine versus placebo or no therapy(21). The analysis showed that L-arginine seems to have a significant beneficial effect on birthweight, gestational age at delivery, intracranial haemorrhage, and neonatal respiratory distress syndrome(21). However, the authors of the meta-analysis state that four of the nine studies were of uncertain quality and there is a high risk of bias(27-30). Furthermore, the number of randomised patients in the trials is relatively small.

By reviewing the existing literature, high-quality evidence is pending for a pharmacological treatment of fetal growth restriction. Apart from the Dutch STRIDER, four other STRIDER trials are presently conducted or are in different phases of preparation, recruitment, and analysis(31). The results of the UK STRIDER trial have been published recently(32) and did not show a difference in pregnancy prolongation between patients allocated to sildenafil versus placebo. To minimise the risks of selective reporting and data-driven analyses, we will here shortly describe the plans for interim analysis and in detail our statistical analysis plans of the Dutch STRIDER trial and how the results will be reported. At first submission of this manuscript, the Dutch STRIDER trial was still recruiting patients and collecting the data, however, during the review of this manuscript, the trial was stopped early based on advice of the DSMB.

Trial overview

Please see the published protocol of the trial for a detailed description of the methodology(33). In short, the Dutch STRIDER trial compares 25 mg sildenafil three times daily orally with matching placebo three times daily in women with severe early-onset fetal growth restriction. The placebo matches the sildenafil in form, size, colour, smell, and solubility. The patients eligible for inclusion are women from 20 weeks and 0 days of gestation until 29 weeks and 6 days, with fetal growth restriction and signs of placental insufficiency, without an alternative explanation for the fetal growth restriction. Participants will use study medication until 32 weeks of gestation or delivery, whichever comes first. The participants, the treatment providers, the outcome assessors, the statisticians, and the

conclusion drawers were planned to be blinded for the treatment allocation(27, 28, 34-40). The treatment allocation was unblinded on early stopping of the trial. The participants, treatment providers, and outcome assessors were blinded up to stopping the trial at the interim analysis.

The original protocol of the Dutch STRIDER trial was approved by the local ethical committee on 22 July 2014. The first patient was included on 20 January 2015. The trial was conducted according to the principles of the Declaration of Helsinki Medical, Dutch legislation on medical research involving human subjects(41-44) and Good Clinical Practice Guidelines (GCP)(45). Patients could only be included in the trial after written informed consent from the pregnant woman was obtained. All study sites are monitored by an independent clinical research associate of the Nederlandse Vereniging voor Obstetrie en Gynaecologie Consortium. An independent data safety monitoring board (DSMB) monitored the study progress, with a special focus on safety (see below). The trial will be reported according to the Consolidated standards of reporting trials (CONSORT) guidelines(46).

Intervention period and data collection
The intervention is sildenafil 25 mg three times daily orally versus placebo three times daily up to 32 weeks gestation or delivery, whichever comes first. Clinical outcome data will be recorded from mother and neonate until discharge to home. Follow up of the child will be assessed at 2 years of age in an outpatient setting.

Concomitant treatments
Patients who participate in the Dutch STRIDER trial will furthermore be treated according to local protocol. The caregivers, blinded for the allocated therapy, will make decisions for the administration of corticosteroids for fetal lung maturity, for the moment of delivery based on fetal and maternal condition and maternal treatment of hypertensive disorder according to the clinical practice in that particular centre, as if patients were not participating in a trial.

Baseline variables
The baseline criteria that are considered to be relevant and are planned to be reported are listed in table 1. The baseline characteristics will be presented by treatment allocation. Binary and categorical outcomes will be expressed in frequencies and percentages. In the case of missing data, there will be a note on how many data were available. Continuous variables will be expressed by either mean and standard deviation (normal distribution) or median and IQR (non-normal distribution). Differences in the treatment arms will not be statistically tested.

Table 1. Baseline criteria

	Sildenafil (n=)	Placebo (n=)
Age (years)		
BMI (kg/m^2)		
Ethnicity		
Caucasian (%)		
African descent (%)		
Asian (%)		
Other (%)		
Highest completed educational level mother		
High (%)		
Middle (%)		
Low (%)		
Unknown (%)		
Highest completed educational level father/partner		
High (%)		
Middle (%)		
Low (%)		
Unknown (%)		
Language spoken at home		
Only Dutch		
Only other language than Dutch		
More than one language, including Dutch		
Maternal smoking (%)		
Gestational age at inclusion (weeks + days)		
Estimated fetal weight at ultrasound (gram)		
Fetal abdominal circumference at ultrasound (mm)		
Notching uterine artery (one-or two-sided) (%)		
PI umbilical artery >95th centile (%)		
PI middle cerebral artery <5th centile (%)		
End-diastolic flow		
Positive (%)		
Absent (%)		
Reversed (%)		
Pregnancy-induced hypertension (%)		
Preeclampsia (%)		
HELLP syndrome (%)		
Systolic blood pressure (mmHg)		
Diastolic blood pressure (mmHg)		

Data collection and storage
Data management was implemented according to GCP guidelines. Patient data up to hospital discharge and long-term follow up data are entered via an electronic case record form (CRF) in a central GCP-proof web-based database to facilitate on-site data entry (RedCap). Security is guaranteed with login names, login codes, and encrypted data transfer. Data collection is performed at multiple time points: at the time of inclusion and randomisation, during the study medication treatment period, at hospital discharge of the child and at 2 years corrected age for follow up. Data on eligible patients not included in the study are also recorded, including patient characteristics and the primary outcome (death or survival with major morbidities).

Serum placental growth factor (PlGf) will be analysed after completion of the study. The PlGf analysis currently is not part of standard care and is not often performed. To investigate the predictive value of PlGf for adverse outcomes in FGR, blood serum samples at inclusion are collected and stored. Samples will not be used before the inclusion and data collection of the study is complete.

Primary outcome
The primary outcome is a composite outcome consisting of either:

1) Neonatal mortality assessed at the time point when the neonate is discharged from the hospital or

2) Major neonatal morbidity defined as
- Intraventricular haemorrhage (IVH) grade 3 or more
- Periventricular leukomalacia (PVL) grade 2 or more
- Moderate or severe bronchopulmonary dysplasia (BPD)
- Necrotising enterocolitis (NEC) grade 2 or more or
- Retinopathy of prematurity (ROP) treated by surgery or laser therapy

• Intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) will be assessed in neonates that were born at a gestational age < 32 weeks or with a birthweight < 1500 g. These neonates will have an ultrasound scan of the brain as standard. Brain magnetic resonance imaging (MRI) will be performed in case different types of abnormalities are seen on ultrasound or in the clinical behaviour of the neonate. The timing and the number of investigations is dependent of the gestational age at birth, the abnormalities seen, and the clinical behaviour of the neonate. Investigations will be performed according to Dutch national recommendations(47). If a neonate is evaluated by ultrasound, the scan showing the most severe abnormalities will be used to assess the neurological morbidity. If a neonate does not have an ultrasound scan because it is born (near-)term and there is no clinical suspicion of neurological morbidity, this will be diagnosed as “no neurological morbidity”.

• Bronchopulmonary dysplasia is assessed at 36 weeks postmenstrual age (PMA) according to the Dutch guideline for BPD and the National Institute of Child Health and Human Development (NICHD) consensus statement using the classification of severity and, if indicated, the oxygen reduction test as described by Walsh et al.(48-53). Neonates that will be born after 36 weeks' gestational age will be diagnosed as "no bronchopulmonary dysplasia".

• Retinopathy of prematurity (ROP) screening will take place according to the Dutch guideline for ROP(54). Screening will be performed by an ophthalmologist in neonates born < 30 weeks gestational age and/or with birthweight < 1250 gram. Neonates born between 30 and 32 weeks and with birthweight between 1250 and 1500 gram will in some situations be screened for retinopathy of prematurity as well. The timing and number of assessments is dependent on the gestational age at birth and the abnormalities found at assessment. Neonates that will not be screened for ROP according to the guideline, will be diagnosed as "no retinopathy of prematurity".

• Necrotising enterocolitis is a clinical diagnosis and staging will be according to the Bell system(55). Whether a neonate will have had an episode of necrotising enterocolitis requiring surgery will be assessed and reported at the time of discharge from the neonatal intensive care.

Secondary outcomes
The secondary outcomes are:

1. The proportion of neonates with neurodevelopmental impairment at 2 years of age, assessed on the 2-year Bayley scales of infant development (BSID)-III(56). Neurodevelopmental follow up will be at the outpatient clinic at the corrected age of the infant of 2 years (2 years after the term age), which is standard in The Netherlands for children born < 30 weeks gestation or born with weight < 1000 g. Neurodevelopmental impairment will be defined using two measures: first, as a cognitive Bayley III score < 85 (or an estimated cognitive delay of more than 3 months when a Bayley test cannot be carried out), composite motor score < 85, cerebral palsy, with a Gross Motor Function Classification System (GMFCS) grade > 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted). The second definition of NDI is similar except it does not include the motor score <85. Second, we will describe the different components of the composite outcome, including all cases of CP and their GMFCS classifications.

2. The mean composite cognitive Bayley III score (continuous outcome), assessed at the 2-year Bayley scales of infant development BSID-III(56).

3. The mean composite motor score for the Bayley scales of infant development BSID-III(56), and the mean standard scores on the fine and gross motor subscales.

4. The proportion of mothers experiencing either preeclampsia or haemolysis, elevated

liver enzymes, and lowplatelets (HELLP) syndrome. Preeclampsia is defined as hypertension in combination with proteinuria. Hypertension is defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg (Korotkoff V), measured at least twice, after 20 weeks of gestation in a patient that had no hypertension before. Proteinuria is defined as ≥ 300 mg protein measured on 24-h urine collection(57). HELLP syndrome is defined as elevated lactate dehydrogenase (LDH); either elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT); and low platelets, according to local laboratory reference values(58). Second, the proportion of patients with preeclampsia and the proportion of patients with HELLP syndrome will be reported individually as well. Whether or not a patient will have had preeclampsia or HELLP syndrome, will be assessed when the mother is discharged to go home after delivery. Development of preeclampsia or HELLP syndrome after discharge home for which readmission is necessary will be considered as a serious adverse event (SAE) and will be line-listed, as described in "Severe adverse events".

5. Pulsatility index of umbilical artery: we will use the first pulsatility index measured on ultrasound performed > 24 h after starting study medication.

6. Birthweight (grammes): we will separately describe the birthweight of live-born neonates and the birthweight of fetuses that experienced intra-uterine death.

7. Gestational age of either delivery or intra-uterine death (weeks and days).

Exploratory outcomes
The relevant exploratory outcomes we plan to report, are listed in table 2 for mother and fetus/neonate.

The percentage of infants that have been assessed for each particular diagnosis will be described for all neonatal outcomes. A table will be presented with line-listing of the primary causes of neonatal death as well. Frequencies and the proportion of total neonatal deaths will be reported.

Table 2: Maternal and fetal/neonatal outcomes

	Intention to treat			Intention to treat, adjusted for GA and EFW at inclusion			Per protocol		
	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value
Maternal outcomes									
Treatment duration (days)									
Gestational age at delivery (weeks + days)									
Pregnancy prolongation after randomisation (days)									
Abdominal circumference at ultrasound closest to two weeks after randomisation (mm)									
Mode of delivery									
Caesarean section on fetal indication (%)									
Caesarean section on maternal indication (%)									
Induced vaginal delivery on fetal indication (%)									
Induced vaginal delivery on maternal indication (%)									
Spontaneous vaginal delivery (%)									
Induction of labour after intra-uterine death (%)									
Pregnancy induced hypertension (%)									
Preeclampsia (%)									
HELLP syndrome (%)									
Maternal use of antihypertensive treatment antenatal or postnatal									
One antihypertensive									
Two antihypertensives									
Three or more antihypertensives									
Maternal need for magnesiumsulphate for hypertension (%)									
Neonate born between 48 h and 14 days after antenatal corticosteroids course (complete course) (%)									

	Intention to treat			Intention to treat, adjusted for GA and EFW at inclusion			Per protocol		
	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value
Neonate born between 0 and 48 h after antenatal corticosteroids course (incomplete course) (%)									
Neonate born during maternal administration of intravenous magnesium sulphate (%)									
Fetal/neonatal outcomes									
Intra-uterine death (%)									
Neonatal death (%)									
Survival at hospital discharge (%)									
Survival with relevant morbidity at hospital discharge (%)									
Survival without relevant morbidity at hospital discharge (%)									
Birthweight of neonates with intra-uterine death (gram)									
Birthweight of neonates with live birth (gram)									
Postmenstrual age at first discharge home (weeks + days)									
IVH Grade III or IV (%)									
PVL Grade II or more (%)									
Moderate or severe BPD (%)									
No BPD (%)									
ROP treated by laser or surgery (%)									
One or more culture-proven episode of infection or clinical episode of infection with antibiotic treatment necessary ≥ 5 days (%)									
NEC grade II or more (%)									

Severe adverse events
Severe adverse events (SAEs) were pre-defined as any medical occurrence that results in death, is life-threatening, causes or prolongs hospital admission, results in persistent or significant disability or incapacity, or results in congenital anomaly. Due to the characteristics of the included patient group, mortality, morbidity and hospital admission are common. In the study protocol maternal and fetal/neonatal SAEs were divided into a group of "context-specific" and "non-context-specific" SAEs. Fetal/neonatal context specific SAEs consist of the events that are explained by and related to the prematurity and dysmaturity due to fetal growth restriction, for example intra-uterine death, neonatal death due to complications of prematurity/dysmaturity. Non-context-specific SAEs will be considered to be unfavourable events that are not explained by the prematurity/dysmaturity as result of the fetal growth restriction. Hospital admission for delivery, hypertensive disorders or fetal monitoring will be considered as context-specific. Other maternal SAEs will be considered to be non-context-specific. All SAEs are evaluated by the Data Monitoring Committee: the context-specific SAEs are monitored during the safety analysis and performed after every 50 patients that completed the study. Non-context-specific SAEs will be sent to and evaluated by the committee right away.

Due to the character and the expected high prevalence of SAEs we did not define SAEs as primary or secondary outcome and will not perform statistical testing on the SAEs, but report them through line-listing.

Adverse effects
Patients are asked to keep note of the adverse effects they experience during the use of study medication in order to evaluate the percentage of women experiencing adverse effects and evaluate the character of experienced adverse effects.

Subgroup analysis
Pre-defined subgroup analyses are:
- An abnormal or normal serum level of placental growth factor (PlGF), defined as PlGF < 5th percentile of the reference value and ≥ 5th percentile of the reference value.
- Placental growth factor (PlGF) < 25th percentile of all samples of the study population and PlGF ≥ 25th percentile of all samples of the study population.
- Gestational age at inclusion, categorized as < 25 weeks of gestation and ≥ 25 weeks of gestation.
- Estimated fetal weight (EFW) at inclusion, categorised as < 300 g, 300-599 g and ≥ 600 g.
- Neonates that appear to have a congenital anomaly, which was not known in the antenatal period, and thus at the time of randomisation, will be included in the final analysis. However, we propose a subgroup analysis in this group of patients and if we find a significant difference in primary outcome of these neonates, we will consider excluding them.

We plan to perform a prognostic study and aim to have the methodology published in a separate statistical analysis plan.

Stratification and design variables
The only stratification variable in the randomisation will be trial site (hospital). 11 Hospitals participated in the study.

Sample size and power estimations
The sample size of the Dutch STRIDER trial has been previously estimated(59). With an acceptable risk of type I error of 5% and risk of type II error of 80% we aim to investigate a decrease on the primary outcome from 71%(23) in the control group to 56% in the experimental group, which is equal to a relative risk reduction just above 21%. Allowing for one interim analysis according to the O'Brien-Fleming spending function ($p < 0.005$), 175 women are needed per group. This sensitivity analysis was taken into account in the sample size analysis, if the anticipated inclusion target is reached the final analysis will still be powered at 80% to test at a significance level of 0.05. We will include an extra 10 women to account for loss to follow up. The total sample size has been modified to 360 women.

A total of 796 patients will be participating if all STRIDER trials include the number of patients indicated in the sample size calculations. With this number of participants, we will have 80% power to detect a difference of 8.6% in primary outcome between the intervention and placebo group, having a risk of 5% type I error.

Power estimations for secondary outcomes: based on the estimated sample size of 360 women and an acceptable risk of type I error of 5%, we estimated the statistical power of the secondary outcomes:

1. Neurodevelopmental impairment: 60% power to confirm or reject an increase in neurodevelopmental impairment from 10%(60) in the control group to 20% in the experimental group, equal to a relative risk reduction of just above 21%, having a risk of 5% for type I error.
2. Bayley III score: 80% power to confirm or reject a minimal relevant difference of 5.5 points on the mean composite motor score of the Bayley scales of infant development BSID-III(56), when assuming that 148 children will be alive at 2 years of age and that the mean composite score in the placebo group is 99 (SD 12) with an acceptable risk of 5% for type I error(60).
3. The proportion of mothers experiencing either preeclampsia or HELLP syndrome: 80% power to detect an increase from 50%(23, 26, 61) in the placebo group to 65% in the sildenafil group.
4. Pulsatility index (PI) of the umbilical artery: 80% power to confirm or reject a mean difference of 0.03 in PI, when assuming that PI before sildenafil administration is 1.13 (SD 0.10)(22) with an acceptable risk of 5% for type I error.
5. Birthweight (grammes): 80% power to confirm or reject a mean difference of 45 g in the birthweight, when assuming the mean birthweight in the placebo group is 422 gram (SD 159) with an acceptable risk of 5% for type I error(23).

6. Gestational age at either delivery or intra-uterine death: 94% power to confirm or reject a mean difference of one week in the gestational age at delivery (SD 2.7 weeks(26)).

Interim analysis

Safety analyses are planned after every 50 patients completing the trial (defined as hospital discharge of the neonate) in which no statistical testing will be performed. The Data Safety Monitoring Committee (DSMB) consists of gynecologists and neonatologist and an independent statistician(62). One interim analysis is planned after outcomes are available for the first half of the anticipated inclusions 180 patients have completed the trial. During the interim analysis, the trial will be stopped if a significant difference in primary outcome between the two treatment arms is observed ($p < 0.005$ according to O'Brian-Fleming rule)(63). The study can be stopped at any time in case the safety of the patients or fetus is considered to be in danger. Also, evidence from other trials and data from the ongoing STRIDER trials will be considered during interim analysis(64).

Statistical analysis

Data on all outcomes will be analysed by two independent statisticians blinded to treatment allocation. Two independent statistical reports will be sent to a third statistician and if there are discrepancies, then the three statistical experts will discuss possible reasons and identify the most correct result.

General analysis principles

The analysis of the Dutch STRIDER trial will be an intention-to-treat analysis, including all patients randomised in the trial. Random intercept models will be used for all primary analyses to account for a center effect. This method assumes that the effect is constant across the centers, but that the background risks differ. Additionally, we will secondly also adjust all primary analyses for design variables by adding them to the regression model. The design variables will be estimated fetal weight at inclusion and gestational age at inclusion. The course of pregnancy can be difficult to predict. In some women, there will unexpectedly be signs of fetal distress or worsening of the maternal condition due to a hypertensive disorder and therefore emergency delivery might be necessary, even before starting study medication. Therefore, a per-protocol analysis is planned as well, including only patients that used at least one tablet of study medication.

STATA 15 will be used for the statistical analysis and analysis is planned to follow the 5-step procedure for evaluation of intervention effects in randomised clinical trials, as proposed by Jakobsen et al.(65). The five steps consist of (1) reporting the confidence intervals and the exact P values for the primary, secondary, and exploratory outcomes; (2) reporting Bayes factor for the primary outcome; (3) adjusting the confidence intervals and the statistical significance threshold if the trial is stopped early or if interim analyses have been conducted(66, 67); (4) adjusting the confidence intervals and the P values for multiplicity due to number of outcome comparisons; and (5) assessing clinical significance of the trial results.

We plan to publish the results of the trial with a primary publication, reporting the primary and secondary outcomes assessed at discharge home of the neonate. The results of the 2-year neurodevelopmental assessment will be published separately.

The Bayes factor is the ratio between the probability of obtaining the result assuming the null hypothesis (H0) is true divided by the probability of obtaining the result assuming the alternative hypothesis (HA) is true. This factor will be calculated, as the P value may be misleading in the case of a low probability of the trial results being compatible with the hypothethical intervention effect in the sample size calculation, even though the P value is below the pre-specified threshold(68). A result < 1.0 supports the conclusion that the sildenafil improves healthy survival in fetal growth restriction, while a Bayes factor > 1.0 supports the inverse conclusion. The suggested threshold in literature is 0.1 for Bayes factor as an indicator of a high probability of an intervention effect similar to or even greater than the hypothetical intervention effect used in the sample size calculation.

Dichotomised outcomes will be presented as proportions of participants in each group with the event, and risk ratios with 95% confidence intervals. Relative risks will be analysed using generalised linear models (bireg) using a log link function(69). Additionally, absolute risk reductions and number needed to treat will be presented for interpretability.

Continuous outcomes will be presented as means, standard deviations, and 95% confidence intervals or medians and interquartile ranges for each group and mean differences, standard deviations, and 95% confidence intervals for the difference between the groups. Continuous outcomes will be analysed using linear regression.

Missing data

In case of missing data, we will follow the principles described by Jakobsen et al.(70) and decide how to handle missing data based on the type of variable or outcome, type of missingness, and proportion of missing data. Either complete case analysis or single or multiple imputation are possible solutions for missing data.

As we expect to have some missing data on the secondary outcome of neurodevelopment, we expect to perform imputation on this outcome. Imputation will not be performed for baseline criteria.

Outline of figures and tables

Figure 1 will be the CONSORT diagram with the flow chart of eligible and randomised patients.

Figure 1: CONSORT flow diagram

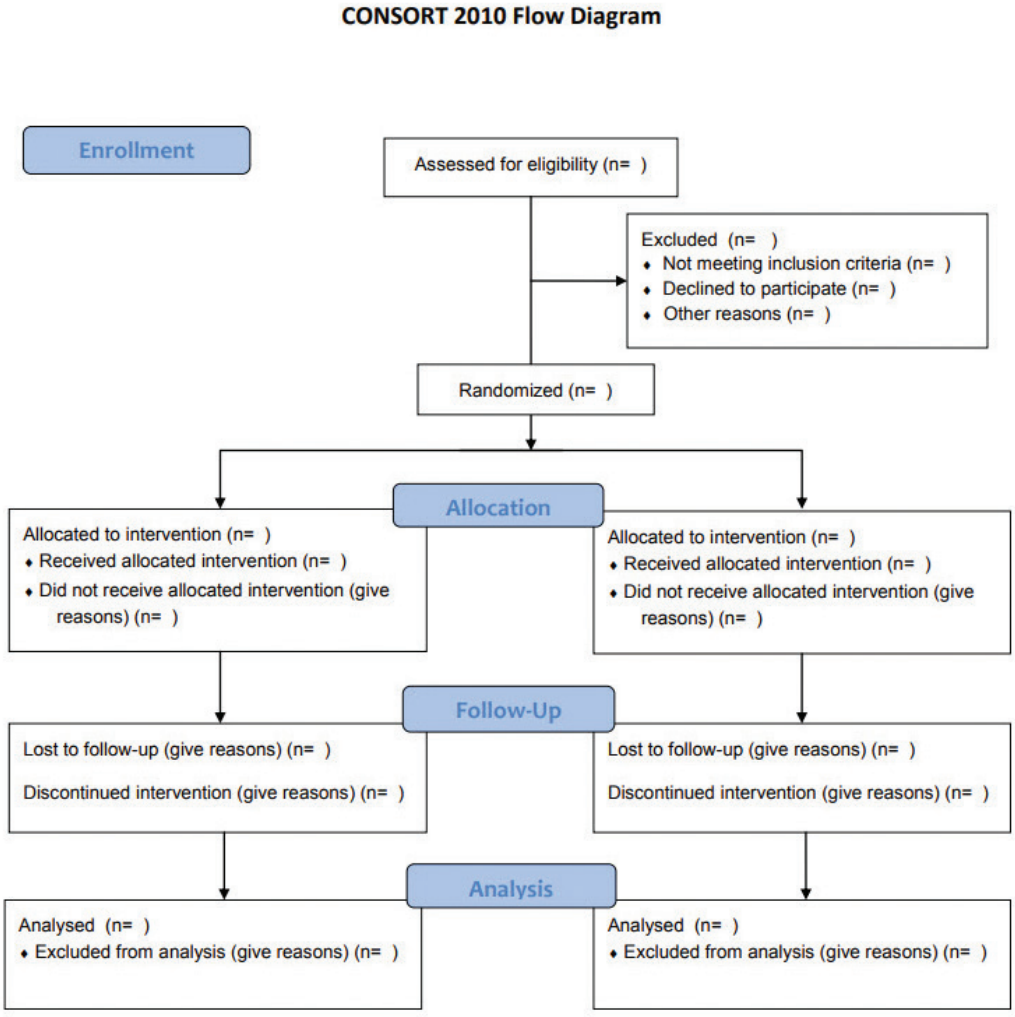

Table 1 will be the table with baseline criteria. The maternal and fetal/neonatal outcomes will be expressed in Table 2, showing both the intention-to-treat and the per-protocol analysis. The neonatal outcomes will not be available for all patients, as some patients will have died before assessing a certain variable, for example bronchopulmonary dysplasia, which is assessed at 36 weeks of gestation. In the table will be noted how many neonates have been assessed for that specific variable.

A table will be presented with line-listing of the primary causes of neonatal death as well. Frequencies and proportion of total neonatal deaths will be shown.

Table 3 will express the Doppler measurements at inclusion and first measurement after starting medication (at least 24 h after starting medication) will be expressed for treatment allocation and will only show the women who at least had one Doppler measurement after inclusion.

Non-context specific maternal and fetal/neonatal SAE's in both treatment groups will be line-listed in a table (Table 4) and the maternal side effects of the study medication will be expressed in Table 5 per treatment allocation. Table 6 will express the 2-year neurodevelopmental outcomes and Table 7 the physical outcomes at 2 years. Table 6 and 7 will not be part of the primary publication, but will be published separately.

Table 3: Doppler measurements at inclusion and first measurement > 24 hours after start medication

	Sildenafil (n=)		Placebo (n=)	
	At inclusion	After start medication	At inclusion	After start medication
Mean PI uterine artery				
PI umbilical artery				
PI middle cerebral artery				
PI ductus venosus				

Table 4: Linelisting of non-context specific SAE's

	Sildenafil (n=)	Placebo (n=)
Maternal		
…		
…		
Other, namely: …		
Fetal/neonatal		
…		
…		
Other, namely: …		

Table 5: Adverse effects of study medication

	Sildenafil (n=)	Placebo (n=)
Headache (%)		
Flushing (%)		
Stuffy nose (%)		
…		
Other		

Table 6: Two year neurodevelopmental outcomes

	Intention to treat			Intention to treat, adjusted for GA and EFW at inclusion			Per protocol		
	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value
Cognitive composite score (mean)									
Motor score (mean)									
Fine motor score (mean)									
Gross motor score (mean)									
Bayley III cognitive composite score and motor score									
<70									
70-84									
85-99									
≥100									
Bayley III motor composite score and motor score									
<70									
70-84									
85-99									
≥100									
Cerebral palsy, all*									
GMFCS grade 1									
GMFCS grade 2									
GMFCS grade 3									
GMFCS grade 4									
GMFCS grade 5									
Normal vision									
Impaired vision despite glasses or lenses									
Mildly abnormal vision despite glasses or lenses									
No useful vision									
Strabismus or amblyopia with normal (corrected) vision									
Normal hearing									

	Intention to treat			Intention to treat, adjusted for GA and EFW at inclusion			Per protocol		
	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value
Subnormal hearing for those cases that do need need aids and have mild hearing loss at time of testing at age two (ie mostly conductive in origin)									
Hearing loss (partly) corrected with aids									
Hearing loss not corrected with aids									
Normal communication									
No normal communication									
Growth Height mean Z score, corrected age									
Weight mean Z score corrected age BMI Z-score corrected age Head circumference mean Z-score corrected age									
Neurodevelopmental impairment I and II**									

**We will score all CP cases and then subdivide them in GMFCS levels; a child that does not have CP will not have a GMFCS score.*
***Defined as either a cognitive Bayley III score of less than 85 or an estimated cognitive delay of more than 3 months, cerebral palsy, with a GMFCS of more than 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted)*

Table 7: Physical outcomes at two year

	Intention to treat			Intention to treat, adjusted for GA and EFW at inclusion			Per protocol		
	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value	Sildenafil (n=)	Placebo (n=)	P value
Number of readmissions since primary discharge									
Number of surgery procedures since primary discharge									
Number of medications used in last year									
Current medication use									

Changes between the protocol and the statistical analysis

The primary outcome in the original protocol is stated as "intact survival at term age". For purpose of the analysis we will express the primary outcome as a composite outcome of mortality and survival with major morbidity. In the outcome table the distinction will be made between the proportion of patients that have intra-uterine death and that have neonatal death. Also, survival without major morbidity as well as the proportions of neonates surviving with the different morbidities including grades will be reported separately.

Other changes between the original protocol and the proposed statistical analysis presented here are the sample size calculation, as the stopping rule was changed from Haybittle-Peto to the Lan-DeMets-O'Brian Fleming-rule to avoid early stopping of the trial if sildenafil seems to be more effective than placebo(66).

Patient and Public Involvement

The development of the research question, outcome measures, and trial design was based on expert consensus in an international collaboration(31). No patients were involved in the design stage of the randomised controlled trial. However, patient representatives of the relevant patient organizations were consulted for the funding application and they eagerly supported the trial and recommended it for funding. No patients were involved in the recruitment to and conduct of the study. After completion of the study, study participants will be informed by the study team about the results and the drug allocation received. The burden of the intervention was not assessed by patients themselves. The dissemination of the results will also be through the relevant patient organizations.

Current trial status

At the moment of submission of this manuscript, the number of inclusions was 186, which corresponds to 52% of anticipated sample size. However, during interim analysis performed on 19 July 2018, evaluating the results of the first 183 patients, the DSMB had advised stopping the trial due to safety concerns and a lack of evidence of positive effects. At that time, 216 patients (60% of anticipated sample size) were recruited in the trial. The patients that were still using study medication stopped taking the tablets. The treatment allocation of all patients was unblinded and was seen by the researchers. This manuscript was submitted on 15 March and was under review. Despite the smaller sample size and early unblinding of the drug allocation, we will try as much as possible to perform the analyses according to the previously described statistical analysis plan. The consequence is that our study might not have enough power for the primary and all of the secondary outcomes. The performance of the previously planned IPD meta-analysis with the other STRIDER trials will become more important. We plan to analyse patients that stopped taking the study medication due to the stopping of the trial, in both the intention-to-treat and in the per-protocol analyses. However, we will perform subgroup analysis in which we will exclude these patients to see whether this will change the primary and secondary outcomes significantly.

Discussion

With the described statistical analysis plan we try to minimise the risks of reporting bias and data-drive analysis in reporting the main results of the Dutch STRIDER trial. We described the pre-defined baseline criteria and primary and secondary outcomes and the analysis plan per outcome.

Four other STRIDER trials with similar inclusion criteria, intervention, and outcome measures are undertaken simultaneously. By performing an individual patient data (IPD) meta-analysis over the results of the five trials, more reliable conclusions can be drawn than from this single trial. However, until all the trials have been performed and individually analysed, we hope that the described statistical approach for the Dutch STRIDER trial will help to give a temporary conclusion to the question of whether or not sildenafil increases the chance of healthy survival in women with severe early-onset fetal growth restriction and whether or not this therapy needs to be applied in clinical practice.

Conclusions

The Dutch STRIDER trial investigates if sildenafil compared with placebo increases the chance of intact neonatal survival at term age in pregnancies complicated by fetal growth restriction. The present statistical analysis plan for the main outcomes of this trial is presented to minimise the risk of reporting bias and data-driven analysis. The results may have profound effects on the health and quality of life of 700-900 patients in The Netherlands each year, and globally the number could be 700.000 patients.

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Chapter 9

Maternal sildenafil vs placebo for severe early-onset fetal growth restriction: A randomized clinical trial

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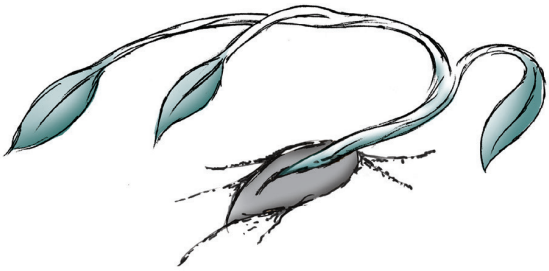

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Abstract

Importance: Severe early onset fetal growth restriction caused by placental dysfunction leads to high rates of perinatal mortality and neonatal morbidity. The phosphodiesterase-5 inhibitor sildenafil, inhibits cyclic guanosine monophosphate hydrolysis, thereby activating the effects of nitric oxide, and might improve uteroplacental function and subsequent perinatal outcomes.

Objective: To determine whether sildenafil reduces perinatal mortality or major morbidity.

Design, setting, and participants: This placebo-controlled randomized clinical trial was conducted at 10 tertiary referral centers and 1 general hospital in the Netherlands from January 20, 2015, to July 16, 2018. Participants included pregnant women between 20 and 30 weeks of gestation with severe fetal growth restriction, defined as fetal abdominal circumference below the third percentile or estimated fetal weight below the fifth percentile combined with Dopplers measurements outside reference ranges or a maternal hypertensive disorder. The trial was stopped early owing to safety concerns on July 19, 2018, whereas benefit on the primary outcome was unlikely. Data were analyzed from January 20, 2015, to January 18, 2019.

Interventions: Participants were randomized to sildenafil 25 mg 3 times a day vs placebo.

Main Outcomes and Measures: The primary outcome was a composite of perinatal mortality or major neonatal morbidity until hospital discharge.

Results: Out of 360 planned participants, a total of 216 pregnant women were included, with 108 randomized to sildenafil (median gestational age at randomization 24 weeks 5 days [interquartile range, 23 weeks 3 days to 26 weeks 0 days]; mean [SD] estimated fetal weight, 458 [160] g) and 108 women randomized to placebo (median gestational age, 25 weeks 0 days [interquartile range, 22 weeks 5 days to 26 weeks 3 days]; mean [SD] estimated fetal weight 464 [186] g). In July 2018, the trial was halted owing to concerns that sildenafil may cause neonatal pulmonary hypertension, whereas benefit on the primary outcome was unlikely. The primary outcome, perinatal mortality or major neonatal morbidity, occurred in the offspring of 65 participants (60.2%) allocated to sildenafil vs 58 (54.2%) allocated to placebo (relative risk, 1.11; 95% CI 0.88-1.40; P=0.38). Pulmonary hypertension, a predefined outcome important for monitoring safety, occurred in 16 (18.8%) neonates in the sildenafil group vs 4 neonates (5.1%) in the placebo group (relative risk 3.67; 95% CI 1.28-10.51; P=0.008).

Conclusions and Relevance: These findings suggest that antenatal maternal sildenafil administration for severe early onset fetal growth restriction did not reduce the risk of perinatal mortality or major neonatal morbidity. The results suggest that sildenafil increases the risk of neonatal pulmonary hypertension.

Introduction

Severe early onset fetal growth restriction is a rare condition, complicating approximately 0.4% of all pregnancies(1, 2). It is associated with a high risk of fetal death, iatrogenic preterm birth, long-lasting stay at the neonatal intensive care unit, neonatal mortality and long-term morbidity(3, 4). Severe early onset fetal growth restriction is also strongly associated with neurodevelopmental impairment later in childhood(5, 6). To our knowledge, no effective treatment to promote fetal growth has been identified, and management consists of intensive monitoring to determine the best moment to deliver the fetus, balancing the consequences of prematurity vs undernutrition and hypoxia(7).

Recently, phosphodiesterase type 5-inhibitors, most often sildenafil, have been investigated as potential treatment for fetal growth restriction(8-16). The Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (STRIDER) consortium designed and conducted in synchrony 4 randomized clinical trials to study sildenafil's hypothesized improvement of placental circulation through its effects on the uteroplacental circulation(8-16).

In the Dutch STRIDER trial, the hypothesis that sildenafil reduces the chance of perinatal mortality and morbidity was tested using a composite outcome of perinatal mortality and major neonatal morbidity.

Methods

We conducted this placebo-controlled randomized clinical trial in 10 tertiary care centers and 1 general hospital in the Netherlands. Ethical approval was granted by Amsterdam UMC. All participating women provided written informed consent. The protocol was registered on September 29, 2014 (link to Trial Protocol in Supplementary material), before the first participant was randomized. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study design

An independent data safety monitoring board (DSMB) monitored the safety of the participants after data were available for each 50 participants, as well as the efficacy after the outcomes were known for half of the participants(17). The DSMB charter included the provision to recommend stopping the trial in case safety of current or future participants was considered to be compromised. Furthermore, a stopping rule was included, indicating that the trial would be stopped if a significant difference between the 2 treatment groups would be observed at interim analysis (according to the O'Brien-Fleming spending function, $P<0.005$).

Participants
Pregnant women were eligible if they were between 20 weeks and 0 days and 27 weeks and 6 days of gestation if the fetal abdominal circumference was below the 3rd percentile or the estimated fetal weight (EFW) below the 5th percentile, combined with either unilateral or bilateral notching of the uterine artery, Pulsatility Index (PI) of the umbilical artery above the 95th percentile, PI of the middle cerebral artery below the 5th percentile, or a maternal hypertensive disorder. Participants with gestation between 28 weeks and 0 days and 29 weeks and 6 days were eligible if the EFW was less than 700 grams, combined with the aforementioned Doppler anomalies or a maternal hypertensive disorder, to select the patients with unfavorable prognosis. Gestational age estimation was based on a first trimester ultrasound. Exclusion criteria were anticipated imminent termination of pregnancy for maternal or fetal indications, multifetal pregnancy, identified congenital anomalies (affecting outcomes), identified congenital infection, maternal age younger than 18 years, cocaine use, current use of sildenafil, current use of cytochrome P450 3A5 isozyme inhibitors, and recent myocardial infarction or stroke.

Maternal race/ethnicity was collected because maternal race/ethnicity is associated with placental dysfunction and pregnancy outcomes(18, 19). Whether the maternal race/ethnicity was European descent, African descent or Asian descent, was indicated by the investigator. In case of doubt, the patient was asked to report her race/ethnicity.

In participating centers, samples of maternal blood were collected at randomization by venipuncture and stored at -80^{o}C for batch testing of placental growth factor (PlGF) level. Measurement of PlGF level was performed on the Kryptor immunoassay (Thermo Fisher Scientific) and compared with the fifth percentile of a reference population (ie 106.54 pg/mL)(20).

Randomization and masking
The web-based randomization had a 1:1 ratio, random block sizes of 2 to 6, and was stratified per participating center. Participants, clinicians, investigators and outcome assessors were blinded for the treatment allocation.

Procedures
Trial medication was manufactured specifically for this trial by Tiofarma, and tablets contained either sildenafil 25 mg or placebo and were taken orally 3 times daily. Active and placebo medications were matching in color, size, weight, and taste. The dosage regimen was based on previous studies by the collaborators on this project(12, 15).

Participants used the trial medication until fetal death, 32 weeks of gestation, or birth. Compliance was participant-reported at each antenatal outpatient clinic visit. Additionally, at the end of the exposure period, medication bottles were collected, and the remaining number of tablets was counted. Participants kept a record of adverse effects. Trial medication was ended at the discretion of the patient. The fetal monitoring (ultrasound and cardiotocography) and interventions other than the trial medication were at the

discretion of the attending gynecologist and in line with Dutch national guidelines and local protocols, depending on the gestational age and EFW. In most participating centers, active management was installed after extensive counseling of parents by a gynecologist and neonatologist and at a minimum gestational age of 26 weeks and 0 days combined with an EFW of 500 g. Data were collected from the patient's electronic health record and entered into a secure electronic database (REDCAP).

Outcomes

The primary outcome was a composite of either perinatal mortality or major neonatal morbidity before the neonate was discharged from the hospital. Major neonatal morbidity was defined as intraventricular hemorrhage grade 3 or more(21-23), periventricular leukomalacia grade 2 or more(24, 25), moderate or severe bronchopulmonary dysplasia (26-30), necrotizing enterocolitis Bell stage 2 or more(31, 32), or retinopathy of prematurity requiring laser therapy(33, 34). We defined the neonatal period as the time until hospital discharge. Mortality after hospital discharge was considered not to be the mortality of interest in the primary outcome, since the chance of this mortality being associated with the intervention was considered small.

The secondary outcomes were (1) the proportion of mothers experiencing either pre-eclampsia or hemolysis-elevated -liver-enzymes-low-platelets syndrome(35); (2) PI of umbilical artery: The first PI measured at the ultrasound performed more than 24 hours after start trial medication; (3) birthweight, with birthweight of live born neonates and birthweight of stillborn fetuses described separately; (4) gestational age at birth or fetal death; and (5) the proportion of neonates with neurodevelopmental impairment at age 2 years, assessed on the 2-year Bayley Scales of Infant Development, Third Edition (BSID-III)(36) and its cognitive and motor subscales. The latter secondary outcome is not reported here because the 2-year follow-up is not yet complete. When possible, we reported outcomes according to the core outcome set for fetal growth restriction that was developed after the start of the trial(37).

Statistical analysis

We aimed to find a decrease in the incidence of the primary outcome from 71%(15) in the control group to 56% in the experimental group, which is equal to a relative risk reduction of 21%. Allowing for 10% loss to follow-up and interim analysis for efficacy according to the O'Brien-Fleming spending function ($P<0.005$), and with an accepted type I error of 5% and type II error of 80%, we needed to randomize 180 women per group.

The statistical analysis plan, published elsewhere(38), provides the details of the statistical analysis. In short, the prespecified primary analysis was an intention-to-treat analysis including all randomized participants. Additionally, several prespecified sensitivity analyses were conducted for the primary outcome: adjusting for gestational age and EFW at randomization; only including participants who had a fetus or neonate without any congenital anomaly that could either explain the small fetal size in hindsight or would have a likely effect on the primary outcome (originally defined as a subgroup analysis, since not

all congenital anomalies can be known antenatally); and a per-protocol analysis for the primary outcome that included only participants who used at least 1 tablet of trial medication. Relative risks were calculated using generalized linear models (log link function), and continuous outcomes were analyzed using linear regression(38).

Predefined subgroup analyses were conducted for participants with a serum level of PlGF (categorized as less than the fifth percentile and fifth percentile or higher), gestational age at randomization (categorized as <25 weeks of gestation and ≥25 weeks of gestation) and EFW at randomization (categorized as <300 g, 300 to 599 g, and ≥600 g).

All statistical analyses were conducted independently by 2 researchers (C.N. and R.G.D., supervised by J.C.J.) using R statistical software version 3.5.1 (R Project for Statistical Counting) and SAS statistical software version 9.4 (SAS Institute). P Values were 2-sided, and statistical significance was set at P<0.05. Data were analyzed from January 20, 2015, to January 18, 2019.

Results

Between January 20, 2015 and July 16, 2018, 281 women were eligible, of whom 216 were randomized (Figure 1). Among these, 108 were randomized to sildenafil (median gestational age at randomization, 24 weeks and 5 days [interquartile range, 23 weeks 3 days to 26 weeks 0 days]; mean [SD] estimated fetal weight, 458 [160] g) and 108 women were randomized to placebo (median gestational age, 25 weeks and 0 days [interquartile range, 22 weeks 5 days to 26 weeks 3 days]; mean [SD] estimated fetal weight 464 [186] g). On July 19, 2018 the DSMB recommended to discontinue the trial based on the findings at the interim analysis on the data from the first 183 participants (Supplementary Material). The main consideration for the DSMB to recommend stopping was an increased incidence of neonatal pulmonary hypertension (a predefined outcome important for monitoring safety), whereas it was considered unlikely that benefit would be shown on the primary outcome of perinatal mortality or major neonatal morbidity until hospital discharge if the trial were continued to its completion. Moreover, no positive effects on the primary, secondary or exploratory outcomes, as defined in the statistical analysis plan(38), were seen. The results of the recently published STRIDER UK trial(39) as well as the (at that time unpublished) data of the STRIDER New Zealand/Australia trial(40) were included in the DSMB deliberations, as was foreseen in the DSMB charter(17). The trial leadership stopped the trial immediately on July 19, 2018, at which point 7 remaining participants using trial medication were advised to stop using the trial medication and drug allocation of all participants was unblinded for the participants and the researchers. Owing to the unforeseen stopping of the trial, we were not able to carry out all analyses as planned (Supplementary Material).

Of the 216 participants randomized at the time of halting the trial, 1 participant was lost to follow-up for all outcomes after having moved abroad, and 12 participants did not start

trial medication and were therefore excluded from the per-protocol analysis. The mean adherence in the per-protocol group was 91% [23%] of the tablets taken. Baseline characteristics are shown in Table 1. There were no clinically relevant differences between the sildenafil and placebo groups in the maternal or fetal baseline characteristics, other than a slight imbalance in fetal sex (sildenafil: 51 [47.2%] boys; placebo: 59 [54.6%] boys).

Figure 1: CONSORT Flow Diagram

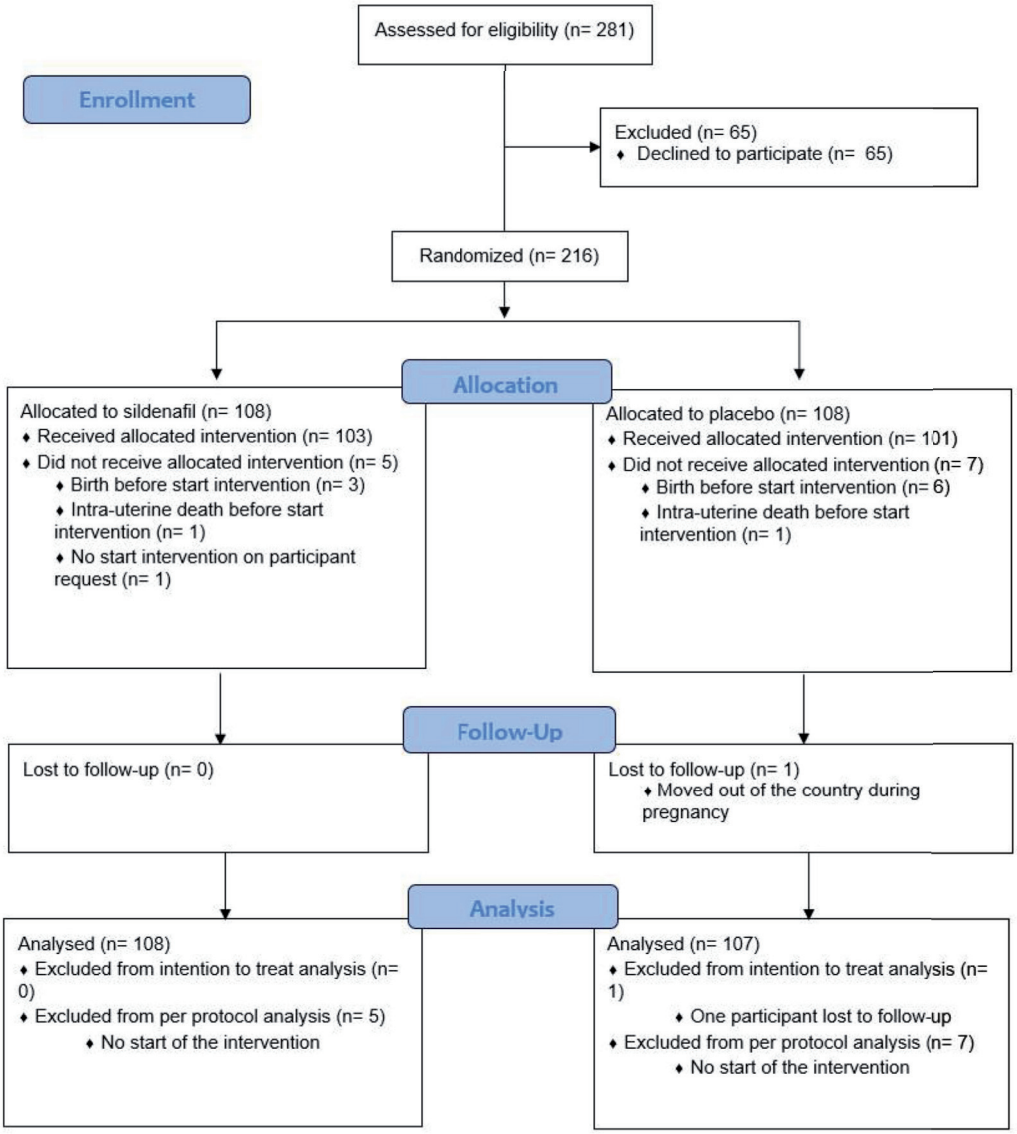

Table 1: Baseline characteristics

	No. (%)	
	Sildenafil (n = 108)	**Placebo (n = 108)**
Age, mean (SD), y	31 (5.1)	31 (5.0)
BMI, mean (SD)	26 (4.7)	26 (5.8)
Race/ethnicity, descent		
European	84 (77.8)	86 (79.6)
African	7 (6.5)	11 (10.2)
Asian	2 (1.9)	5 (4.6)
Other (%)	13 (12.0)	6 (5.6)
Maternal smoking	13 (12.0)	10 (9.3)
Gestational age at randomization, median (IQR), wk	24 5/7 (23 3/7 to 25 5/7)	25 0/7 (22 5/7 to 26 3/7)
Ultrasonagraphic examination results, mean (SD)		
Estimated fetal weight, g	458 (160)	464 (186)
Fetal abdominal circumference, mm	165 (2)	164 (26)
Sex		
Boys	51 (47.2)	59 (54.6)
Girls	57 (52.8)	48 (44.4)
Notching uterine artery (1- or 2-sided)	61 (56.5)	64 (59.3)
PI		
Umbilical artery >95th percentile	51 (47.2)	53 (49.1)
Middle cerebral artery <fifth percentile	47 (43.5)	43 (39.8)
End-diastolic flow		
Positive	73 (67.6)	65 (60.2)
Absent	27 (25.0)	33 (30.6)
Reversed	7 (6.5)	7 (6.5)
Pregnancy hypertension	22 (20.4)	24 (22.2)
Preeclampsia	23 (21.3)	26 (24.1)
HELLP syndrome	1 (0.9)	2 (1.9)
Blood pressure, mean (SD), mmHg		
Systolic	132 (22)	132 (20)
Diastolic	83 (15)	83 (15)
PlGF <fifth percentile of reference value, No/total No.[a]	56/61 (91.8)	53/59 (89.8)

BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); HELLP = hemolysis, elevated liver enzymes, and low platelets; IQR = interquartile range; PI = Pulsatility Index; PlGF = placental growth factor

[a] *Reference value was 106.54 pg/L; 5th percentile of reference population*

No difference was observed in the composite primary outcome of perinatal mortality or major neonatal morbidity until hospital discharge: 65 participants (60.2%) in the sildenafil-group and 58 participants (54.2%) in the placebo-group experienced perinatal death or major neonatal morbidity (relative risk [RR] 1.11; 95% CI, 0.88-1.40; P=0.38) (Table 2).

Bayes factor analysis indicated that the results on the primary outcome were 3.7-fold more likely compatible with no effect than with the risk reduction hypothesized in the sample size calculation. No differences were observed in the subcomponents of the primary outcome. Perinatal mortality was comparable (sildenafil: 44 deaths (40.7%); placebo: 40 deaths (37.4%); RR 1.09; 95% CI, 0.78-1.52; P=0.61). Two more children in the sildenafil group died after hospital discharge: 1 died 1 day after hospital discharge owing to sepsis resulting from necrotizing enterocolitis; another died at age 18 months owing to cardiogenic shock resulting from sepsis. Trial Sequential Analysis on the data from this trial showed that the boundary for futility was crossed for the primary outcome (Supplementary Material).

The proportion of mothers experiencing either preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome was 46 mothers (42.6%) in the sildenafil group vs 48 (44.9%) mothers in the group allocated to placebo (RR, 0.95; 95% CI, 0.70-1.29) (Table 3). The mean PI of the maternal uterine artery or the fetal umbilical and middle cerebral artery arteries after treatment with study medication did not differ between groups (Table S1).

No difference in birthweight was observed between the treatment groups. Mean (SD) birthweight of the neonates that were stillborn was 414 (143) g in the sildenafil group vs 362 (115) g in the placebo groups (P=0.15). Mean gestational age at birth or fetal death was 29 weeks 3 days (SD, 4 weeks 0 days) in the sildenafil group vs 29 weeks 3 days (SD, 4 weeks 3 days) in the placebo group (P>0.99).

The results of all exploratory outcomes are reported in Table 2 and 3. Because the DSMB based their advice to stop the trial on the increased occurrence of neonatal pulmonary hypertension in the sildenafil group, we composed an expert adjudication committee of 4 neonatologists (W.O., A.F.J.v.H., I.K.M.R. and E.L.), experienced in treating neonates who are preterm and growth restricted, and a pediatric cardiologist (R.M.F.B.), knowledgeable on the subject of neonatal and pediatric pulmonary hypertension, to carefully review this outcome. The committee, blinded for treatment allocation, reviewed all neonatal records with the purpose of consensus validation of this diagnosis after discontinuation of the trial. Persistent pulmonary hypertension was defined as either confirmed by cardiac ultrasound examination or as a difference in oxygen saturation between the right upper extremity and either lower extremity (ie, post-ductal) of more than 10%. There was an increase of neonates in the sildenafil group who experienced pulmonary hypertension vs the placebo group (16 of 85 neonates (18.8%) vs 4 of 78 neonates (5.1%); RR, 3.67; 95% CI, 1.28-10.51; P=0.008). The adjudication committee observed that 2 different forms of pulmonary hypertension had occurred (Table S2), including persistent pulmonary hypertension in the neonate and later-onset pulmonary hypertension associated with either sepsis or bronchopulmonary dysplasia. Neonatal death was attributable to pulmonary hypertension in 4 infants, 2 in each group (Table S2 and Table S3). We plan to publish a separate article on the diagnosis of pulmonary hypertension and the validation process within the trial.

Table 2: Fetal or neonatal outcomes

	Intention to treat analysis[a] No./total No.(%)				
	Sildenafil	**Placebo**	**RR (95% CI)**	**Mean difference (95% CI)**	**P value**
Primary outcome[b]	65/108 (60.2)	58/107 (54.2)	1.11 (0.88 to 1.40)	NA	0.38
Birthweight, mean (SD), g	829 (537)	884 (627)	NA	-55 (-211 to 101)	0.49
Stillbirth	23/108 (21.3)	29/107 (27.1)	0.79 (0.49 to 1.27)	NA	0.32
Birthweight, mean (SD), g	414 (143)	362 (115)	NA	53 (-17 to 123)	0.15
Percentile[c]					
<Tenth	10/13 (76.9)	11/11 (100)	0.77 (0.57 to 1.04)	NA	0.08
<Third	8/13 (61.5)	10/11 (90.9)	0.68 (0.42 to 1.08)	NA	0.10
Live birth	85/108 (78.7)	78/107 (72.9)	1.08 (0.93 to 1.26)	NA	0.32
Birthweight, mean (SD), g	942 (549)	1078 (628)	NA	-136 (-318 to 44)	0.14
Percentile[c]					
<Tenth	33/73 (45.2)	30/68 (44.1)	1.02 (0.71 to 1.48)	NA	0.90
<Third	20/73 (27.4)	19/68 (27.9)	0.98 (0.57 to 1.67)	NA	0.94
Apgar Score 5 min <7	32 (37.6)	25 (32.1)	1.17 (0.77 to 1.79)	NA	0.46
Cord blood gas pH <7.10	2/48 (4.2)	0/31 (0)			
Neonatal death	21/85 (24.7)	11/78 (14.1)	1.75 (0.9 to 3.39)	NA	0.10
Survival					
At hospital discharge	64/85 (75.3)	67/78 (85.9)	0.88 (0.75 to 1.02)	NA	0.09
With major morbidity at hospital discharge	21/85 (24.7)	18/78 (23.1)	1.07 (0.62 to 1.85)	NA	0.81
Without major morbidity at hospital discharge	43/85 (50.6)	49/78 (62.8)	0.81 (0.61 to 1.06)	NA	0.12
Postmenstrual age at first discharge home, mean (SD), wk	42 (7.9)	40 (2.3)	NA	2.04 (0.04 to 4.03)	0.047
IVH grade III or IV	3/85 (3.5)	2/78 (2.6)	1.38 (0.24 to 8.02)	NA	0.72
PVL grade II or more (%)	0/85 (0)	0/78 (0)			>0.99
BPD					
Moderate or severe	23/85 (27.1)	16/78 (20.5)	1.32 (0.75 to 2.31)	NA	0.33
None	41/85 (48.2)	47/78 (60.3)	0.80 (0.61 to 1.06)	NA	0.13
ROP treated by laser or surgery	8/85 (9.5)	3/78 (3.8)	2.45 (0.67 to 8.9)	NA	0.17
1 or more culture-proven episode of infection or clinical episode of infection with antibiotic treatment necessary ≥5 d	44/85 (51.8)	35/78 (44.9)	1.15 (0.84 to 1.59)	NA	0.38
NEC grade II or more	7/85 (8.3)	8/78 (10.3)	0.80 (0.31 to 2.11)	NA	0.66
Abdominal circumference, initial growth rate between randomization and 14 d, mean (SD), mm/week	7.4 (6.2)	8.8 (7.3)	NA	-1.4 (-3.43 to 0.69)	0.19

BPD = bronchopulmonary dysplasia; EFW = estimated fetal weight; HELLP = hemolysis, elevated liver enzymes, low platelets; IVH = intra-ventricular hemorrhage; NA = not applicable; NEC = necrotizing enterocolitis; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; RR = relative risk

[a] *Intention-to-treat analysis corrected for gestational age and EFW at randomization, and per-protocol analysis had similar results*

[b] *The primary outcome was perinatal death or major neonatal morbidity before discharge*

[c] *Birthweight percentiles were only calculated for infants born after 23 weeks gestational age*

Table 3: Maternal outcomes

	Intention to treat analysis[a] No./total No. (%)				
	Sildenafil	**Placebo**	**RR (95% CI)**	**Mean difference (95% CI)**	**P value**
Treatment duration, mean (SD), d	24/108 (18)	20/107 (43)	NA	3.73 (-5.44 to 12.91)	0.43
Gestational age at birth, mean (SD), wk	29 3/7 (4 0/7)	29 3/7 (4 3/7)	NA	-0.01 (-1.12 to 1.11)	0.99
Preterm birth, wk					
<28	46/108 (42.6)	48/107 (44.9)	0.95 (0.70 to 1.29)	NA	0.74
<37	97/108 (89.8)	90/107 (84.1)	1.07 (0.96 to 1.18)	NA	0.22
Pregnancy prolongation after randomization, mean (SD), d	34 (28)	33 (32)	NA	0.64 (-7.4 to 8.67)	0.88
Mode of delivery					0.46
Cesarean					
On fetal indication	57/108 (52.8)	51/107 (47.7)	NA	NA	
On maternal indication	14/108 (13.0)	14/107 (13.1)	NA	NA	
Induced vaginal birth					
On fetal indication	7/108 (6.5)	12/107 (11.2)	NA	NA	
On maternal indication	8/108 (7.4)	3/107 (2.8)	NA	NA	
Spontaneous vaginal birth	9/108 (8.3)	11/107 (10.3)	NA	NA	
Induction of labor after intra-uterine death	12/108 (11.1)	16/107 (15.0)	NA	NA	
Pregnancy hypertension	74/108 (68.5)	72/107 (67.3)	1.02 (0.85 to 1.22)	NA	0.85
Preeclampsia	42/108 (38.9)	44/107 (41.1)	0.95 (0.68 to 1.31)	NA	0.74
HELLP syndrome	12/108 (11.1)	10/107 (9.3)	1.19 (0.54 to 2.63)	NA	0.67
Maternal use of antihypertensive treatment antenatal or postnatal					0.61
None	50/108 (46.3)	53/107 (49.5)	NA	NA	
1	32/108 (29.6)	34/107 (31.8)	NA	NA	
2	16/108 (14.8)	15/107 (14.0)	NA	NA	
≥3	10/108 (9.3)	5/107 (4.7)	NA	NA	
Maternal magnesiumsulphate for hypertension	14/108 (13.0)	15/107 (14.0)	0.92 (0.47 to 1.82)	NA	0.82
Antenatal corticosteroids for fetal lung maturation					
48 h to 14 d (complete course)	52/85 (61.2)	56/78 (71.8)	0.85 (0.68 to 1.06)	NA	0.15
<48 h (incomplete course)	4/85 (4.8)	7/78 (9.0)	0.52 (0.16 to 1.72)	NA	0.29

NA = not applicable; RR = relative risk

[a] Intention-to-treat analysis corrected for gestational age and EFW at randomization and per protocol analysis had similar results

Table 4: Prespecified sensitivity and subgroup analyses on the primary outcome according to treatment

	No./total No. (%)			
	Sildenafil	**Placebo**	**RR (95% CI)**	**P value[a]**
Sensitivity				
Per protocol	60/103 (58.3)	54/100 (54.0)	1.08 (0.85 to 1.38)	0.54
Adjusted for EFW and GA at randomization	65/108 (60.2)	58/107 (54.2)	1.23 (0.69 to 2.23)	0.48
Post-hoc adjustment for sex	65/108 (60.2)	58/107 (54.2)	1.33 (0.77 to 2.30)	0.31
Excluding				
Neonates who appeared to have a congenital anomaly	60/102 (58.8)	54/101 (53.5)	1.10 (0.86 to 1.40)	0.44
Participants who were pregnant or for whom the neonate was admitted at NICU when trial was stopped (post hoc)	60/97 (61.9)	55/98 (56.1)	1.10 (0.87 to 1.39)	0.42
Placental growth factor, percentile of the reference value				
<Fifth	36/56 (64.3)	25/53 (47.2)	1.36 (0.96 to 1.93)	0.99
≥Fifth	4/5 (80.0)	3/6 (50.0)	1.60 (0.64 to 3.98)	
GA at randomization, wk				
<25	42/60 (70.0)	36/54 (66.7)	1.05 (0.82 to 1.35)	0.85
≥25	23/48 (47.9)	22/53 (41.5)	1.15 (0.75 to 1.78)	
EFW at randomization, g				
<300	15/19 (78.9)	21/26 (80.8)	0.98 (0.73 to 1.32)	0.70
300 to 599	44/67 (65.7)	23/48 (47.9)	1.37 (0.97 to 1.93)	
≥600	3/18 (16.7)	10/26 (38.5)	0.43 (0.14 to 1.36)	

EFW = estimated fetal weight; GA = gestational age; NICU = neonatal intensive care unit; RR = relative risk
[a] The P value is from the interaction term for subgroup analyses and from the treatment effect for the sensitivity analyses

No subgroup differences were detected when assessed by adding interaction terms to the models, and the sensitivity analyses did not lead to statistically significant results on the primary outcome (Table 4). However, the RR slightly increased when the analyses were adjusted for gestational age and EFW at inclusion (RR 1.23; 95% CI, 0.69-2.23; P=0.48) and in a post hoc analysis that explored the potential effect of the imbalance of sex at inclusion (RR, 1.33; 95% CI, 0.77-2.30; P=0.31).

We observed 10 maternal and 2 fetal or neonatal serious adverse events in the sildenafil group vs 8 maternal and 2 fetal or neonatal serious adverse events in the placebo group that could be directly attributed to the high-risk nature of the study population (eg, hospitalization of the neonate) (Table S4 in Appendix 2). Other than pulmonary hypertension, there were no differences in the other serious adverse events. Several adverse effects of the trial medication with different frequencies were reported by the participants and are presented in Table S5. The primary causes of neonatal death and the congenital anomalies observed are described in Table S6 and Table S7.

Discussion

This randomized clinical trial found that sildenafil compared with placebo did not reduce the risk of perinatal mortality or major neonatal morbidity. This finding is in line with 2 other published STRIDER trials from the UK(39) and from New Zealand and Australia(40) and is confirmed by trial sequential analysis of this outcome that includes all 3 trials.

Our present finding of an increased incidence of pulmonary hypertension after antenatal sildenafil administration was not observed in the 2 other STRIDER trials(39, 40). This difference may be explained by definition differences, diagnostic strategies, or thresholds of suspicion. Our finding may indicate an important safety signal, and causality is a possibility because sildenafil targets the pulmonary vasculature. We hypothesize that the causal mechanisms might be rebound vasoconstriction (or lack of dilatation) of the pulmonary arteries to structural changes within the pulmonary vasculature.

The Canadian STRIDER trial (NCT02442492) was terminated based on the results of this STRIDER trial. The planned individual patient data analysis that combines our data with all other STRIDER trials will have more power to draw conclusions based on all available data and hopefully to allow meaningful subgroup analysis to identify if there are specific participant groups that experience harm or benefit from the intervention(41).

Limitations

Our trial has limitations. First, the trial was stopped before the planned sample size was reached because of an increased incidence of pulmonary hypertension in the sildenafil group, as well as indications of futility on our primary outcome. Pulmonary hypertension was predefined as an important safety outcome to monitor, but it was neither defined as a primary or secondary outcome, and pulmonary hypertension is a nonvalidated surrogate outcome regarding more patient-centered outcomes. Although each adverse event should be seriously regarded(42), it might be argued that the pulmonary hypertension result should only be regarded as hypothesis-generating and should be tested in the planned individual patient data analysis(41). Second, when assessing the primary outcome of perinatal mortality or major neonatal morbidity, the trial sequential analysis showed that the boundary for futility was crossed, indicating that we could reject that sildenafil reduces the risk of the primary outcome by 20%. However, we cannot reject that

sildenafil reduces the risk of the primary outcome by smaller and perhaps clinically important margins, or that sildenafil reduces the risk of any of the secondary outcomes.

It could be argued that the trial was stopped too soon owing to the lack of robustness on the findings of harm. However, the advice of the independent DSMB was not only based on potential harms but also on lack of benefits. In addition to the increase in pulmonary hypertension observed at the interim analysis, it became evident that it was unlikely that benefit of sildenafil treatment would be shown on the primary outcome if the trial were continued to its completion. This was also demonstrated in the trial sequential analysis on the primary outcome that showed that the boundary for futility was crossed when taking the results of the UK(39) and Australian/New Zealand(40) STRIDER trials into account.

It could also be argued that the STRIDER trials were premature. However, there was extensive evidence in appropriate animal models of fetal growth restriction and increasing human evidence suggesting potential for a positive effect on fetal growth(8). The dosage used in this study (ie, 25 mg 3 times daily) was based on a previous trial(15) and is slightly higher than the dosage used for the treatment of pulmonary hypertension in adults. A meta-analysis of animal studies(8) suggested that a higher dosage than in the current study might be necessary to reach adequate serum levels of sildenafil. Sildenafil is approved to improve exercise ability and delay clinical worsening of pulmonary arterial hypertension in adult patients (World Health Organization Group I). In 2012, the US Food and Drug Administration recommended that sildenafil should not be prescribed to children ages 1 through 17 years for pulmonary arterial hypertension(43). However, there were no reported safety concerns for the use of sildenafil in fetal growth restriction. In contrast, there was even an ongoing inclusion of this drug into clinical practice in this at-risk patient category(44). Adequately powered randomized clinical trials are necessary to assess the validity of an intervention before it is implemented. This concerted approach of the STRIDER trials aimed to prevent premature implementation of sildenafil based on a few underpowered trials and sought to thoroughly test the beneficial claims before implementation(12, 14, 15).

Conclusions

This randomized clinical trial found that antenatal maternal sildenafil administration for severe early onset fetal growth restriction did not reduce the risk of perinatal death or major neonatal morbidity. Our results suggest that sildenafil increases the risk of neonatal pulmonary hypertension.

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Supplementary information

Link to study protocol

ClinicalTrials.gov, NCT02277132

Letter of DSMB regarding interim analysis

DSMB Recommendation STRIDER Study (NL)

July 19, 2018

On July 11th 2018, the NVOG DSMB for the STRIDER study met to discuss the planned (planned at completion of 175 subjects) interim analysis for the second time. At the first discussion on May 23rd it was decided to make sure safety data from the STRIDER study was as complete as possible and to obtain (mainly safety) data of the two completed sister studies (UK and New Zeeland and Australia) before arriving at a final recommendation. The NVOG DSMB allowed only a maximum time of one month for completion of the data to minimise risks to participants. For the meeting on July 11th the interim analysis was updated, with data cut off July 5th.

The interim analysis included endpoint data from 183 patients, of whom for 182 (89 on placebo, 93 on sildenafil) the primary endpoint of was available.

The DSMB has carefully evaluated the totality of data based on the interim analysis report and included the results from the two sister studies in its considerations, however not deviating from the principle that the interim data from the present STRIDER study should guide its recommendation. The DSMB also requested several additional analyses to ensure its interpretation of the data was correct.

The DSMB recommends stopping recruitment and treatment for the STRIDER study at the earliest possible occasion that allows proper communication to the participants and other stakeholders. The main consideration for the DSMB to recommend stopping is that there is serious concern that sildenafil may cause harm to the newborn children, whereas given the results of 182 children it is extremely unlikely that any benefit can be shown on the primary endpoint of *intact neonatal survival until term age* if the trial is continued to its completion (conditional power < 0.01).

The main potential harm observed is persistent pulmonary hypertension, with an incidence of 17/64 (26.6%) on sildenafil and 3/58 (5.2%) on placebo.

The following results summarize the key results underlying the DSMB recommendation.

	Sildenafil		*Placebo*	
Intact neonatal survival until term age	*32/93*	*34.4%*	*39/89*	*43.8%*
Death prior to discharge	*19/71*	*26.8%*	*9/63*	*14.3%*
Persistent pulmonary hypertension	*17/64*	*26.6%*	*3/58*	*5.2%*

Concluding, the DSMB recommends not to continue the trial from a safety perspective, while sufficient data appears to be available to assess benefit - risk of sildenafil for this treatment objective.

Prof Kit C.B. Roes, chair

Differences between the pre-defined statistical analysis plan and the final analysis

We submitted the statistical analysis plan of this trial before the discontinuation due to the interim analysis and was in a second review stage at discontinuation of the trial.

The inclusion criterium 'PlGF < 5th percentile' was removed. In clinical practice, it appeared that no participating centres performed measurement of PlGF during standard patient care, but only for purpose of research. In clinical practice this pre-specified inclusion criterium was not known for potentially eligible patients.

In Table 1 we pre-defined the outcomes 'highest completed educational level mother', 'highest educational level father/partner' and 'language spoken at home'. These variables are important for the neurodevelopmental outcomes at two years of age. Since these variables are not collected systematically during pregnancy, we had a high proportion of missing data. During the neurodevelopmental assessment at two years, these variables will be collected systematically and we will report them in the publication of the long-term outcomes.

The variables 'Female sex (%)' and 'PlGF < 5th percentile of the reference value (%)' were added to Table 1, since this variable was considered to be clinically relevant.

In Table 2 and 3 the relative risk with 95% confidence interval was added for all outcomes.

The variable "Neonate born during maternal administration of intravenous magnesium sulphate (%)" has been removed from Table 3, since this outcome was not systematically registered and collected within the trial.

The variables 'Preterm birth < 28 weeks', 'Preterm birth < 37 weeks', 'Birth weight < 10th percentile', 'Birth weight < 3rd percentile', 'Apgar score 5 minutes < 7' and 'Cord blood gas pH < 7.10' were added to table 2 and 3, since these variables were considered to be clinically relevant and are part of the identified core outcome set(37).

The variable 'Birthweight' was added to Table 2 after peer review of the manuscript on request of the reviewers.

In Table 4 a post-hoc analysis adjusting for the imbalance in fetal sex was added, since this imbalance was observed in the results.

The pre-planned subgroup analysis, comparing placental growth factor (PlGF) < 25th percentile of all samples of the study population and PlGF ≥ 25th percentile of all samples of the study population, has not been reported, since most available PlGF outcomes were low. Therefore, this subgroup analysis was considered to have minimal clinical impact.

The pre-defined subgroup analysis, comparing participants who had a fetus or neonate

without any congenital anomaly that could either explain the small fetal size in hindsight or would have a likely impact on the primary outcome, was changed to a sensitivity analysis. This analysis was wrongly defined as a subgroup analysis, since we do not test the effect of sildenafil in the participants who had a fetus or neonate with any congenital anomaly that could either explain the small fetal size in hindsight or would have a likely impact on the primary outcome.

Table 6 and Table S1 were added, since we considered it important to present the different types of pulmonary hypertension, the association between pulmonary hypertension, neonatal death and treatment allocation. We also considered it important to explore the pregnancy characteristics of the neonates that did and did not develop pulmonary hypertension in order to improve interpretation of the results.

Table S2, S3 and S4 were moved to the appendix for purpose of readability of the manuscript.

In the statistical analysis plan we planned to use random intercept models for all primary analyses to account for a center effect. However, due to a lower power after early discontinuation of the trial the models did not converge for all outcomes, we decided to use fixed-effect models and not to account for a center effect.

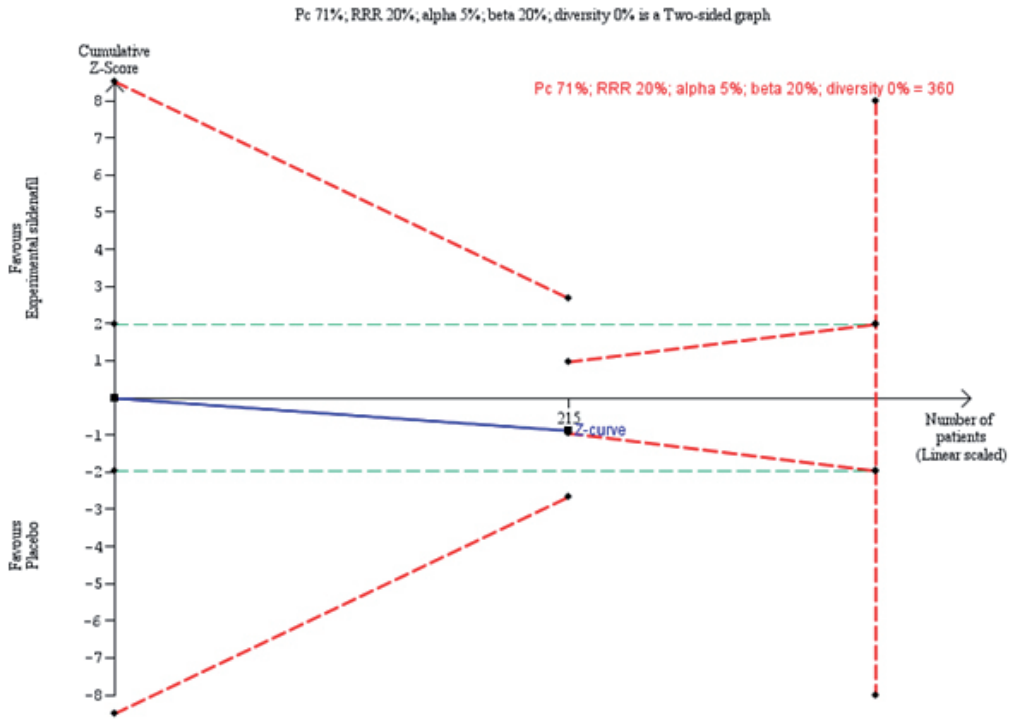
The two statisticians that independently conducted the statistical analyses, were unblinded due to the fact that pulmonary hypertension was not excluded from the data set and via their knowledge of the results of the interim analysis.

Trial Sequential Analysis

We followed our published statistical analysis plan(38).

Primary neonatal outcome
When we applied the data of the interim analysis of the Dutch STRIDER trial to the Trial Sequential Analysis program we observed that futility had been reached regarding the primary neonatal outcome of intact neonatal survival (Figure S1).

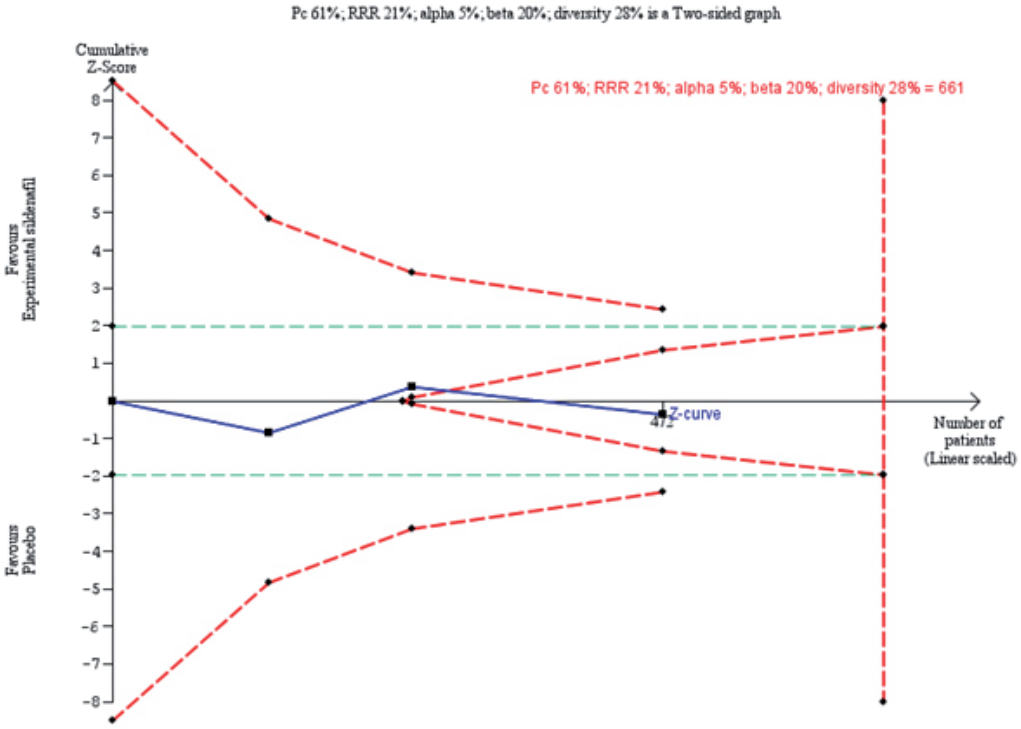
Figure S1. Trial Sequential Analysis of the interim data of the primary outcome from the Dutch STRIDER trial



The cumulative Z curve after 215 participants have been randomized and followed up penetrates the monitoring boundaries for futility. The required sample size of 360 participants is calculated based on the anticipated proportion of neonates with the primary outcome of 71%; a relative risk reduction of 21%; alpha of 5%; beta of 20%; and 0% diversity

When we conducted a Trial Sequential Analysis of the two published STRIDER trials plus the interim data from the Dutch Strider trial we found again that the cumulative Z curve entered the futility area (Figure S2). The observed relative risk (RR) is 1.05 with 95% confidence interval (CI) of 0.90 to 1.20. We are able to demonstrate futility down to intervention effects of 16% relative risk reduction (data not shown). For smaller intervention effects we could not demonstrate futility (data not shown).

Figure S2. Trial Sequential Analysis of the primary outcome from the two published STRIDER trials(39, 40) plus the interim data from the Dutch STRIDER trial



The cumulative Z curve after addition of the Dutch trial participants enters the area of futility. The diversity-adjusted required information size of 661 participants is calculated based on the observed proportion of neonates with the primary outcome of 61%; a relative risk reduction of 21%; alpha of 5%; beta of 20%; and the observed diversity 28%

Table S1: Doppler measurements at randomization and first measurement > 24 hours after start of medication

	Sildenafil (n= 108)		Placebo (n= 107)		P value*
	At randomization	After start medication	At randomization	After start medication	
Mean PI uterine artery	1.76 (±0.66)	1.29 (±0.61)	1.70 (±0.61)	1.65 (±1.03)	0.90
Mean PI umbilical artery	1.89 (±0.79)	1.97 (±1.04)	2.37 (±3.95)	1.92 (±0.86)	0.62
Mean PI middle cerebral artery	1.57 (±0.56)	1.51 (±0.41)	1.46 (±0.47)	1.58 (±0.44)	0.06
Mean PI ductus venosus	0.79 (±0.32)	0.88 (±0.40)	1.06 (±0.99)	0.73 (±0.32)	0.80

Plus-minus values are standard deviations (SD)
PI = pulsatility index
** P value for the comparison of the difference in Doppler measurements at randomization and after start of medication between the sildenafil and placebo groups*

Table S2: Types of pulmonary hypertension within live born neonates in the Dutch STRIDER trial, per randomization allocation

	Sildenafil (n=85)		Placebo (N=78)	
	Neonatal death (n=21)	Survival to discharge (n=64)	Neonatal death (n=11)	Survival to discharge (n=67)
Total pulmonary hypertension	10	6	3	1
PPHN	7	3	1	1
PH associated with sepsis	1	1	0	0
Late-onset PH associated with (developing) BPD	1	0	1	0
PPHN followed by late-onset PH associated with (developing) BPD	1	2	1	0

PPHN = persistent pulmonary hypertension of the neonate; PH = pulmonary hypertension; BPD = bronchopulmonary dysplasia
The total number of neonates in the sildenafil group with pulmonary hypertension compared with the placebo group was 16/85 (19%) versus 4/78 (5%); RR 3.67; 95% CI 1.28 to 10.51; P=0.008

Table S3: Characteristics of neonates with and without pulmonary hypertension

	Neonates with PH (n=20)	Neonates without PH (n=143)	P value
GA at randomization (weeks + days) (median, IQR)	24 + 6 (23 + 1 to 25 + 4)	25 + 3 (24 + 0 to 26 + 4)	0.05
EFW at randomization (g) (median, IQR)	475 (323 to 536)	518 (377 to 645)	0.06
Absent or reversed EDF at randomization (%)	9 (45.0%)	35 (24.5%)	0.04
GA at delivery (weeks + days) (median, IQR)	26 + 6 (26 +0 to 28 + 2)	29 + 4 (27 + 6 to 34 + 1)	<0.0001
Birthweight (g) (median, IQR)	573 (484 to 650)	805 (639 to 1460)	<0.0001
Female sex (%)	7 (35.0%)	71 (49.7%)	0.24
Maternal preeclampsia or HELLP (%)	6 (30.0%)	34 (23.8%)	0.58

PH = pulmonary hypertension; GA = gestational age; EFW = estimated fetal weight; EDF = end-diastolic flow; HELLP = hemolysis, elevated liver enzymes and low platelets

Table S4: Non-context specific SAEs

	Sildenafil (n= 108)	Placebo (n=107)
Maternal		
Spontaneous preterm labor	0	3
Admission due to threatened preterm labor	1	1
Hospital admission due to headache	1	0
Admission due to vaginal blood loss	1	0
Admission for observation after fall on abdomen	1	0
Hospital admission due to pain, itch and hypertension	1	0
Admission due to suboptimal CTG, headache and itch	0	1
Asymptomatic hyponatremia and hyperkaliemia	0	1
Hydronephrosis for which double J stent placement	0	1
Infected hematoma cesarean scar for which opening of the wound and antibiotic treatment	1	0
Admission due to fever and malaise, due to wound infection combined with upper airway infection, for which antibiotic treatment	1	0
Subcutaneous hematoma after cesarean section for which re-laparotomy	1	0
Severe HELLP postpartum, or antiphospholipid syndrome flare	1	0
Hospital admission due to delirious postpartum	1	0
Hospital admission due to endometritis postpartum	0	1
Fetal/neonatal		
Atypical hemorrhagic lesions in the wall of lateral ventricles	0	1
Progressive cholestasis	0	1
Intrahepatic portal venous shunt	1	0
Death 18 months postpartum due to cardiogenic shock based on sepsis	1	0

SAE = serious adverse event; CTG = cardiotocography; HELLP = hemolysis, elevated liver enzymes and low platelets

Table S5: Side effects of study medication, as reported by the participants

	Sildenafil (n= 103)	Placebo (n= 100)
One or more side effects (%)	25 (24.3%)	9 (9.0%)
Headache (%)	13 (12.6%)	4 (4.0%)
Flushing (%)	8 (7.8%)	1 (1.0%)
Congested nose (%)	5 (4.9%)	0
Nausea/ reflux (%)	4 (3.9%)	3 (3.0%)
Bleeding nose (%)	3 (2.9%)	0
Fatigue (%)	3 (2.9%)	0
Abdominal pain (%)	2 (1.9%)	2 (2.0%)
Edema (%)	2 (1.9%)	1 (1.0%)
Hot sensation (%)	1 (1.0%)	1 (1.0%)
Dry mouth/throat (%)	1 (1.0%)	1 (1.0%)
Diarrhea (%)	1 (1.0%)	1 (1.0%)
Dizziness (%)	1 (1.0%)	0
Stuffiness (%)	1 (1.0%)	0
Redness face (%)	1 (1.0%)	0
Spider naevi (%)	1 (1.0%)	0
Skin rash (%)	1 (1.0%)	0
Blood blister (%)	1 (1.0%)	0
Night sweating (%)	0	1 (1.0%)
Muscle ache (%)	1 (1.0%)	0
Blurry vision (%)	0	1 (1.0%)
Reduced fetal movements (%)	1 (1.0%)	0
Braxton hicks contractions (%)	1 (1.0%)	0
Palpitations (%)	1 (1.0%)	0
Numb feeling in legs (%)	0	1 (1.0%)
Malaise (%)	1 (1.0%)	0

Table S6: Primary causes of neonatal death

Cause of neonatal death	Sildenafil (n = 21)	Placebo (n = 11)
Sepsis/infection	7 (33.3%)	2 (18.2%)
Pulmonary hypertension	2 (9.5%)	2 (18.2%)
Necrotizing enterocolitis	3 (14.3%)	1 (9.1%)
Bronchopulmonary dysplasia	1 (4.8%)	1 (9.1%)
Intestinal perforation	2 (9.5%)	0
Intestinal ischemia	0	2 (18.2%)
Intracerebral hemorrhage	1 (4.8%)	1 (9.1%)
Non-intervention due to non-viability/dismal prognosis	2 (9.5%)	0
Result of a congenital anomaly	1 (4.8%)	1 (9.1%)
Choking	1 (4.8%)	0
Pericardial tamponade	0	1 (9.1%)
Respiratory distress syndrome	1 (4.8%)	0

Table S7: Congenital anomalies

Diagnosis	Further information
Silver Russell syndrome	DNA-confirmed
Silver Russell syndrome	DNA-confirmed
Silver Russel syndrome	Neonatal death, 4 major clinical criteria, not DNA-confirmed
Hartnup's disease	Macrocephaly, receding skull seams, abnormality of the ear (relative macrocephaly due to brain sparing
Atresia of the ductus venosus	Neonatal death, finding confirmed at autopsy
Mosaicism trisomy 16	Amniocentesis after randomization. Termination of pregnancy after finding
Multiple congenital anomalies, no confirmed syndrome	Neonatal death with multiple anomalies confirmed at autopsy. Esophageal atresia with tracheo-esophageal fistula, tethered cord, hypertelorism
ADA-SCID (adenosine deaminase deficiency - severe combined immune deficiency)	Neonatal death due to late necrotizing enterocolitis and sepsis, in the setting of a primary T-cell immunodeficiency (DNA-confirmed)
Multiple congenital anomalies, no confirmed syndrome	Single umbilical artery, hemivertebrae, wide fontanelle No confirmed DNA-diagnosis
Unbalanced translocation	Amniocentesis after randomization. Termination of pregnancy after finding
Congenital nephropathy RMDN1 gene mutation	Neonatal death, homozygous mutation of RMND1 gene (p.Leu393Val)
Multiple congenital anomalies, no confirmed syndrome	Large neurocranium, arthrogryposis, hypospadia, syndactyly No confirmed DNA-diagnosis

Chapter 10

Neonatal pulmonary hypertension after severe early-onset fetal growth restriction in the Dutch STRIDER-trial: the need for a consensus definition

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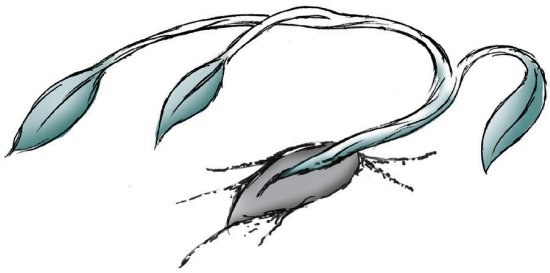
Submitted



Abstract

Background: The Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction) trial randomly assigned pregnant women with severe early-onset fetal growth restriction (FGR) to sildenafil versus placebo. Sildenafil did not reduce perinatal mortality and morbidity, but did show a higher rate of neonatal pulmonary hypertension (PH) in the sildenafil group.

Methods: A blinded expert committee assessed by consensus the diagnosis of PH, as previously made by the treating physician, and compared the prevalence and definition reported in published studies.

Results: Of the 25 infants initially labeled as having PH (15% of 163 participants), 20 (12%) were confirmed. Of these, 12 infants had persistent PH of the neonate (PPHN), and four had PH associated with sepsis or bronchopulmonary dysplasia. Four neonates with PPHN subsequently developed PH associated with bronchopulmonary dysplasia in later life. Published literature reported a highly variable prevalence (5% to 50%) of PH after FGR depending on the population and definition used.

Conclusions: PH was more frequent among infants of mothers allocated to antenatal sildenafil compared with placebo. The validation process showed that the diagnosis of neonatal PH is complex and in need for an unambiguous definition. This would reduce the reported variance of PH incidences.

Introduction

Fetal growth restriction (FGR) is a condition of placental insufficiency in which the fetus does not reach its own intrinsic growth potential(1). In the extreme phenotype of early-onset FGR (before 32 weeks' gestation), the root cause lies in early pregnancy when the necessary low-resistance high-flow placental bed circulation is inadequately established. The ensuing placental insufficiency is reflected in impaired growth and abnormal umbilical and fetal Doppler velocity patterns and a high risk of stillbirth(2). If born alive, usually through iatrogenic premature birth, the neonate is likely to be admitted to neonatal intensive care unit (NICU) and is prone to neonatal mortality and long-term morbidity(3). Common complications are intra-ventricular haemorrhage (IVH)(4-6), periventricular leukomalacia (PVL)(7, 8), bronchopulmonary dysplasia (BPD)(9-13), necrotizing enterocolitis (NEC)(14, 15), retinopathy of prematurity (ROP)(16, 17), sepsis and pulmonary hypertension (PH), either persistent pulmonary hypertension of the neonate (PPHN) or late-onset pulmonary hypertension, often associated with BPD(18-20).

PPHN refers to a persistence of transductal and interatrial right-to-left shunting after birth and is associated with a variety of conditions, including developmental lung diseases, perinatal infections, meconium aspiration syndrome, and cardiac diseases, or in the absence of such conditions referred to as idiopathic(21, 22). PPHN is a clinical syndrome, commonly defined by the presence of extra-pulmonary right-to-left shunt across the foramen ovale or patent ductus arteriosus, which leads to hypoxaemia. Importantly, no specific level of estimated pulmonary artery pressure has been defined. While an absolute value of mean pulmonary artery pressure (mPAP) of > 25 mmHg is generally accepted for infants above three months of age, the premise that a single threshold is appropriate for neonates at all gestations is likely invalid. A diagnostic threshold for preterm infants has not been agreed upon. Also, irrespective of the timeframe after birth during which symptoms occur, the syndrome is still called PPHN. Also after the neonatal transition period, the best diagnostic tools and the exact criteria to be used to define pulmonary hypertension in premature born infants with FGR are subject of international debate, since heart catheterization, which is the diagnostic golden standard for measuring the PAP, is generally regarded not suitable for this purpose in this vulnerable population(23).

In the Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction) trial(24), the phosphodiesterase 5-inhibitor (PDE5) sildenafil was evaluated as treatment for severe early-onset FGR in a randomised controlled setting. The primary outcome of this trial was a composite of fetal and neonatal mortality or major neonatal morbidity. This randomised, placebo-controlled trial was terminated immediately after the pre-planned interim analysis after 60% of inclusions, based on advice of the data safety monitoring board (DSMB) who found potential harm for the neonates in the face of futility. The concerns of harm were based on the increased incidence of PH, as diagnosed by the treating physician, and neonatal deaths in neonates whose mothers were allocated to the sildenafil group. The reported diagnoses PH included both PPHN as well as PH of later onset. However, both were documented asd PPHN in the study database, so at first,

no distinction was made. Based on the data of 182 patients that completed the study at that time, 17 neonates in the sildenafil group had been labeled PPHN compared with three neonates in the placebo group.

Since no standardised echocardiographic screening in all neonates was performed, after the trial was stopped, we aimed to validate, typify and characterise the diagnosis of PH, and establish the relationship with neonatal deaths. The aim of this paper is to describe the findings of the expert adjudication committee and compare these to available literature on definitions and prevalence of PPHN and PH in preterm growth restricted neonates.

Methods

In the Dutch STRIDER trial, the completion of the study database case record form for mother and infant, was mostly based on the discharge letter(s). If any of the diagnoses IVH, PVL, BPD, NEC, ROP, sepsis, and PH were mentioned in the discharge letter, the conditions were marked as present. In case of doubt of the presence of certain conditions, a local neonatologist was asked to check the particular diagnosis in the patient records. In the study database, no distinction was made between PPHN and late-onset PH, associated with (developing) BPD and/or sepsis. Echocardiography was performed only on clinical indication at discretion of the treating physician.

After discontinuation of the trial and because of the unexpected finding, the study team decided to install a blinded external adjudication committee of neonatologists (WO, AFJvH, EL, IKMR) and a pediatric cardiologist (RMFB) with expertise in PPHN/PH and preterm infants with fetal growth restriction to review all potential cases of PH. In two face-to-face sessions, the relevant documents (letters, notes, results of cardiac ultrasound, saturation measurements etc.) of all neonates that were either reported in the database with PH and/or died, were reviewed. To verify that no infant with clinically relevant PH had been missed, the treating physicians were asked post hoc to review the patient records of all infants that had received any respiratory support during NICU-admission and to confirm that these infants had not shown signs of PH. All these infants were discussed in these meetings for the diagnosis and type of PH as well as the cause of death. In accordance with criteria defined in consensus within the expert committee, a diagnosis of PPHN was applied when there was a clinical suspicion of PH, confirmed by either right-left-shunting through an open foramen ovale and/or an open ductus arteriosus on echocardiography and/or by a more than 10% transcutaneous oxygen saturation difference between the upper right and lower limb (pre- and postductal differences). A diagnosis and evaluation of severity of late-onset PH was made when PH was diagnosed after an initial period without signs of PH and based on echocardiographic signs of increased systolic right ventricular pressure (PRV:PLV > 0.5), including right-to-left shunting through persistent foramen ovale or ductus arteriosus, or in the absence of shunts increased maximal flow velocity of tricuspid or pulmonary regurgitation jets, septal flattening, pulmonary acceleration time, all in the absence of structural heart disease, including

pulmonary vein stenosis or left ventricular dysfunction. For the distinction between PPHN and late onset PH associated with sepsis or (developing) BPD, the clinical course of the neonate was discussed, and the final diagnosis was set by consensus between the experts. In the clinical course the most important factor for the distinction between the different types of PH was the timeline in onset of symptoms. When signs of PH were present roughly within the first days of life, this was classified as PPHN. When the symptoms of PH occurred after 28 days of life in combination with an episode of sepsis, or in association with (developing) BPD, the diagnosis of late-onset PH associated with sepsis or (developing) BPD respectively was made. For all children presenting with symptoms of PH between 48 hours and 28 days, the course of symptoms and cardiorespiratory condition was reviewed and discussed in order to distinguish between the different forms of PH. Consequently, an infant could be diagnosed with more than one type of PH, presenting initially with PPHN and later with late-onset PH.

Literature review

We performed a scoping literature search to compare the prevalence and the definition of PPHN in neonates and definition of PPHN born after fetal growth restriction. An information specialist (JL) performed an electronic search in Ovid Medline from inception to July 10th 2019 using MESH-terms and text words for the concepts 'fetal growth restriction' and 'pulmonary hypertension' or 'persistent fetal circulation'. Animal studies were excluded. There were no language, date or study restrictions. The references and citations of eligible publications were screened for additional relevant studies. Original publications were eligible for inclusion if the outcome PH and/or the definition of PH was described in neonates born after FGR/placental dysfunction. One author (AP) screened the titles and abstracts and, if potentially eligible, the full-text.

Results

The interim analysis and the termination of the Dutch STRIDER trial took place in July 2018. The discussions held with this expert committee were in September and October 2018. The interim analysis planned to include the completed data of 50% of the intended trial population (N=360). At the time of the interim analysis, the DSMB evaluated the data of 183 patients. At that time, 216 (60%) pregnant women had been randomised in the trial, 20 of whom were still pregnant or the infant was still admitted to the NICU at the time of the interim analysis. One participant was lost to follow-up for all maternal and fetal/neonatal outcomes due to moving abroad during the pregnancy. Additional information on inclusion criteria and baseline characteristics has been described elsewhere (24). During the meetings, 47 infants were discussed. Among these infants, 25 infants who had initially been diagnosed with PPHN and 19 infants died without the diagnosis of PPHN. Furthermore, among these 47 infants, two were discussed after the treating physician found signs of possible PH during the post hoc review of infants that had survived and were not initially reported as having PPHN. One infant was discussed upon request of the gynecologist, since an Abernathy vascular malformation (congenital portosystemic shunt)

was observed, but no PPHN or late-onset PH was reported. The shunt resolved spontaneously.

After consensus, the labeling with the presence or absence of the diagnosis of PH changed for nine infants in the study. Of these nine infants, six had received the PH label by the treating physician because of a clinical suspicion of PH but did not match the more rigorous definition after review. In another infant the labeling in the databases was incorrect due to a data entry mistake. Two previously undetected infants were identified in this validation procedure as having PPHN because of their need for oxygen and they had pre-postductal saturation differences of more than 10%. The first infant was from the placebo group and was diagnosed with PPHN and the other infant was from the sildenafil group who was born with a birthweight of 440 gram at 27 weeks and 1 day of gestation, and whose treatment was stopped at the fourth day due to apparent non-viability.

In total, of the 85 infants allocated to sildenafil, 16 (19%) experienced PH (either PPHN or late-onset PH or both) whereas this was the case for only 4 (5%) of the 78 neonates in the placebo group (risk ratio (RR) 3.67; 95% confidence interval (CI) 1.28 to 10.51; p = 0.008) (Table 1). Of the 16 infants with PH in the sildenafil group, ten died (63%). In the placebo group, three of four infants died (75%) (RR 0.83; 95% CI 0.42 to 1.65; p = 0.60).

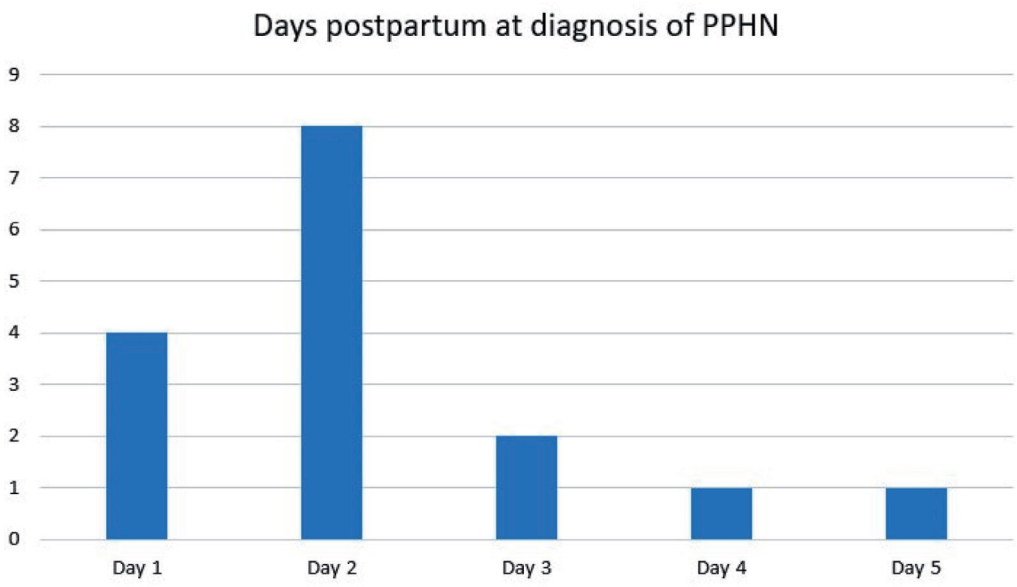
Table 1: Types of pulmonary hypertension within live born infants in the Dutch STRIDER trial, per randomization allocation group

	Sildenafil (n=85)		Placebo (N=78)	
	Neonatal death (n=21)	Survival to discharge (n=64)	Neonatal death (n=11)	Survival to discharge (n=67)
Total pulmonary hypertension	10	6	3	1
PPHN	7	3	1	1
PH associated with sepsis	1	1	0	0
Late-onset PH associated with (developing) BPD	1	0	1	0
PPHN followed by late-onset PH associated with (developing) BPD	1	2	1	0

PPHN = Persistent pulmonary hypertension of the neonate; PH = Pulmonary hypertension; BPD = Bronchopulmonary dysplasia
The total number of neonates in the sildenafil group with any PH compared with the placebo group was 16/85 (19%) versus 4/78 (5%); RR 3.67; 95% CI 1.28 to 10.51; P=0.008

Of the 16 infants diagnosed with PPHN, the timing of occurrence of PPHN is presented in figure 1. All infants with PPHN received the diagnosis on day one to five after delivery (the day of delivery was considered as day zero). Most were diagnosed with PPHN on day one or two, and the most prevalent day was day two (nine out of 16 infants). PH associated with sepsis occurred in two children: on day 2 and day 5. The occurrence of PH associated with BPD was widespread: on day 20, 61, 85, 88, 103 and 106 after delivery.

Figure 1: Timing of diagnosis of persistent pulmonary hypertension of the neonate (PPHN)



Number of infants with PPHN. Day of delivery is considered as day 0.

In summary, the expert committee confirmed the diagnosis in twenty infants with PPHN or PH according to the above-mentioned definitions (Table 1). Of these preterm infants, 16 presented with PPHN (13 allocated to sildenafil and three to placebo), of who four subsequently developed late-onset PH associated with (developing) BPD later in the disease course (three allocated to sildenafil and one to placebo). Two infants allocated to antenatal sildenafil experienced PH associated with sepsis, whereas two infants experienced late-onset PH associated with (developing) BPD (one allocated to sildenafil, one to placebo).

When reviewing the cause of death, the committee of neonatologists concluded that PH was the primary cause of death in four infants: two allocated to sildenafil and two to placebo.

Table 2 presents the characteristics of the infants experiencing one or more forms of PH, compared with the infants that did not experience PH. The median gestational age at delivery and median birthweight were lower in the infants that experienced PH. Furthermore, a higher percentage of the infants that experienced PH, had absent or reversed EDF in the umbilical artery before birth (nine out of twenty (45%) versus 35 out of 143 (24.5%), p = 0.04).

Table 2: Characteristics of neonates with and without any pulmonary hypertension

	Neonates with PH (n=20)	Neonates without PH (n=143)	P value
GA at randomization (weeks + days) (median, IQR)	24 + 6 (23 + 1 to 25 + 4)	25 + 3 (24 + 0 to 26 + 4)	0.05
EFW at randomization (g) (median, IQR)	475 (323 to 536)	518 (377 to 645)	0.06
Absent or reversed EDF at randomization (%)	9 (45.0%)	35 (24.5%)	0.04
GA at delivery (weeks + days) (median, IQR)	26 + 6 (26 +0 to 28 + 2)	29 + 4 (27 + 6 to 34 + 1)	<0.0001
Birthweight (g) (median, IQR)	573 (484 to 650)	805 (639 to 1460)	<0.0001
Female sex (%)	7 (35.0%)	71 (49.7%)	0.24
Maternal preeclampsia or HELLP (%)	6 (30.0%)	34 (23.8%)	0.58

PH = pulmonary hypertension; GA = gestational age; IQR = inter quartile range; EFW = estimated fetal weight; EDF = end-diastolic flow; HELLP = Haemolysis Elevated Liver enzymes Low Platelets

Synthesis of the results of the literature review

The literature search identified 108 records. 92 Records were excluded based on title and abstract. One full text was not available; the other 15 full text manuscripts were screened, of which 11 records were excluded since they did not meet the inclusion criteria. One additional reference was found via references checking.

Table 3 describes the definition or echocardiographic criteria used to define PH, the definition for FGR used by the study population and prevalence of PPHN of the five included studies. These studies report a prevalence of 50%(25), 12%(26), 5%(18) and 22%(19) in FGR infants. However, some of the included studies included neonates below a certain absolute birthweight or with SGA instead of FGR. A more extensive description of the individual study results is presented in the Supplementary Information.

Table 3: Definition and prevalence of PH in the included studies from the literature review

First author, year	Study population	Definition	Prevalence
Bhat, 2012(25)	145 neonates with an extreme very low birthweight (≤ 1000 gram)	Pulmonary hypertension: At least one of the following echocardiographic findings: (1) right ventricular hypertrophy, (2) flattening of interventricular septum, (3) presence of tricuspid regurgitation in the absence of pulmonary stenosis, and (4) elevated right ventricular pressures as estimated by Doppler studies of tricuspid regurgitation jet	26 out of 145, of whom 12 (46%) were SGA at delivery. Of the 52 SGA neonates, 26 (50%) developed PH
Check, 2013(27)	Neonates with BPD that were delivered ≤ 28 completed weeks of gestation.	Pulmonary hypertension was defined following a standardized algorithm: if tricuspid regurgitation (TR) was present, the Bernoulli equation was used to estimate the right ventricular (RV) pressure and to determine whether pulmonary arterial pressure was elevated (RV > 33% systemic). If TR was not present, demonstration of at least two of the following four findings must be made: RV enlargement, RV hypertrophy, interventricular septal flattening and/or abnormal pulmonary artery Doppler (sawtooth pattern or shortened acceleration time)	39 out of 138 infants with BPD (28.3%). The prevalence among infants without BPD is not described
Danhaive, 2005(26)	153 newborns with a birthweight below 1000 gram	Pulmonary hypertension: Tricuspid regurgitant jet velocity or, when impossible, on the systolic configuration of the ventricular septum. RV pressure greater than half-systemic or a flattened septum were reported as ''moderate'', whereas RV pressure equal or superior to systemic or a septum bulging into the left ventricle were reported as ''severe''	Six out of 49 (12%)
Turan, 2013(18)	94 neonates born after FGR	Pulmonary hypertension: Right to left shunt is described. The definition of PH itself is not described in this secondary analysis of a prospective multicenter study	Right to left shunting was observed in 5 (5%) neonates
Vyas-Read, 2017(19)	556 neonates born < 32 weeks and a birthweight below 1500 gram	Pulmonary hypertension: An echocardiogram that showed: 1) a moderate-to-large patent ductus arteriosus (PDA) with bidirectional or right-to-left shunting; 2) a tricuspid regurgitation jet gradient of ≥ 32 mmHg with septal flattening, right ventricular hypertrophy, or right ventricular dilation; or 3) a tricuspid regurgitation jet velocity of ≥45 mmHg	59 Neonates were diagnosed with late PH of which ten (18%) were born after FGR. Of the 45 neonates born after FGR, ten (22%) developed late PH

SGA = small for gestational age; PH = pulmonary hypertension; BPD = bronchopulmonary dysplasia; RV = right ventricle; TR = tricuspid regurgitation; FGR = fetal growth restriction; PDA = patent ductus arteriosus

Discussion

The Dutch Strider study revealed an unexpected higher incidence of PH in growth restricted infants antenatally exposed to sildenafil, compared with placebo. We validated the diagnosis of PH in an expert committee. After a thorough review of all cases by an expert committee twenty out of 163 (12%) of the live born infants in the Dutch STRIDER trial were diagnosed with PH. The majority of the infants experienced PPHN immediately after delivery, but also cases of late-onset PH associated with (developing) BPD and PH associated with sepsis were observed.

PPHN was first described by Gersony et al. in 1969(21) as a persistence of the fetal circulation after birth. During normal transition after birth, the lungs of the newborn fill with air together with rhythmic distensions, resulting in a gradual shift from fetal towards neonatal circulation with a decrease in pulmonary vascular resistance in order to increase pulmonary blood flow and oxygenate the blood by the lungs. However, in PPHN the neonatal circulation fails to adapt to the extra uterine situation and a sustained elevation of the vascular resistance persists, resulting in a right-to-left shunting through the foramen ovale and/or the ductus arteriosus(28). As a result, the systemic blood is hypoxemic, potentially leading to a vicious circle of acidosis, vasoconstriction, failing circulation, and eventually heart failure and failure of other organs. PPHN occurs in about two out of 1000 live born neonates(29-31), but recent studies report an increased prevalence in preterm born infants, with higher prevalence in more severe prematurity(32, 33). Clinical chorioamnionitis, premature rupture of membranes(33), fetal myocardial dysfunction, fetal structural cardiac diseases, fetal hepatic and cerebral arteriovenous malformation, maternal metabolic diseases, maternal drugs use, maternal smoking, maternal lung disorders(34), and placental dysfunction(34, 35) have been identified as important risk factors(23). Late-onset PH associated with BPD has been associated with prematurity, severity of BPD, but also with preceding PPHN, small for gestational age, ROP, persistent ductus arteriosus (PDA) and PDA ligation(23).

Some clinicians and researchers, due to lack of compelling evidence, hypothesize that signs of PPHN typically start within the first days of life based on the idea that the fetal circulation should adapt to the extra-uterine life within the first day(s)(28). However, other clinicians hypothesize that PPHN occurs within the neonatal period, defined as the first 28 days of life(36). We consider the timing of occurrence of symptoms of PH important in the distinction between PPHN and late-onset PH. There is scant data on the influence of fetal remodeling and how much time is 'physiologically' appropriate to adapt from intrauterine towards neonatal life and the variety on factors influencing the pulmonary vascular resistance. This adaptation process most likely differs for different gestational ages. It may be that neonates can remain haemodynamically stable directly after birth by compensating for the shunting, while after a few days (when an additional haemodynamic problem occurs), the fetus might show symptoms of PH, since compensation is no longer possible due to the adaptation of the right ventricle in the transition period. We recognise that the diagnoses of PPHN and late-onset PH might form a continuum, representing evolving

pulmonary vascular disease due to a disturbed vascular and airway development already in utero combined with environmental injuries(37). However, because of the unknown mechanisms associated with prenatal sildenafil exposure and the occurrence of neonatal or infantile pulmonary hypertension, we considered the distinction between the clinical phenotypes PPHN and late-onset PH associated with BPD or sepsis important. The distinction between a primary and a secondary problem is not straightforward, especially in this group of vulnerable infants, as reflected in the results of the literature search. This resulted in lengthy discussions about the diagnoses within our expert group. In our opinion, the discussions about subtle differences in the interpretation of the diagnosis PPHN, underline the need for a consensus definition to use in clinical practice and in research.

After extensive review of data of the infants of the Dutch STRIDER trial, the finding at interim analysis that there was an excess of any PH in infants after antenatal sildenafil exposure was confirmed, 19% versus 5%. This study does not provide answers as to the reason for the high incidence of PPHN in the infants who were antenatally exposed to sildenafil in the Dutch STRIDER study. Although hypotheses can be given that the medication may have induced structural or functional changes of the pulmonary vasculature, this relationship is not necessarily causal, and needs to be further explored. Additional studies, including histology of the placenta and biomedical studies of maternal and fetal materials may progress knowledge in this matter. Also, an individual data (IPD) meta-analysis including the other international STRIDER trials is planned and will provide additional data(38).

In the Dutch STRIDER trial, the diagnosis PH was recorded as a predefined exploratory outcome important for monitoring safety. PPHN was defined before the start of the trial as a clinical suspicion 'confirmed by echocardiography or saturation differences of more than 10% between the upper right and lower left or right limb', without pre-defined timeframe. Echocardiography was not performed as standard screening in premature neonates, but rather at the discretion of the treating physician when there was clinical suspicion of PH or suspicion of another cardiac problem. The incidence of PH in the Dutch STRIDER trial (12%) is comparable to the UK STRIDER trial(39)(16%; 15 out of 92 infants, six allocated to sildenafil and nine to placebo, personal communication), but higher than in the NZAUS STRIDER trial(40)(2%; two out of 103 infants, one allocated to sildenafil and one to placebo). These differences may be explained by definition differences, diagnostic strategies, severity of the condition in the different STRIDER cohorts, or thresholds of suspicion. Of note is the fact that neonates received no standardised screening for PH, only based on clinical suspicion. Clinical vigilance may play a role, although the infants with PPHN were spread equally across participating centers. We do not expect many differences in the use of definitions, diagnostic strategies or thresholds of suspicion between the participating centers within our country. Therefore, this is unlikely to explain the difference between randomisation groups in the Dutch STRIDER.

Nine infants of the total 163 live born infants (6%) in our trial were misclassified regarding a diagnosis PH, of whom one was a data entry mistake and eight infants were wrongly reported as having or not having PH. The fact that six neonates were incorrectly scored as

PPHN and two neonates were incorrectly scored as not having PPHN seem to underline the fact that a diagnosis of PPHN is not straightforward in clinical practice. In this study, systematical evaluation was only carried out after the trial was stopped. In one infant inhaled NO treatment was initiated for clinical 'PPHN' even though the definition of PPHN as defined in the study protocol was not met (yet). This underlines the conception that PH is a continuum of transition of the vascular bed, with many factors influencing the pulmonary arterial pressure. Furthermore, a systematical evaluation and a more detailed definition of PH could be described in our study protocol.

In total, the overall proportion of infants experiencing any type of PH in the Dutch STRIDER trial was 20/163 (12%). The studies we reviewed report a prevalence of 50%(25), 12%(26), 5%(18), and 22%(19). Even though there are few studies reporting the prevalence of PH among neonates born after FGR, the percentage of 12% that we found, does not seem to be an outlier. However, we found a prevalence of 5% (4/78 infants) of PH in our placebo group, which corresponds to the lowest percentage reported in the study of Turan(18). The observed differences in incidence between studies and the incidence of the Dutch STRIDER are related not only to the definition of PH, but also to how infants were screened or identified. Many of the studies report the outcomes of a group of infants born below a certain gestational age or below a certain birthweight, which is not fully comparable with our study population. Furthermore, in most studies (also in our current study) selection bias was present due to the design of the studies in which the infants are not systematically screened.

Internationally the definition of PH that is generally accepted is a mean PAP of > 20 to 25 mmHg, independent of gestational age or birthweight, measured by heart catheterisation. However, in the vulnerable population of preterm and growth restricted infants, this invasive measurement is not preferred or even impossible in some. Currently the most commonly used method of diagnosis in newborns is cardiac ultrasound in order to confirm the right-to left or bidirectional shunt and/or the increased PAP. The limitation of this technique is that it is dependent on the investigator and measurements are often derived values and estimations. In addition, no timeframe is included as part of the definition of PPHN. As discussed earlier, some clinicians hypothesize that PPHN occurs within the first days of life and others to the hypothesis that it is possible that PPHN was not obvious during the first days of life, but symptoms can occur later. A clear international accepted definition, including the timeframe, is still lacking(34, 41, 42).

We propose that a consensus definition of PPHN should be formed including the timeframe to discriminate between PPHN and late-onset PH. Furthermore, we propose that the performance of a cardiac ultrasound should be considered in trials investigating maternal medication that could influence the hemodynamics in the infants.

The strength of the Dutch STRIDER trial is the design. The allocation to either sildenafil or placebo was blinded for the patient and all caregivers, including the treating neonatologists and the outcome assessors. The drug allocation was unblinded as soon as the trial

was stopped and thus during the validation of the diagnosis of PH by the expert committee, but the randomisation code was not revealed to the experts before, during, or after the meetings(24). Another strength is the rigorous evaluation of all infants with neonatal death, PPHN, and other neonatal morbidities by a group of experts in the management of this disease(24). Since all experts involved in this committee work in the academic hospitals participating in the Dutch STRIDER trial, they theoretically could have known the drug allocation from some infants. However, all outcomes were assessed in consensus by the entire group and we think this theoretical bias was adequately prevented.

We acknowledge that in the Dutch STRIDER trial there was no systematic screening for PH. A systematic screening of all infants in both groups at similar time points would be a prerequisite for a valid comparison of the two groups. Furthermore, systematic screening could have increased the number of misclassified infants for the diagnosis PH. We also acknowledge that although the literature search was extensive, it was not a systematic review. We can therefore not exclude the chance that by this scoping review we have missed relevant records. Also by focusing on FGR and placental dysfunction, studies describing subgroups of SGA infants, might have been missed.

After a thorough review of all infants with suspicion of PH by an expert committee 20/163 (12%) of the live born infants in the Dutch STRIDER trial were diagnosed with PH. The majority of the infants experienced PPHN immediately after delivery, but also infants with late-onset PH associated with (developing) BPD and PH associated with sepsis were observed. Any form of PH occurred more often after antenatal exposure to sildenafil. Our study discusses that the definition, detection, and characterisation of neonatal PH is complex and difficult and requires (clinical and echocardiographic) standardised screening in risk groups, such as preterm infants born after FGR. A definition of PH is needed. Considering the fact that it is not possible to come to a definition based on empirical evidence nor is it possible to do the necessary assessments to prove the currently used diagnosis in the most vulnerable neonates, the authors suggest that an expert-based consensus definition of PH, both PPHN and late onset PH in (preterm or SGA) infants should be established, to assist correct diagnosis and compare data on short-term neonatal and long-term outcomes.

The Dutch STRIDER Trial Group

Please find the list of members of the Dutch STRIDER Trial Group in the Supplementary Information of chapter 9.

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Supplementary Information

Bhat et al. evaluated a group of 145 neonates with an extreme very low birthweight (≤ 1000 gram) for the presence or absence of PH(25). Infants were diagnosed with pulmonary hypertension if at least one of the following echocardiographic findings was present: [1] right ventricular hypertrophy, [2] flattening of interventricular septum, [3] presence of tricuspid regurgitation in the absence of pulmonary stenosis, and [4] elevated right ventricular pressures as estimated by Doppler studies of tricuspid regurgitation jet. 26 Neonates were diagnosed with PH, of whom 12 (46%) were small for gestational age (SGA) at delivery. Of the 52 SGA neonates, 26 (50%) developed PH(25).

Check et al. performed a retrospective cohort study, in which the medical records of infants that were delivered ≤ 28 completed weeks of gestation were reviewed and the characteristics of neonates with BPD were analyzed(27). PH was defined following a standardized algorithm: if tricuspid regurgitation (TR) was present, the Bernoulli equation was used to estimate the right ventricular (RV) pressure and to determine whether pulmonary arterial pressure was elevated (RV > 33% systemic). If TR was not present, demonstration of at least two of the following four findings must be made: RV enlargement, RV hypertrophy, interventricular septal flattening and/or abnormal pulmonary artery Doppler (sawtooth pattern or shortened acceleration time). Among the neonates with BPD in this group, birthweight percentile was in the univariate and multivariate analyses associated with PH, but the prevalence of PH among neonates without BPD was not described(27).

Danhaive et al. described a case series report of 153 newborns with a birthweight below 1000 gram, 49 (32%) of which had a birthweight below the 10th percentile for gestational age(26). The diagnosis of pulmonary hypertension was established on the basis of tricuspid regurgitant jet velocity or, when impossible, on the systolic configuration of the ventricular septum. RV pressure greater than half-systemic or a flattened septum were reported as ‘‘moderate’’, whereas RV pressure equal or superior to systemic or a septum bulging into the left ventricle were reported as ‘‘severe’’. Six out of 49 (12%) of neonates with a birthweight below the 10th percentile were diagnosed with PH; whereas one out of 104 (1%) neonates with a birthweight above the 10th percentile was diagnosed with PH. Three out of six growth restricted neonates with PH were born from a twin pregnancy.

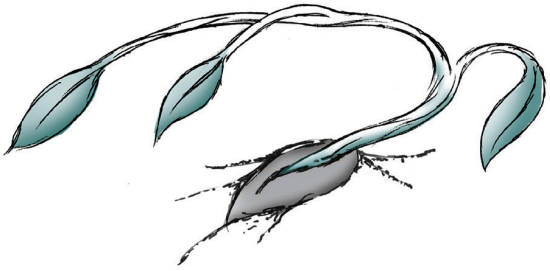
Turan et al. studied the cardiovascular transition of 94 neonates born after FGR(18). The neonatal echocardiographic findings showed right to left shunt in five out of 94 neonates (5%). The definition of PH itself is not defined in this secondary analysis of a prospective multicenter study(18).

Vyas-Read et al. performed a retrospective observational cohort study and included 556 neonates born < 32 weeks and a birthweight below 1500 gram(19). The primary outcome was late PH on the final echocardiograph prior to death or discharge from the neonatal intensive care unit. Pulmonary hypertension (PH) was defined as an echocardiogram that

showed: [1] a moderate-to-large patent ductus arteriosus (PDA) with bidirectional or right-to-left shunting; [2] a tricuspid regurgitation jet gradient of ≥32 mmHg with septal flattening, right ventricular hypertrophy, or right ventricular dilation; or [3] a tricuspid regurgitation jet velocity of ≥45 mmHg. 59 Neonates were diagnosed with late PH of which ten (18%) were born after FGR. Of the 45 neonates born after FGR, ten (22%) developed late PH. The median timing of final ultrasound was 77 days (13-136) in the group diagnosed with late PH(19).

Chapter 11

Summary



Summary

This thesis aimed to answer questions on important aspects of early-onset FGR: its definition, prognosis and management.

In **Chapter 2** we describe which definitions of fetal growth restriction in the existing literature are used over time and our findings underline the need for a uniform definition. In our literature review of used definitions in the years 1994, 2004 and 2014(1) we showed that through the years an increasing number of studies have been published on FGR (56, 75 and 116 respectively). Many definitions of FGR are used, of which the majority in all time frames was 'birthweight below the 10th percentile', which is unfitting from an obstetric perspective. This has shown improvement over the years: in 2014 the highest percentage of the studies used antepartum findings instead of postpartum findings (neonatal weight): 34% in 1994, 30% of the studies in 2004 and 47% in 2014 used antepartum findings in defining FGR. Still, the majority of definitions essentially defined SGA, i.e. smallness, rather than the pathological syndrome of FGR. This chapter points out the lack of heterogeneity and imperfections in the definition of FGR and we conclude that in order to ensure adequate interpretation from a clinical perspective as well as data synthesis from a research perspective, a uniform definition of FGR is necessary.

Chapter 3 is a systematic review on the reported fetal and neonatal mortality and short- and long-term morbidity in cohorts of women with early FGR(2). 21 Studies reporting 2334 pregnancies with FGR, diagnosed before 32 weeks of gestation, on fetal and neonatal morbidity in combination with short or long-term outcome were included in the review. Patients included in the different cohorts, had variable pregnancy characteristics such as gestational age and estimated fetal weight at diagnosis of FGR. Overall, 12% antenatal deaths and 7% neonatal deaths occurred. Only a few studies focused on the long-term neurodevelopment of the surviving children, with an overall neurodevelopmental impairment rate of 11%, but the variation was large, as were the applied methods. We conclude that, although it is obvious that early-onset FGR carries a high burden of disease for affected children, to improve counseling of individual patients about the fetal prognosis, a more detailed analysis of individual patient data would be useful.

The neurodevelopmental outcomes at five years of age in a cohort of children born after severe early-onset FGR is reported in **Chapter 4**(3) These children were born from mothers participating in the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study(4). Of the 74 children that were assessed at five years of age, the mean full-scale IQ (FSIQ) was normal, but 15% of the children had an abnormal score (FSIQ below 85) and in 35% either verbal or performance or processing speed quotient was below a score of 85. Of the assessed children, 38% had an abnormal score in the motor assessment. The factors associated with an abnormal FSIQ were the end-diastolic flow (EDF) of umbilical artery, gestational age at delivery, birthweight and neonatal morbidity. The abnormal motor score was found more often in boys and in children that experienced bronchopulmonary dysplasia (BPD) in the neonatal period. In summary, the findings at five years

showed an overall better outcome than anticipated, but higher risk of an adverse neurodevelopmental outcome remained, in particular the motor and processing speed outcomes. Because of the selective sample no conclusion could be made regarding the initial aims of the TRUFFLE trial.

Chapter 5 is a systematic review of the prognostic accuracy of short-term variation (STV) of the fetal heart rate on the cardiotocography (CTG) in pregnancies complicated by FGR(5). This review shows that in pregnant women with early-onset FGR (before 32 weeks of gestation), the STV is not statistically significant associated with acidemia. Due to the limited data, no conclusion can be drawn for the association between STV and fetal/neonatal mortality, morbidity and long-term (neurodevelopmental) outcomes. Therefore, we conclude that even though the STV seems a logical and promising tool for deciding on the optimal moment of delivery during fetal surveillance, a randomized controlled trial (RCT) is necessary to investigate whether a management strategy that includes a decision algorithm based on STV improves outcomes over visual evaluation of the CTG.

In **Chapter 6** a secondary analysis of the Control of Hypertension In Pregnancy Study (CHIPS)(6) is presented(7). In this analysis the association has been investigated between level and duration of blood pressure control and fetal growth. The associations between gestational age at randomization to 'less tight' control versus 'tight' control of hypertension in pregnancy and the proportion of children with a birthweight below the tenth percentile were explored. The results of this analysis show that less tight control starting before 24 weeks was associated with fewer babies with a birthweight below 10th centile but a higher rate of preterm birth. There was no effect on perinatal death or high-level neonatal care for more than 48 hours. For the mother, 'less tight' (vs. 'tight') control was associated with more severe hypertension at all gestational ages, but in particular before 28 weeks. This leads to the hypothesis that 'tight' control of hypertension might cause some reduction in birthweight. However, this association was not powered for in the RCT and further research would be necessary to explore this hypothesis.

Chapter 7, 8, 9 and 10 are on the STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) trials, in particular the Dutch STRIDER study. This is a set of five trials that were designed in international collaboration, as described in **Chapter 7**. The aim was to investigate whether the phosphodiesterase 5-inhibitor sildenafil would decrease fetal and neonatal morbidity, mortality and long-term neurodevelopmental impairment in pregnant women with severe early-onset FGR, compared to placebo. The international study protocol of the five STRIDER trials is presented in chapter 7(8).

Chapter 8 consists of the detailed statistical analysis plan for the Dutch STRIDER trial(9).

Chapter 9 reports the results of the Dutch STRIDER trial(10). The trial was stopped early based on advice of the Data Safety Monitoring Board (DSMB) due to serious concern of harm combined with futility at interim analysis and at that time 216 patients had been

randomized. The primary outcome (mortality or survival with serious neonatal morbidity) occurred in the offspring of 65 participants (60%) allocated to sildenafil and in 58 (54%) allocated to placebo (RR 1.11, 95% CI 0.88 to 1.40; P=0.38). The conclusion of this trial was that antenatal sildenafil administration, compared to placebo, did not reduce the chance of neonatal mortality and morbidity. Moreover, an unexpected and yet unexplained increase in neonatal pulmonary hypertension was observed in the infants born in the sildenafil group compared with placebo (16 (19%) compared with 4 (5%) (RR 3.67, 95% CI 1.28 to 10.51; P=0.008)).

Chapter 10 describes the process and outcomes of neonatal outcome validation within the Dutch STRIDER trial and discusses the hypotheses on the possible association between antenatal sildenafil treatment and Persistent Pulmonary Hypertension of the Neonate (PPHN). This data validation found a total rate of 12% pulmonary hypertension in the Dutch STRIDER trial. The lack of a standardized definition of pulmonary hypertension makes the diagnosis and interpreting data complex. There is need for a consensus definition of pulmonary hypertension to reduce the reported variance of pulmonary hypertension incidences in prospective studies in which neonates born preterm after FGR are actively screened for right to left shunting after 24 hours of life in order to be able to start treatment in an early stage of disease.

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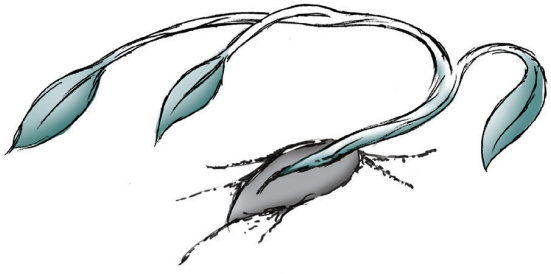
Chapter 12

General discussion



General discussion

Severe, early-onset FGR is an uncommon condition in pregnancy and affects about 700 pregnant women in The Netherlands yearly(1). The definition of FGR is by consensus defined as an AC or EFW below 3rd percentile or AEDF; or as an AC or EFW below 10th percentile with a PI of the uterine artery above 95th percentile and/or PI of the umbilical artery above 95th percentile(2). When a fetus is identified as smaller than expected based on the gestational age either by symphysial fundal height measurements and/or ultrasound, his/her parents enter a 'rollercoaster' of diagnostics, decision-making and fetal surveillance. This care is concentrated in specialized centres. The differential diagnosis work-up is essential, as there is a chance that the fetus has underlying syndromal pathology or is small-for-gestational age based on a congenital infection. The first condition is less likely if there are no structural anomalies on ultrasound and can be minimized by investigating the genetic pattern in cells from the amniotic fluid (amniocentesis). Alternatively, cell-free fetal DNA derived from maternal blood may be an option, but is currently mostly used to find numeric chromosomal anomalies. Congenital infection can be excluded by investigating maternal serum. When these examinations turn out negative, the diagnosis placental dysfunction is more likely if abnormal Doppler measurements are present on ultrasound. Regular ultrasounds are performed to estimate fetal weight and monitor Doppler velocimetry of maternal and fetal vessels as a surrogate measure of placental function. The worsening of placental dysfunction is typically progressive(3). When the fetus has reached viability and the parents agree to this, a strategy to deliver the fetus when the intra-uterine risks increase above estimated risks of neonatal survival becomes appropriate. There is practice variation as to what is considered the 'limit of viability' both between and within countries. In the Amsterdam UMC this was per consensus at a gestational age of at least 26 weeks and an estimated fetal weight (EFW) of at least 500 grams. From the TRUFFLE study, the conclusion was drawn that when using these limits of viability, perinatal death is 8% and survival without severe morbidity occurred in 70% of cases(4). This threshold is subject to change over time, within center, country and internationally. If parents and the team of gynecologists and neonatologists agree to an active intervention strategy, fetal surveillance is installed, corticosteroids for fetal lung maturity are administered and a caesarean section is performed when monitoring shows deterioration of the fetal condition.

To date, no effective treatment has been found to improve placental function, fetal growth and the (healthy) survival rate of the fetus and neonate. Also, predicting the course of growth and therefore predicting the gestational age at birth and the birthweight are difficult. Since the suboptimal feto-maternal circulation is the cause of the growth restriction, researchers world-wide have aimed to find an intervention influencing this circulation in a positive way. Interventions that have been investigated are marine oil and other prostaglandin precursors(5), vitamin C(6), vitamin E(7), magnesium(8), omega-3(9), statins(10), aspirin(11) and antithrombotic agents(12). The last years the nitric oxide (NO) pathway has become a pathway of interest and therefore L-arginine(13) and phosphodiesterase 5-inhibitors(13, 14) have been subject of case-reports, cohorts and RCT's. In this

thesis we report on our studies on the safety and efficacy of the phosphodiesterase 5-inhibitor sildenafil.

The existing literature suggested a positive effect on birthweight, gestational age at delivery and in some studies even the rate of maternal hypertensive disorders(14-21). In contrast, the STRIDER-trials, organized in an international collaboration, did not confirm these positive effects(22-24). From the five intended trials, two (New Zealand/Australia and United Kingdom) were completed before the Dutch STRIDER was stopped prematurely. One trial had just started (Canada) and one had been abandoned during set-up due to regulatory restraints. The three RCT's showed combined fetal and neonatal mortality rates of 36.1% in the sildenafil treated group and 41.1% in the group patients treated with placebo. Mortality varied among these three trials and was lowest in the New Zealand/Australian trial, possibly due to the slightly higher EFW at inclusion and higher birthweight. Median gestational age at inclusion was comparable between the three trials. The reason for these RCT's not finding a positive effect on fetal and neonatal prognosis, while other reports did, might be a matter of power and patient selection. The STRIDER trials were relatively large and of good quality, including a well-defined group of patients with a placental insufficiency. Due to these strict inclusion criteria, our patient population might be slightly different than previous trials that could have included a proportion of small-for-gestational age (SGA) fetuses as well, since we know that many trials in patients with FGR, only used birthweight percentile or AC or EFW for the diagnosis, while antenatal Doppler measurements could distinguish between SGA and FGR(25). On top of the fact that we were not able to confirm that sildenafil improves the outcomes in pregnancies complicated by FGR, the Dutch trial showed a suggestion of potential harm of the medication (24). There was a statistically significant increase in neonatal pulmonary hypertension, but this was not associated with an increased rate of neonatal death or other neonatal morbidity. This potential harm may have been based on chance or is based on a causal association with the antenatal administration of sildenafil or that is was based on chance. The other two finished STRIDER trials did not find similar rates of pulmonary hypertension, but had not clearly defined it as an outcome measure either. The fact that pulmonary hypertension was diagnosed pro rato within the Dutch participating centers and the validation of the diagnosis by an independent expert committee, supports the rate of pulmonary hypertension we found. We hope that data from autopsies that have been performed and detailed investigations of the placental tissue by the pathologist will contribute to this distinction. We are preparing for an Individual Patient Data (IPD) meta-analysis of RCT's investigating sildenafil in early-onset FGR to further investigate these associations(26). Another possibility why no improvement of fetal growth was found in the STRIDER trials, could be the dosage that was used in the trials, however, the dosage used corresponds with the dosage used in the study of von Dadelszen that showed improved growth of the fetal AC(21). The RCT of Trapani used 50 mg three times daily and concluded that sildenafil resulted in pregnancy prolongation in pregnancies complicated by preeclampsia(20). It is possible that the dosage (25 mg three times daily) was too low to reach the optimal concentration or that reducing the dosage over the first days after delivery might have prevented the PH in the neonates(14). At this point, however, we

conclude that antenatal treatment with sildenafil in the current dosage and administration schedule does not benefit mother or fetus and should not be prescribed for this indication.

	STRIDER UK(22)		STRIDER Aus/NZ(23)		Dutch STRIDER(24)	
	Sildenafil (n= 70)	Placebo (n= 65)	Sildenafil (n= 63)	Placebo (n= 59)	Sildenafil (n= 108)	Placebo (n= 107)
Fetal death	21 (30%)	22 (34%)	7 (11%)	12 (20%)	23 (21%)	29 (27%)
Neonatal death	10 (14%)	7 (11%)	5 (8%)	4 (7%)	21 (19%)	11 (10%)
Total mortality	35%	46%	19%	27%	40%	37%

Besides the pharmacological agent sildenafil, this thesis discusses other aspects of management. A crucial element of management in these pregnancies is fetal surveillance. Some centers have adopted a policy in which ductus venosus and computerized CTG are used for the monitoring of the foetal condition. Fetal heart rate variation in the CTG is quantified by software-calculation to reduce observer variation in the appraisal of the CTG. The TRUFFLE-criteria to perform a cesarean section are a consistent STV value below 3.5 ms at gestational age below 29 weeks and a value below 4.0 ms at gestational age between 29 and 32 weeks(27). The systematic review performed in light of this thesis finds no conclusive support for STV-based management, although this is mainly due to the lack of adequate studies. Most importantly, there are no randomized trials. Within the selected studies there was no obvious association between STV and umbilical cord acidemia immediately after birth. Because of low power, a statement on the association between STV and fetal or neonatal mortality or long-term neurodevelopment cannot be made(28). The subanalyses of TRUFFLE and other studies, and the logical hypothesis behind STV are however compelling to the extent where an RCT comparing STV to the visual inspection of CTG is justified to answer the question whether there is a role for the STV calculation in fetal surveillance. It could be a crucial step, because optimal timing of delivery in pregnancies complicated by severe early-onset FGR to date still is the only known effective intervention, and optimizing this intervention would be of benefit. From the available data currently known, there is insufficient basis to determine that STV should be advised as parameter to guide the decision for delivery should be made.

Fifteen to 50% of the pregnant women with FGR are also diagnosed with a hypertensive disorder of pregnancy(3, 19, 21, 22). Even though the absolute chance of maternal mortality in developed countries is low, hypertensive disorders cause 13% of maternal mortality and is the second leading cause of death from pregnancy-related conditions(29). Even though the level of evidence is very low, the WHO recommends strongly to treat pregnant women with severe hypertension with antihypertensive drugs(30). The Control of Hypertension In Pregnancy Study (CHIPS)(31) addressed the issue of the blood pressure target in pregnancies complicated by nonproteinuric chronic hypertension or gestational hypertension between 14 and 34 weeks of gestation and showed no differences in the risk of

pregnancy loss, need for high-level neonatal care or overall maternal complications between the 493 women randomized to 'less-tight' control (target diastolic blood pressure 100 mmHg and 488 women randomized to 'tight' control of hypertension (target diastolic blood pressure 85 mmHg. However, there are 'believers' and 'non-believers' of the hypothesis that lowering maternal blood pressure negatively affects fetal growth(32-34). The CHIPS trial did not show differences in the rate of neonates with a birthweight below the tenth centile. Our secondary analysis of the CHIPS trial investigated the association between timing of randomization to the different study arms and the risk of SGA and showed a possible association between randomization to 'tight' control of hypertension early in pregnancy and the rate of SGA babies (defined as birthweight below the tenth percentile)(35). Randomisation before (but not after) 24 weeks' to 'less tight' (vs. 'tight') control was associated with fewer babies with birthweight <10th centile, but more preterm birth, and no effect on perinatal death or high-level neonatal care >48hr. This large, well-designed RCT was not powered for this post-hoc analysis and FGR is not defined as an outcome, since the Dopplers and serial growth measurements were not systematically recorded as an outcome. Therefore, the question remains whether these children were SGA or FGR. As long as we do not have more information on a possible harmful effect of blood pressure lowering on fetal growth and possible long-term effects on the neonates, the 'tight' approach might be advocated for, since less maternal hypertension was observed in women allocated to this treatment(31, 35).

As said earlier, a crucial element of management of pregnancies complicated by FGR, is the counselling of parents regarding the management on whether or not to perform fetal surveillance, administer corticosteroids for fetal lung maturity and to have the fetus delivered. Delivery by a caesarean section is associated with a higher risk of maternal mortality(36), ectopic pregnancy and placental problems in following pregnancies(37) and the risk of uterine rupture in next pregnancies(38). Risk of death after cesarean section was 21.9 per 100.000 cesarean sections (86 out of 393,443) versus 3.8 deaths per 100.000 vaginal births (88 out of 2,291,503): Relative Risk (RR) 5.7 (95% CI 4.2-7.7). Death directly related to complications of caesarean section occurred in 8/86 women: 2 per 100,000 caesarean sections(36).These risks are believed to be even slightly higher when a premature caesarean section is performed(39), although evidence is scarce. Around the thresholds of viability it should be weighed if the chances of (healthy) survival of the fetus after delivery are high enough to outweigh the maternal risks of the caesarean section in the current pregnancy and possible future pregnancies. Also, what is considered as 'healthy' survival, is not generally defined and individual judgement on acceptable neonatal and long-term risks need to take place. As stated above, the perception of this risk balance is different between patients and between caregivers in time and place. It therefore requires an individual judgement and balancing arguments, also taking (a wish for) possible future pregnancies into account. The systematic review on perinatal mortality, morbidity and long term neurodevelopment performed in this thesis aimed to inform patients and their caregivers on the rates of mortality and morbidity in their individual situation(40). Even though this review has some disadvantages with respect to the different patient populations in the included studies, a striking outcome is that the rate of

stillbirths is almost twice as high as the rate of neonatal death. In general, when reaching viability, the chances of neonatal survival are fair, however, the live born neonates are possibly the children with the more favourable (genetic) prognosis, resulting in live birth. However, only a minority of the studies reporting on fetal/neonatal mortality, also focussed on the long-term development of the children, while adverse long-term developmental outcome rate can only be truly judged if perinatal mortality is accounted for. From the studies that investigated long-term neurodevelopment, 11% (varying from 0% to 27%) of the surviving children were diagnosed with neurodevelopmental impairment, mostly at the age of two years. In the TRUFFLE study no formal five years outcome measurement was scheduled. In The Netherlands, a subset of children participating in this study were seen at five years because of the Dutch follow-up protocol. In this five years follow-up, assessment of 74 children after severe early-onset FGR found a rate of neurodevelopmental impairment of 16%, and full scale IQ was in the normal range %(41). But not included in this definition were deficits in processing speed and motor outcome. These were found, in 27% and 38% respectively. It would be interesting to know how well these various scores predict academic achievement and later participation as an adult in society. The subset was the lower gestational age of the Dutch TRUFFLE sample. But it is possible that neurodevelopmental impairment has a similar prevalence at higher gestational age, because of longer exposure to a non-optimal fetal circulation. Therefore, the importance of our findings are only limited. The importance of long(er) term follow-up in all participants of a trial lies in the fact that this gives a complete evaluation of efficacy and safety of an intervention; we aim to follow the children born from the Dutch STRIDER trial up to later age, in order to improve the counselling of parents in the future.

Considerations for the future

Unfortunately, a promising therapeutic strategy with the phosphodiesterase 5-inhibitor sildenafil for severe, early-onset FGR turned out to be ineffective and even potentially harmful. This is a disappointing finding given the ample promising early reports from animal and human studies suggesting the positive potential. It is also an important finding given the fact that there were unpublished reports and communications suggesting there was a creep into practice(42). The STRIDER initiative is an excellent example of the importance of a robust evidence base before new therapies are implemented and how international concerted efforts can provide conclusive evidence.

Other potential therapeutic options to improve rates of healthy survival in this patient group should be explored. Statins could be a possible target drug to investigate further as potential therapy or the phosphodiesterase 5-inhibitors could be produced in such way that the medication does not cross the placenta in order to prevent fetal side effects. In order to investigate possible new interventions in FGR, we firstly propose an overview of the preclinical evidence and an (international) RCT with sufficient power to answer the research question. From the Dutch STRIDER study we can learn that the role of the DSMB is crucial for the safety aspects of the participants. Clear definitions of outcome measures and complete and timely data-entry is important for the DSMB to judge on the safety and efficacy of the intervention. From the international STRIDER consortium, we can learn

how useful it is when similar protocols are being used in various trial setting. Furthermore, the optimization of fetal surveillance and determining the optimal moment of delivery is an important target as well. In order to reach this, a trial on computerized versus visual evaluation of the CTG will be useful. Besides, the combination of reporting short term and long term outcomes (up to adult age) in trials will give a complete evaluation of the interventions that have been investigating. Meta-analyses (if possible with individual patient data) need to combine the results of all relevant trials that have been carried out on a specific intervention in order to be able to draw reliable conclusions with sufficient power to guide clinical practice.

Above all, this thesis underlines the importance of evidence-based guidance of patients by their health care providers. Obstetricians, midwifes, nurses and neonatologists (also using data from pediatricians and psychologists on child follow up) take part in a very intense and important period of parents' lives. Therefore, clear and honest counseling on what we know and what we still need to learn is important and professional involvement can make a difference.

We thank all parents on behalf of women who will experience FGR in future pregnancies for their contribution to this valuable knowledge.

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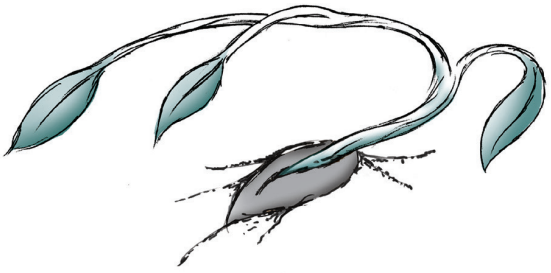
Chapter 13

Nederlandstalige samenvatting



Nederlandstalige samenvatting

Dit proefschrift belicht belangrijke aspecten van vroege ernstige foetale groeirestrictie (FGR), namelijk de definitie, prognose en de behandeling.

In **Hoofdstuk 2** beschrijven we welke definities van FGR in de bestaande literatuur gebruikt zijn door de tijd heen. In onze literatuur review over de gebruikte definities in de jaren 1994, 2004 en 2014(1) hebben we laten zien dat een toenemend aantal studies gepubliceerd is over het onderwerp FGR (56, 75 en 116 respectievelijk). De meeste studies gaan over 'small-for-gestational-age' (SGA), oftewel lichte baby's, en niet noodzakelijk kinderen met het ziektebeeld FGR. Omdat in deze studies veel verschillende definities van groeivertraging gebruikt zijn, waarbij in de onderzochte jaren de meerderheid van de studies FGR definieerden als een 'geboortegewicht onder het 10e percentiel', kijkend naar het oorzakelijke mechanisme is dit niet helemaal juist, pleiten wij voor herbezinning op de definitie. De gebruikte definities zijn veranderd door de tijd heen als gevolg van de verbeterde antenatale diagnostische mogelijkheden, namelijk nauwkeurigere gewichtsschatting met de echo en Doppler metingen in plaats van het uitwendig onderzoek. In 2014 gebruikte het grootste gedeelte van de studies antepartum metingen in plaats van postpartum metingen (kindsgewicht): 34% van de studies in 1994, 30% in 2004 en 47% in 2014. Dit hoofdstuk benadrukt het gebrek aan eenduidigheid en de onvolkomenheden in de definitie van FGR in de literatuur en onze conclusie is dat een uniforme definitie van FGR nodig is voor adequate en juiste interpretatie van data voor klinisch gebruik, maar ook in het kader van wetenschappelijk onderzoek.

Hoofdstuk 3 bevat een systematische review over de gerapporteerde foetale en neonatale sterfte en de kinderlijke korte- en lange-termijn morbiditeit in cohorten van moeders met kinderen met de diagnose vroege FGR(2). 21 Studies die 2334 zwangerschappen beschrijven die gecompliceerd waren door FGR vòòr 32 weken zwangerschapsduur, werden opgenomen in deze review. De moeders die deel uitmaakten van de verschillende onderzochte cohorten hadden verschillende zwangerschapskarakteristieken, zoals zwangerschapsduur en geschat foetaal gewicht bij het stellen van de diagnose FGR. De groeivertraging resulteerde bij 12% van de onderzochte zwangerschappen in een sterfte van het kind voor de geboorte en bij 7% in een sterfte na de geboorte. Opvallend was dat slechts enkele studies de lange-termijn ontwikkeling van de overlevende kinderen hebben onderzocht, waarbij bleek dat onder de onderzochte kinderen 11% een ontwikkelingsstoornis had. Echter de variatie tussen de verschillende studies was groot, net als de methodes die gebruikt zijn om de diagnose ontwikkelingsstoornis te stellen. We concludeerden dat een meer gedetailleerde analyse van data van individuele patiënten nodig is en bijdraagt aan een betere counseling van individuele patiënten over de prognose van de kinderlijke overleving en ontwikkeling. Los daarvan staat buiten kijf dat vroege ernstige FGR een hoge ziektelast met zich meebrengt voor de aangedane kinderen en dus een grote belasting en zorg voor hun ouders.

De ontwikkeling op vijfjarige leeftijd in een cohort met kinderen die geboren zijn na vroege ernstige FGR, wordt beschreven in **Hoofdstuk 4**(3). Deze studie beschrijft de Nederlandse subgroep van kinderen van moeders die hebben meegedaan aan het onderzoek genaamd "Trial of Randomized Umbilical and Fetal Flow in Europe" (TRUFFLE study)(4). Van de 74 kinderen die op vijfjarige leeftijd onderzocht zijn, was het gemiddelde totale IQ (FSIQ) normaal, maar 15% van de kinderen had een abnormale IQ-score (FSIQ lager dan 85) en 35% van de kinderen had een afwijkende score op het gebied van ofwel het verbaal IQ, het performaal IQ (praktisch vaardigheden waarbij ruimtelijk inzicht ook een rol speelt en die minder met taal zijn) of de verwerkingssnelheid. Van de onderzochte kinderen, had 38% een afwijkende score bij onderzoek naar de motorische vaardigheden. De factoren die geassocieerd zijn met een abnormaal totaal IQ, waren de antenataal gemeten eind-diastolische stroomsnelheid (EDF) in de arteria umbilicalis, zwangerschapsduur bij geboorte, geboortegewicht en neonatale morbiditeit. De afwijkende score op het gebied van de motoriek kwam vaker voor bij jongens en bij kinderen die bronchopulmonale dysplasie (BPD) hadden doorgemaakt in de neonatale periode. Samenvattend, de uitkomsten op vijfjarige leeftijd lieten in het algemeen een betere ontwikkeling zien dan verwacht, maar een verhoogd risico op ontwikkelingsproblemen werd ook hier gevonden, waarbij in het bijzonder beperkingen in motorische ontwikkeling en verwerkingssnelheid bij de aangedane kinderen gevonden werd.

Hoofdstuk 5 bestaat uit een systematische review over de voorspellende waarde van de korte-termijn variatie (STV) van de foetale hartslag, geregistreerd middels cardiotocografie (CTG) bij zwangerschappen die gecompliceerd werden door FGR(5). Deze review laat zien dat bij zwangere vrouwen met vroege ernstige FGR (vòòr 32 weken zwangerschapsduur) de STV niet statisch significant geassocieerd is met een verhoogde zuurgraad van het kind (acidemie). Doordat er weinig data zijn over dit onderwerp, kan er geen conclusie getrokken worden over de associatie tussen STV en foetale/neonatale mortaliteit, morbiditeit en lange-termijn (ontwikkelings-)uitkomsten. Daarom concludeerden we dat, ondanks dat de STV een logische en veelbelovende techniek is om het optimale moment te bepalen waarop de bevalling plaats zou moeten vinden bij zwangere vrouwen die foetale bewaking ondergaan, er een gerandomiseerde studie (RCT) nodig is om te onderzoeken of een aanpak die een beslissing op basis van de STV maakt, de foetale/neonatale uitkomst verbetert, ten opzichte van de tot nu toe veel gebruikte visuele beoordeling van het CTG.

In **Hoofdstuk 6** wordt een secundaire analyse van de "Control of Hypertension In Pregnancy Study" (CHIPS)(6) gepresenteerd(7). Bij deze analyse werd de associatie tussen de hoogte en duur van de behandeling van verhoogde moederlijke bloeddruk tijdens de zwangerschap en foetale groei onderzocht. Dit werd gedaan door de relatie tussen de duur van een milde verlaging van de bloeddruk na randomisatie en het percentage kinderen met een geboortegewicht onder het 10e percentiel te vergelijken met de relatie van dat percentage kinderen bij moeders met een grotere verlaging van de bloeddruk. De resultaten van deze analyse lieten zien dat de behandeling met milde verlaging van de bloeddruk die gestart werd vòòr 24 weken zwangerschapsduur, geassocieerd was met

minder baby's met een geboortegewicht onder het 10e percentiel, maar met een hoger percentage vroeggeboorte. Er was geen effect op perinatale sterfte of de noodzaak tot intensive care behandeling van de neonaat langer dan 48 uur. De minder sterke verlaging van de bloeddruk was voor de moeder geassocieerd met een hogere kans op ernstige hypertensie bij alle zwangerschapsduren, maar met name vòòr de 28 weken. Dit heeft geleid tot de hypothese dat behandeling van hypertensie in de zwangerschap mogelijk een reductie in het geboortegewicht geeft. Echter, de RCT had onvoldoende power, om een definitieve uitspraak te doen over deze associatie en verder onderzoek is nodig om deze hypothese verder uit te werken.

Hoofdstuk 7, 8, 9 en 10 gaan over de STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) studies, met name over de Nederlandse (Dutch) STRIDER-studie, studies over medicamenteuze behandeling tijdens de zwangerschap bij verdenking op groeivertraging gericht op een verbetering van de groei van het kind. STRIDER bestaat uit een vijftal studies die binnen een internationale samenwerking opgezet zijn, zoals beschreven in **Hoofdstuk 7**. Het doel van de studies was om de vraag te beantwoorden of de phosphodiesterase 5-remmer sildenafil de foetale en neonatale sterfte, morbiditeit en lange-termijn ontwikkelingsstoornissen kan verminderen bij zwangere vrouwen met vroege ernstige FGR, vergeleken met placebo. Het internationale studie protocol van de vijf STRIDER studies wordt gepresenteerd in hoofdstuk 7(8).

Hoofdstuk 8 beschrijft het gedetailleerde statistisch analyse plan van de Dutch STRIDER studie(9).

Hoofdstuk 9 rapporteert de resultaten van de Dutch STRIDER studie(10). De studie is gestopt naar aanleiding van de interim analyse na advies van de Data Safety Monitoring Board (DSMB) omdat er serieuze zorgen waren dat sildenafil schade veroorzaakte bij de pasgeboren kinderen, in combinatie met een zeer hoge kans op futiliteit, oftewel er was een verwaarloosbare kans dat de studie alsnog een positief resultaat zou laten zien als er meer patiënten zouden meedoen. Op het moment van stoppen hadden 216 patiënten meegedaan aan de studie. De primaire uitkomst (sterfte voor of na de geboorte of overleving met ernstige neonatale morbiditeit) kwam voor bij 65 kinderen (60%) waarvan moeder geloot had voor sildenafil en bij 58 (54%) geloot voor placebo (RR 1.11, 95% CI 0.88 tot 1.40; P=0.38). De conclusie van dit onderzoek is dat behandeling in de zwangerschap met sildenafil, vergeleken met placebo, de kans op neonatale sterfte en morbiditeit niet verlaagt. Daarnaast werd een onverwacht, en ook niet geheel verklaard, toegenomen percentage hoge bloeddruk in de bloedvaten van de longen (pulmonale hypertensie) gezien bij de kinderen wiens moeder aan sildenafil blootgesteld was, vergeleken met placebo (16 (19%) versus 4 (5%) (RR 3.67, 95% CI 1.28 to 10.51; P=0.008)).

Hoofdstuk 10 beschrijft het proces en de uitkomsten van de validatie van de uitkomsten van de pasgeborenen binnen de Dutch STRIDER studie en reflecteert op de hypotheses achter de mogelijke associatie tussen sildenafil blootstelling in de zwangerschap en pulmonale hypertensie bij de kinderen, gedefinieerd als Persistent Pulmonary Hyperten-

sion of the Neonate (PPHN). Na deze data validatie bleek dat 12% van de kinderen in de Dutch STRIDER studie pulmonale hypertensie had doorgemaakt. Het gebrek aan een gestandaardiseerde definitie van pulmonale hypertensie maakt de diagnosestelling en het interpreteren van data over dit onderwerp complex. Er is consensus nodig over de definitie van pulmonale hypertensie om de gerapporteerde variatie in het vóórkomen in wetenschappelijke studies te reduceren.

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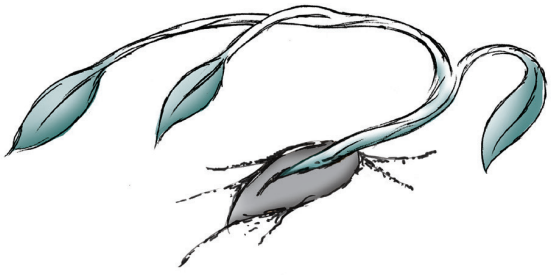
Chapter 14

Appendices



Abbreviations

AC	Abdominal circumference
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATI	Algemene taal index
BMI	Body mass index
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
BW	Birthweight
BWR	Birthweight ratio
CBCL	Child Behavior Checklist
cCTG	Computerized cardiotocography
CHIPS	Control of Hypertension In Pregnancy Study
CTG	Cardiotocography
CI	Confidence interval
CNS	Central nervous system
CP	Cerebral palsy
CRF	Case record form
dBP	Diastolic blood pressure
DQ	Developmental quotient
DSMB	Data safety monitoring board
DV	Ductus venosus
EDF	End-diastolic flow
EFW	Estimated fetal weight
FGR	Fetal growth restriction
FSIQ	Full-scale intelligence quotient
GA	Gestational age
GCP	Good clinical practice
GMFCS	Gross motor function classification system
GMH	Germinal matrix cerebral haemorrhage
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HC	Head circumference
HELLP	Hemolysis elevated liver enzymes low platelets
HIV	Human immunodeficiency virus
IQ	Intelligence quotient
IQR	Interquartile range
IPD	Individual patient data
IUFD	Intra-uterine fetal death
IUGR	Intra-uterine growth restriction
IVH	Intraventricular haemorrhage
LDH	Lactate dehydrogenase
M-ABC	Movement Assessment Battery for Children

MRI	Magnetic resonance imaging
NDI	Neurodevelopmental impairment
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NO	Nitric oxide
OR	Odds ratio
PAP	Pulmonary artery pressure
PDA	Persistent ductus arteriosus
PDE	Phosphodiesterase
PE	Preeclampsia
PH	Pulmonary hypertension
PMA	Postmenstrual age
PP	Postpartum
PI	Pulsatility index
PlGF	Placental growth factor
PPHN	Persistent pulmonary hypertension of the neonate
PIQ	Performance intelligence quotient
PSQ	Processing speed quotient
PVL	Periventricular leukomalacia
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
RR	Relative risk
sBP	Systolic blood pressure
SAE	Serious adverse event
SCPE	Surveillance of Cerebral Palsy in Europe
SD	Standard deviation
SGA	Small for gestational age
STRIDER	Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction
STV	Short term variation
TOP	Termination of pregnancy
TRUFFLE	Trial of Randomized Umbilical and Fetal Flow in Europe
UK	United Kingdom
US	Ultrasound
vCTG	Visual cardiotography
VIQ	Verbal intelligence quotient
WHO	World health organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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Chapter 2: Temporal variation in definition of fetal growth restriction in the literature
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Chapter 3: Early-onset fetal growth restriction: a systematic review of literature on mortality and morbidity
Study design and concept: A Pels, IM Beune, AG van Wassenaer-Leemhuis, W Ganzevoort. Data analysis and interpretation: A Pels, IM Beune, J Limpens. Manuscript preparation: A Pels, IM Beune. Manuscript editing and review: A Pels, IM Beune, AG van Wassenaer-Leemhuis, J Limpens, W Ganzevoort.

Chapter 4: Neurodevelopmental outcomes at five years after early-onset fetal growth restriction: analyses in a Dutch subgroup participating in a European management trial
Study design and concept: A Pels, OC Knaven, W Ganzevoort, AG van Wassenaer-Leemhuis. Data analysis and interpretation: A Pels, OC Knaven, W Ganzevoort, AG van Wassenaer- Leemhuis. Manuscript preparation: A Pels, OC Knaven. Manuscript editing and review: A Pels, OC Knaven, BJ Wijnberg-Williams, MJC Eijsermans, SM Mulder-de Tollenaer, CSH Aarnoudse-Moens, C Kooopman-Esseboom, J van Eyck, JB Derks, W Ganzevoort, AG van Wassenaer-Leemhuis.

Chapter 5: The prognostic accuracy of short-term variation of fetal heart rate in early onset fetal growth restriction: a systematic review
Study design and concept: A Pels, NA Mensing van Charante, W Ganzevoort. Data analysis and interpretation: A Pels, NA Mensing van Charante, J Limpens, W Ganzevoort. Manuscript preparation: A Pels, NA Mensing van Charante. Manuscript editing and review: A Pels, NA Mensing van Charante, CA Vollgraff Heidweiller- Schreurs, J Limpens, H Wolf MA de Boer, W Ganzevoort

Chapter 6: Influence of gestational age at initiation of antihypertensive therapy – secondary analysis of CHIPS trial data
Study design and concept: A Pels, LA Magee. Data analysis and interpretation: A Pels, T Lee, LA Magee. Manuscript preparation: A Pels. Manuscript editing and review: A Pels, BW Mol, J Singer, T Lee, P von Dadelszen, W Ganzevoort, E Asztalos, LA Magee.

Chapter 7: STRIDER (Sildenafil TheRapy in Dismal prognosis Early onset fetal growth Restriction): an international consortium of randomised placebo-controlled trials
Study design and concept: LC Kenny, Z Alfirevic, PN Baker, P von Dadelszen, BW Mol, W Ganzevoort, KM Groom. Data analysis and interpretation: A Pels, C Gluud, W Ganzevoort. Manuscript preparation: A Pels. Manuscript editing and review: A Pels, LC Kenny, Z Alfirevic, PN Baker, P von Dadelszen, C Gluud, CT Kariya, BW Mol, AT Papageorghiou, AG van

Wassenaer-Leemhuis, W Ganzevoort, KM Groom.

Chapter 8: Detailed statistical analysis plan for the Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) randomised clinical trial on sildenafil versus placebo for pregnant women with severe early onset fetal growth restriction
Study design and concept: A Pels, JC Jakobsen, W Ganzevoort, C Gluud. Data analysis and interpretation: A Pels, JC Jakobsen, W Ganzevoort, C Gluud. Manuscript preparation: A Pels, JC Jakobsen. Manuscript editing and review: A Pels, JC Jakobsen, W Ganzevoort, CA Naaktgeboren, W Onland, AG van Wassenaer- Leemhuis, C Gluud.

Chapter 9: Maternal sildenafil vs placebo for severe early-onset fetal growth restriction: A randomized clinical trial
Study design and concept: A Pels, W Ganzevoort. Data analysis and interpretation: A Pels, C Naaktgeboren, JC Jakobsen, C Gluud, W Ganzevoort. Manuscript preparation: A Pels, C Naaktgeboren, JC Jakobsen, C Gluud, W Ganzevoort. Manuscript editing and review: A Pels, J Derks, A Elvan-Taspinar, J van Drongelen, M de Boer, JJ Duvekot, J van Laar, J van Eyck, S Al-Nasiry, M Sueters, M Post, W Onland, AG van Wassenaer-Leemhuis, C Naaktgeboren, JC Jakobsen, C Gluud, RG Duijnhoven, T Lely, SJ Gordijn, W Ganzevoort.

Chapter 10: Neonatal pulmonary hypertension after severe early-onset fetal growth restriction in the Dutch STRIDER-trial: the need for a consensus definition
Study design and concept: A Pels, W Onland, W Ganzevoort. Data analysis and Interpretation: A Pels, W Onland, RMF Berger, AFJ van Heijst, E Lopriore, IKM Reiss, J Limpens, SJ Gordijn, W Ganzevoort. Manuscript preparation: A Pels, W Onland, W Ganzevoort. Manuscript editing and review: A Pels, W Onland, RMF Berger, AFJ van Heijst, E Lopriore, IKM Reiss, Limpens, SJ Gordijn, W Ganzevoort.

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- Pels A, Onland W, Berger RMF, Van Heijst AFJ, Lopriore E, Reiss IKM, Limpens J, Gordijn SJ, Ganzevoort W. Neonatal pulmonary hypertension after severe early-onset fetal growth restriction in the Dutch STRIDER-trial: the need for a consensus definition. Submitted.
- Scott G, Gillon TER, Pels A, Von Dadelszen P, Magee LA. Guidelines - similarities /dissimilarities. A systematic review of international clinical practice guidelines for pregnancy hypertension. Am J Obstet Gynecol. 2020 Aug 20;S0002-9378(20)30846-2.
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- Pels A, Jakobsen JC, Ganzevoort W, Naaktgeboren CA, Onland W, van Wassenaer-Leemhuis AG, Gluud C. Detailed statistical analysis plan for the Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) randomised clinical trial on sildenafil versus placebo for pregnant women with severe early onset fetal growth restriction. Trials. 2019 Jan 11;20(1):42.
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Portfolio

Courses Graduate School, AMC

January 2019	June 2015 Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers; January 2019 re-certification
December 2018	Randomized clinical trials
June 2018	Didactical skills
May 2018	Research data management
January 2018	Evaluation of medical tests
March 2017	Oral presentation in English
May 2016	Observational epidemiology
January 2016	Systematic Reviews
November 2015	Scientific Writing
January 2015	Practical Biostatistics (SPSS)

International presentations

14-2-2019	Oral presentation SMFM's 39th Annual Pregnancy Meeting (Las Vegas, United States): 'Maternal sildenafil for severe early-onset fetal growth restriction: the Dutch multicentre placebo-controlled double-blind STRIDER-trial'.
9-10-2018	Oral presentation ISSHP (Amsterdam, Nederland): 'Influence of gestational age at initiation of antihypertensive therapy –secondary analysis of CHIPS trial data'.
8-10-2018	Poster presentation ISSHP (Amsterdam, Nederland): 'Neurodevelopmental outcomes at five years after early-onset fetal growth restriction: analyses in a Dutch subgroup participating in a European management trial'.
2-10-2018	Oral presentation 7th International Fetal Growth Meeting (Milan, Italy): 'Neurodevelopmental outcomes at five years after early-onset fetal growth restriction: analyses in a Dutch subgroup participating in a European management trial'.
18-11-2016	Poster presentation 5th International Fetal Growth Meeting (Toronto, Canada): 'Computerised versus visual analysis of the CTG in early-onset fetal growth restriction: a literature review'.

Supervising

2017 – 2018	R.M. De Voogt, medical student, bachelor thesis: 'In antenatally detected extreme early-onset fetal growth restriction, what is the actual prognosis at the time of diagnosis?'
2017	O.C. Knaven, medical student, scientific internship: 'A five year neurodevelopmental follow-up study of children with early fetal growth restriction.'

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Lieve ooms, tantes, neven en nichten: wat kan ik genieten van onze hechte band en vreselijk goede Pelsen-tradities.

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Oom Tom, wat ben ik dankbaar voor al je hulp en creativiteit in de opmaak van het Noukieboekie. Dankjewel!

Lieve oma, wat ben ik blij met onze band en wat ben ik enorm trots op u.

Emile en Iris, in de afgelopen jaren zijn er een hoop life-events geweest en ik ben trots op de onvoorwaardelijke eenheid die we vormen. En uiteraard excuus voor de goede verloskundige anekdotes en niet te vergeten, die keer dat ik te laat bij het vaderdag-etentje was. Nu was dé beruchte DSMB-vergadering toch wel een redelijk excuus.

Stephen, how's your 'Dutch for Dummies'?

Pa, dankjewel voor de enorme liefde en trots die jij voor ons drieën hebt; ik weet dat ik maar hoef te bellen en je verzet de hele wereld voor me. Ik ben ongelooflijk trots op jou en zie steeds meer hoeveel ik op je lijk.

Scott, ik mag mezelf gelukkig prijzen dat jij hier naast me staat. Bij jou kan ik dromen, intellectueel sparren en ordinair klagen. En uiteraard heerlijk en gezellig eten na jouw kookkunsten. Jij maakt dat ik regelmatig de laptop dichtklap, wat misschien nog wel meer heeft opgeleverd dan de laptop vaker openklappen. Ik ben superblij dat wij de afgelopen tijd hebben mogen delen en kijk uit naar nog heel veel meer.

Lieve mama, jij bent de grote afwezige vandaag. Ik zou niets liever willen dan jou dit eindresultaat laten zien. Als geen ander weet jij hoe het is om ziek te zijn van je zwangerschap en de impact die dat de rest van je leven heeft. Ook weet jij als geen ander hoe het is om een groeivertraagd kind te krijgen. Een kind dat vandaag haar werk met trots verdedigt.

Curriculum vitae

Anouk Pels werd geboren op 27 september 1990 in Haarlem, als oudste van drie kinderen. In 2008 haalde zij haar gymnasiumdiploma aan het Herbert Vissers College in Nieuw Vennep. Hierna begon zij aan de studie geneeskunde bij de Universiteit van Amsterdam.

Nadat gedurende de studie haar interesse gewekt werd voor de verloskunde, ontmoette zij Wessel Ganzevoort, gynaecoloog in het AMC, via wie zij in 2012 voor een wetenschappelijke stage naar Vancouver, Canada, vertrok. Hier werkte zij onder supervisie van Laura Magee en Peter von Dadelszen aan een update van de Canadese richtlijn van hypertensieve aandoeningen in de zwangerschap.

Eenmaal terug, begon zij aan de co-schappen en kreeg intussen de kans om te helpen met de opzet van de Dutch STRIDER trial. In 2015 haalde zij haar artsendiploma, waarna zij met veel plezier een jaar als ANIOS in de TerGooi Ziekenhuizen heeft gewerkt. Hierna ging de aandacht weer terug naar het onderzoek, gecombineerd met het werk als ANIOS in het AMC. In mei 2019 is zij in het Spaarne Gasthuis gestart met de opleiding tot gynaecoloog.