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Standardization in fetal growth restriction

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Chapter

4

Temporal variation in definition of fetal growth restriction in the literature

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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.

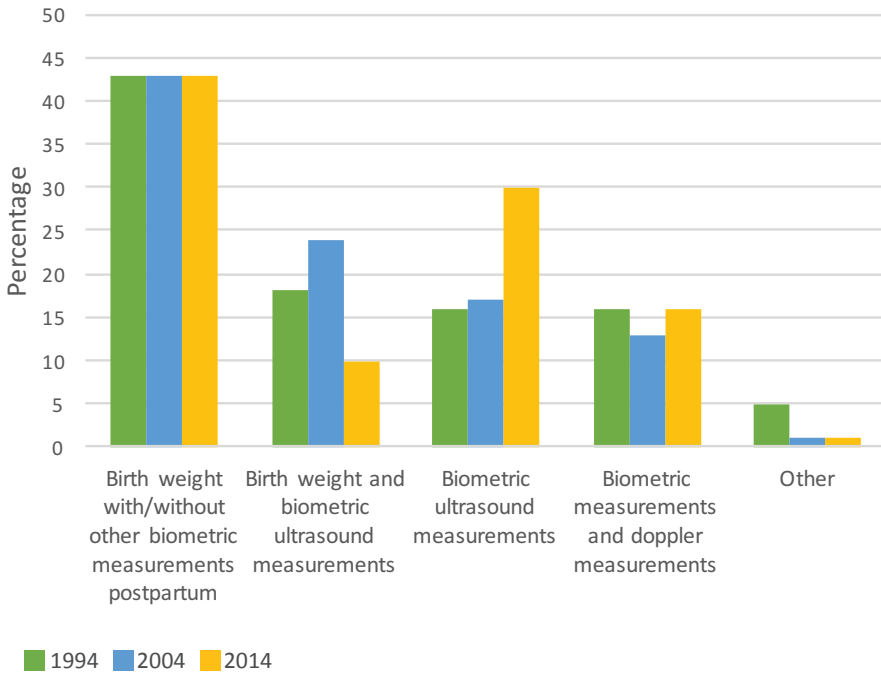
We aimed to describe different definitions of FGR used in the literature and how these changed over the past two decades, between 1994 and 2014, before a consensus-based definition for early and late FGR was established through a Delphi procedure.(15)

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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Supplement 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 subscapular 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 pulsatility 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 pulsatility 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
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 cerebropoplacental ratio; REDF reversed end-diastolic flow; DV ductus venosus; FGR fetal growth ratio

Figure S1 Flowchart on record selection

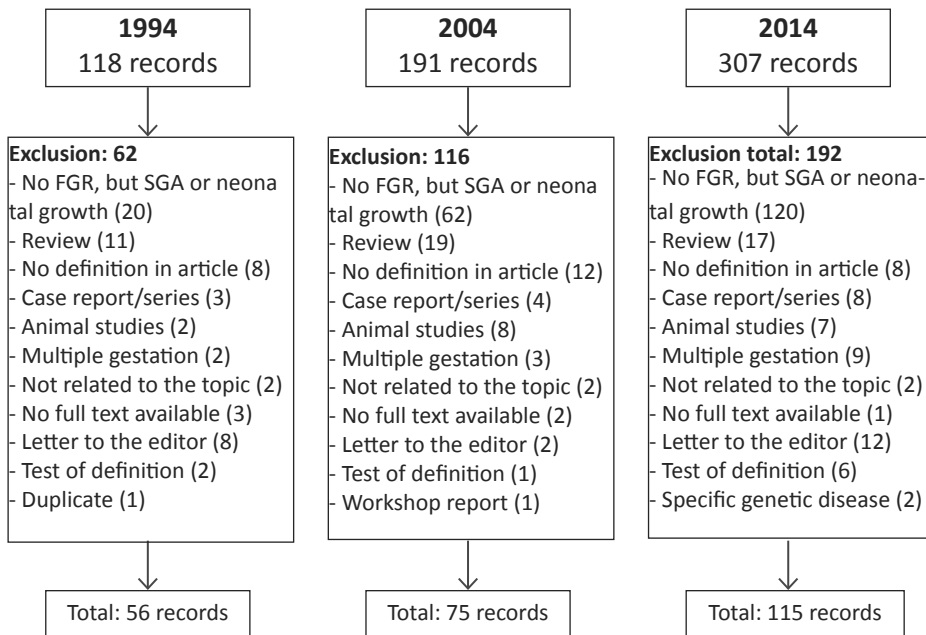
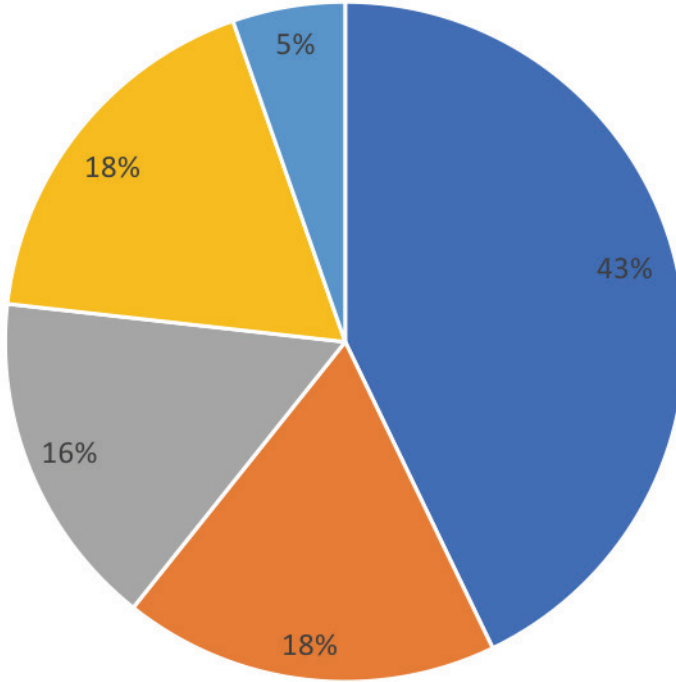
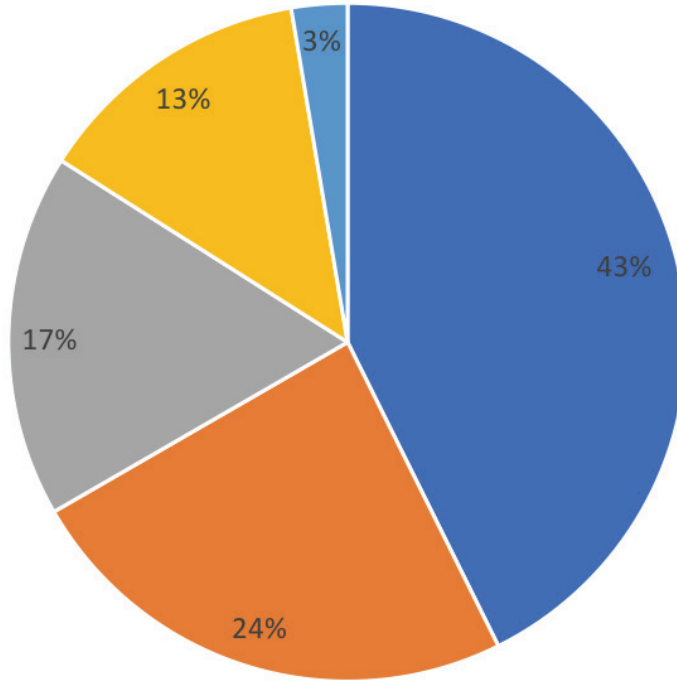


Figure S2 Variation in used definitions in 1994



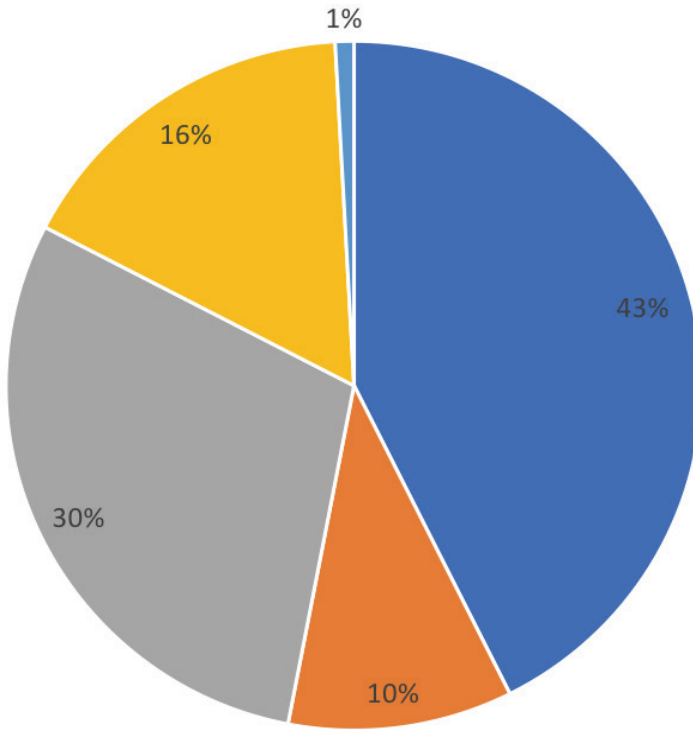
- Birth weight with/without other biometric measurements postpartum
- Birth weight and biometric ultrasound measurements
- Biometric ultrasound measurements
- Biometric ultrasound measurements and Doppler measurements
- Other

Figure S3 Variation in used definitions in 2004



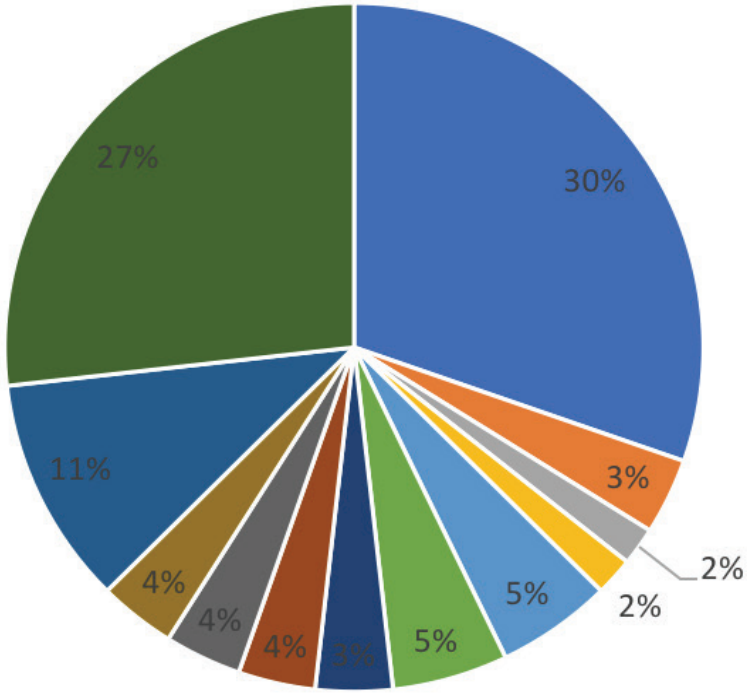
- Birth weight with/without other biometric measurements postpartum
- Birth weight and biometric ultrasound measurements
- Biometric ultrasound measurements
- Biometric ultrasound measurements and Doppler measurements
- Other

Figure S4 Variation in used definitions in 2014



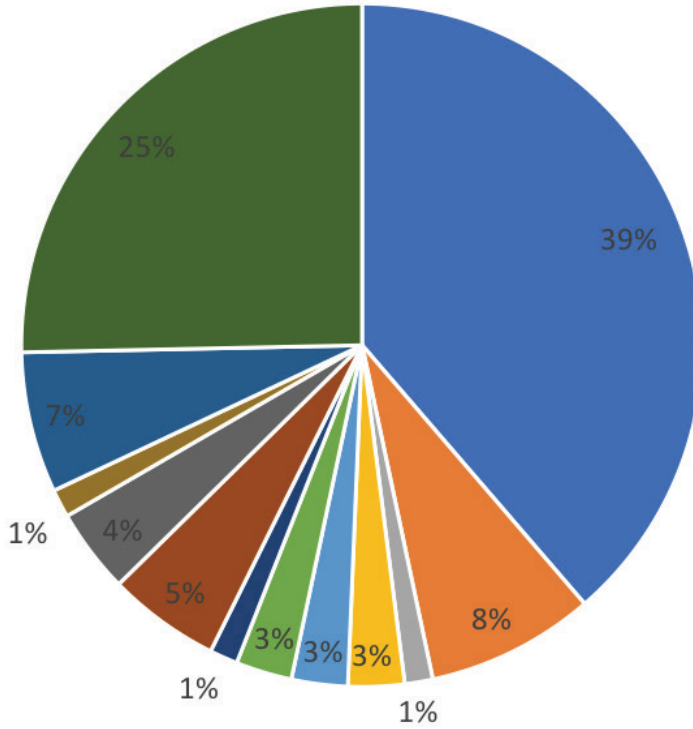
- Birth weight with/without other biometric measurements postpartum
- Birth weight and biometric ultrasound measurements
- Biometric ultrasound measurements
- Biometric ultrasound measurements and Doppler measurements
- Other

Figure S5 Growth formulas used in 1994



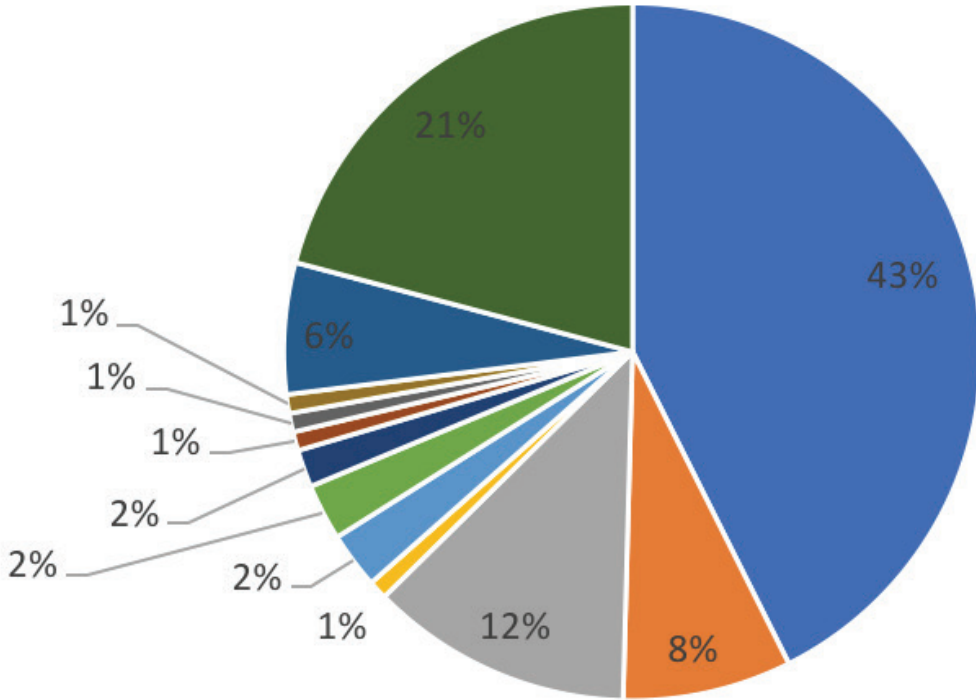
- Local population based centiles
- Customized centiles
- Kloosterman
- Brenner et al
- Lubchenco et al
- Campbell et al
- Usher and McLean
- Leroy and Lefort
- Yudkin
- No centiles, but absolute birth weight
- Other
- Not stated

Figure S6 Growth formulas used in 2004



- Local population based centiles
- Customized centiles
- Hadlock
- Kloosterman
- Todros et al
- Alexander et al
- Marsal et al
- Brenner et al
- Snijders et al
- No centiles, but absolute birth weight
- Other
- Not stated

Figure S7 Growth formulas used in 2014



- Local population based centiles
- Customized centiles
- Hadlock
- Kloosterman
- Todros et al
- Alexander et al
- Kramer et al
- Marsal et al
- Brenner et al
- No centiles, but absolute birth weight
- Other
- Not stated

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.



PART

3

Is there a possibility to come to consensus how to diagnose fetal growth restriction antenatal, postnatal and after fetal demise?

