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REPRODUCTIVE AND PERINATAL EPIDEMIOLOGY (R PLATT, SECTION EDITOR)

Longitudinal Ultrasound Measures of Fetal Growth and Offspring Outcomes

Tricia L. Larose[1] · Steve W. Turner[2] · Jennifer A. Hutcheon[3] · Tormod Rogne[1] · Ingrid I. Riphagen[4] · Marit Martinussen[5,6] · Geir W. Jacobsen[1]

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Abstract
Purpose of Review In this narrative review, we outline recent evidence relating longitudinal ultrasound (US) measurements to offspring outcomes in the perinatal period and in childhood, with an emphasis on the methodological approaches for describing fetal growth.
Recent Findings The utility of longitudinal ultrasonography (US) to measure fetal growth and determine fetal trajectories is valued in both clinical and research environments. Evidence shows that repeated measures of US throughout pregnancy are useful for distinguishing between a growth-restricted and constitutionally small fetus, the former burdened by adverse clinical outcomes. Fetal growth restriction and small for gestational age are not interchangeable terms, although both can exist in the same individual.
Summary The application of longitudinal US may have predictive value when determining longer-term health and disease outcomes in offspring born growth-restricted. However, it is important to remember that associations between fetal growth restriction and increased risk for non-communicable diseases are likely modified by postnatal growth.

Keywords Serial ultrasound · Prenatal ultrasonography · Fetal growth · Intrauterine growth restriction · Infant development · Child development

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✉ Tricia L. Larose
tricia.larose@ntnu.no

[1] Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[2] Department of Child Health, University of Aberdeen, Aberdeen, UK

[3] Department of Obstetrics and Gynaecology, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

[4] Unit for Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[5] Department of Laboratory Medicine, Women and Children's Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[6] St. Olav's University Hospital, Trondheim, Norway

Introduction

Fetal growth restriction (FGR) is defined as a pathologic inhibition of intrauterine growth and failure of the fetus to achieve its full growth potential [1]. FGR offspring face increased risk of perinatal mortality [2] and adverse perinatal morbidity [3]. Offspring born with FGR also face a wide range of longer-term consequences, such as respiratory disorders in childhood [4] and neuropsychological deficits in early adulthood [5].

Small-for-gestational-age (SGA) and FGR are frequently, but mistakenly, used synonymously in the medical literature. FGR is a clinical definition applied to the neonate born with pathological features of malnutrition and/or intrauterine fetal growth restriction, irrespective of birthweight percentile [1]. In contrast, SGA is derived from a single cross-sectional measurement of birthweight most often defined as a birthweight below the 10th percentile for sex and gestational age. The use of SGA as a proxy for FGR is common, but has serious clinical limitations. Most notably, the SGA definition can be applied to offspring who are both pathologically growth restricted and constitutionally small (small but healthy offspring). Moreover, the SGA definition may fail to capture offspring

born at appropriate weight but with clinical features related to growth restriction.

Obstetrical ultrasonography has the potential to improve the distinction between SGA and FGR by measuring fetal size at repeated times throughout pregnancy and identifying fetuses whose growth trajectories are decreasing. Thus, studies examining longitudinal ultrasound measurements may yield new insights into the consequences of FGR for longer-term child health. The focus of this review is to summarise the relationship between longitudinal US measurements of fetal growth and offspring outcomes. We start by exploring the methodological challenges faced when analysing serial fetal US results, and then relate fetal US results to perinatal and childhood outcomes.

Search Strategy

An earlier systematic review [6] of the literature, with search end date July 2014, described associations between prenatal fetal measurements and childhood outcomes. Given the large number of recent publications in this area, we conducted a new comprehensive review of the literature. We searched MEDLINE and Embase databases for relevant articles published in English from 2014. Searches were run in October 2016. We also reviewed bibliographies of relevant articles and included papers previously known to the authors. Search details are reported in Appendix 1.

Methodological Approaches for Describing Fetal Growth Patterns

Prior to the introduction of obstetrical ultrasound, intrauterine growth was a hidden process that could only be assessed based on the end result, fetal size at birth [7]. As such, growth charts describing patterns of intrauterine growth have conventionally been derived by joining the cross-sectional birthweight measurements of infants born at different weeks of gestation. However, estimating longitudinal patterns of fetal growth using the birthweights of different infants born at different gestational ages is problematic. Intrauterine growth restriction is a common cause of preterm birth, and as a result, infants born at preterm gestational ages are systematically smaller than their healthier peers remaining in utero [8, Secher 1987, p. 2494, 9–11]. This introduces bias to conventional birthweight-for-gestational-age charts, whereby the weight percentiles at preterm ages (reflecting the birthweights of preterm births) are shifted to artificially lower values. The bias means that birthweight-derived charts will misclassify small fetuses as normal, potentially missing cases of true intrauterine growth restriction [12]. For this reason, more recent charts to describe intrauterine growth patterns have been derived from serial ultrasound estimates of fetal weight throughout gestation, rather than birthweight [13–15].

The statistical methods recommended for summarising population-level patterns of fetal growth, typically for the purpose of producing size-for-gestational-age charts [14, 16, 17], have previously been outlined [18]. For researchers wanting to link individual-level fetal growth patterns with child health outcomes, however, the best approach for empirically summarising each growth trajectory is less clear. As outlined below, several different approaches have been used, each with their own strengths and limitations.

The simplest approach is to consider each serial ultrasound measurement in isolation (i.e. independent of past or subsequent measurements). For example, biometric measurements from each of 28, 33, and 38 weeks separately were linked with infant fat mass at birth [19]. The primary advantage of this approach is its ease of implementation, as the inclusion of only a single measurement per fetus eliminates the need for more advanced analytic approaches to account for the correlation between serial measurements. Interpretation of the model estimates is also straightforward. However, analysing fetal size measurements separately does not take advantage of the serial measurements available to describe growth, not size.

A more common method is to express growth as a change in standard deviation *z*-scores (or percentiles) between two time points. In this approach, fetal size measurements are standardized to a gestational-age-specific *z*-score or percentile using a previously derived reference chart or standard, and growth is calculated as the difference in *z*-scores/percentiles between two gestational ages. The *z*-scores or percentiles can be further "customised" to account for maternal influences on fetal growth (such as parity, ethnicity and height) [20], although some research suggests this may be too little to improve identification of growth-restricted fetuses [21–24]. In several papers [25, 26], an increase or decrease of more than 0.67 standard deviations was considered abnormal growth. The difference in *z*-score can then be included as a single summary measure of growth in a model estimating predictors of a child health outcome. A variation of this approach is to categorise the *z*-scores (e.g. into thirds) and describe fetal growth in terms of a change in category between time points [27].

The change in *z*-score approach makes better use of serial ultrasound measurements than examining each ultrasound measurement in isolation. Nevertheless, by using only two data points to describe a growth trajectory, the approach is highly sensitive to the effects of measurement error in ultrasound biometry [28]. Further, the approach does not account for regression to the mean (whereby extreme values are more likely to be closer to average on subsequent measurement), or the time interval between the two times (as time points separated by a short interval would be expected to be more similar than time points separated by a longer interval). Finally, the approach produces multiple summary measures of growth per

fetus (e.g. the change between second and third trimester ultrasounds, third trimester ultrasound and birth, and second trimester ultrasound and birth). This creates concerns about multiple comparisons (i.e. an increased risk of false positive findings by chance alone due to the large number of hypothesis tests performed). Especially since fetal growth is already often examined using multiple biometrics measurements (e.g. head circumference, abdominal circumference, femur length and estimated fetal weight). Its ease of calculation and clinical interpretation, however, likely explains its common use.

Conditional fetal growth measurements classify a fetus' current size given (conditional on) its size earlier in the pregnancy. Fetal growth is calculated as the difference between a fetus' observed weight and that predicted based on prior size. The predicted weight can be calculated using estimates of within- and between-fetus variation obtained from a hierarchical regression model of repeated ultrasound measurements [29, 30] or as the residual of a model regressing the current measurement on previous measurement [4, 31, 32]. The conditional growth measurement—either a standardized residual or conditional growth percentile—can then be linked with child outcomes in a separate model. Conditional measurements calculated with a hierarchical model address several of the limitations associated with the change in *z*-score method (such as regression to the mean, and accounting for the time interval between measurements), but are still focused on the difference between two measurements rather than the trajectory and potential problems with multiple comparisons.

Finally, conventional growth models, such as those used to produce size-for-gestational-age charts, estimate a single-population average growth trajectory, as well as the extent to which fetuses' trajectories vary about this average. Latent class models assume that the population does not consist of a single homogenous group, but instead consists of different heterogeneous subgroups (such as those with underlying pathological conditions affecting growth). The model estimates the number and size of latent classes (subgroups) in a given population and assigns class membership to individuals. Latent class models have been applied by several researchers to the study of longitudinal fetal growth ("growth mixture models"), with the goal of identifying distinct subgroups of fetuses with suboptimal fetal growth patterns [33, 34].

By using all available measurements from each fetus, the approach maximizes available information on each fetus' growth pattern and makes each trajectory less sensitive to measurement error in a given value. The approach also eliminates the use of conventional size thresholds (such as the 3rd or 10th percentile) to define abnormal growth, which are driven by statistical distributions rather than risks of adverse outcomes. Nevertheless, the number of groups chosen by the model is data-driven rather than based on clinical insight. As a result, the number of groups could differ based on sample size or study population, and may not reflect clinically meaningful divisions. Further, the fetal growth subgroups are established using datasets with complete measurements including birthweight, and it is unclear how well the postnatally established groups could be translated into a tool to inform prenatal care. As a result, the approach is likely best suited to studies seeking to understand disease etiology rather than identify high-risk fetuses in the clinical setting.

The extent to which the choice of modelling methodology influences our understanding of the relationship between serial fetal growth measurements and offspring outcomes is unclear. No study has directly compared the impact of these methodologic differences on substantive conclusions. Thus, the approach to quantifying individual fetal growth trajectories chosen by each study should be carefully considered when comparing research findings.

Birth Outcomes

Our search identified four independent studies that reported the association between longitudinal fetal growth and perinatal outcomes [35–38]. Each of these four studies assessed fetal growth based on change in standardised size between two time points.

Mode of Delivery

One study evaluated 48 singleton pregnancies that resulted in term birth of newborns with a birthweight greater than the 10th centile (i.e. non-SGA) [35]. Fetal growth restriction was defined based on change in customized fetal weight centile from gestational week 28 to birth. Labor was induced in 44% of pregnancies with a fall in centile greater than 20 percentage points (moderate to severe decline) compared with 37% in the other pregnancies (maintained growth). In pregnancies with moderate to severe decline, emergency cesarean delivery was carried out 22% of the time, compared with 3% of the time in pregnancies with maintained growth. Similarly, operative vaginal delivery was more common in pregnancies with moderate to severe decline (33%) compared to pregnancies with maintained growth (13%). Elective cesarean delivery, however, was more common in the latter group (17%) compared to the former group (0%).

A second study evaluated 970 pregnancies with estimated fetal weights (EFW) consistently below the 10th centile at multiple ultrasound measurements in the second half of pregnancy [36]. Fetuses that had a biparietal diameter below the 10th centile were classified as *symmetric* SGA (29%), while those who had biparietal diameter consistently above the 10th centile were classified as *asymmetric* SGA (71%). The latter group was interpreted to present "head-sparing." Induction of labor was more common in asymmetric pregnancies (50 vs. 40%, $p = 0.011$). There was no difference in the proportion of emergency cesarean deliveries or operative vaginal delivery

between the asymmetric and symmetric groups (25 vs. 28%, $p = 0.334$, and 8 vs. 5%, $p = 0.113$). Elective cesarean deliveries, however, were less common in asymmetric pregnancies (15 vs. 25%, $p = 0.003$).

Use of asymmetric vs. symmetric SGA as a proxy of restricted growth has been much debated. Symmetric SGA was first thought to represent an increased risk of morbidity, due to lack of "head sparing" [35, 36]. More recent studies have reported greater neonatal morbidity in *asymmetric* SGA than in AGA newborns [37]. Many now advise against the classification of symmetric vs. asymmetric [38]. For example, SGA pregnancies without FGR can be defined as risk pregnancies which may explain a higher rate of elective cesarean deliveries. However, it is generally accepted that growth restriction may be an important indication of delivery, and that FGR pregnancies have a higher rate of cesarean deliveries [39–41].

Gestational Age at Birth

A study from the Generation R Study evaluated the association between fetal growth in all trimesters and length of gestation and newborn size in 8636 pregnancies [37]. A greater crown rump length (CRL) in the first trimester was associated with reduced risk of preterm birth (<37 weeks). In this analysis, length of gestation was ascertained by the last menstrual period method, and sensitivity analyses revealed that timing of ovulation was an unlikely explanation for the observed association. A similar association was found in the third trimester, while there was no clear association between second trimester fetal weight and preterm birth. A positive change in fetal weight centile from the second to third trimester was associated with a reduced risk of preterm birth (OR 0.71 (95% CI 0.64 to 0.80)) for a one SD increase in second to third trimester change in EFW.

Greater EFW in the second and third trimesters were associated with a reduced risk of post-term birth (>42 weeks). A positive change in EFW from the second to third trimester, however, was associated with an increased risk of post-term birth (OR 1.31 (95% CI 1.18 to 1.46)) for a one SD increase in second to third trimester change in EFW.

O'Connor and colleagues found that gestational age at delivery was shorter in symmetric SGA pregnancies compared with that in asymmetric SGA pregnancies (36.6 vs. 37.1, respectively, $p = 0.033$) [36]. Smaller than expected first trimester CRL has previously been shown to be associated with an increased risk of preterm delivery [42, 43]. Later in pregnancy, FGR may be an important indication of induction of labor [44].

Size at Birth

A Generation R Study found that greater fetal size from the first through the last trimester to be associated with a reduced risk of birthweight <5th percentile for gestational age, with a stronger association later in pregnancy [37]. Hence, a positive change in EFW centile from the second to third trimester was also associated with reduced risk of SGA birth. Correspondingly, fetal size in all the trimesters was positively associated with a greater risk of LGA birth. A growth spurt from the second to the third trimester increased the risk of LGA birth.

Asymmetric SGA pregnancies carried a smaller risk of birth <10th centile compared with symmetric SGA pregnancies, in the study by O'Connor and colleagues (77 vs. 84%, respectively, $p = 0.017$) [36]. Accordingly, asymmetric SGA newborns were heavier compared with the symmetric SGA newborns (2.301 vs. 2.135 g, respectively, $p = 0.001$).

Thus, even in early pregnancy, fetal size predicts birth size, as has been previously reported [42, 43]. This supports the use of ultrasound as a measure of fetal growth. While birthweight is affected by both length of gestation and fetal growth, findings from the Generation R Study suggest fetal growth variation is more strongly associated with size at birth as compared with gestational age at birth [37].

Neonatal Morbidity and Mortality

Three studies reported the association between fetal growth and neonatal morbidity and mortality [35, 36, 38].

The pregnancy outcome prediction (POP) study evaluated 3977 singleton pregnancies and measured fetal growth in gestational weeks 20, 28 and 36 [38]. Newborns with an EFW <10th centile were stratified into two groups: a growth restricted group with an abdominal circumference growth velocity <10th centile between gestational week 20 and the latest ultrasound scan before birth; and the rest classified as non-growth restricted. Newborns that were small and growth restricted in pregnancy had distinctively increased risk of metabolic acidosis (RR 4.1), 5-min Apgar score <7 (RR 4.6), admission to neonatal intensive care unit (RR 2.1), and the three outcomes combined (RR 2.5), compared with newborns with EFW >10th centile. Those with an EFW <10th centile, but without restricted fetal growth, had no increased risk of these neonatal outcomes.

Conversely, in the study by O'Connor and colleagues, asymmetric SGA infants had reduced risk of perinatal morbidity (composite score of intraventricular hemorrhage, periventricular hemorrhage, hypoxic-ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia and death) compared with symmetric ones (5 vs. 12%, respectively, $p = 0.003$) [36]. Bardien and colleagues observed that 33% of those with moderate to severe decline in expected fetal weight from gestational week 28 to birth had a cord pH <7.2, compared with 24% in the maintained growth group [35]. Small numbers, however, left imprecise results.

The study by O'Connor found a slightly lower mortality among asymmetric SGA newborns, 0.1%, compared with

symmetric ones, 1.4%, but the results were uncertain ($p = 0.086$) [36].

These results are somewhat conflicting, which may owe to the fact that O'Connor and colleagues have applied an unspecific proxy for restricted fetal growth (i.e. asymmetric vs. symmetric SGA). The two other studies showed that pathological fetal growth on top of small fetal size seems to increase the risk of neonatal morbidity and mortality. This is in line with previous reports, and may explain why some studies that have only evaluated small size without accounting for longitudinal growth patterns have failed to find increased morbidity and mortality [45]. However, some studies found that there may also be increased neonatal morbidity among newborns with declined fetal growth, but with weight >10th percentile [40, 45].

The most recent 2013 RCOG guidelines [39] argue that routine serial ultrasound measurements of the fetus are not justified, despite positions to the contrary [40–42]. For example, while the RCOG guidelines advise serial assessment in pregnancies with EFW <10th centile, others argue that serial ultrasound measurements of non-SGA pregnancies have predictive value in terms of risk of emergency cesarean delivery [40].

Childhood Outcomes

Our search identified ten papers that reported the association between longitudinal US measures of fetal growth and childhood outcomes. Six papers were from a single study cohort in the Netherlands (the Generation R cohort), two were from the Scandinavian Successive SGA Births cohort, and a further two papers were from independent study cohorts in Ireland and Saudi Arabia.

Respiratory Outcomes

One Generation R paper described how individuals with obstructed lung function (i.e. the 15% of the total population ($n = 3954$) with the highest total respiratory resistance at 6 years of age) had a subtle faltering in fetal length and weight from 20-week gestation which was equivalent to approximately 0.15 z-scores at birth [4]. In this study, postnatal growth did not modify the relationship between fetal growth and childhood respiratory resistance, but accelerated postnatal weight gain was associated with increased risk for asthma [4]. These findings confirm the results from the only cohort to link fetal measurements to lung function and also support the paradigm that reduced lung function per se is not sufficient to cause asthma [46].

Allergy Outcomes

A 2015 paper described links between faltering fetal size and early childhood eczema in a Saudi population [47]. Three studies in European populations had previously described associations between increasing fetal size and increased risk for skin prick positivity or eczema [6], but in this Saudi population of 1076 children, the opposite relationship was seen, i.e. each z-score increase in abdominal circumference was associated with a 33% reduced risk for reported eczema at 2 years of age. The contrasting finding between the Saudi and European populations may reflect differences in fetal environments, e.g. Saudi mothers rarely smoke and have different diet compared to their peers in Europe.

Obesity

The nature of the relationship between fetal size and obesity remains unclear, partly because obesity outcomes in most studies have been reported at early follow-up. Early obesity can be difficult to diagnose due to the natural changes in adiposity which take place during the preschool years. A recent paper used data from 6464 participants in the Generation R cohort to link fetal and early childhood anthropometric measurements to body mass index (BMI) and indices of fat distribution (including total body fat and hip to waist fat ratio) at 6 years of age [26]. Fetal and childhood increased weight were positively associated with increased BMI. Accelerating growth in both stages was associated with overall increased BMI of 0.66 z-scores, of which the 80% was related to early childhood growth. Increasing early childhood weight trajectory, but not fetal growth, was linked to increased fat deposits. The findings of a second study from Ireland ($n = 62$) are consistent with the study of Gishti et al. and reported associations between deposits of fat in the fetus and neonate but only from 38-week gestation [19].

Neurodevelopment

Two studies from the Scandinavian Successive SGA Births cohort give insight into how faltering fetal growth is associated with intelligence quotient (IQ) scores and brain volume in adolescence and early adulthood [48, 49]. The first paper identified 13 SGA term births with faltering fetal weight gain from 25-week gestation, 36 constitutionally small SGA term births, and 105 non-SGA term births. At 5 and 9 years of age, those with SGA after faltering weight gain had lower IQ (approximately 5 points relative to controls) and, at 15 years, had reduced volumes of the thalamus and cerebellar white tissue [48]. A subset of those assessed at 5, 9 and 15 years were followed up at 19–20 years, and those born SGA after faltering fetal weight had a 14-point reduction in IQ compared to peers with normal birthweight [49].

Cardiovascular Outcomes

Ischemic heart disease is a common condition where "fetal origins" are implicated but where symptoms and signs are not present in childhood. Three papers from the Generation R

cohort have related growth before and after birth to outcomes whose clinical relevance is unknown, but which might plausibly reflect a predisposition to ischemic heart disease. In the first paper, Gishti et al. [26] describe associations between fetal and infant growth and caliber of retinal arterioles and venules; among 4122 individuals, there were associations between accelerated growth in infancy (but not fetal life) and reduced retinal arteriolar caliber. The second paper tested the hypothesis that the "level" of vascular resistance is determined in late fetal life by relating indices of fetal vascular resistance at 30-week gestation to blood pressure at 6 years of age; there were no associations seem among the 917 participants [50]. The third paper related fetal growth to blood pressure at 6 years of age in 6239 individuals. Faltering fetal growth (i.e. a fall in estimated fetal weight *z*-score of >0.67) followed by accelerated infant growth (i.e. a rise in infant weight *z*-score of >0.67) was associated with a number of adverse outcomes including increased systolic blood pressure (SBP) (typically 0.1 mmHg). Being born SGA was also associated with increased SBP (typically 0.16 mmHg) compared with non-SGA births. Children with the highest 15% values for SBP had faltering growth during the third trimester but not during infancy [25]. Together, these studies support the paradigm that factors which determine growth during late fetal and especially in infant life may be relevant to cardiovascular well-being in later life.

Bone Mineralization

A study from the Generation R cohort related growth as a fetus and young child to bone mineral density, bone mineral content and bone area at 6 years of age in 5431 individuals [31]. There were positive associations between growth before and after birth and indices of bone mineralization, and growth during infancy was most strongly associated with outcomes. These findings are consistent with outcomes already described in children aged 6 months and 4 years.

Conclusions and Steps Forward

Despite longstanding recognition of the inherent limitations of the SGA concept [51, 52], the use of SGA has persisted in both clinical and research environments. One reason may be the inherent ease with which birthweight-by-gestational age is understood and applied, notwithstanding a constant debate about choice of cut offs to define high-risk. The dilemma regarding false/true positive or true/false negative birth outcomes is ongoing, particularly in reference to the following question: is the newborn growth restricted, or is (s)he not? In some ways, the utility of prenatal ultrasonography has come to our aid by describing longitudinal fetal growth patterns that allow for the design of trajectories from the prenatal period toward later development of health and disease. Yet, longitudinal US may not be without its own inherent limitations. For example, what is faltering growth? And who are the symmetrical versus asymmetrical growth restricted fetuses?

Nevertheless, the current narrative review demonstrates that longitudinal surveillance of fetal growth has favorably influenced obstetric management through increased knowledge, improved vigilance and more precise selection of mothers for cesarean delivery birth. Other important findings, including better predictions of premature births and size at birth, indicate a continued if not growing need for targeted neonatal care.

More generally, the summary of literature in this review shows a glimpse of the FGR offspring perspective beyond birth and the neonatal period. In quite different domains of medicine, "faltering" fetal growth is rapidly emerging as a condition of fetal growth that ought to be considered. The impact of FGR on later health is documented in areas where the etiological characteristics are known to be modifiable. Of particular note are the short-term and long-term influences that FGR birth has on neurodevelopment, cognition and psychiatric disorders. It should be noted that the follow-up time for studies summarised in this review is relatively short; hence, our conclusions on the utility of longitudinal US to measure fetal growth and offspring outcomes may be limited to studies covering only the first and second decades of the life course.

The literature describing the application of fetal ultrasound measurements to research and clinical outcomes is still incomplete in a number of ways. First, few published studies include data from more than 1000 participants. Larger studies are needed, as are additional meta-analyses [53]. A second limitation from the current body of literature includes inter-operator variability. Standardization of measurements is challenging to achieve, and international consensus statements would be helpful. A third deficit in the fetal ultrasound literature is the lack of substantial data from low- and middle-income countries.

Overall, our findings suggest that prenatal fetal measurements are a useful predictor of fetal well-being, and that factors driving fetal growth may also be important to childhood outcomes and beyond. Looking ahead, work from the Generation R Study needs to be replicated in other populations from around the world, and in cohorts with older children and young adults. To the extent for which it is feasible, systematic data from longitudinal ultrasounds could be collected from newly formed or already existing cohorts.

Take home points:

1. SGA and FGR are not interchangeable terms, although both can exist in the same individual.
2. Perinatal outcomes (including mode of delivery) are worse in fetuses with decreasing ultrasound growth

trajectories. However, it is unclear whether if outcomes are worse in fetuses with FGR than fetuses who are SGA (based on a single measurement).

3. Fetuses with reduced measurements are at increased risk for non-communicable diseases but this association is modified by postnatal growth.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Appendix 1. MEDLINE through Ovid (1946–2016 October 17)

MEDLINE through Ovid (1946–2016 October 17).

Resource selected: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present October 17th 2016

Search History

# ▲	Searches	Results	Type
1	Fetal development/ or "Embryonic and fetal development"/ or Fetal growth retardation/ or ((Fetus/ or Fetus weight/) and (Growth/ or Gestational age/))	50,896	Advanced
2	(anthropometr* or ultrasound or ultrasonograph* or echograph* or sonograph*).mp. or ((conception or fetal or fetus* or foetal or foetus* or in utero or antenatal* or prenatal* or intrauterine) adj15 (measure* or assess* or growth pattern* or growth trajector*)).ti,ab.	440,831	Advanced
3	Child/ or Child, Preschool/ or Child development/ or exp Child development disorders/ or Child Health/ or Pregnancy Outcome/ or Long term adverse effects/ or Infant/ or "Infant, newborn"/ or "Infant, small for gestational age"/ or exp. "Infant, Low birth weight"/ or Child*.ti,ab. or "Prenatal exposure, delayed effects"/	2,567,632	Advanced
4	1 and 2 and 3	4398	Advanced
5	4 and (Humans/ not Animals/)	4165	Advanced
6	limit 5 to yr. = "2014 -Current"	433	Advanced
7	6 not review.pt.	387	Advanced

Embase through Ovid (1974 to 2016 October 14)

Resource selected Embase 1974 to 2016 October 14

Search History

# ▲	Searches	Results	Type
1	Fetus growth/ or Intrauterine growth retardation/ or Fetus development/ or Prenatal growth/ or (("Fetus"/ or Fetus weight/) and (Growth rate/ or Growth retardation/ or Gestational age/))	74,954	Advanced
2	(anthropometr* or ultrasound or ultrasonograph* or echograph* or sonograph*).mp. or ((conception or fetal or fetus* or foetal or foetus* or in utero or antenatal* or prenatal* or intrauterine) adj15 (measure* or assess* or growth pattern* or growth trajector*)).ti,ab.	739,868	Advanced
3	Child/ or Childhood/ or Child development/ or Preschool child/ or Toddler/ or School child/ or Child health/ or Child growth/ or Early childhood/ or child*.ti,ab. or Pregnancy outcome/ or exp Childhood disease/ or Infant/ or Newborn/ or Infancy/ or Postnatal growth/ or Postnatal development/ or "Small for date infant"/	2,821,960	Advanced
4	1 and 2 and 3	8882	Advanced
5	4 and ((Human/ or Normal human/) not (Animal/ or Animal experiment/ or Animal model/ or Nonhuman/))	7813	Advanced
6	limit 5 to yr. = "2014 -Current"	2162	Advanced
7	6 not review.pt.	2040	Advanced

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