STILLBIRTH AT TERM: DOES SIZE REALLY MATTER?

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SYNOPSIS: Fetal nutritional and respiratory demands change differentially with advancing gestation explaining the different presentation of early/late placental dysfunction and the ineffectiveness of a policy of assessing fetal size to prevent term stillbirth.

KEYWORDS: Stillbirth, placental dysfunction, fetal growth restriction, small for gestational age, estimated fetal weight, fetal growth charts, fetal growth reference standards, customized fetal growth

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ABSTRACT

Placental dysfunction has a deleterious influence on fetal size and is associated with higher rates of both perinatal morbidity and mortality. This association underpins the strategy of fetal size evaluation as a mechanism to identify placental dysfunction and prevent stillbirth. The optimal method of routine SGA detection remains to be clarified with choices between symphyseal-fundal height estimation versus routine third trimester ultrasound, various formulae for fetal weight estimation by ultrasound and the use of national, customized or international fetal growth references. Despite this controversy, the strategy of SGA detection is undermined by data demonstrating that the relationship between fetal size and adverse outcome weakens significantly with advancing gestation such that near term, the majority of stillbirths and adverse perinatal outcomes occur in normally-sized fetuses. The use of maternal serum biochemical and Doppler parameters near term appears to be superior to fetal size in the identification of fetuses compromised by placental dysfunction and at increased risk of damage or demise. Multiparameter models and predictive algorithms using maternal risk factors, biochemical and Doppler parameters have been developed, but need to be prospectively validated to demonstrate their effectiveness.

INTRODUCTION

Stillbirth conventionally refers to the demise of a fetus in the second half of pregnancy. Not only is stillbirth a devastating obstetric outcome, it is a potential trigger to major economical and psychological consequences for women, families, health-care providers and communities. There are an estimated 4.2 million women living with depression secondary to a previous fetal death (1). Global estimates of stillbirth rate usually take into account only those occurring after 28 weeks, as there is some inter-country variation in the classification of early stillbirth. In 2015, the estimated average global SB rate was 18.4 per 1,000 births, with an approximate annual total of 2.6 million late fetal deaths (2). This equates to more than 7,000 families worldwide experiencing the burden of a fetal loss every day, with 80% of cases occurring in South Asia and sub-Saharan Africa - especially in rural settings and conflict zones (3). In these low and middle income countries, half of stillbirths are diagnosed in labor, in contrast to high-income countries only 16% of stillbirths occurred intrapartum (2,4).

Although the majority of stillbirths at term are labelled ‘unexplained’, this is often repeatedly and incorrectly interpreted as being unpreventable. In a total of 18 national reports from several different economic zones, only 7.4% of stillbirths were attributable to congenital anomalies (3). Impaired fetal growth secondary to placental dysfunction is considered to be one of the main reasons for perinatal morbidity and mortality. Fetuses weighing below the 10th centile are found approximately 2 to 3-times more frequently amongst stillbirths than live births (5). Small for gestational age (SGA) infants also contributed to 22% of neonatal deaths in a recent study of over 22 million infants born in low and middle income countries (6). Combined with the finding that up to 8 in 10 SGA neonates are born at term, it has become routine clinical practice to screen for SGA fetuses in order to detect placental dysfunction and prevent of adverse pregnancy outcomes (7). In this article, we discuss the rationale for the strategy of stillbirth prevention by fetal size-based screening and management in the light of contemporary scientific evidence.

ESTIMATED FETAL WEIGHT

Classically, screening for SGA has been embedded into routine prenatal care by assessing maternal risk factors identification, serial symphyseal-fundal height measurements and identifying pregnancy complications such as preeclampsia. Increased risk of placental dysfunction identified by any of these means usually triggers ultrasound evaluation for fetal growth and well-being (8). This is still the strategy currently practiced in the majority of obstetric units (9), although an universal third trimester ultrasound screening approach has been shown to double the detection of SGA fetuses and triple the detection of severe SGA with estimated fetal weight (EFW) below the 3rd centile for gestational age (10,11). Ultrasound assessment under these circumstances follows two main steps: measurement of fetal biometry to calculate EFW and plotting the EFW on a chart to establish a fetal weight centile for the given gestational age.

EFW formulae

There are currently more than 60 published single or multi-parameter formulae to estimate fetal weight. A recent study using a population of more than 5,000 non-anomalous singleton pregnancies scanned between 22 to 43 weeks and within days of birth evaluated the accuracy of EFW formulae (12). The authors showed that EFW calculated by Hadlock et al.'s 1985 formula (13), which uses head circumference (HC), abdominal circumference (AC) and femur length (FL) predicts birthweight within 10% in 80% of pregnancies even in when SGA or large for gestational age (12). Similarly, the same Hadlock formula performed best in multiple pregnancy with 70% of EFW estimated within 10% of birth weight (14).

FETAL SIZE REFERENCES/STANDARDS

Even though EFW can be calculated with relative accuracy by ultrasound fetal biometry and use of the correct fetal weight, this value will only be clinically useful when plotted on a normal range of EFW for gestational age to establish the fetal weight centile. Several charts have been developed with this purpose – some advocating references for a specific geographical region, some

proposing customization taking into consideration clinical characteristics and others developed with the objective of being international reference standards.

National/Local charts

Locally developed reference charts have been widely used on the basis that they account for variations in environment, ethnicity and stature between different populations. Although this approach initially may seem to be reasonable on the basis that there are distinct rates of morbidity and mortality related to growth disorders across the world, there are many aspects that must be considered before adopting such local/national charts. First is related to the method of construction, since local/national charts are generally constructed retrospectively based on birth weight databases rather than ultrasound biometry. Prospectively developed charts would be better able to avoid including women with occult or hidden morbidities (15). Furthermore, reference charts should be created from ultrasound EFW, especially at preterm gestations where birthweights are liable to be affected (lowered) by the pathology that resulted in preterm birth (16,17). Other issues with implementing regional charts is that there are currently at least 116 definitions of self-reported ethnicity in the biomedical literature (18), and that the latter is variably defined by different populations (19) and the increasing frequency of mixed ethnicity. The final barrier to the adoption of local/national charts is the lack of a real biological explanation for why geographical location or the maternal passport would result in differences in fetal growth. Where putative reasons are proposed for geographical variations in adult stature, the arguments for socioeconomical and nutritional origins for this variation outweigh possible genetic causes.

Customized charts

Some authors support the point of view that fetal weight charts should be adjusted for maternal constitutional characteristics, making it possible to estimate an individualized gestation related optimal weight (GROW) for each fetus (20,21). Proponents of this policy argue that this customization only takes in consideration physiological maternal variations rather than pathological variables which reflect health, social and economic disparities among

populations. For example, a recent NICHD Fetal Growth Study prospectively evaluated 1,737 low-risk women and reported that fetal growth not only differed significantly by self-identified ethnic group, but also by marital status, level of education and annual income (22). At odds with this policy of customization is that many of the variables that are included in customization such as maternal age, weight and ethnicity are known to be associated with adverse pregnancy outcome and stillbirth suggesting that they are not physiological variables that should be used to 'normalize' poor fetal growth. Furthermore, artificially setting SGA rates at 10% by customization does not adequately reflect the known variation in neonatal malnutrition rates between low and middle income countries, as well as the higher rates of obesity in high income countries (15). These limitations explain why despite repeated evaluations, customization for fetal growth has not been shown to improve prediction and prevention of stillbirth. A cohort study conducted in almost one million pregnant women at term in Scotland failed to show that customization improved prediction of stillbirth when compared to non-customization (23). This same study demonstrated that EFW below the 25th centile would provide better prediction for increased risk of stillbirth than the 10th centile (Figure 1).

International fetal growth standards

Local and customized descriptive charts are *fetal growth references*, which should be differentiated from prescriptive *fetal growth standards*. The former show how fetuses from a determined population have grown at a particular time, while the latter are developed to reflect how healthy pregnant fetuses should grow when free from nutritional, environmental and health restrictions (15). Two charts were developed with the purpose of being international standards for fetal growth in healthy populations, the INTERGROWTH-21st project (24,25) and the World Health Organization (WHO) sponsored study (26). The former was constructed prospectively from 2,404 fetuses at low risk for adverse outcomes from 8 delimited geographical areas and following WHO recommendations for assessment of human size and growth (27). This design made it possible to better exclude potential confounders and to reach the conclusion that human fetal growth is similar across different nationalities in low-risk situation (28). On the other hand, the WHO study followed-up 1,387

pregnant women from 10 countries, reported that fetal growth varied modestly between populations influenced by age, height, weight parity and fetal sex (22). This difference could be explained by the less stringent screening, sample recruitment methods and follow-up parameters used by the two studies. In particular, being hospital-based studies can introduce selection bias as patients attending may not be representative of the population. INTERGROWTH-21st has been compared to few local and customized references, with reported decreased rates of identification of SGA and LGA (21,29). It is relatively evident that international standards will result in variable rates of pathology depending on the populations to which they are applied – similar to international thresholds used for diagnosing chronic hypertension of diabetes mellitus.

FETAL GROWTH VELOCITY

Another strategy used to identify fetuses affected by placental dysfunction is to study the fetal growth velocity obtained by sequential scans in pregnancy. The advantages of this approach include avoidance of individual measurement errors by the use of multiple scans and also the possibility of better identifying at-risk fetuses through the differentiation of normal versus abnormal growth profiles. However, previous studies of fetal growth velocity have reported inconsistent results, probably because of the lack of consensus of what constitutes a suboptimal fetal growth velocity, whether this varies with gestational age and the relationship of growth velocity to adverse pregnancy outcome. The prospective TRUFFLE randomized controlled study prospectively evaluated 503 cases of severe fetal growth restriction between 26 and 32 weeks and reported that fetal growth was not predictive of adverse outcome (30,31). Conversely, the POP study, which evaluated 3,977 pregnant women for selective or universal ultrasound in the third trimester, showed that AC growth velocity was associated with adverse pregnancy outcome, but only in 4% of the sample where the EFW was already below the 10th centile, but not in appropriate for gestational age (AGA) fetuses (11). In a larger retrospective study, Ciobanu *et al.* showed that the predictive performance of a single EFW at 35 to 36+6 weeks for SGA was not improved neither by the addition of estimated growth velocity between 20 and 36 weeks in a population of 44,000

pregnant patients (32) nor between 32 and 36 weeks in a 14,000 patient sample (33).

RELATIONSHIP BETWEEN FETAL SIZE AND STILLBIRTH

There is a an overrepresentation of SGA fetuses amongst stillbirths, especially those that occur before 32 weeks of gestation, where 70% have birthweights below the 10% centile (4). The latter observation combined with the finding that up to 80% of SGA neonates are born at term, it has become routine clinical practice to screen for SGA fetuses in order to detect placental dysfunction and prevent of adverse pregnancy outcomes (7). However, this strategy is undermined by the finding in several large population-based studies, that only 30-40% of stillbirth after 32 weeks are SGA (4,29,34,35) (Figure 2). Confounding the relationship between SGA and stillbirth is the finding that intrauterine stillbirths progressively lose 20-25% of bodyweight in utero through maceration and after being delivered due to shrinkage in fetal mass by dehydration (36). Accounting for postmortem fetal weight loss suggests that the true prevalence of SGA birth in stillbirth at term is nearer 20-25%, meaning that the majority of adverse pregnancy outcomes occur in appropriately grown fetuses.

Definition of fetal growth restriction

Small for gestational age is the statistical deviation of fetal size from a reference standard, with an agreed threshold of less than the 10th centile. In contrast, fetal growth restriction (FGR) is a functional problem caused by uteroplacental insufficiency, where the definition should ideally include functional biophysical and biochemical indices of placental function. Uteroplacental dysfunction resulting in FGR is far more strongly associated to perinatal morbidity and mortality than SGA. Until recently there has been no gold standard for its diagnosis and many definitions have been used in the medical literature, making it difficult to compare results among published papers (37). In 2016, a definition of FGR through a Delphi procedure stressed marked differences between early and late-onset FGR. The expert consensus recommended taking into consideration not only fetal biometric parameters, but also functional

ones such as Doppler indices and cardiotocography (Table 1). For the first time, there was consensus that placental dysfunction resulting in fetal hypoxemia in FGR may occur in fetuses with AC/EFW above the 10th centile. The latter was marked by marked reduction in AC/EFW growth centiles and/or fetal Doppler abnormalities (37). The author's opinion was that the updated definition would better differentiate pathological growth restricted fetuses from the constitutionally small and healthy ones (37).

Although early and late-onset fetal growth restriction were defined as occurring before or after 32 weeks' gestation, it's important to emphasize that they are not different disorders, but instead the consequences or signs of placental dysfunction following distinct patterns depending on the gestational age at onset of placental dysfunction (38,39). Early-onset FGR pregnancies diagnosed before 32 weeks are less prevalent (<1%), often associated with preeclampsia, present with greater weight deficit, abnormalities of fetal Doppler indices and more severe hypoxemia resulting in higher morbidity and mortality (38,40). In contrast, late-onset FGR is more common (3-5%), often occurs without concurrent maternal hypertension, less likely to have abnormal fetal Doppler indices but also associated with significant perinatal morbidity and mortality (38,40). The differing presentations of the same disorder (placental dysfunction) as two apparently distinct entities (early and late-onset FGR) are explained by the differing fetal nutritional and respiratory demands observed with advancing gestation (38,39,41). Fetal nutritional demands follow a logarithmic expansion whilst respiratory demands increase exponentially (Figure 3). As a consequence, early-onset placental dysfunction will have a disproportionate effect on fetal growth before respiratory compromise develops – hence fetal stunting is a characteristic feature of early-onset fetal growth restriction. In contrast, late-onset placental dysfunction will primarily compromise fetal respiratory function before fetal nutrition and growth are affected – presenting as fetal hypoxemia even in apparently 'normally-sized' fetuses (38,39).

MANAGEMENT OF LATE-ONSET FETAL GROWTH RESTRICTION

There appears to be effective early pregnancy screening for early-onset preeclampsia and fetal growth restriction. The ASPRE randomized double-blind placebo controlled trial in 1776 high-risk patients reported a reduction of 62% of early-onset preeclampsia with the use of 150mg aspirin from 16-36 weeks (42). In the ASPRE cohort, management of early-onset FGR is optimized using a combination of both computerized cardiotocography, fetal umbilical and ductus venous Doppler assessment interpreted using TRUFFLE criteria (30). The TRUFFLE study demonstrated a neurologically intact survival at 2-years of age in 95% of pregnancies presenting with early-onset FGR at 26-32 weeks' gestation (30,31). However, no equivalent exists to screen for late-onset placental dysfunction and FGR near term, with the ASPRE and other screening algorithms performing poorly in this regard. In the absence of effective screening tools, detection of SGA near term is a substitute proxy target for many antenatal care protocols. The randomized blinded POPS study has clearly demonstrated that routine third-trimester ultrasound is three-times more effective that serial symphysis to fundal height measurement for the detection of SGA <3rd centile (11).

The main limitation of an ultrasound-based programme for SGA detection at term is effectively differentiating physiologically small babies from SGA babies compromised by placental dysfunction (reducing false-positives) and identifying the burden of disease in placental dysfunction where fetuses are still normally-sized (reducing false-negatives). There is growing evidence here that the use of uterine, umbilical and middle cerebral artery Doppler indices - even in fetuses with AC/EFW above the 10th centile. These Doppler parameters have utility in detection of placental hypoperfusion (uterine Doppler) and fetal redistribution (umbilical and middle cerebral artery Doppler), as functional parameters with superior performance to isolated biometric measurements (39). Low cerebroplacental ratio (CPR) values in the third trimester of pregnancy has been shown to better reflect respiratory compromise and to be an independent predictor of stillbirth and perinatal mortality (43) - being at least two-times more predictive of adverse outcomes than fetal size alone (44). In this sense, it seems reasonable that multiple parameters should be assessed

for a better prediction of fetuses at risk of stillbirth (43,45,46). Although the use of biomarkers such as PLGF and sFlt1 have been proved useful for prediction and timely diagnosis of preeclampsia (47,48), in pregnancies at 35-37 weeks of gestation the routine assessment of these markers provided poor prediction of perinatal outcomes in both SGA and non-SGA fetuses (49). Maybe the incorporation of these markers to more comprehensive algorithms should be the key to a better predictive performance regarding SGA and term stillbirth.

Examples of the potential effectiveness of this approach have been shown in two recent studies. Akolekar et al, used 36 weeks ultrasound data in 45,000 singleton pregnancies to identify fetuses with EFW <40th centile and stratify them into high, intermediate, low and very low-risk management groups according uterine, umbilical and middle cerebral artery pulsatility indexes (50). This approach identified 22% of women as moderate-high risk requiring further monitoring as this cohort contained 84% of adverse perinatal events occurring in term newborns with birthweight above the 10th centile. Other authors have proposed a multiparameter validated algorithm with the objective of identifying fetuses at high risk for fetal demise - the **I**ndividual **RI**sk a**S**sessment (IRIS) prediction model (51,52). The combination of three antenatal (gestational age, parity and CPR) and three intrapartum (epidural use, labor induction and oxytocin use) can be used to assess the risk for intrapartum compromise requiring operative delivery. The IRIS algorithm demonstrated moderate to good discrimination and no sign of poor fit – and is available as a smartphone app to aid clinical decision making regarding the mode of delivery for SGA fetuses (https://mail13240.wixsite.com/website). Whether such management protocols or algorithms could improve pregnancy outcome can only be evaluated in adequately powered, blinded trials. Nevertheless, it seems inevitable that in the future, algorithms combining maternal characteristics, fetal size, placental biomarkers and Doppler indices will become available to aid in the management of pregnancies affected by placental dysfunction.

CONCLUSION

Placental dysfunction has a deleterious influence on fetal size and is associated with higher rates of perinatal morbidity and mortality. This observation has underpinned the evaluation of fetal size as the conventional strategy to identify placental dysfunction and prevent stillbirth. An effective policy of SGA detection requires routine third trimester ultrasound, EFW estimation using the Hadlock HC-AC-FL formula and evaluation of the fetal EFW centile using an international fetal growth standard such as INTERGROWTH-21st. However, this strategy is undermined by recent data which demonstrates that the relationship between fetal size and adverse outcome weakens significantly with advancing gestation such that near term, the majority of stillbirths and adverse perinatal outcomes occur in normally-sized fetuses. The use of fetal Doppler and maternal serum biochemical parameters near term appear to be a superior to fetal size in the identification of fetuses compromised by placental dysfunction and at risk of demise. Such multiparameter models and algorithms using maternal risk factors, biochemical and Doppler parameters have been developed, but need to be prospectively validated to demonstrtate their effectiveness.

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TABLES LEGENDS

Table 1. Delphi consensus-based definitions for early and fetal growth restriction (FGR) in absence of congenital anomalies [adapted from Gordijn et al. (37)].

FIGURES LEGENDS

Figure 1. Stillbirth rate according to birthweight centiles [adapted from Iliodromiti et al. (23)].

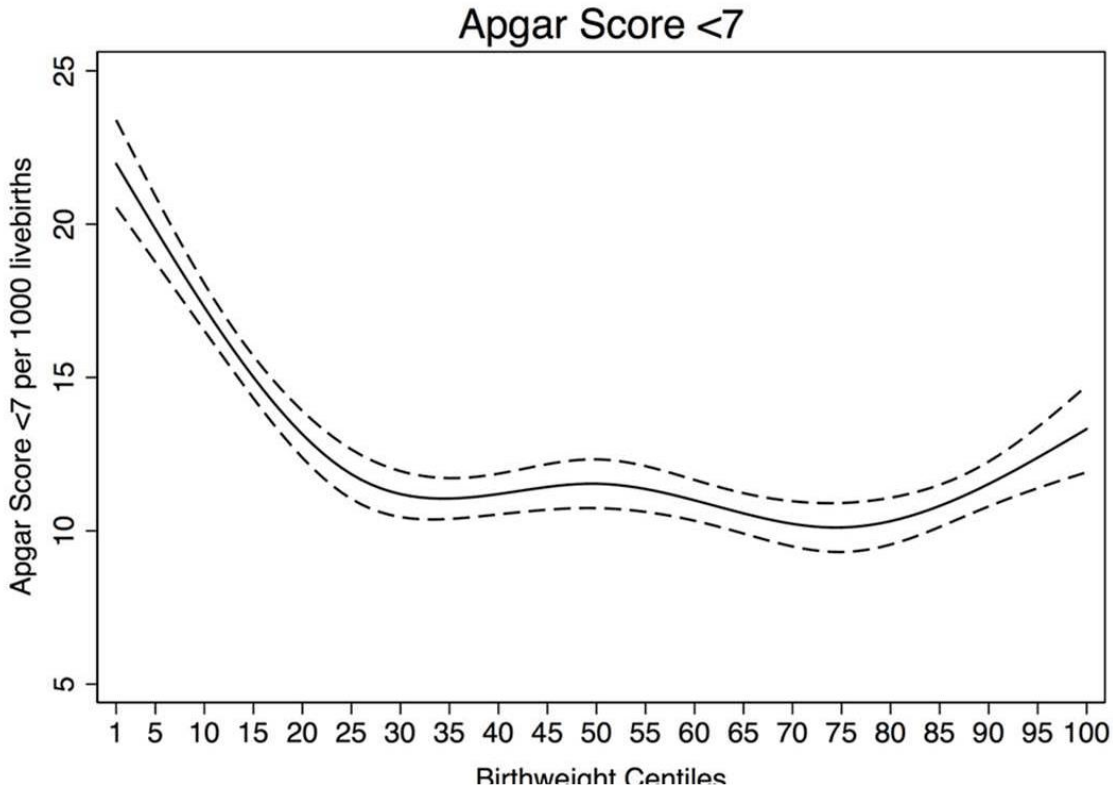
Figure 2. Birth weight according to gestational age at delivery in 436 pregnancies complicated by stillbirth, plotted against the 10^{th}, 50^{th} and 90^{th} centiles of a multiethnic population of 113,456 women normal range (solid lines) and those of the INTERGROWTH-21^{st} standard (dotted lines). Adapted from Poon et al. (29).

Figure 3. Increase in fetal nutritional (green line) and respiratory (red line) demands with advancing gestation [adapted from Thilaganathan B. (39)]. Early-onset placental dysfunction (vertical gray solid line) will impact at a time when fetal nutritional demands (green arrows) rise exponentially and therefore will have a disproportionate effect on fetal growth compared with development of fetal hypoxemia and demise. Placental dysfunction at term (vertical gray dotted line) will impact at a time when fetal respiratory needs (red arrows) rise exponentially and therefore likely to compromise fetal wellbeing before fetal growth is impaired.

Table 1. Delphi consensus-based definitions for early and fetal growth restriction (FGR) in absence of congenital anomalies [adapted from Gordijn et al. (37)].

Early FGR: GA < 32 weeks in absence of congenital anomalies	Late FGR: GA ≥ 32 weeks in absence of congenital anomalies
AC/EFW < 3rd centile *or* UA-AEDF *Or* 1. AC/EFW < 10th centile *combined with* 2. UtA-PI > 95th centile *and/or* 3. UA-PI > 95th centile	AC/EFW < 3rd centile *Or at least 2 out of 3 of the following* 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles > 2 quartiles on growth centiles* 3. CPR < 5th centile *or* UA-PI > 95th centile

* Growth centiles are non-customized centiles. AC = fetal abdominal circumference; AEDF = absent end-diastolic flow; CPR = cerebroplacental ratio; EFW = estimated fetal weight; GA = gestational age; PI = pulsatility index; UA = umbilical artery; UtA = uterine artery.



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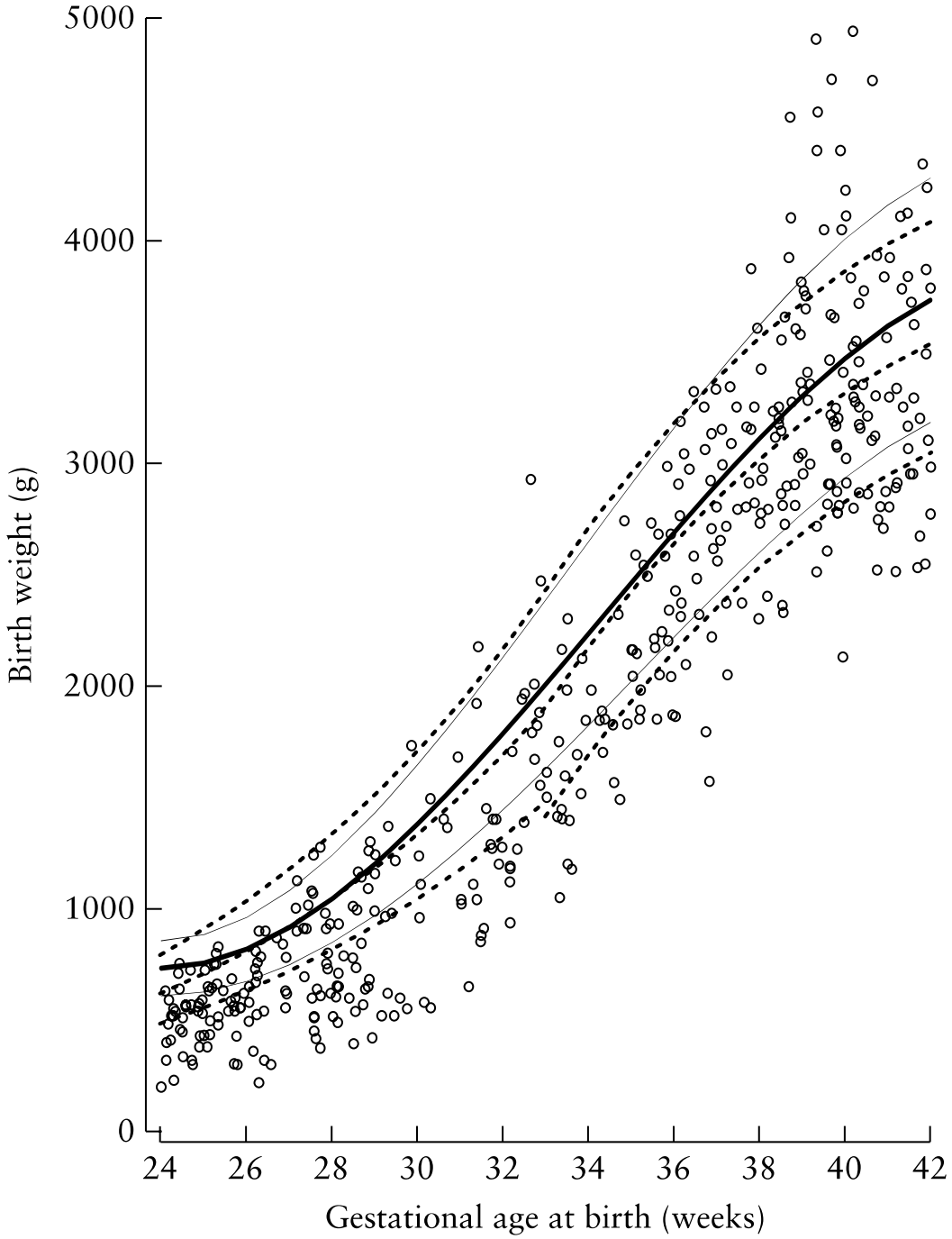

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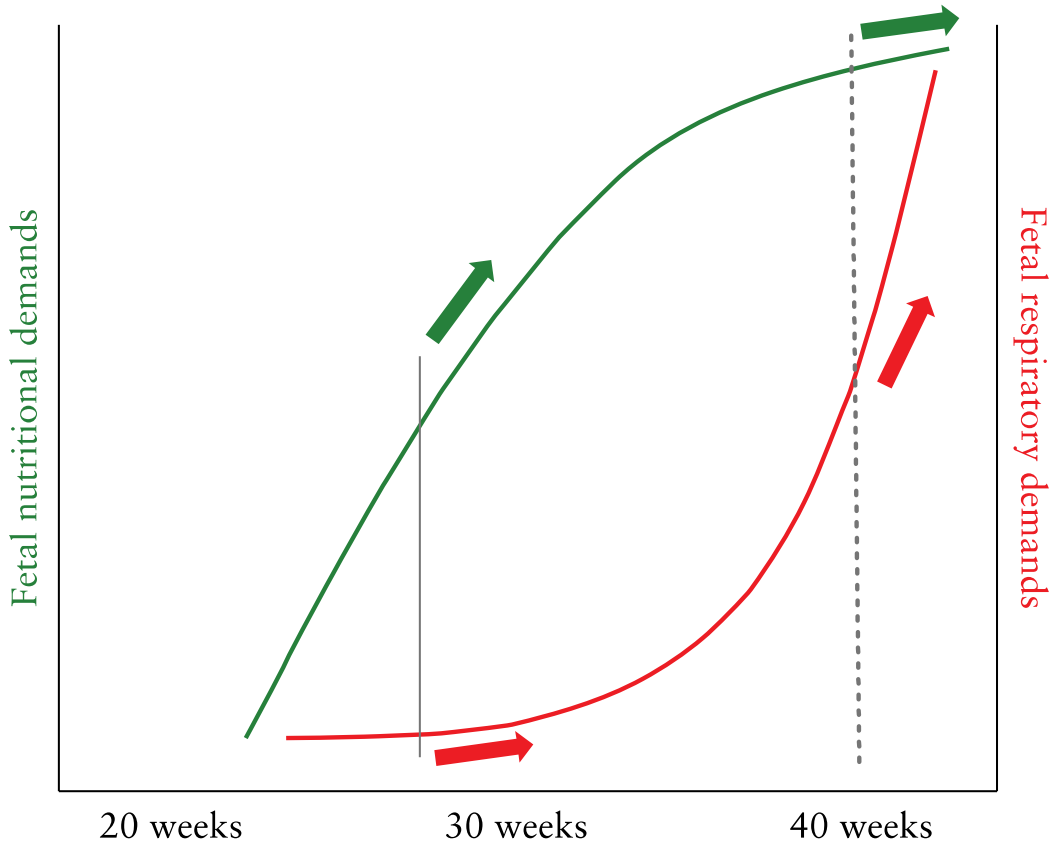

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