Elsevier Editorial System(tm) for Best Practice & Research Clinical Obstetrics & Gynecology
Manuscript Draft

Manuscript Number: YBEOG-D-16-687

Title: Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term

Article Type: Issue on AFS (GE Thilaganathan)

Keywords: uteroplacental Doppler, fetal Doppler, umbilical artery Doppler, middle cerebral artery Doppler, cerberoplacental ratio, fetal growth restriction, term, failure to reach growth potential, growth velocity

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Abstract: Identification of the fetus at risk of adverse outcome at term is a challenge to both clinicians and researchers alike. Despite the fact that fetal growth restriction (FGR) is a known risk factor for stillbirth, at least two thirds of the stillbirth cases at term are not small for gestational age (SGA) - a commonly used proxy for FGR. However, the majority of SGA fetuses are constitutionally small babies and do not suffer from adverse perinatal outcome. Doppler cerebroplacental ratio (CPR) is emerging as a marker of failure to reach growth potential at term. CPR is an independent predictor of intrapartum fetal distress, admission to the neonatal unit at term, stillbirth, perinatal death and neonatal morbidity. Raised uterine artery Doppler resistance in the third trimester is independently associated with significantly lower birthweight and CPR. The combination of the estimated fetal weight, CPR and uterine Doppler in the third trimester can identify the majority of fetuses at risk of stillbirth.

HIGHLIGHTS

- Despite the fact that fetal growth restriction (FGR) is a known risk factor for stillbirth, the majority of fetuses suffering from stillbirth at term are not small for gestational age.
- Serial measurements to assess growth velocity, combined with fetal Doppler, are preferable than a single point estimate.
- The cerebroplacental ratio (CPR) is emerging as a marker of failure to reach growth potential at term
- The combination of the estimated fetal weight, CPR and uterine Doppler in the third trimester can identify the majority of fetuses at risk of stillbirth

Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term

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Word count: 6,657 (inclusive of references and figures/tables)

ABSTRACT

Identification of the fetus at risk of adverse outcome at term is a challenge to both clinicians and researchers alike. Despite the fact that fetal growth restriction (FGR) is a known risk factor for stillbirth, at least two thirds of the stillbirth cases at term are not small for gestational age (SGA) - a commonly used proxy for FGR. However, the majority of SGA fetuses are constitutionally small babies and do not suffer from adverse perinatal outcome. Doppler cerebroplacental ratio (CPR) is emerging as a marker of failure to reach growth potential at term. CPR is an independent predictor of intrapartum fetal distress, admission to the neonatal unit at term, stillbirth, perinatal death and neonatal morbidity. Raised uterine artery Doppler resistance in the third trimester is independently associated with significantly lower birthweight and CPR. The combination of the estimated fetal weight, CPR and uterine Doppler in the third trimester can identify the majority of fetuses at risk of stillbirth.

KEY WORDS: uteroplacental Doppler, fetal Doppler, umbilical artery Doppler, middle cerebral artery Doppler, cerberoplacental ratio, fetal growth restriction, term, failure to reach growth potential, growth velocity

Introduction

Fetal growth restriction (FGR) is a major determinant of stillbirth, perinatal mortality and neonatal morbidity, most importantly hypoxic ischemic encephalopathy and cerebral palsy [1-4]. Despite the fact that two thirds of stillbirths were traditionally considered unexplained, it was revealed that 43% of these fetuses were FGR using a different stillbirth post-mortem classification system [5]. Furthermore, a retrospective population study has shown that the antenatal detection of SGA could potentially halve the risk of stillbirth [6]. Therefore, improving the identification of the small for gestational age (SGA) fetuses potentially could prevent stillbirth, likely through appropriate antenatal surveillance and timely delivery [6-9]. At present, the prenatal detection of SGA is achieved in only about 1 in 4 cases [6-9].

SGA is traditionally defined as birthweight below the 10th centile for gestational age and sex according to population references [10,11]. The use of customized centiles adjusts the birthweight for maternal height, weight, ethnicity, parity, gestational age, fetal sex, and has been shown to classify additional SGA fetuses, which would not have been identified by conventional population-based definitions [12]. Studies have demonstrated that those fetuses identified as SGA only by customized centiles are at increased risk of adverse outcome, while those considered as SGA only by population centiles have similar outcomes to the appropriately grown fetsues [12]. However, the concept of customization is controversial at present, partially due to the fact that some of the factors which influence fetal size, might not have a physiological effect, and that they themselves are known pathological risk factors for stillbirth – such as advanced maternal age, increased maternal weight and ethnic origin [13-15].

The diagnosis of FGR at term is a challenge for clinicians and researchers alike. On the other hand, its management is relatively simple – scheduled birth at term is unlikely to result in significant short- or long-term harm. Moreover, the long-held belief that induction of labour close to term increases the risk of cesarean section has recently been shown in more than

one study not to be the case. Stock *et al.* reported that elective induction of labor at term reduces perinatal mortality without increasing the risk of operative delivery [16]. This was confirmed in a more recent study in which induction of labor at low Bishop scores did not increase the risk of cesarean section or poor neonatal outcome [17].

Estimation of the fetal weight using ultrasound at term also has its limitations. While individual fetal parameters can be measured reasonable accurately, the fetal weight is estimated by applying one of many formulae to these parameters. Even the best of these formulae have a margin of error in the region of +/-15%, and there is evidence that they are least accurate in the very small and very large fetuses. Furthermore, until recently there have been no standard criteria for the diagnosis of FGR at term. One could argue that the diagnosis of FGR is best achieved using longitudinal assessment of fetal biometry. However, this ideal is not always feasible as multiple routine scan assessments performed every 3-4 weeks is required – something that is beyond the scope of resources available in many settings. The application of evidence derived from studies of early-onset FGR would be inappropriate, as early and late-onset FGR might reflect different pathological processes and are known to differ in many aspects [18]. Recently, a consensus definition for late FGR (defined as FGR beyond 32 weeks' gestation) was reached using a Delphi procedure. This definition used four parameters: estimated fetal weight (EFW) <10th percentile, abdominal circumference (AC) <10th percentile, crossing centiles on growth charts of more than two quartiles, and fetal cerebroplacental ratio (CPR) <5th percentile [19].

FGR is a known risk factor for stillbirth. However, approximately two thirds of the stillbirth cases at term have a birthweight more than the 10th centile [20], so relying on the fetal size alone will fail to identify a large proportion of fetuses at risk of stillbirth at term. Furthermore, recently published data also shows that a fetus loses about 10-30% of its body weight between the time of intrauterine demise and subsequent postnatal assessment. The latter finding suggests that the majority of stillborn fetuses may have demised whilst still of normal weight and only become SGA after demise with the onset of maceration. It is also possible

that those stillbirths that result from placental hypoxia represent the tip of the iceberg and that for each fetal loss, a greater number of surviving neonates might suffer neurological impairment as a result of less severe hypoxia.

Assessment of fetal growth at term

For decades, fetal growth has been assessed using ultrasound biometric measurements including head circumference (HC), AC and femur length (FL). It is important to appreciate that biometry measured at single ultrasound scan gives information only about fetal *size*, but tells us nothing about fetal nutrition and growth *velocity*. Impaired fetal growth velocity, defined as a deceleration in the rate of growth measured longitudinally by at least two scans, ideally three weeks apart, can be used as a surrogate marker of FGR [21]. Interval growth assessment, like any other measurement, is potentially susceptible to inaccuracies as a result of intra- and inter-observer variability [22], particularly when the interval between examinations is short.

SGA is often used as a proxy for or, sometimes incorrectly, as synonymous with FGR [23,24]. However, the majority of SGA fetuses are constitutionally small babies whose growth rate is perfectly normal. Only a proportion of SGA babies have true FGR, i.e. suffering a reduction in growth *velocity*. Furthermore, it has recently been shown that a proportion of appropriate for gestational (AGA) fetuses (that is, fetuses whose EFW lies above the 10th centile) also suffer with growth restriction; in other words, despite being a good size, their growth velocity is impaired and they are failing to meet their growth potential. Indeed the majority of stillbirths at term occur in AGA fetuses [25-27]. A population based cohort study using data from the medical birth registry of Norway, which included 1.9 million singleton births at or beyond 37 weeks' gestation, showed that the proportion of stillbirths whose weight lies above the 10th centile (i.e. AGA) has been increasing from the 1960s (when it was 55%) to the early 2000s (when it was 77%) [27].

Unfortunately, there is no consensus around what constitutes normal or abnormal fetal growth velocity. In clinical practice, serial biometric measures (HC, AC and FL) are plotted on a population growth chart. A fall-off of these measures, especially of the AC, across centiles is taken as an indicator of possible FGR. It has been suggested that the use of customized growth charts, rather than population growth charts, can potentially reduce the risk of stillbirth by using maternal characteristics to adjust centile curves more appropriate to the individual fetus [28]. However, the use of customized charts simply shifts the point biometric measures from one centile to another (and so could potentially shift a fetus from AGA to SGA or vice versa), but in itself does not alter the growth velocity. In other words, it can potentially alert the clinician to the fact that a baby is small (according to its customized centile chart) and so trigger more close monitoring, but does not indicate whether the fetus is growth restricted any better than when population growth charts are used.

It has long been recognized that impaired fetal growth is associated with adverse pregnancy outcomes. De Jong showed in 1999 that the fetal growth rate was significantly lower in pregnancies that had operative delivery for presumed fetal distress (20.9 g/day) or neonatal unit admission (20.3 g/day) compared to those with uncomplicated outcome (21.9 g/day) [29]. A large screening study of 4,512 nulliparous woman recruited over a four year period in Cambridge UK [30] found that an EFW below the 10th centile was associated with an increased risk of neonatal morbidity, but only if the fetal AC growth velocity was in the lowest decile (relative risk of 17.6). In 2008, Eixarch showed that only fetuses with signs of cerebral redistribution, identified as those with a low middle cerebral artery (MCA) pulsatility index (PI), suffered from lower communication and problem solving scores in childhood [31]. Interestingly, term SGA fetuses with normal MCA PI had similar neurodevelopmental outcomes to those above the 10th centile with normal MCA PI. All of this evidence supports the concept that it is impaired fetal growth velocity, rather than size *per se*, that puts a fetus at risk of adverse outcome.

It is notable that the improvement of the detection of SGA neonates using assessment of the fetal growth (biometry) was associated with a high false positive rate (two false positives for each additional SGA neonate detected), as shown in the Cambridge screening study [30]. It is clear, therefore, that additional parameters such as fetal Doppler or biochemical markers, such as placental growth factor, are required to optimize the identification of fetuses at risk of adverse outcome [30,32].

Uterine artery Doppler

Conventionally, uterine artery Doppler indices have been measured in the second trimester when increased resistance has been taken as an indicator of impaired trophoblastic invasion of the maternal spiral arteries, and associated with an increased risk of later pregnancy complications due to placental dysfunction, such as preeclampsia, SGA and FGR [33-35]. It has also been demonstrated that uterine artery Doppler indices at the end of the first trimester may also predict preeclampsia, FGR, placental abruption and stillbirth, although with less sensitivity and specificity than second trimester measures [33-39]. More recently, longitudinal studies have reported progressive deterioration of uterine artery Doppler indices in women who go on to develop preeclampsia [34]. This has led to a shift in emphasis from a single point assessment to monitoring the longitudinal trend.

Recently it has been shown that uterine artery Doppler indices in the third trimester might be of clinical value [40-44]. Some studies have suggested that the predictive value of third trimester uterine artery Doppler is comparable to that of umbilical artery Doppler when predicting adverse pregnancy outcomes in late onset FGR [45-47]. More recent findings suggest that third trimester uterine artery Doppler was significantly associated with the risk of stillbirth and perinatal death [48]. Raised uterine artery mean PI in the third trimester is associated with significantly lower birthweight and fetal CPR. Indeed, uterine artery Doppler in the third trimester is an independent predictor of the fetal CPR, even after adjusting for birthweight centile or SGA.

Fetal Doppler

Although it is now well established that fetal Doppler is a valuable tool in the assessment and management of high-risk pregnancies, this is not the case with regard to low risk pregnancies where the evidence of its benefit is lacking. Growth restricted fetuses are characterized by an increase in the resistance to flow in the umbilical artery (increased PI) and may develop a reduction in the MCA PI. This latter finding is an indication of brain sparing in which available oxygen and nutrition is redistributed towards the vital organs (brain, heart and adrenal glands) and away from those less critical organs. These two Doppler findings (increased umbilical artery PI and reduced MCA PI) can be combined in CPR, which is the simple ratio between the MCA PI and the umbilical artery PI. In FGR, as the umbilical artery Pi is increased, and the MCA PI may be reduced, the CPR is low.

Fetal brain sparing (low MCA PI or CPR) has been associated with adverse pregnancy outcomes, even in fetuses with normal umbilical artery Doppler [45,49]. However, the CPR improves the prediction of adverse pregnancy outcomes when compared to its individual components [49-53]. It has been shown that a suboptimal or low CPR is associated with short-term markers of neonatal outcome such as cord blood acidemia, need for emergency operative delivery and neonatal unit admission [54-57], as well as stillbirth and neonatal morbidity [48, 57-59].

Fetuses with late onset FGR, in particular those with abnormal MCA Doppler, were found to have a significantly smaller corpus callosum at term than AGA fetuses [60]; this in turn was associated with an increased risk of neurobehavioral disorders in FGR babies. The same group showed that SGA fetuses with cerebral blood flow redistribution have a higher incidence of neurodevelopmental deficit at the age of two years, achieving a lower mean centile in communication and problem solving [31]. Furthermore, small fetuses with abnormal CPR were more likely to suffer with a deficit in cognitive functioning and academic

achievement in all domains at the age of six to eight years [61]. In this study, abnormal CPR predicted low academic scores in children born at term [61].

In common with studies of individual Doppler parameters, the majority of studies of CPR have until recently focused on SGA fetuses. In a recent meta-analysis, abnormal CPR in SGA fetuses was associated with an increased risk of cesarean section for presumed fetal distress (OR 7.4; 95% CI 2.5 to 21.5), low 5-minute Apgar score (OR 6.9; 95% CI 0.96 to 49.1), neonatal unit admission (OR 13.0; 95% CI 6.0 to 27.9) and neonatal complications (OR 20.4; 95% CI 8.7 to 47.6) [62]. The equivalent sensitivities for each of these outcomes were 44-70%, 50-80%, 40-81%, and 39-86%, respectively. The corresponding specificities were 56-93%, 54-80%, 53-96%, and 53-97%, respectively [62]. Furthermore, the findings of the PORTO study reinforced the importance of CPR in identifying at risk fetuses; FGR fetuses with abnormal CPR had a 11-fold increase in the risk of adverse pregnancy outcomes, in particular neonatal morbidity, when compared to those with normal CPR [59].

We recently reported that the CPR is a marker of failure to reach growth potential and adverse pregnancy outcomes, in both AGA and SGA fetuses [55,56], and this has been discussed in a recent review [63]. Most studies that assessed the utility of CPR in identifying at risk fetuses used point estimates and lacked longitudinal data. Given that fetuses considered to be at risk, such as those diagnosed to be SGA, are monitored with serial ultrasound examinations, it should be possible, and indeed would be preferable, to use reference ranges for CPR based on studies with a longitudinal design [64]. However, the reference ranges currently used for CPR are based on cross sectional studies and thus more suitable for single observations rather than serial monitoring [63-68].

CPR is lower in fetuses suffering with FGR that are therefore at increased risk of stillbirth [48]. However, in normal fetuses, CPR normally falls after 34 weeks of gestation [66,69]. It is conceivable that the rate and/or magnitude of this fall might be greater in at risk fetuses. In a recent study, the conditional centile for CPR ≤5th and

≤10th was associated with adverse perinatal outcomes [70]. Moreover, adding the conditional centile to the conventional centile for CPR has improved the prediction of adverse perinatal outcomes, compared to the use of the conventional centile alone [70]. The adverse perinatal outcomes described in this study included preterm birth, operative delivery for fetal distress, neonatal unit admission, 5-minute Apgar score less than 7, neonatal hypoglycemia and perinatal mortality. It remains to be established whether a steeper than expected fall in the CPR can predict fetal demise.

A model of fetal surveillance

Until recently, it is primarily SGA fetuses that have been considered at risk of adverse outcomes and therefore subjected to increased surveillance, using both biometric and Doppler measurements. Similarly, the focus of most research on FGR has been on SGA fetuses; indeed, many publications have erroneously used the terms SGA and FGR as if they were interchangeable. However, the weight of evidence is increasing that a large proportion of SGA fetuses are not growth restricted, while a significant proportion of AGA fetuses are growth restricted and therefore at increased risk of adverse outcome, including stillbirth. There is a rise in the incidence of stillbirth and perinatal mortality with reducing birthweight centiles, even in those with birthweight centile above the 80th [26,71,72]. This fact is consistent with our recent observation of increasing the proportion of low CPR with reducing birthweight centiles, even in those above the 10^{th} centile (Figure 1) [73].

We have therefore suggested a combined assessment approach for adverse outcomes, using both fetal biometry and CPR [73] (Figure 2). The model combines the data based on the assessment of the fetal biometry, which is the conventional model using the 10^{th} centile of EFW as the cut-off to identify those fetuses at risk of adverse outcome, and hemodynamics. We applied a threshold of the 5^{th} centile of CPR from the group of fetuses least likely to suffer from the consequences of growth restriction (77^{th}-90^{th} centile of birthweight). Accordingly, regardless of fetal weight centile, we proposed that fetuses with

CPR MoM values below this cut-off are considered at increased risk of adverse pregnancy outcomes secondary to late-onset placental insufficiency or insult [73] (Figure 1). Interestingly, AGA fetuses with abnormal CPR were more prone to poor acid-base status at birth compared to those with normal CPR [54].

For both biometry and CPR, the rate of change is likely to be of greater value than point estimates. Such an approach is likely to optimize the identification of fetuses that are failing to reach their individual growth potential [58], regardless of whether their estimated weight is above or below the 10th centile. We recently showed that CPR combined with uterine artery Doppler and EFW in the third trimester could identify the majority of pregnancies complicated by stillbirth and perinatal loss [48]. This is the primary goal of identifying FGR at term; once identified, management is easy by early delivery.

Conclusion

It is increasingly clear that the use of point estimates of biometry is inadequate for assessing fetuses for growth restriction at term and identifying those at increased risk of adverse perinatal outcome. Serial measurements to assess growth *velocity*, combined with Doppler measures to identify those fetuses with redistribution, are preferable. The CPR, a measure combining both umbilical and MCA Doppler indices, appears to be a very promising tool for optimizing the identification of at risk fetuses. It is clear that prospective studies are needed to identify the best markers for the diagnosis of subtle hypoxia at term, the potential for neurological damage in AGA fetuses with abnormal CPR, and the optimal timing for screening for adverse outcomes in the third trimester.

PRACTICE POINTS

- Fetal growth restriction is a major determinant of stillbirth, perinatal mortality and neonatal morbidity
- The majority of fetuses suffering from stillbirth at term are not small for gestational age
- The cerebroplacental ratio (CPR) is emerging as a marker of failure to reach growth potential at term
- The combination of the estimated fetal weight, CPR and uterine Doppler in the third trimester can identify the majority of fetuses at risk of stillbirth

RESEARCH AGENDA

- Diagnostic markers of hypoxia and potential neurological damage at term
- The potential value of the cerebroplacental ratio (CPR), in combination with other biophysical and biochemical markers, in identifying the fetuses at risk of adverse outcome at term
- Optimal timing for screening for adverse outcomes at term

SUMMARY

Despite the fact that fetal growth restriction (FGR) is a known risk factor for stillbirth, the majority of fetuses suffering from stillbirth at term are not small for gestational age. It is increasingly clear that the use of point estimates of biometry are inadequate for assessing FGR at term and identifying those at increased risk of adverse perinatal outcome. Serial measurements to assess growth velocity, combined with Doppler measures to identify those fetuses with redistribution, are preferable. The cerebroplacental ratio (CPR), a measure combining both umbilical and MCA Doppler indices, is emerging as a marker of failure to reach growth potential at term and could help identifying the at risk fetuses. The combination of the estimated fetal weight, CPR and uterine Doppler in the third trimester can identify the majority of fetuses at risk of stillbirth or perinatal death. It is clear that prospective studies are needed to identify the best markers for the diagnosis of hypoxia at term and the optimal timing for screening for adverse outcomes in the third trimester.

Conflict of interest statement

The authors report no conflict of interest.

Role of the funding source

Not applicable

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Figures legend

Figure 1. The proportion of term fetuses with failure to reach growth potential (FRGP) according to their birthweight (BW) centile group (i.e. proportion of fetuses with a cerebroplacental ratio (CPR) multiple of the median (MoM) value below the established FRGP normality threshold (CPR MoM=0.6765), which was calculated after subtracting those cases with CPR MoM below the 5th centile observed in the group with BW >90th centile). Appropriate-for-gestational-age (AGA) fetuses show a progressive decrease of CPR, which is especially important in the group with BW<25th centile. *Chi-square test plus Holms's correction for multiple comparisons.

This figure corresponds to reference [73]

Figure 2. Scattergram showing the combined model for the screening of adverse outcome in late fetal growth restriction, according to cerebroplacental ratio multiples of the median (CPR MoM) and birthweight centile. Group 1, small-for-gestational-age (SGA) fetuses with abnormal CPR; Group 2, appropriate-for-gestational-age (AGA) and large-for-gestational-age (LGA) fetuses with abnormal CPR; Group 3, SGA fetuses with normal CPR; Group 4, AGA and LGA fetuses with normal CPR. Our proposal includes identifies group 3 as fetuses with potential adverse outcome. These fetuses were earlier considered as normal fetuses.

This figure corresponds to reference [73]

Figure
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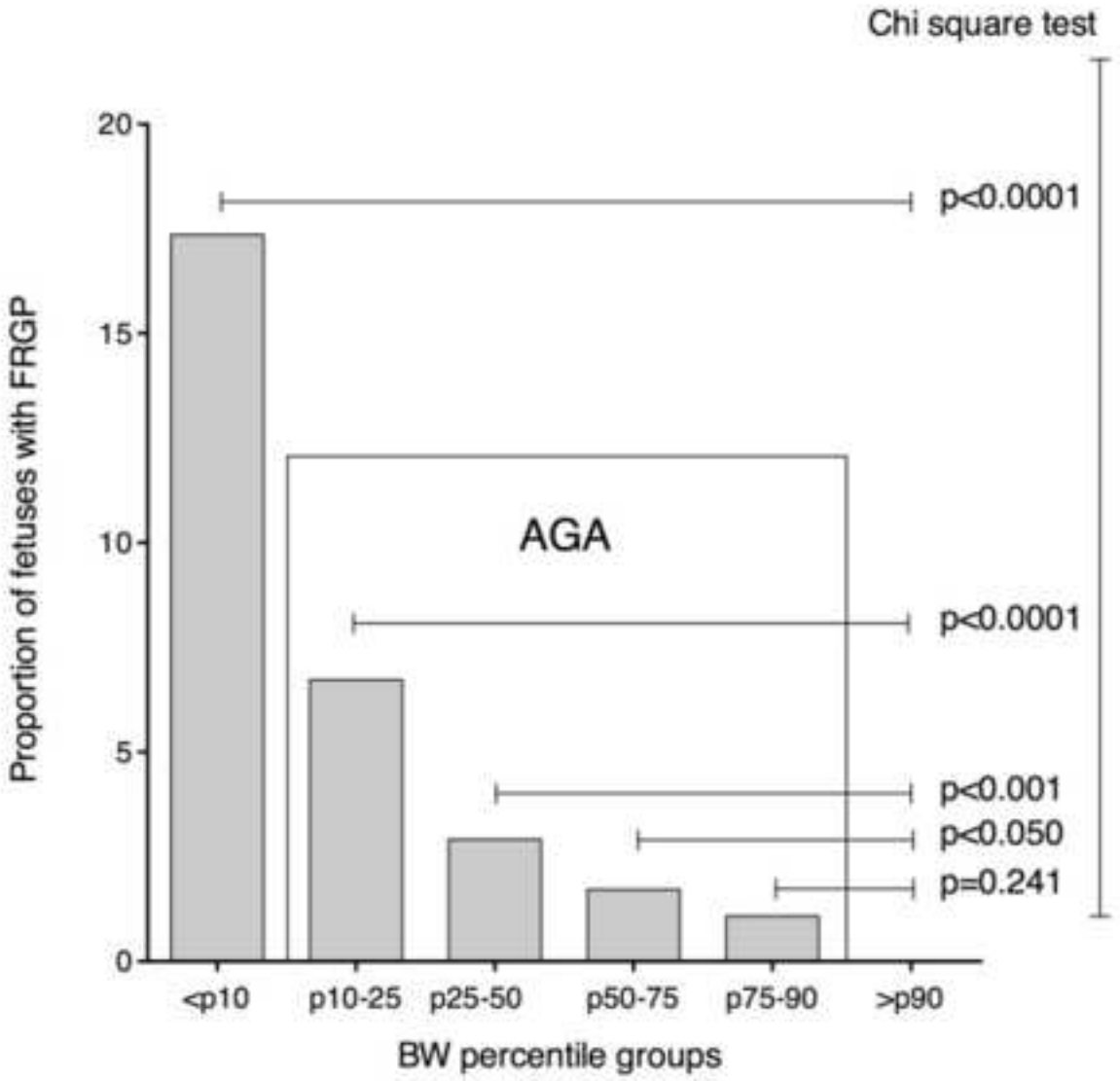

Figure 1

Figure
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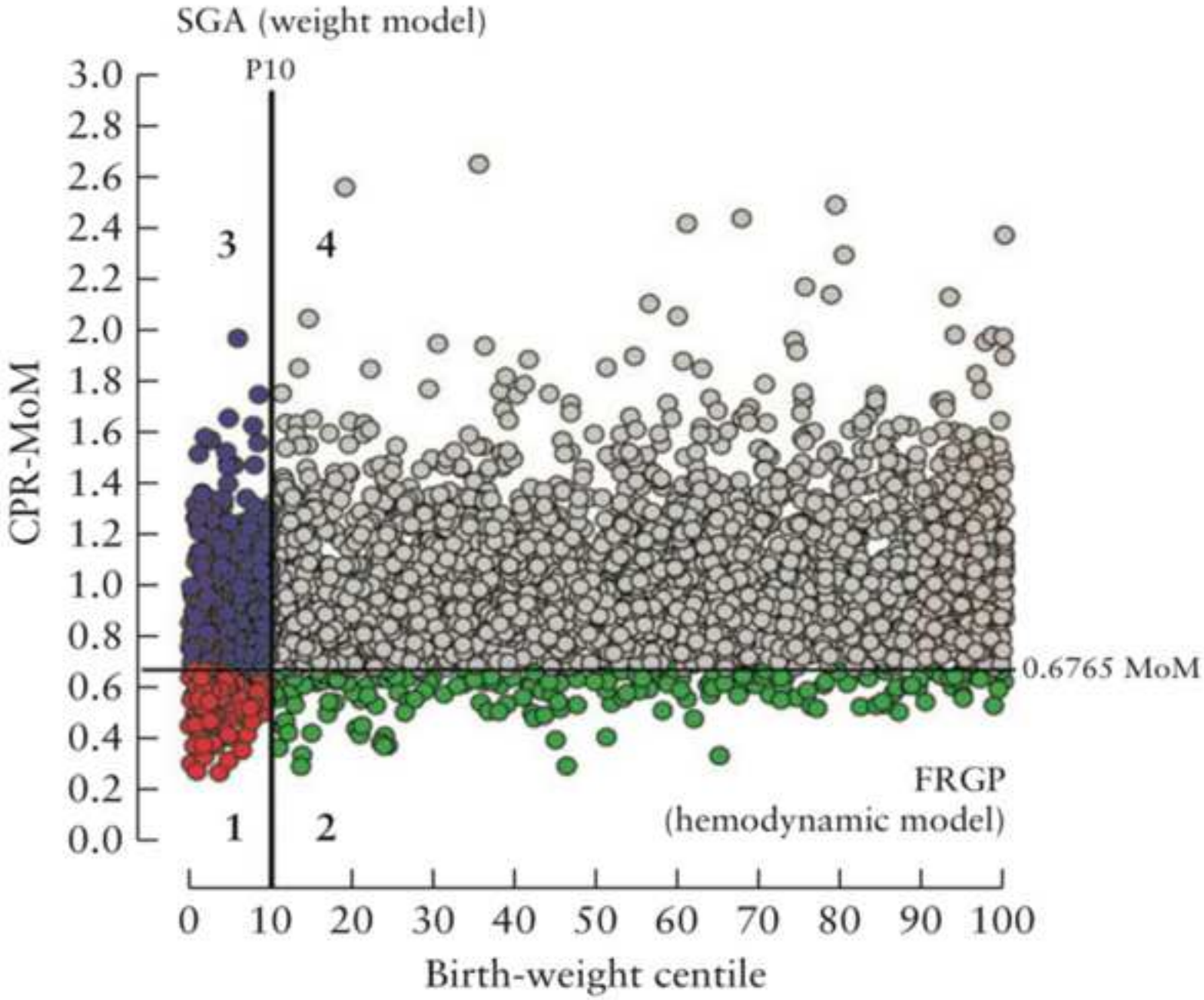

Figure 2