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Diagnosis of fetal growth restriction in perinatal deaths using brain to liver weight ratios

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Summary

We determined brain to liver weight ratio (BLWR) thresholds for fetal growth restriction (FGR) using autopsy information on 395 perinatal deaths comprising stillborn babies who died during labour and neonatal deaths. FGR was defined using two methods: (1) birth weight for gestational age (WGA) less than the 10th percentile; and (2) WGA less than the 10th percentile or discordant birth weight/length. The association between BLWR and FGR was investigated using odds ratios, and classification statistics were calculated for a range of BLWR thresholds. Using WGA, 84 cases (21.3%) were FGR and a further 15 cases ($n = 99$, 25%) had discordant birth weight/length. The BLWR ranged from 1.02 to 7.30 and was positively associated with FGR. BLWR was not associated with FGR for babies with congenital central nervous system or chromosomal abnormalities. Excluding these, for FGR defined using WGA and discordant birth weight/length, a BLWR threshold of 5.0 was 100% predictive of FGR. A BLWR threshold of 3.0 for babies over 28 weeks gestation and 3.7 for more preterm babies optimised case detection while minimising missed and false positive cases. Additional evidence of FGR should be sought for babies with a BLWR of less than 5.0 to confirm FGR.

Key words: Autopsy standards, brain to liver weight ratio, fetal growth restriction, perinatal death, small for gestational age.

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INTRODUCTION

Causes of pathological fetal growth restriction (FGR) are diverse and include many factors such as uteroplacental insufficiency, chronic maternal diseases, congenital and genetic disorders, infections and environmental conditions.[1] Correctly identifying FGR in perinatal deaths is important for understanding the clinical pathway that led to the death and the existence of any preventable factors. A diagnosis of FGR in a perinatal death is important information for clinicians and families, and has implications for the management of subsequent pregnancies.

Historically, FGR has been classified as either symmetrical or asymmetrical. In symmetrical FGR, reduced fetal growth is equally reflected across all developing organs and body parts resulting in a small but proportionally shaped infant. In contrast, asymmetrical FGR refers to cases where the rate of growth is unbalanced between different organs and body parts, and where energy is preferentially redirected to vital organs such as the brain and heart at the expense of other organs such as the liver.[2,3] Consequently, asymmetrical FGR infants are characterised by disproportionate growth manifested as a low birth weight but with relatively spared length and head circumference.[4]

More recently, the classification of FGR has been expanded to three main types.[5] Type I is symmetrical FGR and is characterised by decreased growth in early pregnancy due to altered cell proliferation of the developing embryo. Type II defines asymmetrical FGR, which is manifested later in pregnancy, generally after 30–32 weeks gestation, and is primarily attributed to reduced cell size. Type III cases of FGR are instances where growth restriction occurs due to a combination of reduced cell proliferation and growth and is a mixture of Type I and Type II FGR. The onset of Type III FGR occurs during the second trimester, the period in which cells are still undergoing proliferation while also starting to increase in size.

FGR represents the failure of babies to reach their genetically determined growth potentials,[1] and is associated with an increased risk of mortality and morbidity.[1,6,7] Diagnosis of FGR is commonly based on the comparison of estimated fetal weight to population-based standards and is usually defined as a birth weight for gestational age (WGA) below the 10th percentile.[8,9] However, difficulties arise in using birth weight percentiles to diagnose FGR in stillborn babies due to the maceration that follows death *in utero* and the lack of certainty about the gestational age at death.[10] Additional information that may be used to assess FGR *in* and *ex utero* include fundal height measurements, head circumference to abdominal circumference ratio, femur length to abdominal circumference ratio, amniotic fluid index, maternal arterial umbilical blood flow, placental grading,[1,8,9] thigh wasting and brain to liver weight ratio (BLWR) based on information obtained at post-mortem examination.[11,12]

An increase in BLWR is the result of unbalanced fetal growth in response to stress, where the growth of the brain and other key organs such as the heart are 'spared' at the expense of other, less vital organs such as the liver, kidneys, pancreas and skeletal muscle.[13,14] Several studies have investigated the relationship between brain to liver weight (or volume) ratios and FGR.[11,12,15] Anderson assessed BLWR in fresh stillborn and neonatal deaths using weights obtained from autopsy reports, and found the mean BLWR of infants that displayed normal body weight was 2.8 and that a ratio greater than 4.5 was a strong indicator of dysmature babies with low body weight.[11] Mitchell investigated using the BLWR to predict low body weight in stillborn babies, using a birth weight

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less than the 10th percentile to classify babies as FGR. Mitchell found that the BLWR tended to be elevated in FGR babies; however, the BLWR alone was considered unlikely to be an adequate indicator of FGR due to poor sensitivity and specificity.[12] Boito *et al.* utilised ultrasound technology to estimate brain and liver volumes in a series of pregnancies, and found that developing fetuses that were subsequently classified as FGR at birth displayed a marked elevation in volume ratios at the time of sonographic examination.[15]

The aim of this study is to determine BLWR thresholds for FGR at autopsy in a normative population of perinatal deaths, comprising stillborn babies who died during labour or in the neonatal period in New South Wales (NSW), Australia.

MATERIALS AND METHODS

The study population included all singleton stillborn babies that died during labour and neonatal deaths that were reported to the NSW Ministry of Health from 2000 to 2012 and had post-mortem information on brain and liver weights available. Of the 9364 perinatal deaths in 2000 to 2012 that were reported to the NSW Ministry of Health at the time the study commenced, 3007 were singleton neonatal deaths or stillbirths that died during labour. Of these 3007 deaths, a post-mortem had been carried out on 763. The study population comprised 395 deaths for which complete information on birth weight, gestational age and brain and liver weights was available.

Confidential reviews of perinatal deaths are carried out by the NSW Maternal and Perinatal Committee, which is appointed by the Minister for Health to review maternal and perinatal morbidity and mortality in NSW. Obstetric cause-specific death classifications for stillbirths and neonatal deaths are assigned according to the Perinatal Society of Australia and New Zealand Perinatal Death Classification and Neonatal Death Classification.[16] Stillbirth is defined as: 'Death prior to the complete expulsion or extraction from its mother of a product of conception of 20 or more completed weeks of gestation or of 400 g or more birth weight where gestation is not known. The death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.'[16] Neonatal death is defined as the death of a live-born baby within 28 days of life.

FGR was defined in two ways:

1. Birth WGA below the 10th percentile. This was assessed using Australian birth weight percentile standards.[17]
2. Birth WGA below the 10th percentile or birth weight and length discordance. As with the first approach, WGA below the 10th percentile was assessed using Australian birth weight percentile standards.[17] Birth weight and length discordance was assessed using expected gestational ages based on the baby's birth weight and length, obtained from Australian 50th percentile standards.[17,18] Babies were defined as FGR when the expected gestational age for length was at least 4 weeks greater than the expected gestational age for weight, or the birth WGA was below the 10th percentile. The use of a difference of four weeks or more in expected gestational ages to indicate FGR is based on Australian birth weight percentile standards,[17] which show that the 10th percentile birth weight for a given gestation corresponds to the 50th percentile birth weight for the gestation 2–4 weeks earlier.

Characteristics of FGR and non-FGR cases for both definitions were compared. Logistic regression was used to calculate the odds ratio (OR) for the association between the BLWR (continuous) and FGR, and to investigate variation by the presence/absence of congenital conditions for both definitions of FGR. To compare the definitions of FGR and investigate the performance of selected BLWR thresholds, 2 by 2 classification tables were constructed by cross-tabulating FGR and a dichotomised BLWR variable where values above the threshold were classified as FGR and those below as non-FGR. BLWR thresholds of interest (2.8, 3.0, 3.5, 4.0, 4.5 and 5.0) were selected *a priori* to provide a range of values based on those previously reported in the literature and considered clinically relevant. For the selected BLWR thresholds, the following classification statistics and their exact binomial 95% confidence intervals were calculated:

1. Sensitivity: percentage of true FGR cases classified as FGR.
2. Specificity: percentage of true non-FGR cases classified as non-FGR.
3. Positive predictive value (PPV): percentage of cases classified as FGR that are true FGR.
4. Negative predictive value (NPV): percentage of cases classified as non-FGR that are true non-FGR.

An optimal BLWR threshold was also calculated using Youden's index,[19] a measure of overall diagnostic effectiveness that balances the trade-off between sensitivity and specificity. Finally, counts of true positive, true negative, false positive and false negative cases for the study population were obtained by comparing the classification of babies as FGR by selected BLWR thresholds and WGA below the 10th percentile or birth weight/length discordance. Data manipulation and statistical analyses were carried out using SAS Enterprise Guide 5.1 and R 2.15.1.[20,21]

This study used data collected by the NSW Maternal and Perinatal Committee, which is a quality assurance committee established under the NSW Health Administration Act 1982. As the study conformed to the standards established by the National Health and Medical Research Council for ethical quality review,[22] ethics committee approval was not necessary.

RESULTS

The study population of 395 deaths comprised 135 stillbirths and 260 neonatal deaths. Of these 395 babies, 38.5% had a congenital condition, 68.1% were low birth weight (less than 2500 g) and 53.4% were extremely preterm (less than 28 weeks gestation). The BLWR ranged from 1.02 to 7.30 (Table 1).

Using WGA less than the 10th percentile, 84 (21.3%) babies were defined as FGR, with higher proportions of FGR cases observed in babies with congenital conditions (25.0%), of low birth weight (23.0%), 28 weeks gestation or greater (28.3%), higher BLWR quintiles (3.56–7.30; 45.6%) and birth length less than or equal to the 10th percentile (69.8%). The addition of birth weight/length for gestational age discordance to the WGA definition of FGR identified an extra 15 cases, increasing the total to 99 (25.1%). Comparatively, this led to increases in the proportion of FGR cases observed in babies with a birth weight of 2500 g or more from 17.5% to 28.6%, babies of 28 weeks gestation or greater from 28.3% to 35.9%, and babies with a birth length above the 90th percentile from 3.1% to 18.8% (Table 1).

The study population included 152 babies with congenital conditions of which 25.7% were affected by conditions of the central nervous system (CNS) or had chromosomal anomalies (CA) (Table 1). For the definition of FGR based on WGA only, logistic regression demonstrated that the association between FGR and the BLWR was strongest for babies without congenital conditions (OR 3.3) and without CNS conditions or CA (OR 2.9) (Fig. 1). The association between FGR and the BLWR was weaker when all babies were considered (OR 2.2) and further reduced for babies with congenital conditions (OR 1.5). The association was in the opposite direction for the subgroup of babies with CNS or CA congenital conditions (OR 0.5), although not significantly so. Similar estimates of association were found when using FGR defined with the addition of birth weight/length discordance. CNS conditions and CA therefore were excluded from subsequent analyses.

Sensitivity and PPV for selected BLWR thresholds were very similar for both FGR definitions, with WGA having slightly better sensitivity and the addition of birth weight/length discordance providing a slight increase in PPV (Fig. 2). Higher