Review

Prediction and prevention of the macrosomic fetus

Jennifer M. Walsh*, Fionnuala M. McAuliffe

UCD Obstetrics and Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland

A B S T R A C T

Fetal macrosomia is associated with significant maternal and neonatal morbidity. In the long term, infants who are large for gestational age are more likely than other infants to be obese in childhood, adolescence and early adulthood, and are inherently at higher risk of cardiovascular and metabolic complications in adulthood. With over one billion adults in the world now overweight and more than 600 million clinically obese, preventing the vicious cycle effect of fetal macrosomia and childhood obesity is an increasingly pertinent issue.

Fetal growth is determined by a complex interplay of various genetic and environmental influences. Consequently the prediction of pregnancies at risk of pathological overgrowth is difficult. Many risk factors for fetal macrosomia, such as maternal obesity and advanced maternal age, are also conversely associated with intrauterine growth restriction. Sonographic detection of fetal macrosomia is notoriously fraught with difficulties, with dozens of formulas for estimated fetal weight proposed but few with sufficient sensitivity to alter clinical practice. This calls into question policies of elective delivery based on projected estimated fetal weight cut-offs alone. More recently the identification of markers of fetal adiposity and maternal serum biomarkers are being investigated to improve the antenatal detection of the large for gestational age fetus.

Prevention of fetal macrosomia is entirely dependent upon correct identification of those at risk. Maternal weight, gestational weight gain and glycaemic control are the risk factors for fetal macrosomia that are most amenable to intervention, and have potential maternal health benefits beyond pregnancy and childbirth. The ideal method of optimising maternal weight and glucose homeostasis is yet to be elucidated, though a number of promising advances are recently being reported.

In this review we outline the contemporary evidence for the prediction and prevention of fetal macrosomia, which is indeed a contemporary dilemma.

© 2012 Elsevier Ireland Ltd. All rights reserved.
1. Introduction

The large for gestational age fetus is predisposed to a variety of adverse obstetric and neonatal outcomes, largely accounted for by the excess risks associated with labour and delivery, including shoulder dystocia and brachial plexus injury [1,2]. Delivery of a large infant also significantly increases the risk of birth complications for the mother [3,4]. In the neonatal period, macrosomic infants are predisposed to electrolyte and metabolic disturbances, such as hypoglycaemia, hyperbilirubinaemia and hypomagnesaemia [5]. In the long term, infants that are at the highest end of the distribution for weight or body mass index (BMI) are more likely than other infants to be obese in childhood, adolescence, and early adulthood [6], and are at risk of cardiovascular and metabolic complications later in life [7,8].

Fetal macrosomia is variably defined as either an absolute birthweight greater than 4000 g, 4500 g or 5000 g, or as a customised birth weight centile of greater than the 90th, 95th or 97th percentile for the infant’s gestational age. None of these terms discriminates the fetus of abnormal body composition from normal. Customised centiles based on individual fetal growth potential are recognised to increase the likelihood of differentiating between physiological and pathological growth [9]. Birth trauma rates for the macrosomic fetus appear to be more closely related to absolute birthweight rather than birth weight centile, though there is evidence for a strong correlation between fetal macrosomia with a short maternal stature and the likelihood of birth injury [10]. The metabolic consequences of macrosomia, however, are more likely to be secondary to pathological overgrowth and abnormal fat deposition in utero [11] than to either absolute birthweight or birthweight centile.

With over one billion adults in the world now overweight and more than 600 million clinically obese [12], methods to accurately predict and ultimately prevent fetal macrosomia are now essential to reduce this potential global health burden.

2. Prediction of fetal macrosomia

Prediction of fetal macrosomia is notoriously fraught with difficulties and calls into question policies of elective delivery for estimated fetal weight alone. Possible methods include identification of those at risk, clinical examination, ultrasound assessment and most recently the use of predictive biomarkers.

2.1. Prediction based on risk factors

A number of risk factors for macrosomia are unmodifiable. These include parental height, parity, ethnicity, maternal age, infant gender and previous delivery of a large for gestational age infant. Macrosomia may also be secondary to genetic syndromes which disrupt normal fetal growth regulation, such as the Beckwith–Wiedemann or Perlmann syndromes [10].

Both maternal and paternal heights have been associated with infant birthweight, though to a lesser extent with the latter [13]. There is a recognised association between advanced maternal age and macrosomia [14]. An analysis of over 8 million births in the United States from 1995 to 1997 by Boulet et al. [3] confirmed that mothers of macrosomic infants were significantly more likely than those of normal birth weight infants to be married and older (>35 years old), and less likely to be under 18 years old and primiparous. Male fetuses during the third trimester have been reported to be significantly heavier than females matched for gestational age [15] with a rate of fetal weight gain 0.5 g/day greater than female fetuses.

Women with a history of one macrosomic infant are at significantly increased risk of delivering another macrosomic infant in a subsequent pregnancy, with an odds ratio of 15.8 in one study [16]. For women with two or more macrosomic infants, the risk is even greater (OR 47.4). Overall, a first delivery of a macrosomic infant weighing greater than 4500 g is associated with a recurrence rate of 32%, compared to just 0.3% in those that deliver a normal birthweight infant the first time [17] (Tables 1 and 2).

Potentially modifiable predictors of birthweight include maternal weight, gestational weight gain, gestational age at birth and maternal glucose metabolism.

Maternal weight and maternal weight gain during pregnancy exert an important influence on infant birth weight [18–20]. Increased maternal body mass index (BMI) confers an elevated risk of delivering a heavier infant [21], while increasing maternal weight gain during pregnancy has been shown to be independently related to increasing infant birth weight [22,23]. Maternal weight gain of more than 11 kg is strongly associated with birth of a large for gestational age neonate [24]. A review by Siega-Riz et al. in 2009 [25] of all studies that examined the relationship between gestational weight gain and large for gestational age babies concluded that there is strong evidence to support associations between excessive gestational weight gain and increased birthweight and fetal growth. Excessive interval pregnancy weight gain has also been shown to be associated with an increased risk of macrosomia and its inherent complications [26]. It has been shown that women with lower weight gain in pregnancy deliver smaller infants than women with higher gains [27].

The incidence of macrosomia increases as gestational age advances. Early studies of intrauterine growth suggested that normal fetal weight gain is curvilinear between 37 and 42 weeks gestation, with fetal growth rates declining as gestation advances [28,29]. The hypothesis for this decline in fetal growth rate was that there was progressive uteroplacental insufficiency as a result of placental aging. One may then assume that if placental function remained adequate as gestational age advances that fetal growth rate would be linear, and the post-dates fetus would be at particular risk of fetal macrosomia. Indeed, in a number of studies with strict exclusion criteria which eliminated pregnancies of uncertain gestational age or those associated with adverse medical or obstetric conditions this was found to be the case [15]. Despite the association between post-dates pregnancies and increased infant birthweight, no benefit from elective induction of labour or caesarean delivery in non-diabetic pregnancies with suspected fetal macrosomia has been established [30].

Altered maternal glucose homeostasis is perhaps the most significant risk factor for fetal macrosomia and also one of the factors most amenable to intervention. Glucose is the main energy substrate for fetal growth [31]. Birthweights in infants of diabetic mothers are increased, with up to 35% above the 95th percentile [32]. In terms of predicting which infants of diabetic pregnancies are most at risk it has been suggested that post-prandial, rather than fasting, glucose concentrations are most predictive of subsequent birthweight [33]. The aim of management of diabetic pregnancies is to achieve maternal glucose levels that are similar to a non-diabetic pregnant population and in doing so achieve a similarly good obstetric outcome. The majority of macrosomic infants, however, are born to non-diabetic women. In 2008, a large prospective study of over 23,000 participants was published [34]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study found strong, continuous associations of maternal glucose levels at 24–32 weeks gestation, below those diagnostic of diabetes, and a variety of adverse pregnancy outcomes such as caesarean delivery, neonatal hypoglycemia, birthweight above the 90th centile, shoulder dystocia, birth injury and pre-eclampsia. This large study, and a number that have subsequently followed, support previous experimental evidence that suggested a direct relationship between maternal glucose levels and infant birth weight [35,36].
Table 1
Prediction of fetal macrosomia.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal palpation</td>
<td>Hall et al. [37]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symphysiofundal height assessment</td>
<td>Rosenberg et al. [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td>Belizán et al. [42]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum biomarkers</td>
<td>Moses et al. [31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A summary of current literature relating to prediction of fetal macrosomia.

2.2. Prediction based on clinical findings

Clinical estimation of fetal weight has been found in a number of studies to be poor, with detection rates of just 40–50% [37,38], as has maternal estimated fetal weight estimation [39]. Methods of clinical estimation of fetal size include abdominal palpation and symphysiofundal height measurement. In many settings, symphysiofundal height measurement has replaced clinical assessment of fetal size by abdominal palpation because the latter has been reported to perform poorly, with detection rates between 30% and 50% [40]. Assessment of symphysiofundal height measurement has been reported to perform somewhat better [41,42]; furthermore it has been suggested that serial measurement of fundal height plotted on customised charts leads to increased antenatal detection of small and large babies [43]. A Cochrane review concluded that there is not enough evidence to evaluate the use of symphysis-fundal height measurements during antenatal care, though the author did conclude that it would seem unwise to abandon the use of symphysiofundal height measurement unless a large trial suggests that it is unhelpful [44]. Sonographic assessment of fetal size is likely superior to clinical estimation [45] but it appears that macrosomia detection rates can be improved by a combination of the two [46].

2.3. Prediction based on ultrasound findings

There is much debate in the literature as to which sonographic estimated fetal weight formulation best predicts the macrosomic fetus. Commonly used weight formulas are associated with very large deviations when used in the macrosomic fetus [47]. This is partly because these formulas were derived from heterogeneous groups and were not specifically designed for assessing fetal weight at the upper end of the weight scale. Chauhan et al. in 2005 reviewed 20 articles that calculated the sensitivity and specificity of sonographic estimated fetal weight of >4000 g to accurately identify a macrosomic fetus [48]. The authors found that the post-test probability of sonographic estimated fetal weight of >4000 g to identify a macrosomic newborn varied widely, from 15% to 79%. They found that neither the type of regression equation used in the estimated fetal weight formula, the time interval between ultrasound and delivery, nor the experience of the sonographer influenced the accuracy.

Hoopmann et al. compared the accuracy of 36 commonly used weight estimation formulas in macrosomic fetuses [49]. They concluded that though some formulas showed advantages as far as mean and absolute percentage errors were concerned, none reached a detection rate for the macrosomic fetus that could lead to a clinical recommendation. Melamed et al. compared the accuracy of 21 sonographic fetal weight-estimation models and abdominal circumference (AC) as a single measure for the prediction of fetal macrosomia and found that models based on three or four biometric indices appeared to be more accurate for the diagnosis of fetal macrosomia than models based on only two indices or on AC as a single measure [50]. Pinette et al. examined 975 fetuses that had estimation of fetal weight by ultrasonography within 1 week before birth, and concluded that using either the mean value of multiple formulas or the Hadlock BPD/FL/AC formula provided the best estimate of true weight without a trend in either over- or under-estimation [51].

A number of authors have developed specific formulas for estimating the weight of the macrosomic fetus taking both fetal biometry and maternal weight into account and reported improved macrosomia detection rates [52,53].

More recently measurements of various markers of fetal adiposity have been assessed in terms of more accurately predicting fetal size. These include fetal upper arm or thigh subcutaneous tissue, upper arm soft tissue thickness, fetal cheek-to-cheek diameter and fetal anterior abdominal wall width (AAW). Chauhan et al. conducted a comparison of five new estimation techniques that involve measurements of soft tissue for identifying newborns with birth weights of at least 4000 g [54]. Three of the five newer methods (upper arm or thigh subcutaneous tissue and ratio of thigh subcutaneous tissue to femur length (FL)) were found to be poor diagnostic tests, whilst neither upper arm soft tissue thickness nor cheek-to-cheek diameter were significantly better than clinical predictions for detecting macrosomic fetuses.

Assessment of fetal anterior abdominal wall width has yielded more promising results. In diabetic pregnancies, Higgins et al. reported that the use of a raised AAW measurement better predicted macrosomia than using AC alone [55], while Petrikovsky et al. in a non-diabetic population found measurement of the subcutaneous tissue thickness of the fetal abdomen was useful for ruling out macrosomia [56]. The use of 3-dimensional volume-based estimated fetal weight has recently been reported to more accurately reflect neonatal fat mass and subsequent birthweight when compared to traditional 2-dimensional sonographically estimated fetal weight [57].

It is clear that further, larger studies are needed before assessment of fetal adiposity can reliably predict subsequent birthweight. Assessment of fetal adiposity may however play an
3. Prevention of fetal macrosomia

Despite the limitations of macrosomia prediction as outlined above, there is a clear need for effective and safe strategies to reduce the incidence in at-risk populations.

Maternal weight, gestational weight gain and glycaemic control are the risk factors for fetal macrosomia that are most amenable to intervention, and that should be targeted for the primary prevention of the implications of fetal macrosomia for pregnancy and beyond. Exercise, healthy diet and lifestyle modifications should be recommended to all identified as higher risk. Pre-pregnancy counselling and public health initiatives should stress the importance of attaining a healthy weight prior to pregnancy and the avoidance of excessive gestational weight gain following conception.

3.1. Exercise in pregnancy

Both the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynecologists (RCOG) recommend 30 min of daily moderate-intensity physical activity for pregnant women [63,64] yet only a small proportion of healthy women are meeting current recommendations for exercise in pregnancy [65]. Moreover, the proportion of the general population who exercise is larger than that of women who exercise during pregnancy, indicating that women who exercise regularly outside of pregnancy curtail or cease physical activity prenatally [66]. One possible explanation for this is the perception that exercise in pregnancy is potentially harmful — a belief that may be held by healthcare professionals as well as pregnant women. Vigorous exercise during pregnancy has been linked to preterm birth and low birth weight, but moderate or mild exertion has not [67]. Reported benefits of exercise in pregnancy include a reduced risk of pre-eclampsia and gestational diabetes, less gestational weight gain, and fewer somatic complaints (including insomnia and low mood) [68]. Regular exercise during pregnancy reduces by 23–28% the odds of giving birth to newborns with excessive birth weight [69]. Overall, the benefits of exercise in pregnancy outweigh the risks, and there are implications of a sedentary lifestyle for both pregnancy and later life. Pregnancy is no longer considered a period of confinement and may even present an opportunity for lifestyle modification, because most women are motivated to have healthy infants. Obstetricians, general practitioners and other heathcare professionals should be informed about the benefits of physical activity in pregnancy and encouraged to educate women about its safety to them and their baby.

3.2. Treatment and prevention of diabetes

The benefit of optimising blood sugars in pre-existing and established gestational diabetic pregnancies is clear. Post-prandial, rather than fasting, glucose concentrations are most predictive of subsequent birthweight [33] and continuous glucose monitoring during pregnancy is associated with improved glycaemic control in the third trimester, as well as lower birth weight and a reduced risk of macrosomia [70].

The results of a multicenter, randomised trial of treatment for mild gestational diabetes concluded that although treatment did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death, it did reduce the risk of fetal overgrowth [71]. Oral hypoglycaemic agents are now being used with greater frequency in the treatment of gestational diabetes, with good results [72]. Metformin in particular is increasingly used as a first-line medical treatment for gestational diabetes [73].
Primary prevention of gestational diabetes involves lifestyle and dietary modifications to optimise maternal BMI pre-pregnancy. A number of studies have also evaluated the role of metformin in preventing gestational diabetes in at-risk populations, with promising results [74,75].

3.3. Maternal diet

There is good evidence that maternal diet plays a role in fetal growth. There is evidence of a direct relationship between maternal blood glucose levels during pregnancy and fetal growth and size at birth, even when maternal blood glucose levels are within their normal range [34,35]. Thus, maintaining blood glucose concentrations within normal parameters during pregnancy may reduce the incidence of fetal macrosomia. Maternal diet, and particularly its carbohydrate (CHO) type and content, influences maternal blood glucose concentrations. However, different CHO foods produce different glycaemic responses. The glycaemic index (GI) was conceived by Jenkins in 1981 as a method for assessing the glycaemic responses of different carbohydrates [76]. Pregnancy is a condition where the GI may be of particular relevance, as glucose is the primary fuel for fetal growth. It has been shown that a low glycaemic diet blunts the mid and late pregnancy increase in insulin resistance typically seen in Westernised societies [77]. These studies suggest that the loss of insulin sensitivity, which is typical of Western women in the third trimester of pregnancy and is considered to be physiological, may be diet-induced. Eating primarily high glycaemic carbohydrate results in foeto-placental overgrowth, excessive maternal weight gain and predisposition to fetal macrosomia, while intake of low-glycaemic carbohydrate predisposes to normal infant birth weight and normal maternal weight gain [35].

Gestational weight gain is associated with fetal macrosomia, and it is notoriously difficult for mothers to regain their prepregnancy weight following delivery. The current National Institute for Health and Clinical Excellence (NICE) recommendation [78] that women not be weighed in pregnancy, and the lack of clear guidance on what optimal gestational weight gain should be, appear contrary to the mounting body of evidence pointing toward a detrimental effect of excess gestational weight gain for both mother and baby [25]. The Institute of Medicine has provided clear guidance on optimal gestational weight gain according to maternal early pregnancy BMI [79]. In the light of the known association between excessive gestational weight gain and interval pregnancy weight gain on obstetric outcome, clear guidance for women, particularly for those in at-risk groups, is needed. It would seem that both providing this guidance and assessing its effects are impossible if women are not weighed during pregnancy and gestational weight gain calculated.

Targeting the maternal obesity epidemic would appear to be pivotal in breaking the escalating rates of both maternal and childhood obesity and public health initiatives should be clearly focused toward advocating a healthy lifestyle in pregnancy and beyond.

A recent systematic review of antenatal interventions for overweight or obese pregnant women concluded that the effect of providing an antenatal dietary intervention for overweight or obese pregnant women on maternal and infant health outcomes remains unclear [80]. A randomised control trial assessing the impact of a low GI diet in the prevention of recurrence of macrosomia is awaited [81], as is a cluster-randomised controlled trial of exercise and dietary intervention to prevent gestational diabetes [82].

4. Conclusion

In conclusion, the macrosomic infant poses significant challenges to obstetric care and can have potential implications for both mother and baby long after labour and delivery. Antenatal detection of the macrosomic fetus is inadequate but advances are being made, both in improvements to estimated fetal weight formulas and in first-trimester prediction. Maternal weight, gestational weight gain and glucose homeostasis are targets for primary prevention of fetal overgrowth and its implications. Further work is needed to interrogate the relationship between maternal and fetal metabolic milieus to understand clearly the pathways and metabolic mechanisms underlying fetal overgrowth. Effective public health strategies are required to recognise and combat the incidence of fetal macrosomia as a significant precursor of childhood obesity and adult ill-health.

References

and anterior
Lancet
Chauhan
Nahum
Pinette
Belizán
Hall
Walsh
Shapiro
results
tive
blood
1999;18(December
2009;34(November
M,
Obstet
Study
O,
of
Biol
abdominal
Rosen
Sp
and
and
Yogev
Northern
Robson
DJ,
review.
Aitchison
Obstet
1999;106(April
Markov
data
macrosomia:
Aitchison
Med
CH,
postpartum
Myers
Kinnunen
Obstetrics
Reference
2008;337(September):a1680.
Cochrane
Statement
of
antenatal
fetal
prediction
of
growth
study
fetal
Bakketeig
al.
Ultrasound
Med
(3)):447–50.
Goodwin