51 Can fetal macrosomia be predicted and prevented?

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Introduction

There is no consensus about the definition of macrosomia. Some authors prefer large for gestational age (LGA) (>90th%) and others birth weights (BW) of ≥4.0 kg, ≥4.1 kg, or ≥4.5 kg.[1–3] The American College of Obstetricians and Gynecologists (ACOG) defines macrosomia as an infant with a BW of ≥4.5 kg irrespective of gestational age or other demographic characteristics.[4] The use of centiles depends on the pregnancy being accurately dated by ultrasound, and this may not be possible in resource-poor settings. Macrosomia based on BW >4.0 kg in our hospital would include 12%–13% of neonates.[5] Adverse clinical consequences in this group are uncommon. This definition makes little sense because adverse consequences for a BW of 4.0–4.5 kg may occur, and any interventions have not been shown to improve clinical outcomes.

For the purposes of this chapter, we are defining fetal macrosomia as a BW of ≥4.5 kg. This is based on studies showing increased fetal and maternal trauma at the delivery of a baby weighing ≥4.5 kg.[6] The definition of macrosomia as ≥4.5 kg represents 2%–3% of our neonatal population. The 4.5 kg limit is only appropriate for term babies and can be criticized for being arbitrary as the incidence of shoulder dystocia rises between BWs of 4.0 and 4.25 kg. It could be argued that 4.25 kg be used as the cutoff value.[7,8] However, the ≥4.5 kg limit defines unequivocally and unambiguously a high-risk group that may benefit from accurate diagnosis and management over the peripartum period.[8]

The macrosomic fetus is at risk of perinatal complications such as shoulder dystocia, brachial plexus injury, clavicular fracture, and meconium aspiration.[3,9–12] In the neonatal period, macrosomic infants are at risk of hypoglycemia, hyperbilirubinemia, and hypomagnesemia.[13] The mother of a macrosomic infant is at increased risk of prolonged labor, operative vaginal delivery, perineal trauma, and caesarean section.[9,12,14,15]

The effect of BW on neonatal risk, morbidity, and mortality was studied in a retrospective review in Birmingham, AL, between 1995 and 1997.[6] From this review, it was concluded that babies ≥4.5 kg were at greater risk of labor complications such as cesarean section, shoulder dystocia, brachial plexus injuries, and neonatal morbidity. Based on the finding of this study, a grading system for macrosomia was proposed. Grade I macrosomia was defined as 4000–4499 g, grade II macrosomia as 4500–4999 g, and grade III macrosomia as ≥5000 g. Labor complications, birth injuries, and newborn morbidity increased with increasing gradation. It was found that perinatal mortality was increased in neonates ≥5000 g.[6]

Incidence

The incidence of macrosomia is widely reported to be increasing.[16,17] However, some of this evidence is more than 20 years old. The incidence of fetal macrosomia in our unit has decreased over 20 years whether the definition used is either ≥4.0 or ≥4.5 kg (Figure 51.1).

In the Republic of Ireland, the incidence of macrosomia has not increased over the last 10 years. The rate of the macrosomia (infants ≥ 4.5 kg) has been 2.5%–2.9% (Figure 51.2). The mean BW for singleton births in the Irish population from 1990 to 2012 shows little variation (Figure 51.3).

Similarly in the United States, the incidence of macrosomia across all subgroups is decreasing (Figure 51.4), despite rising obesity rates.[18]

The incidence of macrosomia in Scandinavia may be increasing. This is reflected in studies from Sweden and Denmark. In Sweden in 2001, a large retrospective study reviewed all birth records from 1992 and 2001. This included 874,163 live, term, singleton births. They found that mean BW increased from 3596 to 3631 g and the percentage of infants weighing >4500 g or more increased from 3.7% to 4.6%.[19] This study cites an increasing average maternal BMI and decreasing smoking rate over the same time period as contributing factors to this increase. However, the increase in mean BMI is hardly significant clinically and may reflect the timing of obstetric interventions at term, e.g., caesarean section or induction of labor.

In Denmark a retrospective study in 2001 reviewed all term singleton deliveries from 1990 to 1999. This included 26,392 infants. Similarly, they found that mean BW increased,

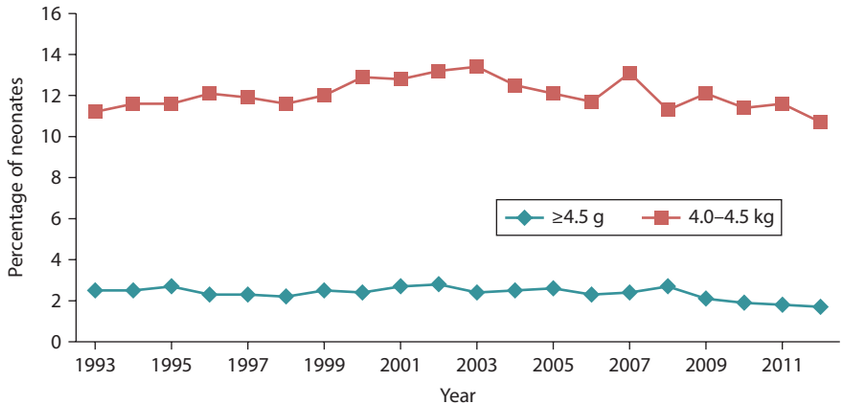

Figure 51.1 Birth weights in 1992–2012, Coombe Women and Infants University Hospital.

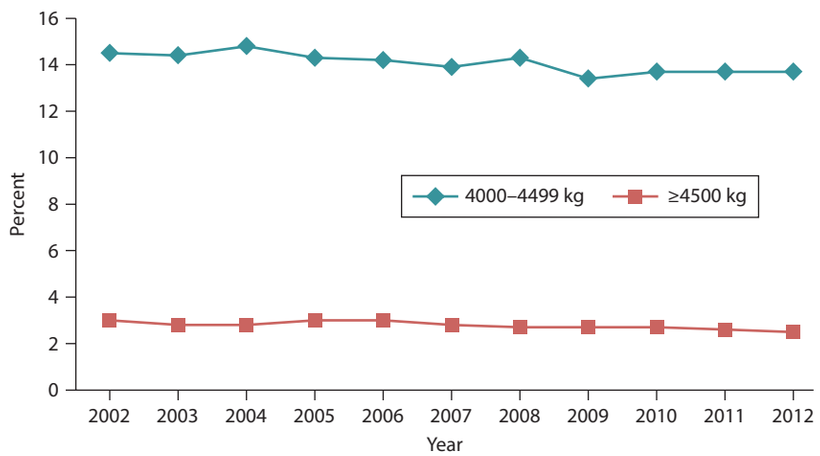

Figure 51.2 Percentage of babies born in the Republic of Ireland in 2002–2012, ESRI/NPRS Perinatal Statistics Report 2003–2012.

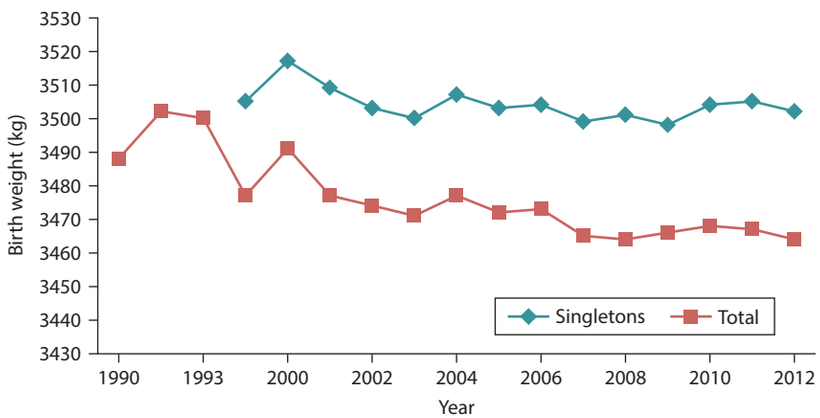

Figure 51.3 Mean birth weight in Ireland, ESRI/NPRS Perinatal Statistics Report.

as did the proportion of infants weighing 4000–4249 g, 4250–4499 g, and 4500 g or more.[20] However, it is worth noting that within their study, only 60.2% had their pregnancies dated by early pregnancy ultrasound. The remaining subjects had their pregnancies dated on the basis of the last menstrual period or on the gestational age recorded as booking. This may explain the apparent increase in BW.

Overall it is observed that the incidence of macrosomia has remained stable over the last 10–15 years. Anecdotally babies are getting bigger. However, with the possible exception of Scandinavia, this is not the case as is reflected in our analysis at local, national, and international level. Commentary in the literature is fraught with discrepancies, assumptions, and inaccurate measurements of gestation at

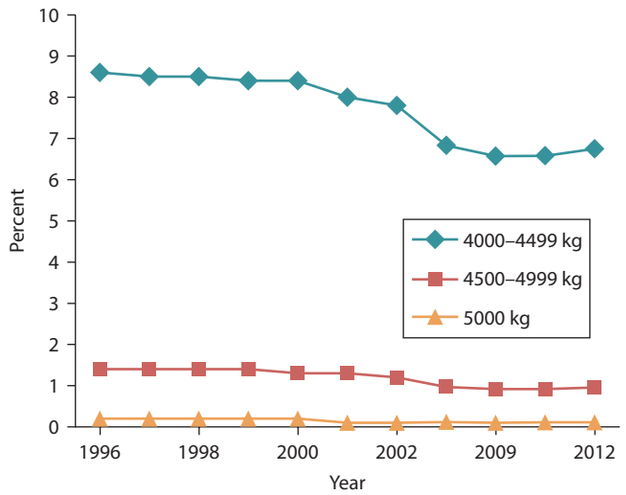

Figure 51.4 Percentage of singleton births in all macrosomic groups in the United States in 1996–2012, National Vital Statistics, CDC.

recruitment and delivery. These discrepancies illustrate the importance of accurate dating of a pregnancy so that any diagnosis of macrosomia is not erroneous.

The reason for any decreasing trends in fetal macrosomia is multifactorial. The increasing rate of assisted reproduction has lead to an increased number of twin and multiple pregnancies.[21] Such an increase of multiple pregnancies leads to a decrease in the overall BW as multiple pregnancies tend to be delivered earlier and overall weigh less than their singleton counterparts.

The diagnosis and management of gestational diabetes mellitus (GDM) also may account for the plateau in the BWs. The criteria for screening remains controversial, but even with selective screening, more women are being diagnosed with GDM.[22] The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial revealed the effects of mild hyperglycemia on fetal size and has subsequently led to changes in the parameters once considered for the diagnosis of GDM.[23]

Larger numbers of women being screened for GDM may lead to earlier intervention and this improves glycemic control. The control of blood glucose levels can be achieved through diet, oral hypoglycemics, and subcutaneous insulin. The overall effect of treatment modalities is stricter glycemic control and subsequent reduction in BW.[24] This may also explain the plateau in the number of macrosomic infants. In the United States, there is a trend toward universal screening for GDM. Therefore, even greater numbers of women are diagnosed with GDM, and their pregnancies are managed ideally within strict glycemic control.[24]

In addition to the regulation of hyperglycemia, the pregnancy complicated by GDM is unlikely to progress past 38 weeks gestation especially in the case of insulin-dependent GDM.[25] As a result, these fetuses are not being given the opportunity for a growth surge in the latter part of pregnancy and in the post dates period. This may impact on the overall percentage of macrosomic infants.

For a variety of reasons, the rate of induction of labor at term is increasing in both primiparous and multiparous women.[26,27] Induction before term will result in the delivery of an infant much smaller than if that infant had been left to deliver at term or beyond, in the postdates period.

Indeed the suspicion of macrosomia may be given as a reason for induction of labor. This diagnosis, often made on clinical examination or ultrasound, is fraught with error and interobserver variation. However, it can drive clinicians to plan an induction before term, again resulting in the delivery of a lighter infant than would have been delivered after term.

Risk factors

The risk factors for macrosomia are either modifiable or unmodifiable (Table 51.1). Unmodifiable risk factors include maternal age, parity, ethnicity, parental height, gender of the fetus, and a history of a previous LGA infant.

The effect of maternal age was demonstrated in a retrospective American review in 1985.[15] A total of 574 infants weighing <4500 kg were compared to a control sample of 18,739 infants weighing 2500–3499 kg. This study found that women delivering macrosomic infants were older and of higher parity.

A prospective observational study in Philadelphia between 1991 and 1994 explored the effect of ethnicity on macrosomia.[28] Macrosomia was defined as a BW >90th centile. Within the cohort, 103 American and 36 Latino subjects were followed prospectively. All subjects had been diagnosed with GDM. They found ethnicity is an independent risk factor for fetal macrosomia. However, ethnic variation in the United States is difficult to interpret as there is such wide ethnic intermingling.

The effect of parental height was extrapolated from the Millennium Cohort Study in the United Kingdom between 2000 and 2002.[29] There were 8053 infants studied. It showed maternal weight was more influential than paternal weight on infant BW.

Women with a history of fetal macrosomia are at risk of delivering another macrosomic infant. A retrospective study in Dublin between 1998 and 1999 reviewed 14,461 pregnancies.[30] From this cohort, 529 infants (3.7%) were macrosomic, with the incidence higher in parous women (4.6%) compared

Table 51.1 Risk factors of fetal macrosomia

Unmodifiable	Modifiable
Maternal age	Hyperglycemia
Parity	Hypertriglyceridemia
Ethnicity	Gestational age at birth
Parental height	Maternal weight
Gender of the fetus	Gestational weight gain
History of LGA infant	Dysfunctional lifestyle

with nulliparas (2.4%, $p < 0.0001$). In the following 5 years, 164 women went on to deliver a macrosomic fetus. They found that women with a history of one macrosomic fetus are at increased risk of another macrosomic fetus in a subsequent pregnancy (OR 15.8, 95% CI 11.45–21.9, $p < 0.001$). For women with two or more macrosomic fetuses, the risk is greater (OR 47.4, 95% CI 19.9–112.9, $p < 0.001$).

While all the previous factors are factored in, there are influences on BW that can be modified. These are of great interest to the clinician, for it is these that we can focus on in an effort to reduce the adverse maternal and fetal outcomes associated with the macrosomic infant. Modifiable risk factors may include maternal hyperglycemia, increased gestational age at delivery, increased maternal weight, increased gestational weight gain, and an unhealthy lifestyle.

The link between maternal and fetal hyperglycemia was first described in Copenhagen in 1952.[31] Maternal hyperglycemia leads to fetal hyperglycemia as glucose crosses the placenta and insulin does not.[32] Glucose is the main substrate for growth in the fetus.[33] In babies of mothers with diabetes, the effect of hyperglycemia is apparent as their BWs are increased. A prospective study in the northern region of the United Kingdom in 1994 enrolled 113 women with preexisting diabetes mellitus. The study found that 35% of those delivered (36 out of 104 deliveries) had a BW >95th centile.[34] In 2008, the HAPO study found that continuous exposure by the fetus to glucose, at levels below those diagnostic of diabetes, had a variety of adverse effects on the pregnancy including BW >90th centile.

Gestational age at delivery is an important risk factor for macrosomia. An observational study in California in 1997 studied the BW of 326 singleton fetuses born between 37 and 42 weeks gestation. They ensured the pregnancies were accurately dated and controlled for obesity, ethnicity, and lifestyle factors, e.g., smoking. The study found that BW was a linear function of gestational age between 37 and 42 weeks.[35] Despite this, however, studies have shown no benefit to induction of labor or caesarean section in nondiabetic mothers with suspected fetal macrosomia.[2]

Prediction

There has long been an interest in accurate methods or models for the prediction of fetal macrosomia. Clinical assessment has been the longest standing method. This involves subjective clinical palpation of the abdomen and measurement of the symphysiofundal height (SFH). These methods are fraught with inaccuracies as interobserver variation occurs. The measurement of SFH does not allow for variables such as polyhydramnios, uterine anomalies, or multiple pregnancies.[36]

Some studies suggest that maternal prediction of macrosomia is accurate. A report in 1995 asked 70 postdates women to predict the fetal weight of their baby.[37] Among the cohort, the sensitivity was 56% and the specificity was 94%. The pretest probability of macrosomia was taken to be 20%, and therefore, the posttest probability was 70%, comparable to the accuracy of ultrasound estimation. However, this study considered those women in the general obstetric population. The accuracy of maternal estimates of BW among women with GDM has not been studied.

Ultrasound has been extensively studied for sensitivity and specificity in detecting fetal macrosomia. Twenty-two articles were reviewed in 2005.[36] The inclusion criteria were any study that considered the sensitivity and specificity of ultrasound-estimated fetal weight to correctly identify a macrosomic fetus. The authors considered macrosomia as fetal weight ≥4000 g. The majority of the reports that met the inclusion criteria were from the United States. Of the 22 reports, 14 were in the general obstetric population, 4 included pregnancies complicated by GDM, and 4 included postdate pregnancies.[36]

The incidence of macrosomia among the general obstetric population (defined as BW >4000 g) ranged from 3% to 55%. The sensitivity and specificity in the detection of macrosomia in this group was wide ranging. The sensitivity ranged from 70% to 99%, while the specificity ranged from 12% to 79%. The time span of the articles included was 10 years (1993–2003). The review considered the possibility that a variation in the regression equation used by each study to predict BW influenced the results. Hadlock's proposed formula was used by 57% of the reports.[38] The posttest probability using this equation ranged from 17% to 76%. Of the 14 studies, 3 used the equation proposed by Shepard with a posttest probability ranging from 16% to 32%, and 1 study used various equations with a posttest probability ranging from 27% to 47%.[39] It concluded that the equation chosen was not a factor in the inconsistent results.

The review found that despite advances in equipment and expertise, our ability to predict the macrosomic infant has not improved over the decade. The expertise of the personnel conducting the ultrasound examination also does not influence the accuracy of prediction of fetal macrosomia.[40] A retrospective review in California recruited 365 women over a 7-month period. The prevalence of macrosomia (BW ≥ 4000 g) was 12%. The prediction of BW in the growth-restricted fetus and the appropriately grown fetus was more accurate among sonographers. However, both sonographers and fetomaternal specialists had similar accuracy in detecting the macrosomic fetus. The posttest probability to detect the macrosomic fetus was 53% and 56%, respectively.

The ability to predict macrosomia in the general obstetric population is fraught with inaccuracy. However, evidence suggests it is feasible to predict macrosomia in pregnancies complicated by diabetes mellitus and in postdate pregnancies. It is most likely that the reason for greater detection is the higher prevalence of macrosomia among these groups. The posttest probability of detection of a macrosomic fetus ranged from 71% to 81% in those with GDM and 61%–63% in postdate pregnancies.[41–44] These studies defined macrosomia as ≥4000 g.

Neonatal morbidity due to birth trauma is more likely to occur when the BW is ≥4500 g.[8] Therefore, it is prudent to consider if macrosomia can be predicted—either clinically or sonographically—in this select group of patients. In the

literature, reviews suggest a posttest probability of detection of macrosomia in infants ≥4500 g varies from 22% to 37% on ultrasound and 12% to 36% on clinical examination.[2,45–47] Present evidence indicates that it remains difficult to predict infants who weigh ≥4500 g either clinically or on ultrasound.

Serum biomarkers that are sensitive and specific could potentially predict fetal macrosomia. This area remains in its infancy, and the results to date show only a relatively small improvement in overall prediction of macrosomia.[48] Low pregnancy-associated plasma protein A and increased beta human chorionic gonadotropin levels have been shown to be predictive in pregnancies complicated by growth restriction. However, the reverse has not proven true when it comes to the prediction of macrosomia. The use of biomarkers for predicting macrosomia, from as early as the first trimester, has been investigated but with only marginal increase in detection.[48] These markers were used in combination with maternal risk profile.

Prevention

The root of macrosomia is multifactorial. Therefore, there are many aspects that can be considered when it comes to preventing this obstetric challenge.

The effect of maternal hyperglycemia on fetal macrosomia is established. Glucose crosses the placenta, while insulin does not. This results in fetal hyperglycemia and a subsequent hyperinsulinemia and fetal macrosomia.[49] In a pregnancy complicated by diabetes, there is central deposition of subcutaneous fat in the abdominal and interscapular areas. However, the skeletal growth is unaffected.[50] A prospective study of 479 healthy, nondiabetic mother and baby pairs concluded that the effect of maternal hyperglycemia on fetal growth is mainly related to fat deposition.[30] Therefore, it stands to reason that control of hyperglycemia is essential to prevent macrosomia. There is some evidence also that altering the carbohydrate type consumed from high to low glycemic index changes glucose and insulin response, in turn altering fetal weight gain.[51]

The impact of maternal obesity on fetal BW may be a factor to be considered in preventing macrosomia. A retrospective observational study in Cleveland reviewed 12,950 deliveries from 1997 to 2001 to evaluate if an abnormal body habitus contributed to the birth of a macrosomic infant.[52] The subjects were classified as underweight, normal, overweight, or obese (defined as >30 kg/m^2). Obesity was not further classified into subgroups. Macrosomia was defined as BW >90th centile. They concluded that obese women had an increased risk of macrosomia (16.8% vs. 10.5%, $p < 0.001$) as were overweight women (12.3% vs. 10.5%, $p < 0.01$). The rate of abnormal body habitus is steadily rising, particularly in the obesity classes. This may impact on the rate of macrosomia and, in doing so, will increase the morbidity associated with macrosomia for both mother and baby. There are also uncertainties about whether any epidemiological associations between obesity and macrosomia may be genetic or may be due to concomitant GDM. Ideally, it is prepregnancy or interpregnancy weight gain that we should be aiming to reduce and also weight gain in the current pregnancy, if BMI is to be optimized.

Maternal obesity may influence fetal macrosomia. However, possibly of more importance is the concept of maternal body composition. Considering the overall body composition and not just BMI may be a more appropriate focus for both the prediction and prevention of fetal macrosomia. In a prospective observational study, our research team studied the correlation between fetal BW and maternal body composition.[53] The study included 2618 subjects of whom 16.5% were obese. We concluded there was no relationship between maternal fat mass and fetal macrosomia. However, fat-free mass was a strong predictor of BW ≥4.0 kg. Women who were in the highest fat-free mass quartile had an odds ratio of 3.6 for a BW >4000 g compared to those in the lowest quartile (Figure 51.5).

The impact of body composition on BW is further demonstrated by work carried out in our unit. This prospective study recruited 368 women across all BMI categories. The BW of babies was recorded and compared against maternal body composition. This shows the range of fetal BW across all BMI categories.

Obstetric interventions are made in a bid to reduce the incidence and impact of fetal macrosomia. It has previously been postulated that elective caesarean section or induction of labor may avoid the adverse outcomes of macrosomia. However, neither approach has shown clear benefit in women with otherwise uncomplicated pregnancies.

A retrospective analysis in 1983 reviewed the outcomes for infants with a BW > 4000 g.[54] They concluded that macrosomia was rare at 37 weeks gestation and increasingly more common thereafter. They advocated ultrasound analysis between 36 and 38 weeks gestation and subsequent induction of labor for suspected macrosomia.

It must also be considered that induction of labor in itself increases the rate of caesarean section. Eleven studies, both observational and randomized, which compared expectant

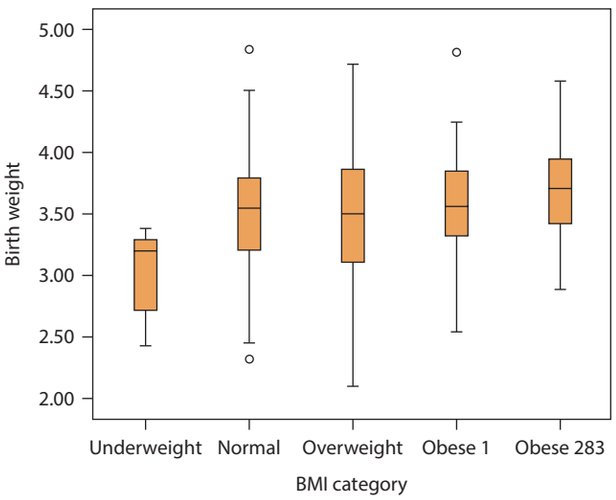

Figure 51.5 The relationship between BMI and birth weight. (From Higgins, O. et al., in press. With permission.)

management versus induction of labor when fetal macrosomia was suspected were reviewed.[55] These 11 studies included 3751 subjects of which 2700 were managed expectantly and 1051 underwent labor induction. Analysis showed that, compared with those whose labor was induced, women who experienced spontaneous onset of labor had a lower incidence of cesarean section (OR 0.39, 95% CI 0.30, 0.50) and higher rates of spontaneous vaginal delivery (OR 2.07, 95% CI 1.34, 319). No differences were noted in rates of operative vaginal delivery, shoulder dystocia, or abnormal Apgar scores in the analyses of the observational or randomized studies.[55]

Pregnancy complicated by GDM is an independent risk factor for neonatal morbidity. Shoulder dystocia was more common in diabetic women.[56] Within this study, it was concluded that the combination of diabetes and a macrosomic infant, with macrosomia defined as ≥4000 g, accounted for 73% of shoulder dystocia cases among women with GDM. Therefore, it was concluded that caesarean section was indicated in those with GDM and an estimated fetal weight ≥4000 g.[56] A similar increased risk of brachial plexus injury associated with GDM has also been demonstrated.[57]

The complications associated with macrosomia in those with GDM are recognized and caesarean delivery in these cases has been widely recommended.[56–58] However, the cutoff value at which caesarean section is advised remains contentious. Some advise a cutoff value of >4000 g, others advise >4250 g, and the ACOG recommends >5000 g.[56,58,59] It remains reasonable that caesarean section should be discussed in the context of GDM and suspected fetal macrosomia >4500 g.

Conclusion

Macrosomia remains a contentious and controversial topic in obstetric practice. There is little doubt that a pregnancy complicated by macrosomia leads to a greater risk of maternal and neonatal morbidity. It is, therefore, a pregnancy complication that we strive to both predict and prevent. However, the effects are wide reaching. Our prediction tools at present are ineffective.

The suspicion of macrosomia heightens both maternal and clinician anxiety and often leads to more investigation and more intervention than in the pregnancy where fetal growth is considered to be normal. The challenges facing us when it comes to macrosomia are wide ranging. It is hoped that through greater research and an agreed definition of macrosomia, the tools for prediction and the strategies for prevention will become more precise and widely used among clinicians worldwide.

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Author Queries

[AQ1] Please provide the expansions of the following acronyms, if appropriate: OR and CI.
[AQ2] Please check if edit to the sentence starting "Of the 14..." is correct.
[AQ3] Please check if edit to the sentence starting "Low pregnancy-associated..." is correct.
[AQ4] Please check if edit to the sentence starting "In a prospective..." is correct.
[AQ5] Please check the citation provided for Figure 51.5.
[AQ6] Please provide complete source line details for Figure 51.5.
[AQ7] Please check the value "319" is correct.
[AQ8] Please provide up to 3 authors before using "et al." in the reference list.
[AQ9] Please provide further details for Refs. [5,26].