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The management of the macrosomic fetus and the assessment of wellbeing in gestational diabetes mellitus.

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Introduction

Diabetes mellitus(DM) in pregnancy is associated with an increased risk of fetal, neonatal, and offspring complications, as well as with long term complications in adulthood. DM may be pregestational (ie, type 1 or 2 diabetes diagnosed before pregnancy with a prevalence 1.8%) or gestational (ie, diabetes diagnosed during pregnancy with a prevalence 7.5%). The outcome mainly is related to the onset and duration of glucose intolerance during pregnancy and the severity of DM. The burden in public health of maternal DM has dramatically increased worldwide. Not only its prevalence rate at present, but the increase of its incidence in the near future will rise a global health problem. Diabetic population will increase from 415 million today to 642 million by the year 2040. In 2015, 199.5 million women counted with DM and 60 million of them were in reproductive age (18-44 years old).[1]

It is estimated that the percentage of gestational diabetes mellitus (GDM) globally is about 5-20% depending on racial and socioeconomic factors. The majority of women remains undiagnosed until usual screening pregnancy tests. According to 7th Diabetes Atlas, hyperglycaemia in pregnancy is classified into three main types: diabetes detected prior to pregnancy or preexisting diabetes (type 1 and type 2), diabetes first detected in pregnancy and GDM which is defined as any degree of glucose intolerance with onset or first recognized during pregnancy.

The 15–45% of diabetic mother babies present macrosomia, which is a 3-fold higher risk compared to normoglycemic ones. Macrosomia is defined as a birth weight above the 90th percentile for gestational age or alternatively over 4,000 g.

Other maternal factors that cause fetal macrosomia ,except maternal hyperglycemia, are maternal

obesity, gestational age at delivery, pregnancy weight gain, maternal height, hypertension and smoking.[2] Obese women have double risk for developing macrosomia[3], excessive insulin levels seems to be a fetal growth accelerating factor. Simmons et al. reported that overgrowth babies from diabetic pregnancies were also hyperinsulinemic.[4]

Pathophysiology

In women with preexisting diabetes, pregnancy is associated with alteration in the regulation of glucose metabolism due to specific placental hormones, like human chorionic gonadotropin (hCG), human placental lactogen (HPL), estrogen and progesterone. During pregnancy, these hormones leads to β-cell hypertrophy and hyperplasia, counteract the action of insulin resulting in insulin resistance and enhance lipolysis[5] which consequently cause free fatty acids elevation in order to provide a different energy source to the mother and to conserve glucose and amino acids for the fetus. In turn, the increasement of free fatty acid levels directly induces insulin-directed entry of glucose into cells.

Adipose tissue produces adipocytokines, including leptin, adiponectin, tumor necrosis factor-α (TNF-α) and interleukin-6, as well as the newly discovered resistin, visfatin and apelin[6-7]. The adipocytokines and elevated lipid concentrations in pregnancy have also been associated with the changes in insulin sensitivity in nonpregnant women[8] as well as in pregnant women[9]. Evidence suggests that one or more of these adipokines might impair insulin signaling and cause insulin resistance[6]. Specifically, TNF-α has a potential role in decreasing insulin sensitivity.

The pathophysiology of macrosomia can be explained by Pedersen's hypothesis of maternal hyperglycemia leading to fetal hyperinsulinemia.

When maternal glycemic control is impaired and the maternal serum glucose level is high, the glucose crosses the placenta. As a result, in the second trimester, the fetal pancreas, which is now capable of secreting insulin, starts to respond to hyperglycemia and secrete insulin in an autonomous fashion regardless of glucose stimulation. This combination of hyperinsulinemia and hyperglycemia leads to an increase in the fat and protein stores of the fetus, resulting in macrosomia.

Macrosomic assessment

Despite that fetal macrosomia is being associated with a 2-3 times risk increasement of fetal, neonatal and long-term maternal complications[10], there are not enough studies in the literature about ultrasound monitoring in pregnancies with suspected fetal macrosomia, in GDM as well as non-diabetic pregnancies. The difficulty in monitoring a macrosomic fetus derives from the complexity of making a diagnosis, as well as the lack of quality evidence as to what should be done if macrosomia is suspected or diagnosed[11].

2D ultrasound is the most widely used method for the diagnosis and monitoring of macrosomia, despite that studies shows a lower accuracy in the prediction of large for gestational age (LGA) compared to normal weight fetus[12]. Some studies show that performing of serial ultrasound scans could provide more accurate data on the estimated fetal weight (EFW)[13,14] and the creation of an individual growth curve special for the fetus, increasing accuracy in the detection of macrosomia[12]. The reassessment should be performed every 3-4 weeks following suspicion of LGA on ultrasound examination. Most often, macrosomia can be predicted after two successive scans when EFW or abdominal circumference (AC) are above the 90th percentile, respectively. Moreover, if after two successive assessments, the EFW weight or AC is below the 90th percentile, it is not necessary to perform further ultrasound examinations because the predictive value does not increase[12].

Regarding the optimal time for ultrasound examination for better prediction of macrosomia at birth,

Souka et al.[15] showed that examination carried out late in the third trimester (between 34-37 weeks) has better accuracy than at the beginning of the third trimester (between 30-33 6/7). Another study reports that ultrasound examinations performed up to 7 days before delivery showed the best results in predicting birth weight [16.] Rigorous vitality monitoring should be performed in cases of suspected macrosomia in post-term pregnancy due to the increased risk of perinatal morbidity and mortality[11].

In patients with pre-gestational diabetes, ultrasound evaluation of amniotic fluid volume and fetal growth is recommended every 4 weeks, starting in the 20th week, and every 2 weeks after the 28th week. Pregestational and GDM are allowed under the same consultation for ultrasound monitoring. However, fetal monitoring may be less rigorous in cases treated only with diet and maintain normal blood glucose levels[17]. Ultrasound is used to measure soft tissue in the shoulder, abdomen, thigh and perioral region of the fetus, based on the fact that adipose tissue that undergoes greatest change in growth disorders. Although some studies have shown good correlation of this assessment with the evaluation of post-natal skin folds, a study comparing soft tissue evaluation with the EFW (head circumference - HC, AC and femur length - FL) has not demonstrated any advantage of such a technique in the detection of macrosomia. The combined use of soft tissue measurements with the EFW could possibly improve the prediction of macrosomia compared to any isolated one[18,12]. A study reports that the assessment of amniotic fluid volume together with the EFW increases the accuracy of prediction of macrosomia at birth[19.] 3D ultrasound provides a better assessment of fetal soft tissues but studies showed no benefit to the estimating of weight compared to 2D ultrasound method[20,21]. In a study which assessed the accuracy of 3D ultrasound fractional limb volume compared with conventional 2D ultrasound in GDM, the 3D ultrasound method showed better sensitivity for prediction of macrosomia than 2D ultrasound (84% vs. 63%)[22.]

Magnetic resonance imaging (MRI) provides a better evaluation of fetal fat. A systematic review and meta-analysis showed that MRI is a more specific method than 2D ultrasound and is apparently also more sensitive despite the limited number of studies and cases[23]. In addition, an MRI study was conducted and showed good correlation of fetal shoulder measurement with shoulder width at birth; this may help in the prediction of shoulder dystocia in macrosomic fetuses[12]. However, MRI is an expensive test and is not as accessible as ultrasound examination, therefore, further studies are required before it can be recommended in clinical practice[23]. The monitoring of fetal growth is an important part of prenatal care. Abnormal fetal growth has shortand long-term consequences. Despite the lack of accuracy, ultrasound improves the monitoring of fetuses with abnormal growth and assists decisions around the timing of delivery[24].

Fetal wellbeing

Literature does not provide many studies regarding the wellbeing of macrosomic fetuses. Most studies focus on the timing and type of delivery for preventing birth trauma and dystocia. In addition to ultrasound fetal growth monitoring, fetal wellbeing can be assessed with the evaluation of amniotic fluid volume, fetal movements, fetal biophysical profile (BPP), electronic fetal monitoring (EFM) and Doppler ultrasound. The evaluation of amniotic fluid volume should also be included in all ultrasound examinations, as polyhydramnios may be indicative of poor glycaemic control[25].

The counting of fetal movements is no-cost method for assessing fetal well-being in the third trimester. There is no consensus on how to instruct the woman to perform this assessment and there are not enough randomized studies to evaluate the various existing protocols; however, maternal percep-

tion of 10 fetal movements in two hours is considered reassuring[26]. If the woman perceives a decrease in fetal movements, another test such as EFM or BPP should be performed. Some authors suggest this method during 26th to 28th week of gestation in pregnancies complicated by diabetes. Studies have demonstrated an increasement in fetal activity associated with elevated glucose levels in maternal blood.

The BPP is usually used as a good predictor of fetal vitality, especially in pregnancies that, in addition to macrosomia, have GDM or pre-gestational diabetes. The BPP has a high positive predictive value for an Apgar score > 7 at 5 minute; however when the test is abnormal, it is not a good predictor of fetal acidaemia[27]. Kjos et al.[28] concluded that a fetal

BPP evaluation carried out twice a week can prevent fetal death in diabetic pregnant women.

Despite the lack of large randomized clinical trials, most protocols recommend that pregnant women with pre-gestational diabetes should perform an antepartum evaluation, including EFM weekly from the 32nd week and twice a week from the 36th week onwards[29]. However, EFM does not provide fetal wellbeing reassurance for no longer than 24 hours and this protocol does not represent a guideline. EFM can be combined with other non-invasive tests such as fetal biophysical profile. Normal results provide greater confidence for doctors and patients for one week[26]. EFM can be classified into reassuring, non reassuring or abnormal, according to NICE classification[30]. When is non-reassuring, it has a low predictive value for fetal distress (<50%) and should be supplemented with BPP[31]. In diabetic pregnant women, loss of fetal heart rate variability at electronic tracing has a higher correlation with impending fetal risk than the decelerations with maintained baseline variability[32]. When computerized EFM was analyzed, an increase in the baseline and short-term variability in diabetic patients was observed[33]. In these patients the short-term variability may not be able to predict hypoxia[34].

Some studies have been conducted to demonstrate changes in patterns of arterial and venous flow in macrosomic fetuses. Ebbing et al.[35] reported increased flow in umbilical vein of these fetuses, increased venous perfusion of the fetal liver, greater distribution of blood to the right liver lobe and decreased pulsatility index (PI) of the umbilical artery. This hyperemic macrosomic fetal liver occurs by the end of pregnancy, in contrast with fetuses of the appropriate weight for the gestational age. thus, a correlation between fetal size and hepatic venous perfusion can be established[36]. It has also been reported that macrosomic newborns have a lower mean umbilical artery PI compared to normal group[37]. Doppler study of umbilical artery and middle cerebral artery(MCA) provides adequate monitoring of placental insufficiency in non-diabetic pregnancies. However, most authors believe that we cannot use the same Doppler criteria of placental insufficiency to evaluate the fetuses of diabetic mothers, since there is a difference in the mechanism which leads to fetal death[38].

There are no published studies which assesses the macrosomic fetal umbilical artery in diabetic pregnant. Current data suggest a closely ultrasound monitoring protocol (twice a week) in pregnancies complicated by preexisting diabetes using EFM or BPP or a combination of both. Furthermore, Doppler ultrasound investigation should be carried out in women with diabetic vasculopahy or with complications of placental insufficiency such as pregnancy induced hypertension, intrauterine growth restriction (IUGR) [26]. Despite the technical difficulty, the evaluation of ductus venosus seems to provide promising data. This is because hypoxia releases catecholamines and diverts more flow from the liver to the fetal heart, thus dilating the ductus venosus. Hepatic artery is also a vessel for further study on the evaluation of the wellbeing of the fetus of a diabetic mother, due to the large metabolic role of the liver in intrauterine life[38].

Complications due to Macrosomia

Maternal complications

If the baby is frandly large, vaginal birth will be more complicated. There is a risk of prolonged labor in which the fetus might be stuck in the birth canal, instrumental delivery may be needed, and even unplanned or emergency cesarean section may be necessary. During birth, there is a greater risk of laceration and tear of the vaginal tissue, and the perineal muscles(perineal tear).

Uterine atony is also a severe complication caused from prolonged labour, macrosomic babies and excessive use of oxytocin. The risk of postpartum bleeding and genital tract injury is about 3–5 times higher in macrosomic deliveries39. Moreover, if the mother has a previous cesarean section, there is a higher chance of uterus tear along the scar line of the previous surgery.

Fetal Complications

Early complications

Premature Birth. Due to early induction of labor before 39 weeks of gestation and/or premature rupture of membranes, there is a risk of preterm delivery. Although all the necessary precautions are undertaken prior to induction of early labor, newborns are still under the risk of complications associated with prematurity, including respiratory distress syndrome, feeding problems, infection, jaundice, admission to neonatal intensive care unit and perinatal death.

Shoulder Dystocia and Erb's Palsy. One of the most serious complications of vaginal delivery in macrosomic babies is shoulder dystocia which is associated with severe birth trauma. Newborns with a birth weight over 4,500g or carry a 6 times higher risk of birth trauma[40], and a 20 times higher risk of brachial plexus injury[41].

Hypoglycemia at Birth. One of the most common metabolic disorder of the neonate of a GDM mother is hypoglycemia. It occurs due to the hyperinsulinemia of the fetus in response to the maternal hyperglycemia in utero. Hypoglycemia leads to more serious complications like severe central nervous system and cardiopulmonary disturbances. Major long-term sequelae include neurologic damage resulting in mental retardation, recurrent seizure activity, developmental delay and personality behavior disorders.

Neonatal Jaundice. Factors which may account for jaundice are prematurity, impaired hepatic bilirubin conjugation and increased enterohepatic bilirubin circulation resulting from poor feeding. In macrosomia, neonates have a high oxygen demand causing increased erythropoiesis and, ultimately, polycythemia. Therefore, when these cells break down, bilirubin levels increases resulting in neonatal jaundice.

Late Complications

Childhood Obesity and Metabolic Syndrome. GDM is a well documented risk factor. There are evidence of fetal reprogramming for late adiposity amongst offspring exposed to diabetes in utero. Pima Indian mothers with preexisting type II diabetes and GDM give birth to larger infants and theese children after the age of are heavier than the offspring of prediabetic or nondiabetic women[42]. The Exploring Perinatal Outcomes among Children (EPOCH) study correlated maternal GDM with a higher BMI, greater waist circumference, increased visceral and subcutaneous adipose tissue and centralized fat distribution pattern in 6- to 13-year-old multiethnic youth[43]. Moreover, teens exposed to maternal GDM in utero had an overall higher average of BMI growth from 27 months through 13 years of age and a higher BMI growth velocity starting at age of 10–13 years[44]. These findings suggest that the long-term effects of in utero GDM exposure are not obvious evident in early childhood, but instead emerge during puberty,

a period during which the development of obesity is to common. Offsprings of diabetic mothers are also susceptible to develop metabolic syndrome during adulthood with increased blood pressure, hyperglycemia, obesity and abnormal cholesterol levels with consequently increase the risk of heart disease, stroke and diabetes.

Management of Macrosomia

There are various recommendations for the management of macrosomia varying from expectant management and elective induction of labor before term to elective cesarean section for an estimated fetal weight of ≥ 4,250 g[45] or >4,500 g [46] depending on the study. Studies have shown that the chance of vaginal delivery is higher when spontaneous labor occurs than when labor is induced[47]. However, waiting strategy is an option limited by gestational age. As the gestational age exceeds 41 weeks, maternal and perinatal morbidity and mortality increase. Hence, timely intervention and induction is needed. The ACOG recommends prophylactic Caesarean section if fetal macrosomia with an EFW >5000 g in pregnant women without diabetes and >4500 g in those with GDM[48].

Early Labor Induction

After 37 weeks of gestation the fetus continues to grow 230 g/week[49] and elective induction of labor before or near term has been proposed to prevent macrosomia and its complications[50]. However, two factors should be assessed prior to the induction: the first is the fetal lung maturation. Fetuses with diabetic mother have been shown to have delayed lung maturity. Normally, the pulmonary maturation happens at a mean age of 34–35 gestational weeks. By 37 weeks, 99% of them are matured. However, the fetal lung under diabetic environment may not be mature until 38.5 weeks. The second factor is that the for a successful induction the Bishop score should be ≥ 6; otherwise, there is an increased chance of failure, which leads to a cesarean section[51]. In one study[52], the outcomes of suspected macrosomic infants of mothers who had expectant management versus elective induction of labor were compared. The rate of cesarean sections was found to be very high (57 vs. 31%) in those who were assigned to the electively inducted group. In some studies, elective induction of labor for macrosomia was found to increase the rate of cesarean delivery with no improvement to perinatal outcomes [47,53].

Elective Cesarean Section

Many studies suggest offering a cesarean section in women with macrosomic infants, especially in these with GDM, insulin-dependent diabetes and a previous high-birth-weight infant, so as to prevent maternal and fetal birth trauma. Unfortunately, measures to estimate fetal weight are inaccurate[54] . Besides that, it has been reported that in general population, it is arbitrary to perform elective cesarean sections to prevent brachial plexopathy[55].

Management of the Neonate

Large-for-gestational-age group include postterm infants and also term and preterm infants. This should be kept in mind as the management and the main concerns in treatment could differ. Neonates of a diabetic mother should undergo a careful physical examination for congenital anomalies(congenital heart defects, tracheoesophageal fistula and central nervous system abnormalities) and birth trauma. They should be observed properly for hypoglycemia, polycythemia, hyperbilirubinemia and electrolyte abnormalities. The blood glucose level should be examined within 1 h of life, then every hour for the next 6–8 h and then as needed. Oral feeding, ideally breast feeding, is recommended as soon as possible, and if oral feeding is insufficient, an intravenous infusion of glucose should be started[11,56].

Conclusion

Fetal macrosomia is an obstetric complication that affects 10% of all pregnancies and is associated with severe maternal-fetal complications such as maternal birth canal trauma, fracture of the clavicle, brachial plexus injury and perinatal asphyxia. Early identification of risk factors such as pre-gestational BMI, excessive weight gain during pregnancy, pre-gestational and GDM can allow the early application of measures to prevent adverse perinatal outcomes. The diagnosis of fetal macrosomia is based on 2D ultrasound formulae in which the EFW is >4000 g. Furthermore, 3D ultrasound could monitor the soft tissue allowing better prediction of birth weight than 2D ultrasound. Elective Caesarean section does not improve the perinatal outcomes in fetal macrosomia cases and induction of labour seems to be better than expectant management for the risk of shoulder dystocia.

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