MINIREVIEWS

What neonatal complications should the pediatrician be aware of in case of maternal gestational diabetes?

Delphine Mitanchez, Catherine Yzydorczyk, Umberto Simeoni

Delphine Mitanchez, Division of Neonatology, Department of Perinatology, Armand Trousseau Hospital, 75012 Paris, France
Catherine Yzydorczyk, Umberto Simeoni, Division of Pediatrics and DOHaD Laboratory, CHUV University Hospital and UNIL, 1011 Lausanne, Switzerland

Author contributions: All the authors made substantial contributions to conception and design of the review, made critical revisions and final approval of the version of the article to be published.

Conflict-of-interest: None.

Correspondence to: Delphine Mitanchez, MD, PhD, Division of Neonatology, Department of Perinatology, Armand Trousseau Hospital, 26 Avenue du Docteur Arnold Netter, 75012 Paris, France. delphine.mitanchez@trs.aphp.fr
Telephone: +33-1-44736191
Fax: +33-1-44736892

Abstract

In the epidemiologic context of maternal obesity and type 2 diabetes (T2D), the incidence of gestational diabetes has significantly increased in the last decades. Infants of diabetic mothers are prone to various neonatal adverse outcomes, including metabolic and hematologic disorders, respiratory distress, cardiac disorders and neurologic impairment due to perinatal asphyxia and birth traumas, among others. Macrosomia is the most constant consequence of diabetes and its severity is mainly influenced by maternal blood glucose level. Neonatal hypoglycemia is the main metabolic disorder that should be prevented as soon as possible after birth. The severity of macrosomia and the maternal health condition have a strong impact on the frequency and the severity of adverse neonatal outcomes. Pregestational T2D and maternal obesity significantly increase the risk of perinatal death and birth defects. The high incidence of maternal hyperglycemia in developing countries, associated with the scarcity of maternal and neonatal care, seriously increase the burden of neonatal complications in these countries.

Key words: Birth defects; Hypoglycemia; Respiratory distress; Preterm; Perinatal mortality; Type 2 diabetes; Obesity

Core tip: Increased mortality and morbidity are historically attributed to neonates of diabetic mothers. A discerning analysis of the literature shows that these adverse outcomes are uncommon among infants born from "pure" gestational diabetes mellitus (GDM) mothers, well managed during pregnancy. Macrosomia is the predominant adverse outcome and the main factor linked to neonatal complications. Poor maternal glycemic control, especially in the context of maternal type 2 diabetes and obesity increases the risk of all adverse neonatal outcomes, most strikingly the risk of perinatal mortality and birth defects. Developing strategies for screening and managing women with GDM must be encouraged notably in middle and low income countries and, also to limit the adverse effects on global health population in the future.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance of any degree with onset or first recognition during pregnancy. In high income countries, but also in middle and low income countries, because of the spreading of industrialized lifestyle, the incidence of obesity and type 2 diabetes (T2D) has dramatically increased, and subsequently the incidence of GDM[1].

In high-resource countries, progress has been made during the past fifty years regarding preconceptional care, screening and management of GDM. However, in low and middle-income countries, quality of antenatal care to detect and manage GDM, are often poorly available. As a consequence, the prenatal and neonatal burden of GDM may be paradoxically higher in these countries, although this point is not well documented[2].

Much of the currently available knowledge on the consequences of maternal diabetes on the offspring has been provided by studies on type 1 diabetes (T1D), while the risks related to GDM, which is much more frequent, need to be clarified in order to improve and to adapt neonatal management[3]. Moreover, extensive data suggest that the offspring of diabetic mothers is furthermore exposed to an increased risk of developing chronic, non-communicable diseases at adulthood[4].

Neonatologists are facing first-line this new epidemiologic setting. This review addresses the currently available knowledge on short term consequences of GDM in neonates and focuses on situations with increased risks of neonatal adverse outcomes.

SHORT TERM OUTCOMES

Macrosomia

Macrosomia is the most constant complication in GDM. The concept of excessive fetal growth is expressed either by the word "macrosomia" or by the expression "large for gestational age" (LGA). Macrosomia is defined by a birth weight (BW) of 4000 or 4500 g and more, depending on the authors. However, in this definition, gestational age (GA) is not taken into account. The term LGA corresponds to a BW $\geqslant$ 90th percentile or > +2SD (> 97th percentile) for GA. This definition allows premature newborns with excessive fetal growth to be identified. Macrosomia in newborns of diabetic mothers is characterized by excess body fat, an increased muscle mass and organomegaly, without increase in brain size.

The Pedersen-Freinkel's hypothesis, expressed sixty years ago, suggested that fetal overgrowth is related to increased transplacental transfer of maternal glucose, which stimulates the release of insulin by fetal pancreatic beta cells[5]. Insulin is a major factor of fetal growth and it up-regulates the Insulin-like Growth Factor (IGF) system, subsequently leading to fetal macrosomia. According to this hypothesis, different studies have characterized the link between maternal glycemia and neonatal macrosomia or fat mass[6,7].

The HAPO study showed a continuous, positive association between maternal glycemia, fetal hyper-insulinism and BW[8]. A linear and continuous relationship between body fat percentage in newborns, maternal glycaemia and fetal insulin levels has been found in this study[9]. More recently, other mechanisms that may also contribute to fetal overgrowth were evoked, like maternal metabolic environment and placental modifications[10]. In particular, maternal lipids availability and transport to the fetus may be enhanced in case of maternal diabetes[11].

Hence, all types of maternal diabetes are risk factors for macrosomia. As discussed below, macrosomia is *per se* a cause increased neonatal adverse outcome and this point emphasizes the importance of recognizing the excess of growth, even in preterm infants. Treatment of GDM significantly reduces the rate of macrosomia[12,13].

Preterm birth

A number of studies have reported an increased risk of preterm births in case of diabetes. However, data are not always available on the respective proportion of induced and spontaneous births, considering the increased maternal and fetal morbidity of diabetes during pregnancy. The benefits of early delivery to avoid fetal death or shoulder dystocia must be balanced against the morbidity linked to preterm birth, especially the respiratory morbidity.

The link between GDM and spontaneous preterm birth is still controversial. Hedderson *et al*[14] showed in a large cohort study that GDM was an independent risk factor for spontaneous preterm birth (RR = 1.42, 95%CI: 1.15-1.77). On the other hand, Yogev *et al*[15] found that the rate of spontaneous preterm delivery was not increased in GDM compared to non-GDM patients. Nevertheless, both studies found a relationship between higher glucose values in the oral glucose tolerance test (OGTT) or higher mean blood glucose levels and preterm birth.

Metabolic disorders

Hypoglycemia: The link between macrosomia, increased cord C-peptide levels that reflects fetal insulin secretion, and neonatal hypoglycemia has long been known. The data collected by the HAPO study confirmed this relationship: neonatal hypoglycemia was strongly associated with elevated cord serum C-peptide levels[16]. The infant of a diabetic mother is

at risk of transient hyperinsulinism, which prevents at birth the normal activation of metabolic pathways producing glucose and ketone bodies, and causes increased glucose consumption by tissues[17].

The exact incidence of hypoglycemia in case of maternal diabetes is difficult to assess due to the various definitions used for neonatal hypoglycemia in the literature. The rate of intravenously treated hypoglycemia was reported between 5% to 7% in two large studies[18,19]. Comparisons with the risk observed in healthy newborns are difficult also because monitoring of blood glucose at birth was different according to the mother was diabetic or not in most of the studies. At last, in many studies, blood glucose level in neonates is checked soon after birth, although the pathologic significance of low blood glucose levels immediately after birth, in the absence of specific symptoms, is still questioned. Indeed, an immediate fall in blood glucose concentration is observed after birth because of the interruption of placental supply, reaching a nadir between 1 and 2 h in healthy term infants[20]. Normal levels at this period cannot be distinguished from abnormal ones in asymptomatic infants and the incidence of hypoglycemia is likely to be overestimated[21]. From 3 h of age, blood glucose then rises spontaneously, even in the absence of any nutritional intake, due to the activation of metabolic regulatory pathways. Therefore, in the absence of abnormal clinical signs, the first blood glucose measurement is recommended after the second feed, which generally allows infants who cannot manage adequate early glucose homoeostasis to be identified[21].

There is currently no consensus on the indications for systematic glucose blood monitoring in asymptomatic infants born to diabetic mothers. It seems reasonable to consider that LGA or growth restricted infants (< 10th percentile) born to diabetic mother may benefit from blood glucose concentration check at 3 to 6 h intervals during the first day of life. On the other hand, normal-grown infants of mothers with diet-controlled GDM should not be monitored[22].

For newborns with no clinical signs, therapeutic intervention can be considered starting at a threshold value of 0.36 g/L (2.0 mmol/L). Early and frequent breastfeeding remains the key in preventing hypoglycemia, whatever the infant's BW, as far as he/she is able to feed autonomously. Therefore, infants of diabetic mothers should be kept aside their mother, in the absence of significant complications requiring a transfer to a special care neonatal unit. Even in mildly or moderately symptomatic infants with low blood glucose levels, sustained breastfeeding, or eventually formula supplements should be tried first, provided a satisfactory clinical response is obtained[22]. In case the infant is unable to feed, an IV glucose supplementation (3-6 mg/kg per hour) should be provided at constant rate of infusion, in order to avoid rebound hypoglycemia.

Hypocalcemia: Hypocalcemia can be defined by plasma calcium concentration below 2 mmol/L or ionized calcium concentration below 1.1 mmol/L, regardless of GA or BW. Transient neonatal hypocalcemia has been mainly reported in neonates of pregestational insulin dependent- diabetic mothers and may be partly related to maternal hypomagnesemia and subsequent fetal hypomagnesemia. The severity of hypocalcemia also appeared to be related to the severity of maternal diabetes, as calcium concentration in the neonates was negatively related to maternal HbA1c levels[23].

It seems that hypocalcemia is rarely of clinical significance, particularly in case of GDM, unless other complications are associated[24].

The mechanism is still unclear but seems to involve an abnormal calcium phosphorus metabolism during pregnancy with a decrease in calcium and vitamin D concentrations especially during the third trimester. Some studies have reported an association between GDM and low maternal vitamin D status, particularly with poor blood glucose control. Conversely, there are growing evidences that women who develop GDM are more likely to be vitamin D deficient[25]. Other factors like prematurity and perinatal asphyxia can contribute to low calcium levels[26].

Therefore, there is no indication to screen healthy baby for hypocalcemia and hypomagnesemia. When treatment is indicated, it consists to give oral vitamin D supplements and calcium gluconate orally or intravenously (40-60 mg/kg per day) and magnesium treatment according to plasma level.

Hyperbilirubinemia: Hyperbilirubinemia is more frequently observed in infants born to diabetic mothers. It is not a serious complication if non-toxic levels are diagnosed and treated, which is usually the case. The risk of nuclear icterus, the severe form of hyperbilirubinemia, is not reported in cases of diabetes as being more frequent. In the HAPO study, hyperbilirubinemia was weakly associated with maternal blood glucose levels[8]. Polycythemia could be one of the reasons, but additional mechanisms, such as preterm birth, poor liver conjugation are likely to be involved.

Hematologic disorders
It has been reported that infants of diabetic mothers may have polycythemia [hematocrit (Ht) higher than 65%]. Mechanisms evoked are reduced transplacental oxygen transport to the fetus and increased fetal oxygen consumption due to fetal hyperinsulinism. This may lead to fetal hypoxia and increased levels of fetal erythropoietin. However, no consistent correlation between plasma erythropoietin level and polycythemia has been reported in human. Increased insulin and IGFs levels can also increase red blood cells production. A strong positive correlation between maternal β-hydroxybutyrate levels and polycythemia was observed in a small observational study[27].

Normovolemic polycythemia seen in infants from diabetic mother can lead to hyperviscosity. Early symptoms are unspecific, feeding problems, plethoric aspect, acro-cyanosis, lethargy, hypotonia, respiratory distress, jitteriness and irritability, seizure (due to multiple cerebral infarcts), necrotizing enterocolitis, hyperbilirubinaemia and hypoglycemia have all been found associated. Polycythemia may also favor deep vessels thrombosis. Hypoglycemia may be aggravated in infants from diabetic mothers in case of polycythemia, due to increased glucose consumption by the increased red cell mass. Partial exchange transfusion with saline solution should be performed in symptomatic infants according to the formula (volume exchanged in mL): (Ht-55) x weight (kg) x 80/Ht.

Respiratory disorders

The rate and the risk of respiratory distress syndrome (RDS) in cases of GDM cannot be accurately established, due to insufficient precise data[28]. In a recent study from the French birth cohort in 2011, including 474 614 births, the risk for neonatal respiratory disorders was slightly but significantly increased in case of GDM [OR adjusted on mother's age and gestational age, 1.2 (1.1-1.3)] (personal data not yet published).

It is generally recognized that, besides RDS, infants born to diabetic mothers are exposed to increased risk of transient tachypnea of the newborn. This is more likely to happen after caesarian section due to delayed reduction of alveolar fluid at birth and when the infants have macrosomia. This was clearly showed in infants of T1D mothers[29].

Diabetes, but also maternal body mass index (BMI), is associated with a higher risk of persistent pulmonary hypertension (PPH). However, other independent risk factors like macrosomia and caesarean deliveries might be in the causal pathway between diabetes, overweight and PPH[30].

Cardiac disorders

Hypertrophic cardiomyopathy: Fetuses exposed to maternal hyperglycemia and hyperinsulinism, are prone to develop hypertrophic cardiomyopathy. It primarily affects the interventricular septum, but can extend to the myocardium in more severe cases[31].

Myocardial hypertrophy has been reported in both pregestational diabetes and GDM with a wide range of frequencies (between 25% to 75% of infants born to diabetic mothers)[32,33]. The incidence was lower in case of pure GDM comparing to pregestational diabetes[34]. The most recent studies showed that good maternal glycemic control does not entirely prevent interventricular septum hypertrophy and minor fetal cardiac function impairment, regardless of the type of diabetes[35,36]. Although myocardial hypertrophy is associated with an overall decrease in ventricular compliance and an increase in contractility of the left and right ventricles, it is most often asymptomatic. It can sometimes lead to severe morbidity and mortality,

according to the severity and the extension of cardiac hypertrophy. Major septal hypertrophy can lead to subaortic stenosis and secondary mitral insufficiency. It is usually considered that heart hypertrophy resolves anatomically within few months. However, the long term effect of diabetic cardiomyopathy on heart function remains to be elucidated.

Cardiac malformations: Some data supports that GDM carries a small but significantly increased of congenital defects (ORs between 1.1 and 1.3), but it is much lower than in women with pregestational diabetes[37]. The malformations described are similar to those reported in pregestational diabetes, especially cardiovascular defects and anomalies involving the musculo-skeletal and central nervous systems[38,39].

The most commonly reported cardiac malformations include transposition of the great arteries, double outlet right ventricle, truncus arteriosus, hypoplastic left heart syndrome and ventricular septal defects[40].

Antenatal ultrasounds play an important role in monitoring fetal cardiac anatomy and function. Antenatal diagnosis of cardiac malformation is helpful to decide the place of birth when specific neonatal cardiologic care is needed. Babies of women with GDM should have an echocardiogram in the presence of clinical signs at birth associated with congenital heart malformations (cyanosis, murmur) or cardiomyopathy (heart failure).

Neurological impairments

Infants of diabetic mothers are prone to neurologic impairments, mainly due to perinatal asphyxia, birth traumas and metabolic disorders.

Perinatal asphyxia: Increased risk of perinatal asphyxia has been reported in diabetic pregnancies in a number of studies. The risks of perinatal asphyxia are increased in case of macrosomia, particularly when there is a shoulder dystocia[28,41]. Impaired fetal environment characterized by fetal hypoxia has also been evoked as a contributing factor.

However, in cases of GDM, the incidence of perinatal asphyxia, defined by a 5-min Apgar score < 7, was very low (1%-2%) in a study including more than a thousand neonates of GDM mothers[18]. In another study, umbilical arterial pH < 7.2 was about 15% in GDM group, comparable to the non-diabetic group[42]. In both studies, the incidence was not influenced by the treatment of maternal diabetes.

Metabolic disorders: Glucose is the main energy substrate for the brain. In newborns, hypoglycemia can lead to the situation where brain energy metabolism cannot be sustained. The consequences of low blood glucose levels depend on the availability of other substrates, such as lactate and ketone bodies also used by the brain to provide energy. These alternative substrates are not routinely measured, and the normal

threshold values are unknown. Their availability also depends on the clinical and nutritional status of the infant.

For infants presenting with clinical signs compatible with hypoglycemia, like apnoea, hypotonia, jitteriness, apathy, hypothermia, tremors and seizures, treatment must ensure that blood glucose levels remain above 0.45 g/L (2.5 mmol/L). An IV bolus dose of glucose (150-200 mg/kg) should be administered urgently, followed by a constant rate infusion. It is necessary to check that thereafter blood glucose concentrations stabilize within normal ranges (20). In case of clinical signs, Cornblath *et al*[43] have suggested that the Whipple triad should be fulfilled: a low blood glucose concentration; signs consistent with hypoglycemia; and resolution of signs and symptoms after restoring blood glucose concentrations to normal values. Therefore, if symptoms persist despite adequate treatment, other causes should be investigated, since these symptoms are not specific.

Symptoms from hypocalcemia are similar to those observed in hypoglycemia, but usually present later, between 24-72 h of life[31]. Then, blood calcium concentration should also be measured in the presence of symptoms suggestive of hypocalcemia.

Brachial plexus injuries: The spinal cord is vulnerable to birth trauma with symptoms related to palsies of the brachial plexus.

The most common type of brachial plexus injury, also called Erb's palsy, involved the cervical roots C5 to C7. The infant presents with internally rotated arm and flexed wrist. The second most common type called total plexus palsy involves cervical roots C5-C8 and sometimes thoracic root T1. The infant presents with a flaccid and insensitive arm and with clawed hand. Paralysis of the hemi-diaphragm is also observed when phrenic nerve is involved, leading to respiratory insufficiency and requirement of mechanical ventilation[44].

Incidence of brachial plexus palsy in newborns of diabetic mothers is low, between 0.2% and 3%. As a consequence, the risk could not be accurately measured[28].

Poor suckling: It has been shown in the early nineties that maternal GDM may impair neonatal behavior, leading to lethargy and hypotonia related to delayed neural maturation. More recently, poorer suckling patterns were found at day 3 only among infants of insulin-managed GDM mothers, but not in the diet-managed mothers[45]. This study confirmed some degree of neurologic immaturity during the early neonatal period.

Digestive impairment
Apart from the difficulties to feed because of poor suckling pattern, neonates of diabetic mothers may also exhibit neonatal small left colon, a cause of functional lower intestinal obstruction that can mimic Hirschsprung disease. The pathophysiology is unknown but it is significantly associated with maternal diabetes. The treatment is always conservative as long as intestinal perforation does not happen. Contrast enema is both diagnostic (abrupt transition zone at the splenic flexure) and curative, promoting the evacuation of meconium relieving the intestinal obstruction[46].

FACTORS THAT INFLUENCE THE SEVERITY OF NEONATAL ADVERSE OUTCOME IN GDM
The adverse neonatal outcomes described above are not constant in all cases but they are significantly influenced by the quality of maternal care and by maternal health. Furthermore, most of these complications are more likely to happen in macrosomic infants.

Maternal conditions and neonatal outcomes
Impact of maternal blood glucose levels and pregestational T2D on neonatal outcomes: Perinatal death, malformations and prematurity are mainly influenced by maternal glucose levels. As discussed above, there is also a linear relationship between glucose maternal level and the frequency of macrosomia[8]. Furthermore, the analysis of the risk of fetal malformation and perinatal death in case of GDM shows that undiagnosed pre-pregnancy T2D has a substantial impact on these serious perinatal complications.

There is a relationship between the malformation rate and maternal fasting blood glucose level[39,47]. This risk also increases with maternal BMI, and when GDM is diagnosed during early pregnancy[48,49]. Most major malformations occur very early in gestation during the embryonic stage. In diabetic pregnancies, they are attributable to unstable periconceptional glycemia. Maternal hyperglycemia results in excess glucose metabolism in the developing embryo that may alter various molecular chain reactions: (1) altered cell lipid metabolism, notably the production of prostaglandin E2 involved in the patency of the ductus arteriosus in utero[50]; (2) high glucose levels induce an excess production of reactive oxygen species which has been shown to cause oxidative stress and subsequently increase the risk for fetal malformations, notably neural tube defect[51]; and also (3) high glucose levels induce the activation of many proteins involved in apoptotic cell death, including members of the caspase families[52]. Although data on the molecular basis of diabetic embryopathy have improved during the last years, mechanisms are still incompletely understood[53].

These clinical and physiopathologic data suggest that the increased risk of congenital defects in GDM reported in some studies is likely to be related to the inclusion of women with undiagnosed T2D in the GDM

groups[54].

Unlike in pregestational diabetes, the increased rate of fetal deaths in the 2nd and 3rd trimesters of pregnancy is debatable in cases of GDM[55,56]. In a large cohort study, the rate of mortality was 16.2/1000 in the GDM group *vs* 12.5/1000 in the general population. Six weeks after delivery, women diagnosed with GDM were re-classified by a post-partum glucose tolerance test. Women having diabetes on post-partum test were considered as "newly presenting T2D". When those women were excluded from the GDM group, perinatal mortality was 8.9/1000 in the "true" GDM group, which was similar to the general population. Mortality was the highest in the groups with T2D diagnosed before and after pregnancy (respectively, 39.1/1000 and 56.2/1000)[57]. These data demonstrated that the increased risk of perinatal death reported in case of GDM in some studies, seems to be attributable to undiagnosed T2D.

Prematurity is one of the leading causes of neonatal death. As discuss above, higher maternal glucose levels were observed in case of prematurity in GDM pregnancies. Furthermore, one of the main causes of induced preterm delivery is maternal pre-eclampsia which is more commonly associated with T2D pregnancies[58].

Impact of maternal obesity in the complications of GDM: Maternal obesity is associated with worse perinatal outcome even in glucose-tolerant women. Macrosomia is the main complication reported in overweight or obese women, independently of diabetes[59-62]. It is well recognized that neonates born to obese women, even if normal glucose tolerant, have increased fat mass[63]. As in GDM, increased adiposity at birth is related to maternal excess of glucose and lipids availability, and placental transfer to the fetus[11].

The risk of fetal and infant deaths are two to three times greater for women with preconceptional obesity, after excluding pregnancies affected by congenital anomalies or pregestational diabetes[64]. It was recently showed that even modest increases in maternal BMI were associated with increased risk of fetal death, stillbirth, and neonatal, perinatal, and infant death. The relative risk per 5-unit increase in maternal BMI ranged from 1.15 to 1.24[65]. Maternal obesity is also associated with an increased risk of a range of structural anomalies, with the higher risk for neural tube defects[66,67]. It is interesting to note that the risk of particular malformations such as omphalocele and diaphragmatic hernia is increased in obese pregnant women, but not in case of diabetes[68,69].

There is a tight link between maternal obesity and diabetes in pregnancy. Indeed, the risk of GDM increases with maternal BMI[70]. The overall population-attributable fraction of GDM related to overweight was estimated at 46.2%[71].

The benefit effect of treatment of diabetes on neonatal outcomes is lower in obese women, even

if targeted levels of glycemic control are achieved. Furthermore, when GDM is untreated or poorly controlled, overweight and obese women have a higher risk of poor neonatal outcome, compared to normal weight GDM women[42,72].

The combination of GDM and obesity shows a greater impact on pregnancy outcomes than either GDM or obesity alone. This cumulative risk was shown for macrosomia, newborn percent body fat and birth trauma[73]. It was also reported for a composite neonatal outcome (BW > 4000 g, birth trauma, shoulder dystocia, hypoglycemia, or jaundice)[74].

Effects of macrosomia on neonatal outcomes

It has long been reported that the delivery of macrosomic infants is associated with a higher risk for adverse neonatal morbidity such as birth injury, respiratory distress and hypoglycemia. Macrosomia (BW > 4500 g), regardless of the cause, is also in itself a risk factor for asphyxia and perinatal death[75].

Macrosomia increases the risk of shoulder dystocia, regardless of the cause. In the study by Zhang *et al*[75], the risk of birth injury was the highest for infants with a birth weight 4500-4999 g and $\geq$ 5000 g, [ORs 2.4 (2.2-2.5) and 3.5 (3.0-4.2), respectively].

In the case of GDM, there is a particularly high risk of respiratory distress in newborns with a BW $\geq$ 4000 g, compared to those with a BW of less than 4000 g [OR = 3.1 (1.11-8.65)][76]. In the other study, the risk of respiratory complications increased with increasing BW $\geq$ 4000 g, irrespective of maternal diabetic status[22]. Furthermore, it seems that clinically significant hypertrophic cardiomyopathy without concomitant fetal macrosomia is rarely observed[40].

The analysis of the data collected by the HAPO study showed that neonatal hypoglycemia was strongly related to elevated cord C-peptide levels. High C-peptide levels are related to the importance of fetal hyperinsulinemia that favors fetal excess of growth. Therefore, infants with excessive size at birth are prone to develop hypoglycemia[16]. It was shown that when BW was $\geq$ 4000 g the risk of hypoglycemia increased, but the risk was higher when BW $\geq$ 4000 g was associated with maternal GDM[76]. In another study, the risk of hypoglycemia increased with increasing BW, irrespective of maternal diabetic status[77].

SIZE OF THE BURDEN IN LOW INCOME COUNTRIES

The prevalence of risk factors for diabetes during pregnancy are increasing all around the world because of increasing incidence of T2D and obesity and the shift of age at onset of diabetes to younger age groups. T2D is an occult disease that can remain undiagnosed, especially in young women of reproductive age. A recent study reported an estimated global prevalence of hyperglycemia in pregnancy worldwide of 170/1000

live births in 2013. A majority of cases occurred in low and middle income countries (91.6%). The prevalence varies widely around the world. The South-East Asia region had the highest prevalence with 23% of live births, followed by the Middle East and North Africa region with 22%[78].

A community-based prospective program in India, with universal screening for GDM, showed that the prevalence of GDM was 13.9%. The frequency varied widely across urban, semi-urban and rural areas, respectively 17.8%, 13.8% and 9.9%. The prevalence also varied according to maternal BMI. For BMI $\geqslant$ 25 mg/m², the incidence was up to 28.4%, 23.8% and 16.1% in urban, semi-urban and rural areas, respectively[79].

A recent analysis of data from World Health Organization (WHO)'s Global Survey on maternal and perinatal outcomes in 23 developing countries described the prevalence of macrosomia, one of the main complications of maternal diabetes and obesity[80]. There was a large variation in the prevalence of babies with BW $\geqslant$ 4 kg, ranging from 0.5% in India, to 15% in Algeria. Maternal diabetes and increased gestational BMI were significantly associated with macrosomia in all regions. For example, in Algeria, where 15% of the babies had a BW $\geqslant$ 4 kg, 25% of the mothers were obese (BMI $\geqslant$ 30 kg/m²). In in Latin America countries, frequency of maternal obesity was more than 30% (Argentina, Mexico, and Paraguay).

It can then be estimated that the burden of neonatal complications is higher in developing countries than in high-income countries, because of the high incidence of maternal hyperglycemia and the absence of screening and treatment of maternal diabetes, and finally because of substandard neonatal care. This is probably even worst within the rural areas, because of limited financial and human resources.

CONCLUSION

It is indisputable that diabetes during pregnancy exposes the fetus and the neonates to increased adverse outcomes. These risks mainly depend on maternal health condition. Thus, awareness of maternal health prior and during pregnancy is essential to pediatricians to anticipate the severity of neonatal adverse outcome. Health systems in low income countries are often insufficiently structured to provide adequate screening and care to diabetic mothers. Such situations seriously increase the burden of adverse fetal and neonatal outcomes, probably still underestimated.

The current definition of GDM does not allow identifying pregestational diabetes from true GDM. The WHO recently proposed new criteria for the diagnosis and definition of hyperglycemia first detected in pregnancy which distinguishes the more serious diabetes in pregnancy from GDM[81]. This is a considerable advance as we say that risks of serious complications for fetuses and the neonates are much higher in true diabetes than in GDM. This will help to better understand the burden of hyperglycemia in pregnancy and its relationship with the growing prevalence of T2D. This will also probably allow in the future to determine precisely the risks linked to GDM compared to those linked to T2D. Such distinction will subsequently help better identifying risks in the neonatal period, but also later in life. Indeed, offspring of diabetic and obese women, or macrosomic infants, are more likely to be obese and to have diabetes and cardiovascular diseases in adulthood[3,4]. These long-term consequences of diabetes in pregnancy are going to be the burden of further generations.

REFERENCES

1   **Roglic G**. Diabetes in women: the global perspective. *Int J Gynaecol Obstet* 2009; **104** Suppl 1: S11-S13 [PMID: 19154995 DOI: 10.1016/j.ijgo.2008.11.022]

2   **Wang Z**, Kanguru L, Hussein J, Fitzmaurice A, Ritchie K. Incidence of adverse outcomes associated with gestational diabetes mellitus in low- and middle-income countries. *Int J Gynaecol Obstet* 2013; **121**: 14-19 [PMID: 23321368 DOI: 10.1016/j.ijgo.2012.10.032]

3   **Mitanchez D**, Burguet A, Simeoni U. Infants born to mothers with gestational diabetes mellitus: mild neonatal effects, a long-term threat to global health. *J Pediatr* 2014; **164**: 445-450 [PMID: 24331686 DOI: 10.1016/j.jpeds.2013.10.076]

4   **Simeoni U**, Barker DJ. Offspring of diabetic pregnancy: long-term outcomes. *Semin Fetal Neonatal Med* 2009; **14**: 119-124 [PMID: 19208505 DOI: 10.1016/j.siny.2009.01.002]

5   **Pedersen J**. Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol* (Copenh) 1954; **16**: 330-342 [PMID: 13206643]

6   **Ostlund I**, Hanson U, Björklund A, Hjertberg R, Eva N, Nordlander E, Swahn ML, Wager J. Maternal and fetal outcomes if gestational impaired glucose tolerance is not treated. *Diabetes Care* 2003; **26**: 2107-2111 [PMID: 12832321 DOI: 10.2337/diacare.26.7.2107]

7   **Ong KK**, Diderholm B, Salzano G, Wingate D, Hughes IA, MacDougall J, Acerini CL, Dunger DB. Pregnancy insulin, glucose, and BMI contribute to birth outcomes in nondiabetic mothers. *Diabetes Care* 2008; **31**: 2193-2197 [PMID: 18697902 DOI: 10.2337/dc08-1111]

8   **Metzger BE**, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358**: 1991-2002 [PMID: 18463375 DOI: 10.1056/NEJMoa0707943]

9   **HAPO Study Cooperative Research Group**. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 2009; **58**: 453-459 [PMID: 19011170 DOI: 10.2337/db08-1112]

10   **Vambergue A**, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. *World J Diabetes* 2011; **2**: 196-203 [PMID: 22087356 DOI: 10.4239/wjd.v2.i11.196]

11   **Catalano PM**, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? *Am J Obstet Gynecol* 2011; **204**: 479-487 [PMID: 21288502 DOI: 10.1016/j.ajog.2010.11.039]

12   **Falavigna M**, Schmidt MI, Trujillo J, Alves LF, Wendland ER, Torloni MR, Colagiuri S, Duncan BB. Effectiveness of gestational diabetes treatment: a systematic review with quality of evidence assessment. *Diabetes Res Clin Pract* 2012; **98**: 396-405 [PMID: 23031412 DOI: 10.1016/j.diabres.2012.09.002]

13   **Horvath K**, Koch K, Jeitler K, Matyas E, Bender R, Bastian

H, Lange S, Siebenhofer A. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* 2010; **340**: c1395 [PMID: 20360215 DOI: 10.1136/bmj.c1395]

14 **Hedderson MM**, Ferrara A, Sacks DA. Gestational diabetes mellitus and lesser degrees of pregnancy hyperglycemia: association with increased risk of spontaneous preterm birth. *Obstet Gynecol* 2003; **102**: 850-856 [PMID: 14551018 DOI: 10.1016/S0029-7844(03)00661-6]

15 **Yogev Y**, Langer O. Spontaneous preterm delivery and gestational diabetes: the impact of glycemic control. *Arch Gynecol Obstet* 2007; **276**: 361-365 [PMID: 17429669 DOI: 10.1007/s00404-007-0359-8]

16 **Metzger BE**, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, Halliday HL, Hennis AJ, Liley H, Ng PC, Coustan DR, Hadden DR, Hod M, Oats JJ, Trimble ER. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics* 2010; **126**: e1545-e1552 [PMID: 21078733 DOI: 10.1542/peds.2009-2257]

17 **Hawdon JM**. Babies born after diabetes in pregnancy: what are the short- and long-term risks and how can we minimise them? *Best Pract Res Clin Obstet Gynaecol* 2011; **25**: 91-104 [PMID: 21237719 DOI: 10.1016/j.bpobgyn.2010.10.005]

18 **Crowther CA**, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; **352**: 2477-2486 [PMID: 15951574 DOI: 10.1056/NEJMoa042973]

19 **Landon MB**, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; **361**: 1339-1348 [PMID: 19797280 DOI: 10.1056/NEJMoa0902430]

20 **Hay WW**, Rozance PJ. Continuous glucose monitoring for diagnosis and treatment of neonatal hypoglycemia. *J Pediatr* 2010; **157**: 180-182 [PMID: 20472249 DOI: 10.1016/j.jpeds.2010.04.007]

21 **Deshpande S**, Ward Platt M. The investigation and management of neonatal hypoglycaemia. *Semin Fetal Neonatal Med* 2005; **10**: 351-361 [PMID: 15922680 DOI: 10.1016/j.siny.2005.04.002]

22 **Mitanchez D**. Management of infants born to mothers with gestational diabetes. Paediatric environment. *Diabetes Metab* 2010; **36**: 587-594 [PMID: 21163423 DOI: 10.1016/j.diabet.2010.11.012]

23 **Demarini S**, Mimouni F, Tsang RC, Khoury J, Hertzberg V. Impact of metabolic control of diabetes during pregnancy on neonatal hypocalcemia: a randomized study. *Obstet Gynecol* 1994; **83**: 918-922 [PMID: 8190431 DOI: 10.1097/00006250-199406000-00003]

24 **Cordero L**, Treuer SH, Landon MB, Gabbe SG. Management of infants of diabetic mothers. *Arch Pediatr Adolesc Med* 1998; **152**: 249-254 [PMID: 9529462 DOI: 10.1001/archpedi.152.3.249]

25 **Alzaim M**, Wood RJ. Vitamin D and gestational diabetes mellitus. *Nutr Rev* 2013; **71**: 158-167 [PMID: 23452283 DOI: 10.1111/nure.12018]

26 **Mimouni F**, Loughead J, Miodovnik M, Khoury J, Tsang RC. Early neonatal predictors of neonatal hypocalcemia in infants of diabetic mothers: an epidemiologic study. *Am J Perinatol* 1990; **7**: 203-206 [PMID: 2372324 DOI: 10.1055/s-2007-999481]

27 **Cetin H**, Yalaz M, Akisu M, Kultursay N. Polycythaemia in infants of diabetic mothers: β-hydroxybutyrate stimulates erythropoietic activity. *J Int Med Res* 2011; **39**: 815-821 [PMID: 21819713 DOI: 10.1177/147323001103900314]

28 **Mitanchez D**. Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. *Diabetes Metab* 2010; **36**: 617-627 [PMID: 21163425 DOI: 10.1016/j.diabet.2010.11.013]

29 **Al-Agha R**, Kinsley BT, Finucane FM, Murray S, Daly S, Foley M, Smith SC, Firth RG. Caesarean section and macrosomia increase transient tachypnoea of the newborn in type 1 diabetes pregnancies. *Diabetes Res Clin Pract* 2010; **89**: e46-e48 [PMID: 20576305 DOI: 10.1016/j.diabres.2010.05.016]

30 **Hernández-Díaz S**, Van Marter LJ, Werler MM, Louik C, Mitchell AA. Risk factors for persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **120**: e272-e282 [PMID: 17671038 DOI: 10.1542/peds.2006-3037]

31 **Hay WW**. Care of the infant of the diabetic mother. *Curr Diab Rep* 2012; **12**: 4-15 [PMID: 22094826 DOI: 10.1007/s11892-011-0243-6]

32 **Veille JC**, Sivakoff M, Hanson R, Fanaroff AA. Interventricular septal thickness in fetuses of diabetic mothers. *Obstet Gynecol* 1992; **79**: 51-54 [PMID: 1727586]

33 **Oberhoffer R**, Högel J, Stoz F, Kohne E, Lang D. Cardiac and extracardiac complications in infants of diabetic mothers and their relation to parameters of carbohydrate metabolism. *Eur J Pediatr* 1997; **156**: 262-265 [PMID: 9128807 DOI: 10.1007/s004310050596]

34 **Ullmo S**, Vial Y, Di Bernardo S, Roth-Kleiner M, Mivelaz Y, Sekarski N, Ruiz J, Meijboom EJ. Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study. *Eur Heart J* 2007; **28**: 1319-1325 [PMID: 17158827 DOI: 10.1093/eurheartj/ehl416]

35 **Garcia-Flores J**, Jañez M, Gonzalez MC, Martinez N, Espada M, Gonzalez A. Fetal myocardial morphological and functional changes associated with well-controlled gestational diabetes. *Eur J Obstet Gynecol Reprod Biol* 2011; **154**: 24-26 [PMID: 20800336 DOI: 10.1016/j.ejogrb.2010.08.002]

36 **Chu C**, Gui YH, Ren YY, Shi LY. The impacts of maternal gestational diabetes mellitus (GDM) on fetal hearts. *Biomed Environ Sci* 2012; **25**: 15-22 [PMID: 22424622 DOI: 10.3967/0895-3988.2012.01.003]

37 **Balsells M**, García-Patterson A, Gich I, Corcoy R. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2012; **28**: 252-257 [PMID: 22052679 DOI: 10.1002/dmrr.1304]

38 **Aberg A**, Westbom L, Källén B. Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. *Early Hum Dev* 2001; **61**: 85-95 [PMID: 11223271 DOI: 10.1016/S0378-3782(00)00125-0]

39 **Schaefer-Graf UM**, Buchanan TA, Xiang A, Songster G, Montoro M, Kjos SL. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am J Obstet Gynecol* 2000; **182**: 313-320 [PMID: 10694330 DOI: 10.1016/S0002-9378(00)70217-1]

40 **Corrigan N**, Brazil DP, McAuliffe F. Fetal cardiac effects of maternal hyperglycemia during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2009; **85**: 523-530 [PMID: 19180650 DOI: 10.1002/bdra.20567]

41 **Anoon SS**, Rizk DE, Ezimokhai M. Obstetric outcome of excessively overgrown fetuses (& gt; or = 5000 g): a case-control study. *J Perinat Med* 2003; **31**: 295-301 [PMID: 12951884 DOI: 10.1515/JPM.2003.041]

42 **Langer O**, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. *Am J Obstet Gynecol* 2005; **192**: 989-997 [PMID: 15846171 DOI: 10.1016/j.ajog.2004.11.039]

43 **Cornblath M**, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000; **105**: 1141-1145 [PMID: 10790476 DOI: 10.1542/peds.105.5.1141]

44 **Zafeiriou DI**, Psychogiou K. Obstetrical brachial plexus palsy. *Pediatr Neurol* 2008; **38**: 235-242 [PMID: 18358400 DOI: 10.1016/j.pediatrneurol.2007.09.013]

45 **Bromiker R**, Rachamim A, Hammerman C, Schimmel M, Kaplan M, Medoff-Cooper B. Immature sucking patterns in infants of mothers with diabetes. *J Pediatr* 2006; **149**: 640-643 [PMID: 17095335 DOI: 10.1016/j.jpeds.2006.07.034]

46 **Ellis H**, Kumar R, Kostyrka B. Neonatal small left colon syndrome in the offspring of diabetic mothers-an analysis of 105 children. *J Pediatr Surg* 2009; **44**: 2343-2346 [PMID: 20006023 DOI: 10.1016/j.jpedsurg.2009.07.054]

47 **Sheffield JS**, Butler-Koster EL, Casey BM, McIntire DD, Leveno KJ. Maternal diabetes mellitus and infant malformations. *Obstet Gynecol* 2002; **100**: 925-930 [PMID: 12423854 DOI: 10.1016/S0029-7844(02)02242-1]

48 **Correa A**, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA, Cleves MA, Riehle-Colarusso TJ, Waller DK, Reece EA. Diabetes mellitus and birth defects. *Am J Obstet Gynecol* 2008; **199**: 237.e1-237.e9 [PMID: 18674752 DOI: 10.1016/j.ajog.2008.06.028]

49 **García-Patterson A**, Erdozain L, Ginovart G, Adelantado JM, Cubero JM, Gallo G, de Leiva A, Corcoy R. In human gestational diabetes mellitus congenital malformations are related to pre-pregnancy body mass index and to severity of diabetes. *Diabetologia* 2004; **47**: 509-514 [PMID: 14770278 DOI: 10.1007/s00125-004-1337-3]

50 **Schneider DJ**, Moore JW. Patent ductus arteriosus. *Circulation* 2006; **114**: 1873-1882 [PMID: 17060397 DOI: 10.1161/CIRCULATIONAHA.105.592063]

51 **Chang TI**, Horal M, Jain SK, Wang F, Patel R, Loeken MR. Oxidant regulation of gene expression and neural tube development: Insights gained from diabetic pregnancy on molecular causes of neural tube defects. *Diabetologia* 2003; **46**: 538-545 [PMID: 12739027]

52 **Zhao Z**, Yang P, Eckert RL, Reece EA. Caspase-8: a key role in the pathogenesis of diabetic embryopathy. *Birth Defects Res B Dev Reprod Toxicol* 2009; **86**: 72-77 [PMID: 19194987 DOI: 10.1002/bdrb.20185]

53 **Reece EA**. Diabetes-induced birth defects: what do we know? What can we do? *Curr Diab Rep* 2012; **12**: 24-32 [PMID: 22167469 DOI: 10.1007/s11892-011-0251-6]

54 **Allen VM**, Armson BA, Wilson RD, Allen VM, Blight C, Gagnon A, Johnson JA, Langlois S, Summers A, Wyatt P, Farine D, Armson BA, Crane J, Delisle MF, Keenan-Lindsay L, Morin V, Schneider CE, Van Aerde J. Teratogenicity associated with pre-existing and gestational diabetes. *J Obstet Gynaecol Can* 2007; **29**: 927-944 [PMID: 17977497]

55 **Dudley DJ**. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. *Obstet Gynecol Clin North Am* 2007; **34**: 293-307, ix [PMID: 17572273 DOI: 10.1016/j.ogc.2007.03.001]

56 **Silver RM**, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, Bukowski R, Carpenter M, Hogue C, Willinger M, Dudley D, Saade G, Stoll B. Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol* 2007; **196**: 433-444 [PMID: 17466694 DOI: 10.1016/j.ajog.2006.11.041]

57 **Cundy T**, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB. Perinatal mortality in Type 2 diabetes mellitus. *Diabet Med* 2000; **17**: 33-39 [PMID: 10691157 DOI: 10.1046/j.1464-5491.2000.00215.x]

58 **Melamed N**, Chen R, Soiberman U, Ben-Haroush A, Hod M, Yogev Y. Spontaneous and indicated preterm delivery in pregestational diabetes mellitus: etiology and risk factors. *Arch Gynecol Obstet* 2008; **278**: 129-134 [PMID: 18193440 DOI: 10.1007/s00404-007-0541-z]

59 **Ehrenberg HM**, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol* 2004; **191**: 964-968 [PMID: 15467573 DOI: 10.1016/j.ajog.2004.06.057]

60 **Jolly MC**, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2003; **111**: 9-14 [PMID: 14557004]

61 **HAPO Study Cooperative Research Group**. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG* 2010; **117**: 575-584 [PMID: 20089115 DOI: 10.1111/j.1471-0528.2009.02486.x]

62 **Owens LA**, O'Sullivan EP, Kirwan B, Avalos G, Gaffney G, Dunne F. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care* 2010; **33**: 577-579 [PMID: 20067952 DOI: 10.2337/dc09-0911]

63 **Sewell MF**, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Am J Obstet Gynecol* 2006; **195**: 1100-1103 [PMID: 16875645 DOI: 10.1016/j.ajog.2006.06.014]

64 **Tennant PW**, Rankin J, Bell R. Maternal body mass index and the risk of fetal and infant death: a cohort study from the North of England. *Hum Reprod* 2011; **26**: 1501-1511 [PMID: 21467206 DOI: 10.1093/humrep/der052]

65 **Aune D**, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA* 2014; **311**: 1536-1546 [PMID: 24737366 DOI: 10.1001/jama.2014.2269]

66 **Stothard KJ**, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009; **301**: 636-650 [PMID: 19211471 DOI: 10.1001/jama.2009.113]

67 **Rasmussen SA**, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neural tube defects: a metaanalysis. *Am J Obstet Gynecol* 2008; **198**: 611-619 [PMID: 18538144 DOI: 10.1016/j.ajog.2008.04.021]

68 **Watkins ML**, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics* 2003; **111**: 1152-1158 [PMID: 12728129]

69 **Waller DK**, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med* 2007; **161**: 745-750 [PMID: 17679655 DOI: 10.1001/archpedi.161.8.745]

70 **Torloni MR**, Betrán AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev* 2009; **10**: 194-203 [PMID: 19055539 DOI: 10.1111/j.1467-789X.2008.00541.x]

71 **Kim SY**, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes mellitus attributable to overweight and obesity. *Am J Public Health* 2010; **100**: 1047-1052 [PMID: 20395581 DOI: 10.2105/AJPH.2009.172890]

72 **Langer O**, Yogev Y, Xenakis EM, Brustman L. Overweight and obese in gestational diabetes: the impact on pregnancy outcome. *Am J Obstet Gynecol* 2005; **192**: 1768-1776 [PMID: 15970805 DOI: 10.1016/j.ajog.2004.12.049]

73 **Catalano PM**, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, Lowe LP, Trimble ER, Coustan DR, Hadden DR, Persson B, Hod M, Oats JJ. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care* 2012; **35**: 780-786 [PMID: 22357187 DOI: 10.2337/dc11-1790]

74 **Roman AS**, Rebarber A, Fox NS, Klauser CK, Istwan N, Rhea D, Saltzman D. The effect of maternal obesity on pregnancy outcomes in women with gestational diabetes. *J Matern Fetal Neonatal Med* 2011; **24**: 723-727 [PMID: 21366395 DOI: 10.3109/14767058.2010.521871]

75 **Zhang X**, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *Am J Obstet Gynecol* 2008; **198**: 517.e1-517.e6 [PMID: 18455528 DOI: 10.1016/j.ajog.2007.12.005]

76 **Esakoff TF**, Cheng YW, Sparks TN, Caughey AB. The association between birthweight 4000 g or greater and perinatal outcomes in patients with and without gestational diabetes mellitus. *Am J Obstet Gynecol* 2009; **200**: 672.e1-672.e4 [PMID: 19376489 DOI: 10.1016/j.ajog.2009.02.035]

77 **Das S**, Irigoyen M, Patterson MB, Salvador A, Schutzman DL. Neonatal outcomes of macrosomic births in diabetic and non-diabetic women. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**: F419-F422 [PMID: 19531522 DOI: 10.1136/adc.2008.156026]

78 **Guariguata L**, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract* 2014; **103**: 176-185 [PMID: 24300020 DOI: 10.1016/j.diabres.2013.11.003]

79 **Seshiah V**, Balaji V, Balaji MS, Paneerselvam A, Kapur A. Pregnancy and diabetes scenario around the world: India. *Int J*

Gynaecol Obstet 2009; **104** Suppl 1: S35-S38 [PMID: 19154999 DOI: 10.1016/j.ijgo.2008.11.035]

80   **Koyanagi A**, Zhang J, Dagvadorj A, Hirayama F, Shibuya K, Souza JP, Gülmezoglu AM. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* 2013; **381**: 476-483 [PMID: 23290494

DOI: 10.1016/S0140-6736(12)61605-5]

81   **World Health Organisation**. Diagnostic criteria and classification of hyperglycemia first detected in pregnancy. Geneva, Switzerland: World Health Organisation; 2013. Available form: URL: http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/