Diabetes in Pregnancy: Health Risks to the Mother, the Growing Fetus, and the Future Child

Shmuel Arnon MD[1,3] and Dorit Ravid MD[2,3]

Departments of [1]Neonatology and [2]Obstetrics and Gynecology, Meir Medical Center, Kfar Saba, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: congenital anomalies, gestational diabetes (GDM), infant of diabetic mother (IDM), neonatal hypoglycemia, pre-gestational diabetes (PGDM)

IMAJ 2020; 22: 578–581

Diabetes in pregnancy can be defined as gestational diabetes mellitus (GDM) or pre-gestational (pre-existing) type I or type II diabetes mellitus (PGDM). GDM is carbohydrate intolerance among women without prior diabetes that begins during pregnancy or is first recognized during pregnancy [1,2].

The prevalence of diabetes in pregnancy has increased worldwide in the last two decades. The increase is in parallel with the epidemic of obesity that has led to a rise in the incidence of both type II diabetes and GDM and a shift of the onset of diabetes to younger ages. Pregnancy is a potent metabolic stressor because of increased insulin resistance and the need for beta-cell adaptation. Therefore, it is not surprising that up to 70% of women with GDM will progress to diabetes during the next 22–28 years [1]. In the United States, diabetes is present in approximately 7% of all pregnancies; 86% of which are defined as GDM [2], in direct proportion to that of type II diabetes [3]. The prevalence of GDM also varies according to screening practices and diagnostic criteria [4].

In this issue of the *Israeli Medical Association Journal* (*IMAJ*), Riskin and colleagues [5] reported data on 526 women who gave birth in a single medical center (Bnai Zion Medical Center, Haifa) during 3 consecutive years from 2015 to 2017. The 5% incidence of diabetes in pregnancy reported in the study is within the range previously reported in the Israeli population [6,7]. The ethnic distribution in this cohort was representative of the general Israeli population, as 70% of the cohort was of Jewish ethnicity.

Diabetes confers significantly greater maternal and fetal risks compared to pregnancy without diabetes, largely related to the degree of hyperglycemia and to chronic complications of diabetes and its co-morbidities. Because GDM represents a milder form of glucose intolerance that usually begins during the second trimester of pregnancy, in women without co-morbidities (apart from obesity), the obstetrical outcome is better than it is among women with PGDM [1,2]. The nature and the prevalence of perinatal outcomes of GDM and PGDM, described by Riskin et al. [5] are comparable to those reported in other countries [1,4].

Maternal obesity often worsens impaired glucose tolerance. GDM and obesity are independently associated with adverse pregnancy outcomes, such as excessive fetal growth and pre-eclampsia. In women with GDM, appropriate weight gain can optimize outcomes, while excessive weight gain is associated with a significantly increased risk of a large for gestational age infant, preterm birth, and cesarean delivery [8,9]

The cohort described by Riskin et al. [5], did not include information on maternal baseline characteristics such as blood pressure, body mass index (BMI), or gestational weight gain, which might confound the incidence of perinatal outcomes, related to diabetes in pregnancy.

In 2008, the landmark, Hyperglycemia and Adverse Pregnancy Outcome study, a prospective, multicenter, blinded study of more than 23,000 pregnant women demonstrated a strong, continuous relationship between maternal glucose load and adverse outcome. There was a linear correlation between glucose levels at the 3-hour, 75 grams oral glucose tolerance test, and cesarean delivery, birth weight above the 90th percentile, neonatal hypoglycemia and fetal hyperinsulinemia. There was also a close correlation between glucose levels and the risk of pre-eclampsia, NICU admissions and shoulder dystocia [9].

Understandably, the management of women with GDM aims to attain the best possible glycemic control, with normal or near normal glucose values, while avoiding hypoglycemia. However, no controlled trials have been performed to identify optimal glycemic targets [1]. Therefore, controversy still exists worldwide regarding the criteria for GDM screening and diagnosis, as well as the best pharmacological treatment.

There is controversy regarding diagnosing GDM with either a one-step or two-step approach. The one-step approach consists of an oral glucose tolerance test with a 75-gram glucose overload that measures plasma glucose concentration at fasting state, 1 hour, and 2 hours after glucose administration. A positive result is defined as 1 blood glucose value above the target value at each interval (92, 180, 153 mg/dl, respectively) [10]. The two-step approach consists of a screening, non-fasting oral 50-gram glucose load, with blood glucose measurement 1 hour later. A positive result is defined as a blood

glucose value of 140 mg/dl or higher. A positive screening test is followed by a diagnostic test that consists of a 100-gram oral glucose load with glucose measurements at fasting and 1, 2, and 3 hours after glucose administration. A positive test is defined when higher blood glucose of the target values (95,180 155,140 mg/dl, respectively) is observed [1].

The Israeli Society of Obstetrics and Gynecology recommends a unique screening approach consisting of a one-step oral glucose tolerance test of 100 grams during the second trimester for women at high risk for GDM, and a two-step approach for women at low-risk [11].

Further randomized controlled trials are needed to decide whether adopting stricter guidelines will improve pregnancy outcomes.

Likewise, there is no consensus regarding management of GDM. Pharmacologic treatment is recommended when target glucose levels cannot be consistently maintained with diet and exercise. The two pharmacologic options for pregnant patients are insulin and the oral antihyperglycemic agents, metformin, and glyburide.

The American College of Obstetricians and Gynecologists (ACOG) and the American Diabetes Association prefer insulin for treating GDM [12] but also endorse the use of oral antihyperglycemic agents, primarily metformin. In contrast, the Society for Maternal-Fetal Medicine regards metformin as a reasonable first-line alternative to insulin [13]. Concerns have been raised regarding more frequent adverse neonatal outcomes (mainly macrosomia and neonatal hypoglycemia) with glyburide, as compared to insulin [14]. The Israeli Society of Obstetrics and Gynecology considers insulin, glyburide, and metformin as comparable options for treating GDM [11].

Riskin et al. [5] found a significant association between intrauterine fetal death or congenital anomalies and diabetes in pregnancy only among mothers with PGDM (12.8% vs. 4.4% and 3.2% in GDM and no GDM, respectively). Although no details regarding congenital anomalies are mentioned, several types, including facial, skeletal, and neural tube defects, are induced in the diabetic environment [4]. Dysmorphology of the cardiovascular and genitourinary systems and caudal agenesis or dysplasia syndrome are seen with markedly increased frequency in PGDM. Dysplasia syndrome consists of agenesis or hypoplasia of the femur in conjunction with agenesis of the lower vertebrae and sacrum. Research studies and animal experiments show that aberrations in intracellular conditions result in a variety of stressors, including oxidative, nitrosative, endoplasmic reticulum, and hexosamine. These changes induce apoptosis and alterations in genetic and epigenetic systems, resulting in dysmorphogenesis [15]. A significant decrease in congenital malformations has been reported with rigorous metabolic regulation in the peri-conception period [4], which may explain the findings of increased incidence of congenital anomalies in the presence of PGDM, in the current study.

Riskin et al. [5] found that 30% of the infants born to mothers with PGDM presented with symptomatic hypoglycemia, as compared to only 2.9% in infants of mothers with GDM and none in the control group [5]. Data from several studies showed that with rigorous management throughout pregnancy, infants of diabetic mothers (IDM) do not become hypoglycemic, and maintain normal glucose production and basal metabolism rates [4,7,16]. Intermittent hyperglycemia in the mother is seen more often in PGDM. It results in fetal hyperglycemia that causes hyperinsulinemia in the fetus; hence, fetal pancreatic islet and beta cell hypertrophy and increased insulin secretion. Because of the lack of significant transfer of insulin from the mother to the fetus in humans, insulin circulating in the fetal compartment is mostly of fetal origin. In addition, the fetus does not mobilize fatty acids from adipose tissue. As a result, circulating levels of free fatty acids remain low. This metabolic picture suggests persistent insulin action and lack of a counter-regulatory hormonal response. The latter is confirmed by the lack of an increase in circulating glucagon and catecholamine levels in IDM during hypoglycemia. The combination of hyperinsulinism and insufficient counter-regulation results in decreased hepatic glucose production, increased peripheral glucose uptake, and impaired lipolysis. Several of these metabolic and morphologic abnormalities can be reversed with fastidious diabetes management in the mother [16].

Riskin et al. [5] found that polycythemia (venous hematocrit > 65%) was more frequent in infants born to mothers diagnosed with diabetes in pregnancy, especially those born to mothers with GDM. However, 11.1% of infants with symptomatic polycythemia needed partial exchange transfusion. All were born to mothers with GDM [5]. Fetal hypoxia caused by increased hemoglobin glycation and reduced 2,3 DPG concentration, leads to increased erythropoietin and red blood cell mass, resulting in polycythemia [16].

They also observed that respiratory morbidity after delivery was significantly associated only with PGDM [5]. An explanation for this finding is that hyperinsulinemia, which is higher in PGDM, has been shown to suppress the production of lung surfactant; thus, predisposing the infant to respiratory distress syndrome after birth [10]. Transient tachypnea of the newborn is another common cause of respiratory distress in IDM, compared to normal neonates. Contributing factors are thought to be poor lung fluid clearance and increased rate of cesarean delivery.

Neonates of women with GDM are characterized by a disproportionate body composition, with a high birth weight relative to length and a high fat mass [17], reflected by increased ponderal index (100 × weight (grams) / height^3 (cm). This disproportion is thought to be the reason for the higher rate of shoulder dystocia observed among diabetic mothers, and is the justification behind the ACOG recommendation to schedule an elective cesarean delivery for fetuses estimated to weigh

over 4500 grams in GDM pregnancies, rather than 5000 grams in non-GDM pregnancies [18]. In the latest Israel Society of Obstetrics and Gynecology statement, 4250 grams is the upper cut-off limit for vaginal delivery trial among women with diabetes in pregnancy [11]. Indeed, Riskin et al. [5] also showed that macrosomia (birth weight > 4000 grams), is the most common medical indication for cesarean delivery in mothers with diabetes in pregnancy, when the risk of shoulder dystocia is high. In the current study, 68% of large for gestational age infants of mothers with diabetes in pregnancy were born by cesarean delivery.

At birth, these infants are obese, plethoric, and large for gestational age. They show evidence of excessive fat, as well as liver, spleen, and cardiac visceromegaly. Because the growth of the brain and possibly the kidneys are not dependent on insulin, these two organs are normal in size. Careful management of maternal metabolism tends to reduce the incidence of macrosomia, but does not prevent it entirely. Alterations in calcium and magnesium homeostasis occur in about 50% of infants born to insulin-dependent diabetic mothers. Unlike hypoglycemia, which happens immediately after birth, hypocalcemia becomes apparent 48 to 72 hours after birth. Plasma calcium concentrations lower than 7 mg/dl are frequently observed [16]. Hypocalcemia has been related to the severity and duration of maternal diabetes. In addition, it may be potentiated by prematurity and asphyxia. The mechanisms of hypocalcemia are probable failure of the IDM to mount an appropriate parathyroid hormone response, persistently high levels of calcitonin, and possible alterations in vitamin D metabolism [19]. Hypomagnesemia (< 1.5 mg/dl) has been observed frequently, as well. It is usually transient and its pathophysiologic significance remains uncertain. Both hypocalcemia and hypomagnesemia may manifest with jitteriness and may require supplemental calcium therapy. However, in most infants, they are transient events that improve spontaneously [16].

Septal hypertrophy and cardiomegaly are specific phenotypic consequences of diabetes in pregnancy and may manifest in heart failure in the neonate. Although Riskin et al. [5] found the rate of cardiomyopathy in infants born to mothers with PGDM to be higher than in GDM and control infants, it did not reach statistical significance, probably due to the small number newborns in the cohort who underwent echocardiography, as only symptomatic infants were evaluated. However, information from asymptomatic IDM revealed alterations in diastolic function and decreased passive compliance of the ventricular myocardium [7,19]. Serial evaluations of cardiac growth in utero in fetuses of diabetic mothers showed that despite good metabolic control, cardiac hypertrophy developed in late gestation (34–40 weeks). Although IDMs with septal hypertrophy may present with obstructive left heart failure, they may also be asymptomatic. Follow-up data show that cardiomyopathy in IDM is transient and usually disappears spontaneously within 6 months after birth [7]. A potential mechanism for hypertrophic cardiomyopathy in IDM is the finding that insulin inhibits expression of glycogen synthase kinase-3b, which down-regulates cardiac hypertrophy [20]. Other functional changes, such as impaired diastolic filling, have been reported in infants of mothers with gestational diabetes but are usually not clinically significant.

Delivery should take place in a hospital, where the newborn can be carefully monitored. Glucose values are checked during the first 3 hours after birth (typically between 30 and 60 minutes), sporadically before feedings, and any time symptoms are suspected. Feedings may be started as soon as the infant is stable, usually within 2–4 hours after birth, and continued at 3- to 4-hour intervals.

Even though physiologic and clinical data clearly demonstrate a marked decrease in fetal and neonatal morbidity and mortality in pregnancies with maternal diabetes, some studies failed to show that this goal was achieved in clinical practice [3,14,16,19]. Continuous, rigorous surveillance of diabetes throughout the pregnancy and fastidious management of metabolism are required.

CONCLUSIONS

The prognosis of IDM is dependent on improvements in antepartum care, fetal monitoring, rigorous control of maternal metabolism, and maternal education, all of which have resulted in reduced perinatal mortality and morbidity. In addition, control of maternal metabolism during the peri-conception period has resulted in a decreased incidence of congenital malformations in IDM. However, certain morbidities, such as premature birth, cesarean section deliveries, hypoglycemia, macrosomia, and polycythemia, persist. In addition, increased birth weight in IDM also increases the risk of type 2 diabetes mellitus and obesity phenotypes later in adult life because of fetal programming [16].

Correspondence

Dr. S. Arnon
Dept. of Neonatology
Meir Medical Center, Kfar Saba 44281, Israel
Phone: 972 53 748 2772
Fax: 972 9 747 1189
email: harnon@netvision.net.il

References

1. Gestational Diabetes Mellitus. *ACOG Practice Bulletin*, No. 190, Feb 2018: e49-e64.
2. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; 43 (Suppl 1): S183-92.
3. Correra A, Bardenheier B, Elixhauser A, Geiss LS, Gregg E. Trends in prevalence of diabetes among delivery hospitalization, United States, 1993-2009. *Matern Child Health J* 2015; 19: 635-42.
4. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. *Diabetes Care* 2014; 37 (6): 1590-6.
5. Riskin A, Itzchaki O, Bader D, Iofe A, Toropine A, Riskin-Mashiah S. Perinatal outcomes in infants of mothers with diabetes in pregnancy. *IMAJ* 2020; 22: 503-9.
6. Sella T, Shalev V, Elchalal U, Chovel-Sella A, Chodick G. Screening for gestational diabetes in the 21st century: a population-based cohort study in Israel. *J Matern Fetal Neonat Med* 2013; 26 (4): 412-6.

7. Leybovitz-Haleluya N, Wainstock T, Landau D, Sheiner E. Maternal gestational diabetes mellitus and the risk of subsequent pediatric cardiovascular diseases of the offspring: a population-based cohort study with up to 18 years of follow up. *Acta Diabetologica* 2018; 55: 1037-42.
8. Cheng YW, Chung JH, Kurbisch-Block I, Inturrisi M, Shafer S, Caughey AB. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. *Obstet Gynecol* 2008; 112 (5): 1015-22.
9. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. HAPO Study Cooperative Research Group. *N Engl J Med* 2008; 358 (19):1991-2002.
10. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. *Diabetes Care* 2010; 33: 676-82.
11. Nacum Z, Zafran N, Salim R, et al. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. *Diabetes Care* 2017; 40: 332-7.
12. Mack LR, Tomich PG. Gestational diabetes diagnosis, classification and clinical care. *Obstet Gynecol Clin N Am* 2017; 44: 207-17.
13. Society of Maternal-Fetal Medicine Publications Committee. SMFM Statement: Pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol* 2018; 218: B2.
14. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015; 350: h102.
15. Eriksson UJ, Wentzel P. The status of diabetic embryopathy. *Ups J Med Sci* 2016; 121: 96-112.
16. Nold JL, Georgieff MK. Infants of diabetic mothers. *Pediatr Clin North Am* 2004; 51: 619-37.
17. Ahlsson F, Lundgren M, Tuvemo T, Gustafsson J, Haglund B. Gestational diabetes and offspring body disproportion. Acta Paediatr 2010; 99: 89-93.
18. ACOG. Practice Bulletin No. 173: Fetal Macrosomia. *Obstet Gynecol* 2016; 128: e195-e209.
19. Mitanchez D, Yzydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother - Short- and long-term implications. *Best Pract Res Cl Ob* 2015; 29 (2): 256-69.
20. Hardt SE, Sadoshima J. Glycogen synthase kinase-3beta: a novel regulator of cardiac hypertrophy and development. *Circ Res* 2002; 90: 1055-63.

Capsule

Preventing protein truncation

A rare neurodegenerative disease called CLN3 Batten disease causes fatality by 20 to 30 years of age. The *CLN3* gene encodes a lysosome membrane protein subject to deletions in exons 7 and 8, which introduces a premature termination codon and truncates the resulting protein by 257 amino acids. **Centa** and colleagues developed an antisense oligonucleotide that restored most of the carboxyl-terminal part of the protein by inducing exon 5 skipping in messenger RNA processing. Injection of these oligonucleotides into the central nervous system of neonatal mice lacking *Cln3* exons 7 and 8 improved motor coordination and survival, indicating that even partial restoration of protein function can be therapeutically beneficial.

Nat Med 2020; 10: 1038/s41591-020-0986-1

Eitan Israeli

Capsule

How uromodulin helps flush out bacteria

Urinary tract infections (UTIs) are one of the most frequent bacterial infections in humans. The glycoprotein uromodulin is the most abundant urinary protein and can provide some protection from UTIs, but the precise mechanism has been unclear. **Weiss** and co-authors found that uromodulin forms stacked, fishbone-like filaments that act as a multivalent decoy for bacterial pathogens with adhesive pili that attach to the uromodulin glycans. The resulting uromodulin-pathogen aggregates prevent bacterial adhesion to glycoproteins of the urinary epithelium and promote pathogen clearance as urine is excreted. This innate protection against UTIs is likely to be particularly important in infants and children.

Science 2020; 369: 1005

Eitan Israeli

Capsule

A deeper look at cancer immunity

A key goal in oncology is diagnosing cancer early, when it is more treatable. Despite decades of progress, early diagnosis of asymptomatic patients remains a major challenge. Most methods involve detecting cancer cells or their DNA, but **Beshnova** et al. suggested a different approach that is focused on the body's immune response. The authors reasoned that the presence of cancer may cause alterations in the T cell receptor repertoire, which could then be detected. They designed a deep-learning method for distinguishing the T cell repertoires in the blood of patients with and without cancer, which they validated in samples from multiple clinical cohorts.

Sci Transl Med 2020; 12: eaaz3738

Eitan Israeli