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Maternal Obesity, Diabetic Pregnancy and Infant of a Diabetic Mother

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Abstract

Two major health care problems in the general population of industrialized countries like the United States and the United Kingdom are obesity and Adult Onset or Type 2 Diabetes Mellitus. The United Kingdom has the highest population obesity in Western Europe. Obesity in childhood and in women of childbearing age is also becoming a significant public health burden with negative short- and long-term economical impacts. In the United States, one third of the adult population is considered to be obese, with a body mass index (BMI) equal or greater than 30. According to the World Health Organization, this healthcare problem is on the rise even in developing countries like those found in the Middle East. A sedentary life style, Western diet and excessive food consumption are the principal causes for such a phenomenon.

Perinatal morbidity and mortality are significantly increased with pregnancies in obese and diabetic women. Diabetic women have increased co-morbidities during pregnancy, such as hypertension and preeclampsia; their infants have associated fetal and neonatal problems, such as the excessive occurrences of congenital anomalies, macrosomia, birth injuries, Respiratory Distress Syndrome, hypoglycemia and other clinically significant morbidities with long-term sequelae and increased mortality.

Based on current literature, this is an attempt to provide a review of the subject of obesity and diabetes mellitus, as well as the multitude of morbidities in infants of diabetic mothers, with emphasis on strategies for their diagnoses, prevention and therapy.

Epidemiology

Diabetes mellitus is a global public health problem with a projected 300 million diabetics by the year 2030 worldwide. In many areas around the globe, including the West as well as many developing and Middle Eastern countries, diabetes has become a major health burden affecting young adults and women in their reproductive years.[1]

According to the World Health Organization, the problem of population obesity is now a worldwide phenomenon. In US, approximately 1.5 million women of childbearing age have diabetes mellitus. With the current obesity epidemic in the United States, it is estimated that the rate of Type 2 Diabetes Mellitus, during pregnancy, will rise with the rate of obesity.

Obese women are at increased risk of developing gestational diabetes compared with women with a normal weight and BMI. A recent meta-analysis exploring the association between Gestational Diabetes Mellitus (GDM) and BMI estimated that the risk of developing GDM is two to four times higher among overweight and obese women respectively compared with normal-weight pregnant women.[2] A recent consensus statement by a European workshop group (an expert committee on women's health) stated that obesity is associated with increased risk of almost all pregnancy complications, such as: gestational hypertension, preeclampsia, gestational diabetes mellitus, delivery of a large for gestational age infant, increased rate of cesarean section delivery. Furthermore, a higher incidence of congenital defects occur more frequently than in women with a normal BMI.[3] Although it is not well-studied yet, maternal obesity may have an imprinting effect and epigenetic changes on the fetus resulting in childhood and adult obesity and diabetes mellitus.

Women who are overweight or obese during pregnancy and childbirth, as measured by increasing maternal BMI, are known to be at risk for significant antenatal, intrapartum, and postpartum and neonatal complications.[4-8]

Physiology of Maternal-Fetal Glucose Relationship

Pregnancy by itself is considered physiologically to be diabetogenic with relative carbohydrate intolerance, higher maternal plasma glucose level during pregnancy and relative insulin resistance. These physiologic changes related to elevated maternal plasma glucose occurs to provide higher glucose to the fetus, the latter being the main energy substrate for fetal metabolic demand and oxidative metabolism. However, glucose represents a quantitatively significant source of fetal energy (fuel); it probably does not supply enough carbon to support the total oxidative demands of fetal life.[9]

A pregnant mother provides a constant supply of glucose to the fetus. There is a linear relationship between the mother and fetal plasma glucose levels at maternal euglycemic and hyperglycemia. At low maternal plasma glucose (less than 4.4 mmol/L or 79 mg/dL), fetal plasma glucose may be even higher than maternal plasma glucose.[10] Glucose is transported across the placenta along a concentration gradient by a facilitated, carrier-mediated diffusion process.[11] Fetal plasma glucose is about 70-80% of maternal plasma glucose within significant range of maternal plasma glucose level. Endogenous production of glucose by the fetus is negligible even with low maternal plasma glucose levels.

Maternal diabetes, being a hyperglycemic state, will result in hyperglycemic state for her fetus. The fetal response to hyperglycemia is a higher production of insulin or hyperinsulinemia.

Diabetes Mellitus and Pregnancy

Transitory disturbances in glucose tolerance occur in 1 to 3% of all pregnancies defined as Gestational Diabetes Mellitus (GDM). The disturbance of glucose metabolism and GDM occurs more frequently in obese pregnant women. Gestational Diabetes Mellitus is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is associated with an increased risk of adverse perinatal outcomes.[12] The etiology of GDM is presumably based on common pathogenic mechanisms with Type 1 and Type 2 Diabetes Mellitus, with pregnancy triggering the manifestation of a glucose metabolism disorder. Therefore, GDM is a disease of pregnancy.

It is currently recommended that GDM be diagnosed in women with at least 2 plasma glucose values on a diagnostic 100-g, 3-hour oral glucose tolerance test (OGTT) that meet or exceed the thresholds recommended by the American Diabetes Association (ADA) of 2004. The 100-g, 3-hour OGTT is only performed in women with abnormal values (7.8 mmol/L) on a 50-g, 1-hour glucose challenge test screening.

The International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) used odds ratios of 1.75 relative to the cohort mean value for each time point in arriving at the following diagnostic criteria: fasting plasma glucose value of 5.1 mmol/L, 1-hour value 10.0 mmol/L, or 2-hour value 8.5 mmol/L. (I mmol is equal to about 18 mg/dL). In a recent publication by the Agency for Healthcare Research and Quality (US); 2008 May, the appropriate diagnosis for GDM is reviewed.[13]

There are two types of diabetes mellitus: Type 1 and Type 2. During pregnancy, 90% of diabetes is Type 2 and 10% are Type 1. According to the American Diabetes Association (2010), Type 1 diabetes results from pancreatic islet beta-cell destruction and usually leads to absolute insulin deficiency; and Type 2 Diabetes Mellitus results from a progressive insulin secretory defect with a background of insulin resistance.

A macrosomic newborn infant (birth weight 5300 g) born at term gestation to a mother with uncontrolled Class B diabetes mellitus. The newborn infant had severe and persistent hypoglycemia, a respiratory problem, and diabetes-related cardiomyopathy.

Classification of Diabetes During Pregnancy

For practical proposes, diabetes in the general population is classified as Type 1, previously called Juvenile Onset Diabetes; Type 2, commonly of Adult Onset. however, is being diagnosed in obese adolescent girls at an earlier age. The former requires insulin therapy, while the later may be managed with insulin in oral anti-hyperglycemic agents. In 2010, the Committee of the Japan Diabetes Society provided a comprehensive report on the epidemiology, classification, and diagnostic criteria for diabetes mellitus in the general population and during pregnancy.[14]

The following is a modified White classification of diabetes during pregnancy currently used in the United States:

- **CLASS A-1:** Abnormal one-hour post-50 g Glucola Test (Blood glucose >140 mg/dl) with normal fasting blood glucose (FBS< 95 mg/dL). Rx: Diet.
- **CLASS A-2:** Abnormal FBS (>95mg/dL) and 3 hours GTT. Rx: Diet and insulin.
- **CLASS B:** Insulin dependent diabetes. Onset: Age > 20 Years. Duration < 10 years; no significant vascular disease or retinopathy.
- **CLASS C:** Insulin dependent diabetes; onset: 10 to 20 years of age. Duration: 10 to 20 years; background retinopathy.
- **CLASS D:** Insulin dependent diabetes; onset < 10 years of age. Duration > 20 years with early and benign retinopathy and proteinuria.
- **CLASS F:** Class D plus clinically significant diabetic retinopathy and nephropathy.
- **CLASS H:** Class F with cardiomyopathy due to coronary artery disease.
- **CLASS R:** Class F with proliferative retinopathy (defined as legally blind).
- **CLASS T:** Pregnancy after renal transplant (renal failure secondary to diabetic complication).
- *CLASS E is CLASS D plus uterine artery calcification; it is not currently used.*

Perinatal Morbidity and Mortality

The perinatal mortality in mothers with Type 1 and Type 2 Diabetes Mellitus is four times higher, and the risk of congenital malformation in the babies of women with diabetes is nearly three times greater.[1,15,16] Perinatal outcome of diabetic pregnancy will depend on the management of maternal plasma glucose levels and maintenance of a tight control of diabetes by appropriate dietary management and insulin therapy. Additionally, chronic complications of diabetes mellitus, which are vascular diseases, will adversely affect perinatal morbidity and mortality.

Pregnancies complicated with diabetes mellitus should be considered "high risk" pregnancies. Diabetes mellitus increases maternal co-morbidities during pregnancy with significant increases also in fetal and neonatal morbidity and mortality. Maternal insulin requirement increases during the course of diabetic pregnancy. Fluctuation of maternal plasma glucose, hyperglycemia, and hypoglycemia occurs as the result of illness, poor and inappropriate dietary intake and medical management. As the result of poorly controlled diabetes during pregnancy, maternal ketoacidosis is more frequently encountered which may result in fetal loss.

Following are the list of perinatal morbidities associated with diabetic pregnancies:
1. Congenital Malformations
2. Increased pregnancy loss
3. Pre-eclampsia
4. Preterm birth
5. Intrauterine Growth Restriction
6. Macrosomia
7. Traumatic Delivery
8. Asphyxia/Hypoxia
9. Hypoglycemia
10. Hypocalcemia
11. Hypomagnesemia
12. Respiratory Distress Syndrome
13. Polycythemia
14. Hyperbilirubinemia
15. Renal Vein Thrombosis
16. Small Left Colon Syndrome
17. Myocardiopathy

Some morbidity from the above list will be discussed in more detail.

Diabetes and Congenital Malformations

Diabetes mellitus in pregnancy causes abnormal development of the embryo and fetus.[17] They have an increased risk of non-syndromic major congenital malformations that are well-established.[18] However, most babies born to women with diabetes mellitus do not have birth defects. An epidemiological study in Norway showed that among the 1,583 births by women with Type 1 Diabetes Mellitus, a total of 91 babies with congenital anomalies were identified. The proportion with congenital anomalies was 5.7% for mothers with diabetes compared to 2.9% in the background population.[19] In this study, the most frequently affected organ system in babies with anomaly within the diabetes group was the cardiovascular system, affected in more than half of the cases. Similar findings were also reported from an epidemiological study in Spain.[20] Although, in the latter study, neural tube defects (NTD) were more prevalent. Significant association was detected between risk of anomalies and duration of diabetes before giving birth.

For pregnant women with poor diabetic control, the risk for a baby to be born with birth defects is about 6-10%. For those with extremely poor control in the first trimester, there may be up to a 20% risk for birth defects. The most significant effect is early in pregnancy, possibly before a woman knows she is pregnant.[21] There is a strong association between elevated HbA1c at the beginning of pregnancy and major congenital anomalies in women with diabetes mellitus. Recent reports using the standardized assays confirm a strong association between HbA1c > 7.0 at the beginning of pregnancy and major congenital anomalies in infants of women with diabetes. Many investigators suggest that women with diabetes achieve HbA1c values as close to normal as possible before pregnancy.

Normal HbA1c during the first trimester of a normal pregnancy is 5.7 to 5.9.[22, 23]

Vitamins C and E intake reduces HbA1c level. Other factors are low serum Iron without anemia, abnormal hemoglobin and fetal Hb > 5%.

The recent American diabetes guidelines set a goal of achieving an HbA1c of less than 7.0% and 6.0% before and during pregnancy, respectively, for women with pre-gestational diabetes.

Types of Congenital Malformations

Almost any organ can be involved in malformations associated with maternal diabetes including the cardiac outflow tract, central nervous system, craniofacial, gastrointestinal, musculoskeletal, and urogenital systems.[24] Certain anomalies are often not detected until well after the neonatal period.

Molecular Mechanism of Central Nervous System Defects

The mechanisms behind the excess risk of congenital malformations are not known in detail. The results of the clinical and basic studies support the view of an early gestational induction of the malformations in diabetic pregnancy by a teratogenic process of multifactorial etiology.[25] Elevated maternal plasma glucose during embryogenesis causes specific gene alterations causing birth defects.[26,27] Hyperglycemia-induced oxidative stress and glyco-oxidative mechanisms are obviously important.[28]

It is known that levels of nitric oxide synthase (NOS) and nitric oxide are elevated in embryos of a mouse model of diabetes. Increased iNOS activity during organogenesis plays a crucial role in the pathogenesis of diabetes-induced malformations and suggests that inhibitors of iNOS might help prevent malformations, especially NTDs, in diabetic pregnancy.[29] Zhao Z. and associates[30,31] have recently provided an elucidation of the molecular mechanisms involved in NTD.

Their findings can be summarized as follow:
1. A failure in closure of the neural folds during the early stage of embryogenesis.
2. Cell death (apoptosis) in the neuroepithelium of the neural tube is a hallmark of maternal diabetes-induced NTD.
3. Caspase-8 (an enzyme: Cysteine Protease, 18 kD molecular weight protein) is an essential factor in hyperglycemia-induced embryonic malformations.
4. Caspase-8 can induce apoptosis through directly cleaving effectors caspases or stimulating the mitochondia/Caspase-9 (37 kD molecular weight protein) pathway.
5. Inhibition of Caspase-8 activity (by antibody) in mouse embryo, subjected to hyperglycemia, decreased the rate of NTD.
6. Molecular mechanisms for the development of other congenital anomalies have yet to be elucidated.

Preconception Care and Prevention of Congenital Malformations

Because major congenital malformations occur early in gestation and are associated with hyperglycemia, investigators have sought to determine whether intensification of diabetes treatment before conception and continued early in pregnancy would reduce the frequency of congenital malformations. Indeed, preconception care is effective in reducing diabetes-related congenital malformations, preterm delivery and maternal hyperglycemia in the first trimester of pregnancy.[5, 32-35]

Women with diabetes mellitus should achieve HbA1c close to normal at conception and early pregnancy in order to reduce major congenital malformations.

Multiple international organizations (NIH, ADA, and IHCE) recommend that preconception care for women with diabetes, designed to avoid teratogenic substances and stabilize nutrient intake, metabolism, and glycemic control, should be used to reduce an adverse pregnancy outcome.

Difficult Task

As noted so well, by Kitzmiller JL, et al,[35] the most challenging issues regarding intensified preconception care of women with diabetes are how to get more women to participate and use effective family planning methods, including those in the population groups at highest risk of developing diabetes, and how to achieve a sufficient level of glycemic control and nutrient intake in women with diabetes who do not plan their pregnancies.

Spontaneous Abortions

The majority of spontaneous abortions occur during the first trimester of pregnancy. Its incidence is greater in diabetic pregnancies compared to normal pregnancies.[36, 37] Spontaneous abortions appear to correlate with the degree of maternal diabetic control, as its incidence is greater with maternal hyperglycemia, poor diabetic control and vasculopathy.[38] Indeed, pregnant patients with long-standing diabetes with high HbA1c have poor perinatal outcome including increased miscarriages.[39] Conversely, recent reports demonstrate a normalization of miscarriage rate with good glycemic control during conception and the first trimester of pregnancy.[40]

Preterm Labor

The incidence of preterm labor and low birth weight infants is more prevalent in diabetic pregnancies.[41,42] Their incidence is increased with poor glycemic control, increased incidence of urinary tract infection in pregnant diabetic mother and a higher incidence of pre-eclampsia associated with diabetic pregnancies.[43] A retrospective study of 482 cases of diabetic pregnancies, during a 13-year period from Japan, showed the rate of preeclampsia to be 25.8%, and the incidence of preterm delivery was 16.6%.[44] Preterm newborn infants from diabetic pregnancies have a higher incidence of Respiratory Distress Syndrome, as well as other morbidities.

Intrauterine Growth Restriction

There is an increased likelihood of pre-eclampsia among diabetic mothers, leading to vasoconstriction, decreased maternal blood volume and decreased placental perfusion. Additionally, intrauterine fetal growth restriction occurs in mothers with long duration of diabetes and vasculopathy.[45,46] As is well-known, a long-term complication of diabetes is vascular disease that affects all organ systems including uterine arteries with decreased utero-placental perfusion.

Fetal Macrosomia

Large for Gestational Age (LGA) and Macrosomia are more frequent in Class A-2, Class B and Class C Diabetic women.

Macrosomia is defined when fetal or neonatal weight is > 4500 g, irrespective of gestational age (American College of Obstetrics and Gynecology or ACOG). In tandem with the increase of obesity, the incidence of fetal macrosomia has been increasing in the West, as well as in developing countries.[47-51]

Fasting plasma glucose demonstrates the most pronounced, linear increase in the risk of LGA across categories of plasma glucose.[52, 53] Skipper (1933) first hypothesized that excess adipose tissue in the infant of a diabetic mother (IDM) resulted from maternal hyperglycemia. Later, Pedersen (1954) proposed that IDM's accelerated growth resulted from fetal hyperglycemia. Fetal hyperglycemia, in turn, causes the fetus to produce higher amount of insulin (hyperinsulinemia). This phenomenon is referred to as "Pedersen Hypothesis," which is maternal hyperglycemia, fetal hyperglycemia, fetal pancreatic beta-cell hyperplasia, and fetal hyperinsulinemia.

Insulin is a mitogenic and growth factor for the fetus resulting in higher fetal body fat and protein deposition. Other hormones and growth factors are also involved in diabetic fetal overgrowth. They are Placenta Growth Hormone (a 22 kDa protein), Insulin-Like Growth Factor-I; Insulin-Like Growth Factor-II; Insulin-Like Growth Factor Binding Protein-3. Prenatally, Pituitary Growth Hormone does not appear to play a significant role in regulating fetal growth.

Body weight distribution of fetal macrosomia in diabetic pregnancy differs from macrosomic fetus of non-diabetic pregnancy or constitutional macrosomia of large and tall women. We have described these body characteristics about 3 decades ago, which was also recently confirmed.[54, 55] We found that the shoulder size to head circumference is significantly greater in macrosomic infant of a diabetic mother compared to the macrosomic fetus of non-diabetic mother.[43] This phenomenon explains the higher incidence of difficult vaginal delivery and shoulder dystocia in diabetic pregnancies.

Difficult Delivery and Shoulder Dystocia

Although macrosomia can be suspected in diabetic pregnancy, the accurate assessment of fetal weight and particularly anthropometric disproportion, shoulder to head circumference, cannot be accurately assessed by current clinical assessment or obstetrical ultrasound. Many assessment tools and formulas have been devised but none achieved good sensitivity or specificity. As the ACOG Practice Bulletin, number 22 of November 2000 states: "An accurate diagnosis of macrosomia can be made only by weighing the newborn after delivery."

We have previously reported that a macrosomic fetus' tolerance to labor is not different from that of a normal-size fetus. Associated clinical problems with fetal macrosomia occur with the process of delivery.[56] A macrosomic fetus is at the highest risk when birth weight is greater than 4300 – 4500 grams. The incidence of shoulder dystocia in diabetic pregnancy versus non-diabetic pregnancy is summarized from a study by Nesbitt TS, et al.[57]

The consequences of difficult delivery and shoulder dystocia are maternal post-partum hemorrhage and vaginal lacerations. Fetal and neonatal problems are shoulder dystocia resulting in asphyxia and central nervous system injury, brachial plexus injury, phrenic nerve paralysis, and clavicular and humeral fractures.

Incidence of Shoulder Dystocia in Large for Gestational Age and Macrosomic infants of Non-Diabetic and Diabetic Mothers in 1992 in California.[57]			
Number of deliveries: 175,886 Vaginal Births > 3,500 g birth weight (BW) Incidence of shoulder dystocia: 6,238 (3%)			
		Non-Diabetic	**Diabetic**
BW:	4,000 to 4,250 g	5.2%	12.2%
BW:	4,250 to 4,500 g	9.1%	16.7%
BW:	4,500 to 4,750 g	14.3%	27.3%
BW:	4,750 to 5,000 g	21.1%	34.8%
Shoulder Dystocia increased by 35% to 45% in Vacuum or Forceps assisted births.			

It is important to note that when shoulder dystocia is suspected, obstetricians should avoid using instruments such as forceps or vacuum extractor to effect vaginal delivery.

Birth Related Asphyxia/Yypoxia

Birth asphyxia and hypoxia with low Apgar scores are of common occurrence in the infant of a diabetic mother.[58, 59] The fetus in a diabetic pregnancy has hyperglycemia and hyperinsulism causing fetal hypermetabolic state and relative fetal hypoxia. Additional factors are: prematurity, intrauterine growth restriction, cesarean section delivery, difficult delivery, shoulder dystocia, instrumentations, and diabetic-related maternal vas-

cular disease. Improved maternal glycemic control has lowered the incidence of birth-related asphyxia and hypoxia.

Neonatal Hypoglycemia

At birth, with the cessation of continuous diffusion of maternal glucose, until feedings have been established, the newborn infant has to rely on endogenous production of glucose for his/her energy demands. In the normal newborn, there is a surge of epinephrine, norepinephrine, glucagon, thyroid hormone and a physiologic decline of plasma insulin. Initially, the energy demand is greater than endogenous production of glucose therefore, plasma glucose concentration declines after birth. The nadir of plasma glucose occurs between 30 to 90 minutes of life and then rises spontaneously, so plateau levels are reached between 2 and 6 hours.

A normal pattern of glucose homeostasis is dependent on maternal glucose during labor and before delivery, i.e., if mother received IV glucose. After the initial decline in plasma glucose, in the first 6 hours of life, a healthy full-term neonate maintains plasma glucose between 40 and 80 mg/dL.

The "normal" range of blood glucose varies for each newborn dependent on birth weight, gestational age, and body glycogen stores, feeding status, presence or absence of disease. The pattern of glucose homeostasis soon after birth is different in the infant of the diabetic mother (IDM). The rate of drop in plasma glucose after birth in IDM is dependent on the maternal status of diabetic control, neonatal blood glucose level at birth, and fetal hyperinsulinemia. The incidence of hypoglycemia in an IDM, despite a large store of hepatic glycogen, is much greater. Within 1-2 hours after delivery, hypoglycemia occurs in 20 to 40% of IDMs.

Although it is very difficult to achieve maternal euglycemic control during diabetic pregnancy, a tight control of maternal plasma glucose with an appropriate regimen of maternal diet and medical management, the incidence of hypoglycemia during the first few hours of life can be significantly decreased. In a review of 211 infants of insulin-dependent diabetic mothers, whose diabetes was tightly controlled during the second and third trimester of pregnancy, and their infants' plasma glucose was monitored on an hourly basis for the first 6 hours of life, the incidence of hypoglycemia was about 10% (authors' unpublished data).

Definition of Hypoglycemia

The definition of hypoglycemia remains controversial. One definition is that the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ. Alternatively, an operational threshold for hypoglycemia is that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature.

For practical purposes, newborns < 24 hours old with plasma glucose < 40 mg/dL and newborns > 24 hours old with plasma glucose < 50 mg/dL should be considered hypoglycemic and evaluated.

Other proposed definitions are plasma glucose < 25 mg/dL in the low birth weight and < 35 mg/dL in the plasma of the term infant up to 72 hours of age. After 72 hours, plasma glucose concentration should be at least 45 mg/dL. Some even suggest plasma glucose level of 30 mg/dL in the first 24 hours and 45 mg/dL in the second 24 hours in

Term newborn infants or two consecutive plasma glucose < 40 mg/dL at any time. The controversies about the definition of neonatal hypoglycemia, the lowest level of blood or plasma glucose, the duration of hypoglycemia, its symptomatology, lack of scientific studies regarding the level of hypoglycemia and central nervous system injury, and the algorithm for the treatment of neonatal hypoglycemia was recently published by the Committee on Fetus and Newborn of the American Academy of Pediatrics.[60]

Signs and Symptoms of Hypoglycemia

Traditionally, hypoglycemia has been defined as symptomatic and asymptomatic.

This distinction is confusing and has no physiological basis. An IDM could be hypoglycemic, but without obvious clinical signs or symptoms. As James Farquhar, a noted British physician, described in 1950's, an IDM appears plethoric and overfed. At a closer look, he/she is not breathing. Non-specific signs and symptoms not unique to hypoglycemia, are changes in levels of consciousness, irritability, lethargy, stupor, apnea, cyanotic spells, poor feeding, hypothermia, hypotonia, limpness, tremor, tachypnea, cyanosis, abnormal cry, seizures and coma.

Diagnosis of Hypoglycemia

Repetitive blood glucose monitoring and rapid treatment even for mild hypoglycemia is recommended for infants in the neonatal period.

To establish the diagnosis of neonatal hypoglycemia some clinicians advocate Whipple's triad, which is:
1. The presence of characteristic clinical manifestations
2. Coincident with low plasma glucose concentrations measured accurately with sensitive and precise methods, and
3. That the clinical signs resolve within minutes to hours once normoglycemia has been reestablished.

Procedure

Serial blood glucose determinations by glucose oxidase methods (oxidase reagent strip i.e. Chemistrip), every 1/2 to 1 hour for the first 4 to 6 hours, or until adequate oral intake has been established is recommended.

If blood glucose is < 40 mg/dl, for confirmation, send blood sample immediately to the lab for plasma glucose determination. A blood sample should be collected in a tube containing a glycolytic inhibitor such as fluoride and the sample should be analyzed as soon as possible.[60] Plasma glucose, done simultaneously with blood glucose determination, is 10 to 18% higher than the latter.[60]

Treatment should be provided based on the Chemistrip value. Do not wait for laboratory results.

Treatment

Severe glucose deficiency leads to cerebral energy failure, impaired cardiac performance, muscle weakness, glycogen depletion, and diminished glucose production.[61] Because of long-term pathological sequelae of the central nervous system as the result of persistent hypoglycemia, prompt diagnosis of hypoglycemia and

its appropriate treatment in a timely manner should be accomplished.[62, 63]

The following treatment plan is recommended. When blood glucose values, by Chemistrip, is 25 to 40 mg/dl, if there is no cardio-respiratory problem, give by nippling and/or gavage, 1 ounce of mixed formula/glucose water (D10W).

Blood Glucose Should be Re-Checked 15 - 20 Minutes Later

For the treatment of blood glucose value < 25 mg/dl give D10W, administer 200 mg/kg, by slow IV push (2 ml of D10W/ Kg of body weight) followed by IV fluid with D10W at a rate of 5 - 6 mg/kg/min. (72 - 80 ml/Kg/day). Monitor blood glucose frequently until stable and resume oral feeding, if infant's condition is stable. Once adequate feeding has been established and blood glucose is in normal range by two consecutive determinations, wean IV glucose accordingly.

Corticosteroids

Corticosteroid should be used only if hypoglycemia persists after 2-3 days of glucose infusion more than 12 mg/kg/min. Determination of plasma insulin level is recommended. Hydrocortisone should be given at 5 mg/kg/day, IV, BID. Alternatively, Prednisone at 2 mg/kg/day, PO may be appropriate. Glucagon 0.2 to 0.3 mg/kg per dose, IV, IM or SQ also has been advocated, however, it should not be used in infants with decrease glycogen stores, i.e., Preterm or IUGR.

Respiratory Distress Syndrome

The infant of a diabetic mother is more significantly affected by respiratory distress than the infant of a mother with a healthy pregnancy. Infants of diabetic mothers are frequently hyperinsulinemic and have an increased incidence of neonatal Respiratory Distress Syndrome (RDS), a disease caused by a deficiency in the production of pulmonary surfactant by alveolar type II cells. It has been hypothesized that insulin inhibits fetal lung type II cell differentiation.[64] Surfactant lines alveoli, decreases surface tension, increases lung compliance, and prevents alveolar collapse. Respiratory Distress Syndrome is the most common cause for respiratory failure in an IDM, particularly those born at preterm gestation.

Fetal hyperinsulinemia causes delayed maturation of pulmonary surfactant production particularly phosphatidylglycerol (PG), a stabilizing alveolar surfactant. Ojomo and Coustan[65] showed that a significant proportion (approximately 21%) of those with gestational diabetes were PG-negative as late as 38 weeks' gestation. A similar proportion of overt diabetic patients were PG-negative as late as 39 weeks' gestation. Therefore, amniocentesis for the presence of PG is recommended when contemplating cesarean section in a diabetic mother. A lecithin to sphyngomyelin ratio of 2.5 rather than 2.0 may indicate fetal lung maturity in diabetic pregnancy.

The preponderance of evidence indicates that rigid maternal glucose control during pregnancy will minimize the incidence of all morbidities in IDM, including RDS.[66] Antenatal management of the diabetic mother to prevent RDS, neonatal diagnosis and management of RDS in the IDM is beyond the scope of this writing.

Hypocalcemia/Hypomagnesemia

Hypocalcemia may occur up to 50% of IDM. The rate of hypocalcemia is dependent on the duration and the severity of maternal diabetes, preterm birth, and birth asphyxia. It is postulated that hypocalcemia in IDM is related to low levels of parathyroid hormone as possible mechanism. Contrary to hypoglycemia, which occurs early, hypocalcemia is generally detected by 24 to 72 hours of life. Serum total calcium of <7mg/dL, ionized Ca<4mg/dL is considered to be diagnostic. The infant is mostly asymptomatic, but can present with jitteriness, lethargy, apnea, tachypnea, and seizures. For its management one should monitor serum Ca

after the first day of life. Most cases of hypocalcemia may resolve with feedings; however, therapy with calcium gluconate should be given to neonates with symptoms.

The incidence of hypomagnesemia is less than hypocalcemia, and will resolve with feeding and rarely require treatment unless adequate oral feeding cannot be established, and the infant is receiving total parenteral nutrition.

As like other morbidities in IDM, strict glycemic control during pregnancy the occurrence of hypocalcemia and hypomagnesemia can be minimized.[66]

Polycythemia/Hyperbilirubinemia

Polycythemia is a frequent finding in the IDM. Its pathophysiology is related to fetal hyperinsulinemia, fetal hypermetabolic state and chronic fetal hypoxia resulting in up-regulation of fetal erythropoietin and excessive hematopoiesis. It occurs more frequently with poor maternal glycemic control, and fetal macrosomia. It may further be exaggerated by the chronic intrauterine hypoxia in mothers with diabetic vascular disease. Its occurrence in an IDM has been reported to be 13-33%. Polycythemia (Hematocrit > 65%) may be associated with hyperviscosity, vascular slugging, ischemia, and infarction. It is recommended that the Hematocrit be measured within 12 hours after birth. The infant should be well-hydrated with adequate glucose intake. In symptomatic infants, due to polycythemia, partial exchange transfusion should be carried out.

Irrespective of blood group incompatibility, hyperbilirubinemia occurs in 11-29% of IDMs. The risk factors are polycythemia and prematurity. Its pathophysiologic mechanism is an increased hemolysis, possibly due to glycosylation of erythrocyte membranes, and increase in RBC numbers.[67, 68] Serum bilirubin should be monitored based on clinical and laboratory appraisal and treatment should be instituted with phototherapy and exchange transfusion if need be.

Renal Vein Thrombosis

Renal vein thrombosis is a rare clinical entity. Most of the literature on this subject is individual case reports.[69, 70, 71] It is more frequent in male than female infants. The majority of cases are unilateral with left side predominance. An IDM, particularly those with polycythemia, hyperviscosity, asphyxia and prematurity are more prone to renal vein thrombosis.[72]

Hypercoagulable states may be an important risk factor. Embolization of the thrombi to other organs and limbs has also been reported.[73, 74]

Recommended therapeutic management is observation, heparin therapy, thrombectomy under real-time ultrasound guidance and surgical removal of the affected kidney.

Small Left Colon Syndrome

Neonatal Small Left Colon Syndrome (SLCS) is the most common cause of intestinal obstruction in offspring of diabetic mothers.[75] It is due to a functional disorder of the lower colon, which produces typical signs, and symptoms of intestinal obstruction.[76]

Forty to 50% of reported cases occur in IDMs. Its etiology has not been clearly elucidated. Newborns with SLCS do not pass meconium within the first 24 hours, and develop abdominal distension with bilious vomiting. A small number of infants develop progressive distension leading to perforation, typically in the cecum, within the first 24-36 hours of life.

This entity may be misdiagnosed, as Hirschsprung disease as the splenic flexure transition zone may be clinically and radiologically indistinguishable from SLCS. As such, some authors suggest that all infants must have a suction rectal biopsy performed to exclude aganglionosis. Characteristic of SLCS is a normal caliber rectum, a small caliber sig-

> *"The care of the IDM by a knowledgeable team of healthcare providers should begin at birth with close evaluation, monitoring and treatment of the newborn infant in a timely and experienced manner."*

moid, and descending colon with an abrupt caliber transition at the splenic flexure.[75]

Treatment for and the resolution of SLCS are by gravity barium enema.

Myocardiopathy

Maternal diabetes mellitus affects the fetal heart both structurally and functionally.[77] Increased risk for hypertrophic cardiomyopathy (thickening of the interaventricular septum) is a common finding in an IDM. Hypertrophic cardiomyopathy and abnormal ventricular diastolic filling in the infant of the diabetic mother is related to poor maternal glycemic control.[78] It is caused by fetal hyperinsulinemia, which increases the synthesis and deposition of fat and glycogen in the myocardial cells. Most commonly, cardiomyopathy is transient and resolves as insulin concentrations normalize. Symptomatic infants typically recover after two to three weeks of supportive care. However, severe fetal and neonatal myocardiopathy with cardiac failure has been reported.[79, 80] Careful diabetic management in pregnancy reduces the severity of hypertrophic cardiomyopathy in IDMs.[81]

Summary

The current epidemic of obesity is adding significant numbers to the pool of pregnant diabetic mothers. For the obvious reasons, prevention of obesity in the general population by early and consistent education should be a national priority. For the reasons enumerated above, diabetic pregnancy should be considered a high-risk condition that carries an increased risk of perinatal morbidity and mortality. Care of the pregnant diabetic mother requires specialized and experienced healthcare personnel prior to conception and during pregnancy. Indeed, referral of diabetic women of childbearing age, particularly those with Type 1 diabetes, is needed in order for them to receive pre-pregnancy counseling, proper dietary management and medical therapy by a highly qualified diabetic team experienced in high-risk obstetrical care.

The care of the IDM by a knowledgeable team of healthcare providers should begin at birth with close evaluation, monitoring and treatment of the newborn infant in a timely and experienced manner.

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Medical News, Products and Information

Mothers of Tiny Babies Suffer Too.

Babies at very low birth weights struggle in their early years and a new study by University of Wisconsin-Madison researchers suggests that their mothers do, too.

The study of families enrolled in the Newborn Lung Project found that by the time the children reached age 5, their mothers suffered much worse health than mothers of normal birth-weight children.

"We found that caring for a baby born with very low birth weight can have negative downstream effects for maternal health," says study leader Dr. Whitney Witt, Assistant Professor of Population Health Sciences at UW School of Medicine and Public Health.

"This suggests that mothers of these babies, and their families, should get help and support both early on and as the child grows up, in order to keep the whole family healthy."

Witt led a research team that interviewed 297 mothers of very low birth-weight babies – defined as babies born weighing less than 1,500 grams or about 3.3 pounds – and 290 mothers of normal birth-weight babies. The Newborn Lung Study includes all very low birth-weight infants born in Wisconsin in 2003 and 2004 and admitted to Neonatal Intensive Care Units (NICU).

They found that:

- Mothers of very low birth-weight children had worse physical health than mothers of normal birth-weight children, partially because of the increased stress experienced by mothers of children born with very low birth weight.
- Among mothers of very low birth-weight children, the higher the number of weeks the baby spent in a NICU, the worse the mother's physical health when the child was age 5. This relationship was independent of whether the mother herself had health problems during pregnancy.
- The mothers of very low birth-weight children who had behavioral problems at age 2 had worse mental health years later. This appears to be partially due to greater levels of stress experienced by mothers of children with behavior problems.

"This study suggests that having a child born with very low birth-weight can have a lasting effect on mothers, and long-term or chronic stress may play a very important role," says Witt. "This is important information for pediatric and family medicine clinicians, so they can monitor, refer, and treat these at-risk mothers as needed."

Other members of the team include: Kristin Litzelman, Lauren E. Wisk and Nataliya Levin, graduate students, and Dr. Mari Palta, all of the UW Department of Population Health Sciences; and Hilary Spear and Beth McManus of the University of Colorado.

New Prenatal Genetic Test Is Much More Powerful Than Standard Chromosome Test at Detecting Fetal Abnormalities

A nationwide, federally funded study has found that testing a developing fetus' DNA through chromosomal microarray (CMA) provides more information about potential disorders than does the standard method of prenatal testing, which is to visually examine the chromosomes (karyotyping). The results of the 4,000-plus-participant clinical study were presented in February at the *32nd Annual Meeting of the Society for Maternal-Fetal Medicine* in Dallas. The study was recently published in the *American Journal of Obstetrics & Gynecology.*

In women having routine prenatal diagnosis, CMA detected additional genetic abnormalities in about 1 out of every 70 fetal samples that had a normal karyotype. When a birth defect was imaged by ultrasound, CMA found additional important genetic information in 6% of cases. These results suggest that CMA may soon replace karyotyping for prenatal testing, says Dr. Ronald Wapner, Director of Reproductive Genetics at NewYork-Presbyterian Hospital/Columbia University Medical Center and Vice Chairman for Research and Professor of Obstetrics and Gynecology at Columbia University College of Physicians and Surgeons.

"Why would anyone want to continue to use the standard method, which gives only part of the answer?" says Dr. Wapner, who led the 34-center study funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. "However, we will have to carefully transition this information into clinical practice — to educate physicians and patients, develop guidelines for its use, and learn how to best use it to improve care."

CMA is not routinely used for prenatal testing, but has become the primary genetic test to evaluate newborns with birth defects, as well as infants and young children with developmental delays.

Dr. Wapner describes the observed difference in accuracy between the two tests this way: "With karyotyping, we can see only when pieces of the genome of about 5 million base pairs are missing from a chromosome. With CMA, we can see missing pieces of fewer than 100,000 base pairs."

CMA is based on a method that determines whether the right amount of genetic material is present at numerous locations in the fetus' genome.

This study was the first to examine the two methods in a blinded head-to-head comparison. Fetal samples were collected from the amniotic fluid or placenta of 4,450 participants. "These were women who were seeking prenatal testing for the usual reasons, which could be age, increased risk of inheritable disease, or a structural abnormality in the fetus," Dr. Wapner says.

Each participant's sample was split and sent, in a blinded fashion, to one of four laboratories that perform CMA — NewYork-Presbyterian Hospital/Columbia University Medical Center, Emory University, Baylor College of Medicine or Signature Genetics. The other portion of the sample was sent to Genzyme Genetics for standard karyotyping.

Results show that CMA and karyotyping were equally effective at identifying chromosomal abnormalities such as the duplicate chromosomes that cause Down Syndrome and Trisomy 18. But CMA provided significantly more clinically relevant information in two situations.

"In 6% of the cases where there's a structural abnormality of the fetus but karyotyping is normal, CMA will provide additional significant information," Dr. Wapner says. "And in about 1.7% of cases where the procedure was done because of the mother's age or similar concerns and the chromosomes were normal, CMA reveals additional information of concern."

Both tests offer information on conditions that can be life-threatening to a newborn baby or that can signal a possible health threat that might be treatable. "We are looking for the same thing in both tests," Dr. Wapner says. "But we find more abnormalities with CMA."

CMA can identify at least 150 known conditions and tell us exactly what the problem is and what it means for a child. Although karyotyping provides the same kind of information, CMA will likely provide more information on other potential disorders that might not otherwise be picked up such as intellectual disability or autism.

"It does not always mean that a child will necessarily develop these disorders, because many are due to multiple influences," Dr. Wapner says. "But it will help parents because they can be on the lookout for a particular disorder and have a treatment plan in place. I believe it is important to give parents as much information as they need about their child."

Global Neonatology Today Monthly Column - MDG #4 and #5 in Russia

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

In Russia, perinatal mortality accounts for the largest share of mortality among children under 5, so its reduction will be important to achievement of the United Nations Millennium Development Goals (MDG) #4, which is to reduce child mortality. The Russian MDGs include: reducing mortality among children under 5 by two thirds in 2015 (to 7/1000) as compared with 1990. It is estimated that Russia could reach its target indicator by 2015 if it sustains its current trend of steady improvement. However, there are problems of underestimation of its Infant Mortality Rate (IMR) because of incomplete registration as mentioned last month in this column. (See discussion of Russia's definition of "live birth" as differing from that of the World Health Organization).

It is recognized that reduction of perinatal mortality requires modern standards of obstetrical care and improvement of support to women from disadvantaged backgrounds, as well as ensuring healthy eating, a healthy lifestyle, prevention of smoking and alcohol consumption.

Maternal Mortality

In 1990, the Maternal Mortality Rate (MMR) was 47/100,000 child births. To reach the MDG #5 of improving maternal health and reducing maternal mortality by 75%, the current rate must be reduced to 12/100,00.

Furthermore, increased and efficient investment in maternal and infant health will further reduce IMR and MMR. However, the over-all health demographic situation does not look optimistic. Russia needs to look beyond the numbers, and develop strong public health measures to improve understanding and avoid undesirable obstetrical outcomes. The National Human Development Report (NDR) recommends the implementation of the World Health Organization's (WHO) *Safe Motherhood Programme*, "which is based on scientifically proven non-medicalized approaches to pregnancy and childbirth."

The report also recommends improvement of obstetrical and perinatal technologies, and monitoring of processes and work methods at maternity homes and departments, as well as assessment of clinical outcomes. Another area of focus should be the reduction in the number of legal and illegal abortions. The report notes that enhancement of safe abortions have led to reduction of maternal mortality. In order to further decrease the MMR, they recommend, "One of five methods recommended by the World Health Organization – confidential enquiries into maternal deaths – is highly valuable for detailed understanding of the real healthcare issues associated with MGD #5 in Russia." However, the country should be able to achieve MDG #5 merely by maintaining the positive trends in abortions.

The authors conclude that, "If modern technologies of prenatal and childbirth care are introduced, and maternal mortality from other causes is reduced, there is every reason to believe that Russia can outperform the MDG #5 target."

Source: National Human Development Report in the Russian Federation, 2010; Millennium Development Goals in Russia: Looking into the Future Moscow 2010 - www.undp.ru/nhdr2010/National_Human_Development_Report_in_the_RF_2010_ENG.pdf.

The 2010 National Human Development Report (NHDR) for the Russian Federation has been prepared by a team of Russian experts and consultants. The analysis and policy recommendations in this report do not necessarily reflect the views of the UN and other institutions by which the experts and consultants are employed. Chief Author: Prof. Sergey N. Bobylev, Dr. Sc. (Economics), Faculty of Economics at Lomonosov Moscow State University; Chapter 5. Reduction of Child Mortality and Better Maternal Care. Health Priorities for Russia Alexey V. Bobrik, PhD (Medicine), Executive Director, Open Health Institute Foundation.

The Clock is Ticking !!!

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