Neonatal Management of the Infant of Diabetic Mother

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Abstract

Many controversies exist about the management of neonatal conditions frequent in the infant of diabetic mother such as asymptomatic neonatal hypoglycemia, hypocalcemia, or polycythemia. In this article, we review the pathophysiology and management of major neonatal complications of diabetes in pregnancy, taking into consideration the major current controversies.

Keywords: Diabetic; Hypoglycemia; Polycythemia

Introduction

A Medline search performed on August, 2013, using the key word of "infant of diabetic mother" and the limit of "clinical guidelines" failed to find any article in the English language that represents some kind of consensus opinion on the neonatal management of the Infant of Diabetic Mother (IDM). We retrieved only one paper, in German, published 15 years ago, and written on behalf of German Professional Societies [1].

Many controversies exist about the management of neonatal conditions such as asymptomatic neonatal hypoglycemia [2], hypocalcemia [3], or polycythemia [4]. In this chapter, we will review the pathophysiology and management of major neonatal complications of diabetes in pregnancy, taking into consideration the major current controversies.

Glycemic Control in Pregnancy and Fetal-Neonatal Complications

Fetal-neonatal complications are directly related to inadequate glycemic control during key periods of pregnancy [5]. Poor periconceptional and early first trimester glycemic control are related to spontaneous abortions, early growth delay, and major congenital malformations [6]. During the second trimester, it is predictive of Pregnancy Induced Hypertension (PIH) [7], preterm labor and delivery [8] and minor congenital anomalies [9]. During the third trimester of pregnancy it is predictive of macrosomia [10], birth trauma, fetal dystocia [11], maternal trauma and high cesarean delivery rate [12]. It is also associated with complications linked to fetal hyperinsulinism such as neonatal hypoglycemia [13], respiratory distress [14,15], cardiac Asymmetric Septal Hypertrophy (ASH) [16], and to decreased fetal oxygenation and its acute [17] or chronic complications such as neonatal polycythemia [18] or thrombocytopenia [19]. Finally, hyperglycemia in labor aggravates the risk of neonatal hypoglycemia and is associated with lowered apgar scores [12,17].

We will here review the major neonatal complications of maternal diabetes, then discuss their management after birth.

Major congenital malformations

Prior to 16-20 weeks, the fetal pancreas secretes insulin in response to amino acids, but not to glucose. Thus, early fetal hyperglycemia is not accompanied by fetal hyperinsulinism [20]. High sugar concentration is toxic to cultured cell growth [21], which may explain the early growth delay highly predictive of congenital malformations of complicated diabetic pregnancies [6]. Maternal magnesium (Mg) depletion may contribute to malformations [22]. All malformations are more frequent in IDM's, but some, such as caudal regression syndrome are highly specific to maternal diabetes [5].

Small left colon syndrome: This entity is, in most cases, transient and resolves on its own [23].

Macrosomia: After 20 weeks gestation maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia, which in turn lead to enhanced growth and macrosomia [10].

Intrauterine growth restriction: A small subgroup of IDMs usually delivered to mothers with advanced diabetic class, with significant vascular disease, may be affected by growth restriction, resulting in compromised nutrient and oxygen delivery to the fetus [5].

Fetal and neonatal hypoxia: Fetal hypoxemia in maternal diabetes has been demonstrated in humans [17] and in animal models [24]. Poorly controlled diabetes may lead to both decreased oxygen supply to the fetus, and increased oxygen consumption by the feto-placental unit [24]. Indeed, fetal oxygen supply may be reduced by a decrease in placental blood flow, possibly aggravated by severe vascular disease. Increased affinity of glycosylated hemoglobin (HbA1c) to O2 may be contributory to decreased O2 maternal-fetal transfer. In the presence of excess fuels or of hyperinsulinemia, the placental metabolic and oxygen consumption rates increase, depriving the fetus of sufficient oxygen [24]. Chronic fetal hypoxemia may lead to a wide range of clinical consequences, from "sudden" intrauterine death, to mild neonatal depression at birth [17]. It also leads to increased production of fetal erythropoietin and increased rates of polycythemia [18]. Decreased platelet counts in IDM's correlate inversely with the circulating nucleated red blood cell counts, which may involve a shift of the pluripotent stem cell toward erythropoiesis, at the expense of thrombocyte formation [19]. Increased red blood cell mass and erythropoietic rate may also play a role in neonatal hyperbilirubinemia.

Neonatal Hypoglycemia (NH): The incidence of NH is difficult to assess, in particular because of the multiple definitions used for NH [25], and because its occurrence is affected by maternal glycemic control [5].

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IDM's often have a rapid fall in Glycemia within hours of birth [2,12], that occurs faster and deeper than in normal infants. The NH is linked to fetal hyperinsulinism caused by maternal hyperglycemia mostly during the third trimester, and is aggravated by maternal hyperglycemia in labor [12]. The gluconeogenic response to NH is blunted in IDM's, and blood fatty acids and postnatal glucagon surge are reduced [26]. Moreover neonatal asphyxia [17] and polycythemia [27] may aggravate hypoglycemia, due to increased glucose demands.

Disorders of mineral metabolism in IDM's:

Decreased bone density in IDM's: Decreased bone density has been reported in IDM's [28] and appears to be due to increased bone resorption, rather than to decreased bone formation [29].

Neonatal hypocalcemia and hypomagnesemia: In a recent past, many IDM's were reported to have Neonatal Hypocalcemia (NHC). With improved management of diabetes in pregnancy, rate and severity of NHC have significantly decreased. Risk factors of NHC in IDM's are birth asphyxia and prematurity [30]. Mg deficiency plays also an important role in the pathogenesis of NHC in IDM's [30]. Poor glycemic control leads to maternal glycosuria, accompanied by urinary Mg loss [22]. In turn, maternal Mg deficiency leads to fetal Mg deficiency [22,30]. Mg is necessary for the appropriate secretion of PTH, as well as in its action upon its target cells [22,30].

Prematurity and Respiratory Distress Syndrome (RDS): A premature delivery is more likely to occur in IDM's because of a higher rate of preterm labor [8], and because of iatrogenic prematurity whenever required to prevent intrauterine fetal death [17]. There is a special risk for RDS in IDM's [15]. With modern management, this risk might match that of the control population, both in preterm infants [15] and in very low birth weight infants [31]. Respiratory symptoms in IDM's are not necessarily equivalent to RDS, and may be the first signs of Transient Tachypnea of the Newborn (TTN), in particular if the infant was born by cesarean delivery [17]. Respiratory symptoms may also be the most obvious signs of cardiac ASH that lead to systolic left outflow obstruction [16].

Neonatal Management of the IDM

Delivery room management

In view of the risk of significant dystocia and that of neonatal depression due to fetal acidemia, a team of professionals highly trained in the pediatric management of complicated deliveries should be present in the delivery room of a planned IDM delivery. This team may be composed of physicians, neonatal nurse practitioners, midwives, or respiratory therapists with formal training and experience in neonatal resuscitation.

Nursery management

a. Vital signs examination and monitoring, at least hourly for the next following 4-6 hours, time during which signs and symptoms of complications such as hypoglycemia or RDS may develop.

b. Complete physical examination by a trained physician as soon as possible after birth. The physical examination will pay meticulous attention to the search for all complications mentioned, in particular trauma and malformations.

c. Screening for and management of NH. The definition of NH is highly controversial. Many reports have arbitrarily defined NH as being a serum, plasma, or whole Blood Glucose (BG)

value below 30-50 mg/dl. It is known that BG determined from one sample differ whether serum, plasma, or whole BG are measured, and vary with the method of measurement. Normal values may be defined using many different approaches [2,25]. A statistical definition (BG concentration more than 2 standard deviations below the mean for a population of well full-term infants) is arbitrary and only defines a population at higher risk. A "metabolic" definition is the BG concentration at which the counter regulatory response becomes activated. A Neurophysiological definition is based upon a threshold associated with disturbed Neurophysiological function, such as auditory evoked response waveform. Finally, a Neuro-developmental definition has been proposed by Lucas et al. [32], who found a threshold value of 47 mg/dl (2.5 mmol/ l) to be more predictive of lower Bayley scores. The following recommendations are an adaptation of those suggested by the American Academy of Pediatrics (AAP) expert committee who published recently (2011) on the topic [2]. The management needs "to account for the overall metabolic and physiologic status of the infant and should not unnecessarily disrupt the mother-infant relationship and breastfeeding" [3].

Screening methods

Glucose reagent strips should only be considered as a screen or an estimate [2], and at least one reliable laboratory plasma glucose value that is significantly low should be obtained to confirm the diagnosis of NH [2]. However, awaiting laboratory confirmation should not delay treatment in a symptomatic infant.

Prevention: IDM's should be fed (preferably at the breast) after delivery or by 1 hour of age and screened 30 minutes after the feeding. This recommendation is consistent with that of the World Health Organization [2]. Gavage feeding may be considered in infants who are not nippling well. Glucose screening should continue until 12 hours of age for infants born to mothers with diabetes and who maintain plasma glucose concentrations > 40 mg/dl [2].

Symptomatic infants: Because severe, prolonged, symptomatic NH may result in neuronal injury, there is a need to intervene rapidly in symptomatic infants. The clinical signs of NH include a wide range of manifestations common in sick neonates. They include jitteriness, cyanosis, seizures, apneic episodes, tachypnea, weak or high-pitched cry, floppiness or lethargy, poor feeding, eye-rolling, and coma. These signs are not specific for NH. It is important to screen such babies for other possible disorders (such as sepsis, hypocalcemia, or polycythemia) as well as NH. Such signs usually subside quickly with normalization of plasma glucose concentrations [2].

A reasonable (although arbitrary) cutoff proposed by the AAP committee for treating symptomatic infants was chosen as 40 mg/dl [3]. This value is higher than the physiologic nadir and higher than concentrations usually associated with clinical signs. Intravenous therapy consists of a "minibolus" of glucose (200 mg of glucose per kg, 2 ml/kg dextrose 10% in water (D10W), intravenously) and/or starting a continuous infusion of glucose (D10W at 80–100 ml/kg per day). The goal is to maintain plasma glucose concentrations in symptomatic infants between 40 and 50 mg/dl.

Asymptomatic infants: A pragmatic approach was developed included a consideration of age of the infant, mode of feeding, and other risk factors. This strategy is based on the observations from Cornblath et al. [25] that: 1) Nearly all infants with symptomatic hypoglycemia during the first hours of life have plasma glucose concentrations < 20

to 25 mg/dl; 2) most infants with persistent or recurrent hypoglycemia have plasma glucose concentrations < 20 to 25 mg/dl; and 3) there is little or no evidence to indicate that asymptomatic NH in the first days of life results in adverse sequelae [2]. The algorithm developed by the AAP separates temporally the infants in 2 time periods (birth to 4 hours and 4-12 hours) and accounts for the changing values of glucose that occur over the first 12 hours after birth.

a. Birth to 4 hours of life: After initial feed before 1 hour of age, the first glucose screen is initiated within half an hour. If < 25 mg/dl and patient still asymptomatic, he/she should be reefed, and checked within an hour. In case BG is still less than 25 mg/dl, IV glucose therapy should be initiated. If BG lies between 25 and 40 mg/dl, the infant should be reefed. Subsequent concentrations lower than 25 mg/dl after attempts to refeed, necessitate treatment with intravenous glucose.

b. 4-12 hours of life: The infant should receive feeds every 2-3 hours, and his BG be checked prior to every feed. The target BG concentration is greater than 45 mg/dl before each feeding. In the event BG is below 35 mg/dl and the patient still asymptomatic, the infant should be reefed, and checked within an hour. In case BG is still less than 35 mg/dl, IV glucose therapy should be initiated. If BG lies between 35 and 45 mg/dl, the infant should be reefed. Subsequent concentrations lower than 35 mg/dl after attempts to refeed, necessitate treatment with intravenous glucose.

If inadequate postnatal glucose homeostasis is documented, the clinician must be certain that the infant can maintain normal plasma glucose concentrations on a routine diet for a reasonably extended period (through at least 3 feed-fast periods) before discharge.

Management of respiratory distress

Respiratory distress in an IDM represents a diagnostic challenge. It may be indicative of congenital pneumonia, or spontaneous Pneumothorax like in any other infant, as well as of TTN, RDS, or heart failure caused by ASH. The management of these conditions is strikingly different. While all may require a similar symptomatic approach, such as administration of oxygen, and ventilatory support as needed, RDS may require administration of surfactant, ASH may require the use of beta-blockers, and TTN will only require time in order to improve. Thus, in every IDM with respiratory distress, careful evaluation of the history and pattern of the respiratory distress is fundamental: maternal fever in labor and prolonged rupture of membranes may point out to potential pneumonia or sepsis, and justify the use of antibiotics; rapidly improving respiratory distress supports the diagnosis of TTN, while rapidly deteriorating distress may indicate the development of RDS or the presence of ASH. All IDM's with respiratory symptoms should undergo: 1) a chest X-ray, and 2) an echocardiogram (to verify the presence or absence of an anatomic heart disease or of ASH). If present, ASH should be managed with beta-blockers (propranolol, starting oral dose: 0.25 mg/kg per dose Q6 hours, increase as needed to maximum of 3.5 mg/kg per dose Q6 hours; starting IV dose: 0.01 mg/kg Q6 hours over 10 minutes, increase as needed to maximum of 0.15 mg/kg per dose Q6 hours) only when symptomatic, and under careful monitoring of the blood pressure [16].

Imaging screen for malformation

We do not advocate routine imaging studies for malformations screening. These studies were probably conducted, in most cases, prenatally (using ultrasonography), and the vast majority of malformations in the IDM should not be a "surprise" at the time of delivery. However, some malformations may not be detected by antenatal ultrasonography, such as a small ventricular septal defect; thus, we advise performing echocardiography only when signs or symptoms pointing out to a possible cardiac problem are present. Similarly, the documentation of ASH, if asymptomatic, is relevant only from an academic standpoint.

Screening for and management of polycythemia

There is no consensus about definition and management of NP, in particular because randomized clinical trials that studied the effect of Partial Exchange Transfusion (PET) upon long term outcome have failed to prove a beneficial effect upon long term outcome [4].

We have recently published a critical review and consensus statement on the topic, on behalf of the Israeli Neonatology Association [4]. The following recommendations are based upon this document. We define NP as a venous hematocrit of at least 65%. Symptoms and complications of polycythemia are unlikely to be related to a hematocrit of < 65%. The need for PET and its efficacy have not been demonstrated when PET is conducted after 6 hours of life in asymptomatic infants. There is no evidence that PET alters the neurologic or developmental outcomes of asymptomatic polycythemic neonates. Thus, routine screening for NP is not recommended, as well as routine PET in asymptomatic infants. Screening for symptoms and for NH should be performed carefully and documented in all infants with polycythemia. IDM's with concomitant NP and persisting NH, as well as those with symptoms of NP should undergo PET [4].

Screening for and Management of Neonatal Hypocalcemia and Hypomagnesemia

We believe that IDM's should be screened for routinely at the age of 24 hours, at the nadir of postnatal calcium [30]. Due to potential effect of NHC on central nervous system heart, there is little controversy on need for treatment of symptomatic hypocalcemia (arrhythmia, pump failure, or seizures) [3]. Intravenous administration of Ca salts is the preferred, most rapid means of correction. Acute correction may be achieved by intravenous bolus infusion, over 10 minutes, with electrocardiographic monitoring, of 18 mg elemental Ca/kg, followed by continuous infusion at 75 mg/kg/24 h. Stepwise reduction of calcium dose over a period of 3 days usually prevents rebound hypocalcemia. Continuous infusion is preferred to bolus, since the latter acutely increases serum osmolality, decreases serum pH by competition of Ca^{++} with H^+ at the bone, is excreted in greater quantity, and may depress parathyroid function. Boluses are more likely to cause arrhythmia, especially bradycardia, and possibly, cardiac standstill. Both bolus and continuous infusion of IV calcium may cause extravasation of calcium into soft tissue with Ca deposition or sloughing of the skin, and sometimes, severe cutaneous necrosis [3]. Intra-arterial infusion is prohibited as organ necrosis such as intestinal necrosis may result.

In case of refractory or relapsing hypocalcemia, it is advised to correct the often associated Mg deficiency. A single dose of 0.12 ml/kg of intramuscular 50% solution of Mg sulfate (6 mg/kg of elemental Mg) will in average increase within 6 hours the serum Mg concentration by 1 mg/dl, and correct the hypocalcemia [3].

Conclusion

The best prevention of the many potential problems of the IDM is adequate maternal glycemic control before and during pregnancy. The IDM may require the full benefits of modern neonatal care. The

IDM that requires respiratory assistance at delivery should be evaluated and monitored at least in a level II or III NICU facility. Otherwise, we believe that its management may well be conducted in a well baby nursery, at the condition that the appropriate evaluation monitoring and follow up are available.

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