

Neonatal management of pregnancy complicated by diabetes

Fauzia Mohsin,¹ Shareen Khan,² Md. Abdul Baki,³ Bedowra Zabeen,⁴ Kiswhar Azad⁵

Abstract

Women with diabetes in pregnancy, either pre-gestational Diabetes Mellitus (Type 1 & Type 2) or Gestational Diabetes, are at increased risk for adverse pregnancy outcomes, including preterm labour and increased foetal mortality rate. Adequate glycaemic control before and during pregnancy is crucial for improving foetal and perinatal outcomes in these babies. Perinatal and neonatal morbidities and mortality rates have declined since the development of specialized maternal, foetal, and neonatal care for women with diabetes and their offspring. However, infants of diabetic mothers are at risk for developing complications as macrosomia, hypoglycaemia, perinatal asphyxia, cardiac and respiratory problems, birth injuries and congenital malformations. In this review article we describe the neonatal management of the offspring of diabetic mothers.

Keywords: T1DM, T2DM, IDM, Barker's Hypothesis, Outcomes.

Introduction

The most common medical complication of pregnancy is diabetes mellitus, with 1 in 7 births being affected by Gestational Diabetes Mellitus (GDM). Despite advances in perinatal care, however, infants of diabetic mothers (IDMs) remain at risk for preterm birth with its attending problems, as well as a multitude of physiologic, metabolic, and congenital complications unique to foetal adaptation to maternal diabetes. Type 1 Diabetes Mellitus (T1DM) is associated with marked risk of embryopathy involving most systems (particularly neural tube defects, cardiac anomalies, caudal regression), poorly controlled T1DM with complications carries a higher risk of intrauterine growth restriction, asphyxia, and foetal death.^{1,2} In later life, IDM is predisposed to obesity, diabetes, and cardiovascular disease.³

Successful management of these high-risk newborns requires close consultation between different specialists

.....
^{1,3,5}Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College, ²Department of Paediatrics, ⁴Consultant and Coordinator, CDiC (Changing Diabetes in Children), BIRDEM General Hospital, Dhaka, Bangladesh.

Correspondence: Fauzia Mohsin. Email: fauzia_mohsin@yahoo.com

involved in the care of the mother and baby, encompassing pre-pregnancy planning, leading on to pregnancy, labour and delivery, and post pregnancy care.⁴

Problems/Complications of IDMs

Perinatal mortality rates in babies from T1DM mothers are increased 3- to 10-fold, and congenital malformation rates are 4- to 10-times higher than in normal infants of the same gestational age, although there is considerable overlap in clinical problems of IDMs from mothers with both type 1 and type 2 diabetes. For example, in a recent survey, Cordero et al noted in a series of 530 infants born to 322 women with GDM and 177 women with T1DM, that, 36% were large for gestational age (LGA); 2% were small for gestational age (SGA), and the rest, the majority were appropriate for gestational age.⁵

The neonatal problems encountered in IDMs are summarized in Table-1.

Table-1: Neonatal morbidities in IDMs.

Clinical presentation

Macrosomia/ LGA (large for gestational age)
 SGA (Small for gestational age) (Mothers with renal, retinal or cardiac disease)
 Birth injury (shoulder dystocia, fractured clavicle)

Metabolic

Hypoglycaemia
 Hypocalcaemia
 Hypomagnesaemia

Respiratory

Perinatal asphyxia
 Respiratory distress syndrome (RDS)
 Transient tachypnoea of newborn (TTN)

Cardiovascular

Hypertrophic obstructive cardiomyopathy/heart failure.
 Septal hypertrophy/septal defects
 Double-outlet right ventricle/ transposition of great vessels

Haematologic

Hyperbilirubinaemia
 Polycythaemia and hyperviscosity
 Renal vein thrombosis

Neurologic

Neurologic instability
 Anencephaly/ spina bifida/ caudal regression syndrome
 Spinal cord birth trauma

Gastrointestinal/urinary

Intestinal atresia
 Small left colon
 Transient haematuria

Pathophysiology

Most, but not all, of the foetal and neonatal sequelae, associated with diabetes during gestation are a function of maternal glycaemic control. According to Pederson hypothesis,⁶ maternal hyperglycaemia results in foetal hyperglycaemia because glucose readily traverses the placenta. The foetal pancreatic response leads to foetal hyperinsulinaemia, which in tandem with maternal hyperglycaemia, causes increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis and augmented protein synthesis. Hyperinsulinism and hyperglycaemia produce foetal acidosis, which may result in increased rate of stillbirth. Separation of placenta at birth suddenly interrupts glucose supply to the infant, such that there is a risk of hypoglycaemia during the first few hours after birth. Diminished epinephrine and glucagon responses also contribute to the hypoglycaemia.

Congenital anomalies correlate with poor metabolic control during the peri-conception and organogenesis periods and may be the result of hyperglycaemia induced teratogenesis. Chronic foetal hypoxia is associated with increased foetal and neonatal morbidity.

Neonatal Management of The IDM

Management of IDMs should ideally start before birth by means of pre-conception counseling and frequent prenatal evaluation of mother and foetus by a dedicated team.⁷⁻⁹

IDMs should breast feed and stay with their mothers, unless there are complications that warrant admission for intensive or special care. The initial assessment of IDMs is summarized in the Table-2.

Table-2: Initial assessment of IDM.

Time	Assessment
Prenatal	Ultrasound for size and anomalies Biophysical profile Maternal HBA1c
Delivery room	Physical examination: Congenital anomalies Size for dates Respiratory distress
Evaluation	Postnatal age (Hour)
Serum glucose	0 (cord blood), 2, 4, 8, 12, 24, 36, 48
Calcium	6, 24, 48 hours
Magnesium	check if calcium low
Haematocrit	4, 24 hours
Bilirubin	Based on clinical jaundice

Continuing Evaluation and Management of IDM

Macrosomia

Infants with birth weight ≥ 4 kg are defined as macrosomic, and a birth weight >90 th percentile for gestational age is defined as large for gestational age (LGA). These infants are prone to hypoglycaemia, hypocalcaemia, polycythaemia, intraventricular cardiac septal hypertrophy, and should be meticulously screened for these complications.^{1,2,7}

Neonatal Hypoglycaemia

Neonatal hypoglycaemia develops in 25-50% of IDMs. The definition of neonatal hypoglycaemia (NH) is controversial. A blood glucose (BG) level above 48mg/dl is considered 'safe' as no babies with BG above this cut-off point, had abnormal sensory evoked brain stem potentials. Babies with NH may be asymptomatic or may display symptoms such as apnoea, respiratory distress, jitteriness, cyanosis, irritability, poor feeding, hypotonia, lethargy, high-pitched or weak cry, hypotonia, and convulsions.^{1,2}

Screening: Capillary blood glucose should be taken from the heel of the newborn using glucose reagent strips. Glucose reagent strips should only be considered as a screen or an estimate, and at least one reliable laboratory plasma glucose value that is significantly low should be obtained to confirm the diagnosis of neonatal hypoglycaemia. However, awaiting laboratory confirmation should not delay treatment in a symptomatic infant.

Prevention: Infants should initiate feeding as soon as possible after birth (within 1 hour) and then at frequent intervals (every 2-3 hours). Post-Caesarian women should begin to breast feed as soon as they are fit.⁸

Treatment: Breastfeed should be initiated by a post-Caesarian mother as soon as she is fit to feed. American Academy of Paediatrics (AAP), advises treatment with intravenous (IV) glucose if plasma glucose is less than 40mg/dl and clinical signs of hypoglycaemia are present. In an asymptomatic infant, IV glucose is needed if blood glucose is between 25mg/dl to 35 mg/dl. According to AAP, screening should continue until 12 hours of age for IDMs and LGA and plasma glucose concentrations should be more than 40mg/dl. A simple calculation for infusion of glucose that can be followed is as below:

Glucose dose = 200 mg/kg (dextrose 10% at 2 ml/kg) and /or IV infusion at 5-8mg/kg/min (80-100 ml/kg/day) achieves plasma glucose level of 40 - 50 mg/dl.

Recurrent or Persistent/Resistant Hypoglycaemia

This condition should be considered when there is a failure to maintain normal blood glucose levels despite a glucose infusion of 12 mg/kg/min or when stabilization is not achieved by 7 days of life. Drugs which can be used include Hydrocortisone: 5mg/kg/day IV or per oral in 2 divided doses for 24-48 hours and Diazoxide: 5-15 mg/kg/day divided every 8 hours. Glucagon is usually only given as a temporary measure. Dose is 0.02-0.3mg/kg/dose IV, intramuscular (IM) or subcutaneous (1 mg maximum dose) Octreotide 2-10mcg/kg/day subcutaneously every 6-12 hours can also be tried.

Hypocalcaemia and Hypomagnesaemia

Hypocalcaemia, is defined as serum calcium level of less than 8mg/dl in a term infant and less than 7 mg/dl in preterm infant. Ionized calcium levels of less than 4 mg/dl are considered as hypocalcaemia. It occurs in up to 50 % of IDMs. The severity of hypocalcaemia is related to the severity of maternal diabetes and involves decreased function of parathyroid gland.^{1,2}

A serum magnesium (Mg) level of less than 1.52 mg/dl indicates hypomagnesaemia. Hypomagnesaemia in IDMs is related to maternal hypomagnesaemia and the severity of maternal diabetes. The signs and symptoms of neonatal hypocalcaemia and hypomagnesaemia are similar to hypoglycaemia and include jitteriness, sweating, tachypnoea, irritability and seizures.^{1,2}

Treatment 100 to 200 mg/kg of 10% calcium gluconate IV slowly over 15 to 20 minutes under constant cardiac monitoring is recommended. Following the initial dose, maintenance calcium should be given as continuous intravenous infusion. In case of refractory or relapsing hypocalcaemia, it is advised to correct the frequently associated Mg deficiency.

For treatment of hypomagnesaemia, Mg sulphate 0.2ml/kg IM is usually given. For maintenance, Mg can be added to IV fluid or given orally as magnesium sulphate 50% 0.2ml/kg/day (4mEq/ml).

Hyperbilirubinemia

Hyperbilirubinemia is extremely common in IDMs, in part because of their tendency to have high red cell mass. Those who have macrosomia tend to be bruised at birth, and resorption of subcutaneous blood can contribute to hyperbilirubinaemia. Such infants have significantly increased bilirubin concentrations compared with IDMs who do not have macrosomia.^{1,2}

Serum bilirubin should be checked according to clinical

judgment. Phototherapy or exchange transfusion are instituted if required.

Polycythaemia

Polycythaemia is defined as a venous haematocrit above 65% or a haemoglobin more than 22gm/dl. It is present in 20-30% of IDMs at birth. The polycythemic IDM is plethoric, sluggish and lethargic. Other symptoms include irritability, poor feeding, jitteriness, apnoea, vomiting, seizure, respiratory distress, tachycardia, congestive heart failure, hypoglycaemia, thrombosis, thrombocytopenia, jaundice and cerebrovascular accidents.^{1,2}

There is no consensus about management of neonatal polycythaemia in particular regarding Partial Exchange Transfusion (PET). In asymptomatic infants with haematocrit (Hct) of 65-70%, close observation and increasing fluid intake are needed. Treatment is controversial in asymptomatic infants with Hct >70-75%. Partial exchange transfusion should be done in symptomatic infants with Hct >65% and in asymptomatic infants with Hct >75%.

Transient tachypnoea of newborn (TTN): This is a parenchymal lung disorder characterized by pulmonary oedema resulting from delayed resorption and clearance of foetal alveolar fluid. TTN is a common cause of respiratory distress in the immediate newborn period and is a self limiting condition.

Respiratory distress syndrome (RDS): Insulin is believed to antagonize the maturing effect of cortisol, which results in blunted production of dimalmityl lecithin. The foetal hyperinsulinaemic state restricts substrate availability for surfactant biosynthesis and impedes fibroblast-pneumocyte factor, which stimulates type II alveolar cells to produce surfactant. Also, previously, inaccurate assessment of gestational age because of foetal macrosomia caused inadvertent preterm delivery with associated RDS. Tight maternal metabolic control and modern obstetric management have greatly reduced the risk of RDS. Treatment consists of definitive or rescue therapy with surfactant.^{1,2}

Perinatal Asphyxia: Perinatal asphyxia can occur in up to 25% of IDMs, almost exclusively born to T1DM mothers, whose DM is chronically unstable and correlates with maternal atherosclerotic vascular disease, hyperglycaemia (before delivery but particularly during labour), maternal nephropathy, and recurrent preterm labour. Management includes oxygen, ventilator support and surfactant as needed. Supportive treatment is given in the form of oxygen, head/total body cooling, and even ventilation.^{1,2}

Hypertrophic Cardiomyopathy and Septal Hypertrophy

IDMs are at increased risk for various cardiomyopathies, including thickening of the interventricular septum and left or right ventricular wall. Fortunately, most are asymptomatic, although aortic outflow obstruction may be sufficiently severe to cause left ventricular failure in a small fraction of IDMs. Such abnormalities generally regress during the first postnatal year. The hypertrophy is a result of foetal insulin secretion stimulating cardiac muscle growth.

The treatment of choice is propranolol. Digoxin is contraindicated because of possible ventricular outflow obstruction. Septal hypertrophy generally resolves by 4 months. Consultation and follow up with a paediatric cardiologist is advised.^{1,2}

Congenital Anomalies

The IDM is at two to four times greater risk of having a congenital malformation than unaffected infants. Any system can be affected. Cardiac anomalies, spinal agenesis-caudal regression syndrome, neural tube defects, and gastrointestinal and urinary tract anomalies are more frequently seen.

One malformation deserves special mention. Sacral agenesis syndrome (agenesis of the lumbar spine, sacrum, and coccyx, and hypoplasia of the lower extremities) is a well-established congenital anomaly associated with maternal diabetes mellitus (not gestational diabetes). However, other etiologic factors are presumably involved, as demonstrated by the rare incidence of caudal regression syndrome (1:60,000) compared to diabetes.^{1,2}

Long-Term Outcome

Achieving optimal metabolic control during pregnancy reduces, but may not absolutely prevent the risk of poor neurodevelopment outcome. IDMs in later life were found to have low intelligence scores and neurodevelopment abnormalities, with some limitations in intelligence and

psychomotor development independent of perinatal complications in the IDM. Maternal hypoglycaemic events were not related to poor infant outcome. Increased maternal glucose values during gestation are associated with smaller brain size and delayed brain maturation in infancy.⁹ The implications of these associations are not clear, although it is recognized that ketones can impair foetal brain development.

Conclusion

There is evidence that good glycaemic control during pregnancy reduces most, but not all complications in IDMs. With proper screening for both GDM and DM, and prompt management, the outcome of diabetic pregnancy can be improved.

Care should be limited not only to pregnancy, but should also focus on the IDM, whose needs and requirements pose unique challenges and risks.

References

1. Hay WW Jr. Care of the infant of the diabetic mother. *Curr Diab Rep* 2012; 12: 4-15.
2. Mimouni FB, Mimouni G, Bental YA. Neonatal management of the infant of diabetic mother. *Pediatr Therapeut* 2013; 4: 186. doi: 10.4172/2161-0665.1000186.
3. Mitanchez D, Zydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother - short- and long-term implications. *Best Pract Res Clin Obstet Gynaecol* 2015; 29: 256-69.
4. Kalra S, Malik S, John M. Gestational diabetes mellitus: a window of opportunity. *Indian J Endocrinol Metab* 2011; 15: 149-51.
5. Cordero L, Treuer SH, Landon MB, Gabbe SG. Management of infants of diabetic mothers. *Arch Pediatr Adolesc Med* 1998; 152: 249-54.
6. Macfarlane CM, Tsakalagos N. The extended Pedersen hypothesis. *Clin Physiol Biochem* 1988; 6: 68-73.
7. VanHaltren K, Malhotra A. Characteristics of infants at risk of hypoglycaemia secondary to being 'infant of a diabetic mother'. *J Pediatr Endocrinol Metab* 2013; 26: 861-5.
8. Kalra B, Gupta Y, Kalra S. Breast feeding: preventive therapy for type 2 diabetes. *J Pak Med Assoc* 2015; 65: 1134-6.
9. Mann JR, Pan C, Rao GA, McDermott S, Hardin JW. Children born to diabetic mothers may be more likely to have intellectual disability. *Matern Child Health J* 2013; 17: 928-32.