Pictorial Essay: Infants of diabetic mothers

Ibrahim A Alorainy, Nauman B Barlas, Amer A Al-Boukai
Department of Diagnostic Radiology, King Saud University, College of Medicine and King Khalid University Hospital, Riyadh, Saudi Arabia

Correspondence: Dr. Nauman B. Barlas, Department of Diagnostic Radiology, Northumbria Healthcare NHS Foundation Trust, Wansbeck General Hospital, NE63 9JJ, U.K. E-mail: naumanbarlas@hotmail.com

Abstract

About 3 to 10% of pregnancies are complicated by glycemic control abnormalities. Maternal diabetes results in significantly greater risk for antenatal, perinatal, and neonatal morbidity and mortality, as well as congenital malformations. The number of diabetic mothers is expected to rise, as more and more of the obese pediatric female population in developed and some developing countries progresses to childbearing age. Radiologists, being part of the teams managing such pregnancies, should be well aware of the findings that may be encountered in infants of diabetic mothers. Timely, accurate, and proper radiological evaluation can reduce morbidity and mortality in these infants. The purpose of this essay is to illustrate the imaging findings in the various pathological conditions involving the major body systems in the offspring of women with diabetes

Key words: Birth defects; diabetic mothers; maternal diabetes

Introduction

Improvements in healthcare have resulted in a decline in neonatal problems. The exception is birth defects which have emerged as the most important cause of perinatal loss in diabetic pregnancies.[1] Presently, it is estimated that 3 to 10% of pregnancies are complicated by glycemic control abnormalities and that 80% of these are caused by gestational diabetes.[2] Validated observations suggest significantly greater risk for antenatal, perinatal, and neonatal morbidity and mortality, as well as congenital malformations in infants of diabetic mothers (IDMs).[3,4] A four-fold higher rate of congenital anomalies of brain, heart, kidneys, intestine, and skeleton has been documented in IDMs, suggesting a strong association between congenital anomalies and maternal glycemic control.[4] Current research suggests that the maternal metabolic milieu has a direct influence on the developing embryo during a critical period of organogenesis.[5] Although anomalies in IDMs tend to encompass a spectrum of organ systems rather than result in any specific syndrome, some individual patterns tend to occur more frequently. Thus, major congenital heart disease, musculoskeletal deformities, and central nervous system (CNS) deformities have been the most commonly reported problems[6] [Table 1].

Table 1: Congenital anomalies in infants of diabetic mothers

| Structural:                                |
|-------------------------------------------|
| Central nervous system                    |
| Neural tube defects (meningocele, encephalocele, anencephaly) |
| Caudal regression syndrome                |
| Holoprosencephaly                         |
| Respiratory system                        |
| Hyaline membrane disease                  |
| Wet lung                                  |
| Cardiovascular system                     |
| Transposition of great vessels            |
| Ventricular and atrial septal defects      |
| Left-sided obstructive lesions (hypoplastic left heart syndrome, aortic stenosis, coarctation) |
| Genitourinary system                      |
| Renal agenesis                            |
| Hydronephrosis                            |
| Ureteral duplication                       |
| Cystic kidneys                            |
| Gastrointestinal                          |
| Duodenal atresia                          |
| Anorectal atresia                         |
| Musculoskeletal system                     |
| Arthrogryposis                            |
| Hypoplastic femur                         |
| Functional:                               |
| Intraventricular septal hypertrophy       |
| Small left colon syndrome                 |
| Others:                                   |
| Renal vein thrombosis                     |
| Adrenal hemorrhage                        |
| Macrosomia resulting in difficult vaginal delivery and birth injuries |

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Gestational diabetes is much more common than nongestational diabetes. The number of diabetic mothers is expected to increase in the future, as more and more of the obese pediatric female population in developed and some developing countries grows to childbearing age. Hence, it is important to address all aspects of this subject. Today, radiologists are part of the teams managing such pregnancies; their role in the detection of congenital anomalies during the antenatal period and in the identification, follow-up, and management of some associated conditions in the perinatal and neonatal period is crucial. It is therefore important for the radiologist to be well aware of the findings that may be encountered in IDMs. Timely, accurate, and proper radiological evaluation can reduce morbidity and mortality in such infants.

The following discussion will address the radiological aspects of abnormalities of the different body systems associated with maternal diabetes.

CNS and Spine

The most common structural abnormalities are those related to the failure of neural tube closure and include meningomyelocele, encephalocele, and anencephaly.\textsuperscript{[4]} CNS malformations, particularly anencephaly [Figure 1], open spina bifida, and holoprosencephaly [Figure 2] have increased ten-fold in patients with maternal diabetes.\textsuperscript{[11]} Maternal diabetes is one of several conditions that lead to neonatal hypoglycemia [Figure 3]. On the other hand, sacral agenesis or caudal regression syndrome (CRS) [Figure 4], which is the congenital defect thought to be most characteristic of diabetic embryopathy, is seen 200 to 400 times more frequently in IDMs;\textsuperscript{[7]} diabetes must be ruled out in mothers who give birth to infants with sacral agenesis.\textsuperscript{[8]} CRS is also known as caudal dysplasia sequence and is characterized by a series of congenital anomalies\textsuperscript{[9]} [Table 2]. Sirenomelia is considered by some to be an extreme form of the CRS, though the single umbilical, persistent vitelline artery in sirenomelia differentiates the two.\textsuperscript{[10]}

Conventional radiographs may demonstrate deformities of the vertebral and pelvic bones as well as of the femur [Figure 4], whereas magnetic resonance imaging (MRI) shows the associated anomalies of the spinal canal, dural sac, and spinal cord [Figure 5].

Respiratory System

The risk for hyaline membrane disease in IDMs is five- to six-fold greater than in infants of nondiabetic women.\textsuperscript{[11]} Reticulonodular shadowing [Figure 6A] is the hallmark of respiratory distress syndrome (RDS). Hypoaeration and air bronchograms are common. A normal chest radiograph at the age of 6 hours of life virtually rules out RDS.\textsuperscript{[12]} Severe RDS, which may lead to death, is characterized by diffuse alveolar opacities [Figure 6B].

In case of metabolically controlled maternal diabetes, fetal lung maturity is not delayed; however, there is an increased risk of wet lung in the neonatal period.\textsuperscript{[13]} Other conditions that predispose to wet lung are prematurity and precipitous pregnancy. The condition is due to delayed resorption and clearance of fluid from the lung. A chest radiograph...
Figure 3 (A,B): Neonatal hypoglycemia: CT scan of the brain shows typical low attenuation in the white matter of the occipital (A) and parietal (B) lobes on both sides.

Figure 5 (A-C): Caudal regression syndrome: Frontal (A) and lateral (B) radiographs of the spine show absence of the sacrum and the entire lumbar spine. The pelvis is very small and the pelvic bones are fused at the midline. Sagittal T2W MRI of the spine (C) shows severe caudal regression with complete absence of the lumbar spine and sacrum. The conus medullaris has a characteristic, abnormal, wedge-shaped (blunted) appearance.

Figure 4: Caudal regression syndrome (complete agenesis of sacrum): Frontal radiograph of the pelvis shows a contracted pelvis due to absence of the sacral segments; the two iliac wings can be seen pseudo-articulating with each other and with the caudal portion of L3 due to the absence of the L4 and L5 vertebrae.

Figure 6 (A,B): Respiratory distress syndrome (RDS): Portable frontal chest radiograph on day 2 (A) shows reticulogranular opacities throughout both lungs with prominent air bronchograms. The cardiac silhouette is preserved and both lungs are hypoaerated. Frontal radiograph of the chest on day 9 (B) shows more severe changes. There is obliteration of the cardiac and diaphragmatic contours due to marked opacification, giving a complete ‘white out’ appearance.

Table 2: Anomalies characterizing caudal regression syndrome

| Musculoskeletal anomalies | Complete or partial agenesis of sacrum | Variable agenesis of lumbar/dorsal spine | Hypoplastic femur | Clubbed feet | Flexion contractures of lower limbs |
|---------------------------|----------------------------------------|------------------------------------------|-------------------|-------------|-----------------------------------|
| Spinal cord anomalies     | High-positioned wedge-shaped termination of conus | Tethered cord | Filar thickening | Presacral meningocele | Lipomyelomeningocele |
| Associated anomalies      | Gastrointestinal system | Anal atresia | Genitourinary system | Neurogenic bladder | Malformed external genitalia | Renal aplasia |

obtained within 2 to 6 hours shows mild cardiomegaly, prominent interstitial pattern in the lungs [Figure 7A], and pleural effusion. In contrast to the findings in RDS, the lungs are hyperinflated in wet lung. The condition is self-limiting and clears spontaneously within 2 to 3 days [Figure 7B].

Cardiovascular System

Cardiac problems may be structural or functional.
Congenital heart disease is about four times more common in IDMs. Structural problems such as transposition of great vessels, truncus arteriosus, and tricuspid atresia are seen three or more times more frequently than expected in IDMs. Wren et al. supported the recommendation that all pregnant women with diabetes should be offered a fetal echocardiography, as antenatal diagnosis of such anomalies leads to an improved postnatal outcome. Ventricular septal defects, atrial septal defects, and left-sided obstructive lesions, such as hypoplastic left heart syndrome, aortic stenosis, and coarctation of aorta are other cardiovascular malformations seen in IDMs. Functional abnormalities which are present in up to 30% of IDMs include intraventricular septal hypertrophy and cardiomyopathy; about 10% may have cardiac failure.

Genitourinary System

Maternal juvenile diabetes mellitus, nephropathy, hydramnios, and poor metabolic control during a pregnancy complicated by diabetes may result in abnormal development of the fetal kidneys. Several renal anomalies are seen in IDMs, including, renal agenesis, ureteral duplication, hydronephrosis, and cystic kidneys.

A known complication in the genitourinary system in IDMs is renal vein thrombosis which is a severe, life-threatening, but rarely occurring condition. The affected infant presents with a flank mass due to renal enlargement. Color Doppler US may show absence of flow, with loss of pulsation and sometimes a clot in the renal vein.

Adrenal hemorrhage Figures 11A,B is also a known entity in IDMs. Large babies such as those seen in diabetic mothers and in the Beckwith-Wiedemann syndrome are predisposed to adrenal hemorrhage. Computed tomography scan and MRI can both diagnose and stage adrenal hemorrhage; however, these modalities usually provide no additional information as compared with ultrasonography (USG) which being free from ionizing radiations can be used in the initial screening and in follow-up.

Early hemorrhage (1 – 2 days), which appears echogenic
on ultrasound USG, liquefies shortly thereafter and a cystic or multicystic appearance develops [Figure 11C]. If this does not happen, neuroblastoma should be considered.\textsuperscript{[19]} Calcification [Figure 11C] can also be seen on as sequelae.

Gastrointestinal system

The most common intestinal anomalies seen in IDM are atresias of the duodenum and rectum, although atretic segments may be seen at any place along the length of the gastrointestinal (GI) tract. Duodenal atresia is considered to be the most common cause of high GI tract obstruction in IDM.\textsuperscript{[20]} Abdominal radiograph is usually diagnostic and shows the classic ‘double bubble’ appearance [Figure 12].

Meconium plug syndrome and small left colon are two overlapping entities in the spectrum of functional neonatal intestinal obstruction.\textsuperscript{[21]} Radiologists use the two term synonymously, or simply the term ‘functional immaturity of colon’ which is a common cause of neonatal distal bowel obstruction in IDM.\textsuperscript{[22]} In meconium plug syndrome, there is distension of the cecum up to the transverse portion of the colon, with the transition near the splenic flexure; the left-sided colon is narrow and the rectum is quite distensible. Inspissated meconium causes multiple filling defects in the distended portion which may include the distal ileum [Figure 13]. Half of these cases are associated with maternal diabetes. It is important to differentiate meconium plug syndrome from Hirschsprung disease [Table 3].

Anorectal malformation is another important cause of lower GI tract obstruction in IDM.\textsuperscript{[23]} The initial abdominal radiograph [Figure 14A] may suggest the level of atresia; however, contrast loopogram [Figure 14B] can confirm not only the level of atresia but also delineate the associated fistula.
Arthrogryposis [Figure 15], hypoplastic femur [Figure 16], and other anomalies of lower limbs are seen more frequently in IDM.[8] Femoral hypoplasia is a rare anomaly with an estimated incidence of 0.11 to 0.2/10000 live births.[24]

Musculoskeletal system

| Table 3: Differences between small left colon and Hirschsprung disease |
|---------------------------------------------------------------|
| **Small left colon syndrome**               | **Hirschsprung disease**                   |
| Type of obstruction                                   | Reversible functional                      | Irreversible functional                      |
| Role of contrast enema                                 | Diagnostic and therapeutic                  | Diagnostic                                    |
| Rectosigmoid ratio*                                    | More than 1                                 | Less than 1                                   |
| Appearance of transition zone                         | Abrupt                                      | Gradual and serrated                          |
| Location of transition zone                           | Splenic flexure                             | Rectosigmoid junction                         |

Figure 12: Duodenal atresia: Frontal radiograph of the chest and abdomen on day 2 shows a dilated stomach and proximal duodenum, with the classical ‘double bubble’ sign. Note the absence of gas shadows in the rest of the abdomen and the bilateral patchy basal pneumonia due to aspiration.

Figure 13: Small left colon syndrome: Frontal radiograph of the abdomen as part of a contrast enema examination using iodinated contrast (gastrografin) shows a narrow caliber of the left colon, with an abrupt transition at the splenic flexure. Multiple filling defects in the left colon are due to meconium plugs (arrow). Also note the rectum is quite distensible.

Figure 14 (A,B): Anorectal malformation: High imperforate anus with recto-urethral fistula. Cross-table lateral radiograph (A) shows absence of air in the anal area (metallic marker at the anal verge). A lucent curvilinear air shadow is seen anteriorly (arrow) representing air in the urinary bladder as a result of the fistula. Loopogram (B) of the same patient confirms the recto urethral fistula and outlines the rectum and the bladder.
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Figure 15 (A–C): Arthrogryposis: Frontal (A) and lateral (B) radiographs of the elbow show extended elbows, pronated forearms, and flexed wrists and fingers in a baby with arthrogryposis. Frontal radiograph of the lower limbs (C) of another baby with arthrogryposis shows bilateral hip dislocations and club feet.

Figure 16: Proximal focal femoral deficiency: Frontal radiograph of the pelvis and both hips shows that the proximal femur is absent and the acetabulum is malformed on the left side. Only a hypoplastic portion of the distal left femur is apparent.

Fetal growth

Macrosomia is usually defined as a birth weight that exceeds some preselected limit, most frequently 4000 g, or more than 90th percentile for gestational age. Fetal macrosomia is observed in 26% of IDM and in 8% of infants of nondiabetic women. Fetal macrosomia can cause difficult vaginal delivery due to shoulder dystocia, with resultant birth injuries and asphyxia. These potential birth injuries include cephalhematoma, subdural hematoma, facial palsy, ocular hemorrhage, clavicular fracture, and brachial plexus injuries (Erb palsy). Hepatomegaly, splenomegaly, and cardiomegaly are detectable on plain radiographs.

Conclusion

There has been significant improvement in the outcome of pregnancies complicated by diabetes mellitus in the last few decades because of the collective efforts of clinicians and researchers. However, there may be a fresh surge of IDM in the near future as a consequence of the expected increase in the numbers of overweight mothers in the developed as well as some developing countries. Radiologists, being part of the teams managing such pregnancies, should be well aware of the common patterns of anomalies and their appearances on various modalities to play their role in an effective manner.

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