HYDROCEPHALY, SCHIZENCEPHALY, SPONDYLOCOSTAL DYSPLASIA, AND HYPOPARATHYROIDISM IN AN INFANT OF A DIABETIC MOTHER

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Abstract

Context. Diabetes mellitus is the most frequent chronic complication in pregnancy and continues to contribute to increased perinatal morbidity and mortality in newborns. Macrosomia, respiratory distress syndrome, metabolic and electrolytic disturbances, and increased rates of congenital structural defects are well-known neonatal complications associated with maternal diabetes, even if well-controlled.

Case report. A macrosomic infant born from an insulin-dependent mother, with uncontrolled diabetes and lack of adequate prenatal care, prenatally diagnosed with hydrocephaly showed a complicated postnatal course. Initial respiratory distress syndrome and transient hypoglycemia, rapidly corrected under treatment, were followed by persistent hypocalcemia and hyperphosphatemia due to hypoparathyroidism and evolving hydrocephaly. Ventriculoperitoneal shunting was followed by resolution of hypocalcemia, but seizures associated with schizencephaly and recurrent respiratory tract infections, aggravated by spondylocostal dysplasia, concurred to infant’s demise at the age of 5 months.

Conclusions. The reported case is rare due to multiple aspects: persistent hypoparathyroidism, uncommon association of schizencephaly, and even rarely association with spondylocostal dysplasia, all these conditions requiring a multidisciplinary therapeutic approach. Also, the reported case is evocative for challenges associated with infants born from diabetic mothers.

Key words: diabetic mother, infant, hydrocephaly, hypoparathyroidism, schizencephaly, spondylocostal dysplasia.

INTRODUCTION

Affecting 1-14% of the pregnancies, diabetes mellitus is the most frequent chronic disease

complicating pregnancy(1, 2). Pregestational diabetes is reported in 13-21% of pregnancies complicated by diabetes (1, 3). Increased maternal age at reproduction and obesity are the highest important factors responsible for the increased prevalence of diabetes mellitus in pregnant women reported in latest years (4, 5). Perinatal outcome of the infant of the diabetic mother (IDM) depends on the onset, duration, and severity of maternal diabetes and is worse for IDM born from mothers with pre-existent insulin-dependent diabetes (2, 3, 5).

Three types of complications are reported in association with diabetes in pregnancy: diabetic embryopathy; diabetic fetopathy; and neonatal complications (7).

Diabetic embryopathy is a spectrum of congenital abnormalities or disruptions and fetal and neonatal complications, including spontaneous abortion, occurring due to maternal diabetes (7). Etiopathogenesis of diabetic embryopathy is still incompletely understood, multiple pathways were suggested as responsible for these effects, but maternal hyperglycemia during the first trimester is considered as the main teratogen (3, 7, 8). The leading role of hyperglycemia is also suggested by decreased rates of congenital defects, almost equal to those of the general population, when diabetes is well-controlled (2, 3, 7). Congenital malformations are the major cause of death in IDM (8) and are frequently associated with pregestational diabetes (8, 9). The risk for congenital structural defects is 2-10 times higher than in general population (9, 10). Diabetes is a teratogen without a specific phenotypic expression (8). All types of congenital malformations were described in IDM but cardiovascular and central nervous system structural defects are the most often cited (8, 9,11-13). Skeletal

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congenital defects are reported with variable rates (11,13,14).

Diabetic fetopathy is another important consequence of maternal hyperglycemia and secondary fetal hyperinsulinism in the second and third trimester of pregnancy (7). Through multiple metabolic effects, fetal insulin excess is producing an additional transfer of nutrients to the fetus, followed by accelerated fetal growth, abnormal fetal composition and macrosomia (8,15). Macrosomia is seen mostly in association with poor glycemic control (16). Chronic fetal hypoxemia is another aspect of diabetic fetopathy, one with multiple consequences: polycythemia (due to erythropoiesis stimulation), cardiomyopathy (due to increased secretion of catecholamine and altered iron distribution), altered fetal growth, and metabolic acidosis (17).

Apart from diabetic embryopathy and fetopathy, a sum of neonatal conditions are occurring with increased rates in IDM, considerably influencing the mortality rate. Infants born from pregnancies complicated with diabetes have increased rates of prematurity, perinatal asphyxia, respiratory distress syndrome, hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia, polycythemia and hyperviscosity syndrome, birth trauma, and hypertrophic cardiomyopathy (8, 18). Neonatal mortality rates are significantly increased in IDMs compared to general population of newborns, the risk of death being almost four times higher (11, 19). Uncontrolled preexistent maternal diabetes and macrosomia are increasing the risk for neonatal mortality (20).

In IDM, hypoparathyroidism is functional and transient, with still unclear etiology, most probably secondary to maternal hyperparathyroidism, fetal magnesium deficiency, increased serum calcitonin concentrations, and increased calcium needs after birth (8).

Hydrocephaly and schizencephaly are cited among central nervous system malformations associated with maternal diabetes as well as vertebral and rib abnormalities, but are not specific to maternal diabetes (12). Spondylocostal dysplasia, characterized by multiple and complex vertebral and costal defects, was reported in the literature only in one IDM (14).

CASE REPORT

The female newborn, birth weight 4650 g (>90th percentile for gestational age), length 53 cm (>90th percentile), cranial circumference 40 cm (>90th percentile), thoracic circumference 39 cm, born at 38

weeks gestation, was admitted in the neonatal intensive care unit (NICU) at 5 hours after birth for respiratory distress syndrome. The mother, secundigesta, primipara (one abortion at request), 24 years old, unmarried, unemployed, living in rural area, with low educational level, had insulin-dependent diabetes diagnosed at 14 years, poorly controlled before and during pregnancy, without significant other pathologies during gravidity. The father, 24 years, unmarried, unemployed, with low educational level, had no significant health problems. Both are with a normal height and weight limits for our country (21). The parents are not consanguineous. Prenatal diagnosis of hydrocephaly was done at around 20 weeks of gestation, termination of pregnancy was suggested and refused by parents. The infant was delivered by cesarean section due to hydrocephaly, macrosomia, and maternal diabetes and had, at birth, a decent general condition - Apgar score 7/8 - followed in minutes by signs of respiratory distress.

At admittance to NICU the infants presented the typical general fluffy, plethoric, and stocked appearance of an IDM, excessive abdominal and cervical fat, mottled skin, mild signs of respiratory distress (polypnea, mild intercostal retractions, and grunting), normal peripheral oxygen saturations in room air, mild generalized hypotonia, very weak sucking reflex, apparently without any congenital defects. Screening test detected hypoglycemia (37 mg/dL), rapidly corrected and stable after starting enteral nutrition and parenteral glucose supplementation (blood glucose of 67 mg/dL after 2 hours). Biochemical investigations performed in the first day of life revealed hypocalcemia (5.68 mg/dL) and increased C reactive protein (18 mg/L). Renal and hepatic tests, serum ionogram, proteins, alkaline phosphatase, blood gases, blood count and differential were in normal limits. Head ultrasound confirmed massive hydrocephaly and also discovered large open-lip left schizencephaly with mass effect on subtentorial structures, compressing cisterna magna (Fig. 1). Patent foramen ovale and interventricular septum hypertrophy (with no significant effect on cardiac functioning) were diagnosed on Doppler echocardiography. Thoraco-abdominal radiography revealed small focal interstitial and perihilar densities (consistent with delayed resorption of fetal pulmonary fluid) but the real surprise were the multiple vertebral and costal defects with secondary thoracic scoliosis unnoticed on general examination of the child: hemivertebrae Th9-Th12-L1, cuneiform vertebra Th11, sinostosis of the VIIth and VIIIth ribs on the median axillary line, bifid apex of the Xth rib on the right side of the thoracic cage, and

Figure 1. Hydrocephaly and large parietal-occipital open-lip schizencephaly - cranial ultrasound.

Figure 2. Thoraco-abdominal radiography showing thoracic scoliosis, costal and vertebral defects.

narrowed Xth and XIth intercostal spaces, with aspect of bifid rib on the left side (Fig. 2). Abdominal ultrasound scan revealed no abnormalities.

The infant was started on antibiotic therapy (continued for 14 days, due to persistently increased values of reactive protein C and procalcitonin despite negative bacteriology, including blood culture) and intravenous calcium supplementation. Correction of hypocalcemia (serum values consistently of total serum calcium < 6 mg/dL) required continuous increase of doses of calcium gluconate and was obtained only after 10 days with doses of about 60 mg elemental calcium/kg/day. Magnesium was not administered since magnesium levels were normal. Persistent hypoparathyroidism was suggested by increased serum phosphate levels (10.5-11 mg/dL; N 2.5-4.5 mg/dL), relatively low serum phosphatase concentrations (188-244 U/L; N 50-500U), normal renal function, and reduced serum parathormone concentration (2.5 pg/mL; N 15-68.3 pg/mL). Interestingly, no clinical signs could be attributed to hypocalcemia since, during this period, the infant had a fairly good general condition, no cardiac and respiratory symptoms (after the first day of life), good tolerance for enteral feeding, good reactivity to stimulation, normal diuresis and intestinal transit, physiological weight loss followed by constant weight gain of about 40-50 g/day. Moderate hyperbilirubinemia (maximum total bilirubin of 13 mg/dL) between the 2nd and the 5th day of life was managed with intermittent phototherapy. Initial generalized hypotonia was followed by marked axial hypotonia and weakness of the sucking reflex persisted, impeding breastfeeding and bottle feeding (the mother left the hospital after one week), forcing supplementation of feedings by gavage.

Persistence of neurological symptoms, rapidly increasing cranial circumference and head ultrasound suggested increased intracranial pressure, confirmed by head ultrasound scan, ophthalmologic examination, and computer-tomography (Fig. 3). At 18 days of life the infant was submitted to neurosurgery ward for ventriculoperitoneal shunting. Intervention went uneventful and the infant was readmitted to NICU for postsurgical care 6 days after the intervention. Investigations repeated after surgery revealed constantly normal values of serum calcium even after interruption of calcium administration (the lowest level in the next 45 days after surgery being 8.63 mg/dL), decreasing values of serum phosphatase (up to 5.2 mg/dL), increasing serum alkaline phosphatase (over 400 U/L, most probably due to prolonged hospitalization

Figure 3. (1) and (2) Massive hydrocephaly and large open-lip schizencephaly - cranial CT, before shunting.

and reduced spontaneous activity), persistent normal levels of serum magnesium. Postoperative anemia was corrected with erythrocyte concentrate.

One month after surgery, the infant presented few short apnea crisis and short tonic focal seizures limited to the left arm. Amplitude EEG confirmed ictal crisis mostly in the right hemisphere and treatment with topiramate was started as indicated by pediatric neurologist. No recurrence of the seizures was noted afterwards and seizures were attributed to schizencephaly. The ventriculoperitoneal shunting functioned normally and head circumference increased only 0.5 cm/month.

The infant was transferred at 2 months after birth from the neonatal ward to pediatric hospital and taken home from there by the parents. During the following one and a half month-period the infant had frequent upper respiratory infections but no seizures were observed and, after neurological re-examination and a normal EEG, the anticonvulsant was stopped. At 4 1/2 months the infant was readmitted in the hospital for tonic generalized seizures occurred during an episode of acute bronchiolitis. Under treatment, the acute respiratory infection episode improved, as did the general condition of the infant, and for about 10 days no seizures were observed (under combined treatment including three anticonvulsants - topiramate, sodium valproate, and levetiracetam). Drainage through ventriculoperitoneal shunting had normal functioning. Occurrence of a new episode of lower respiratory tract infection (interstitial pneumonia) severely affected the general condition of the infant, with respiratory failure

(needing intubation and mechanical ventilation), multiple system organ failure, reoccurrence of epileptic crisis with increased frequency and severity, resistant to treatment, coma, and exitus (at 5 months of age). Macroscopic and microscopic anatomopathological examination confirmed bilateral bronchopneumonia and the above mentioned congenital malformations.

DISCUSSION

The most frequent chronic medical condition in pregnancy, diabetes mellitus is complicating 1-14% of all pregnancies (1, 3), considerably influencing the pregnancy and neonatal outcomes. Pregestational diabetes is representing 13-21% of all pregnancies complicated by diabetes (1, 3) and has an increased rate of complication in offsprings compared to gestational diabetes (6). The incidence and severity of fetal and neonatal complications are depending on the onset, duration, severity, and complications associated with maternal diabetes (mostly vascular complications) (6). Neonatal mortality is reported in 31.7/1000 births associated with maternal diabetes, four times higher than in general population of newborns (11). Poor glycemic control before conception and during pregnancy and macrosomia are risk factors for increased mortality in IDM (20). The same conditions were also noticed in our case: maternal diabetes was diagnosed 10 years before birth and was poorly controlled, the child presented macrosomia, and cesarean delivery favored delayed

resorption of fetal pulmonary fluid. Inconsistent follow-up of pregnancy itself was also noted.

Maternal diabetes, mostly type I, is associated with 2-8 fold increased risk for congenital defects compared to general population of neonates (10). Congenital malformations are responsible for up to 50% of the perinatal mortality rate (11). The etiology and pathogenesis of diabetic embryopathy are still incompletely understood, studies reporting myo-inositol, oxygen free radicals, hyperketonemia, somatomedin inhibitors, arachidonic acid deficiency, hypoxemia, amino acids abnormalities, abnormal glycosylation of proteins, accumulation of sorbitol as possible etiologic agents for congenital structural defects seen in IDM, but maternal hyperglycemia during the first trimester of pregnancy is considered the major teratogen in IDM (1, 6). Multiple types of malformations, all occurring no later than 3-6 weeks of gestation, during organogenesis, have been reported in association with maternal diabetes, but together, cardiovascular and central nervous system defects are the most frequently seen (13). Patent ductus arteriosus was considered as delayed cardiac adaptation to extrauterine life due to respiratory difficulties (closed at 4 months). Absence of congenital heart defects allowed us to exclude di George syndrome, a chromosomal condition evolving with hypoparathyroidism, typical facial stigma, conotruncal cardiac congenital defects, and absent thymus; the syndrome was reported in association with maternal diabetes.

The most often reported central nervous system defects in IDM are spina bifida and anencephaly, conditions occurring 13-20 times more often than in infants of non-diabetic mothers (11, 13). More rarely holoprosencephaly, Arnold Chiari malformation, microcephaly, macrocephaly, olfactory tract agenesis, arrhinencephaly, lissencephaly, cerebellar dysplasia, or hydrocephaly and schizencephaly are reported in IDM (12, 13). We are not aware of reported cases of IDM with both hydrocephaly and schizencephaly, both conditions with unfavorable course, with increased potential to aggravate the outcome. In our case, massive hydrocephalus imposed ventriculoperitoneal shunting relatively soon after birth (3 weeks), while the large open-lip parieto-occipital schizencephaly was associated with recurrent focal epileptic seizures that rapidly become anticonvulsant-resistant. Also, compression of subtentorial structures due to massive hydrocephaly most probably caused deficient sucking reflex, while marked hypotonia, seen since birth may have been caused by schizencephaly.

Skeletal malformations as reported in IDM with an almost similar prevalence as in general population - 8.3/1000 births (9), vertebral defects and scoliosis being the most frequently cited. Absence of cranio-facial characteristic stigma and auricular defects differentiated our case from facio-auriculo-vertebral syndrome (OAVS), also reported in IDM infants (22). Multiple vertebral and costal defects observed in our case, determining thoracic scoliosis, allowed us to match them with spondylocostal dysplasia, an abnormal segmentation abnormality, the dominant-inherited type, occurring sporadically in most of the cases. In the thoracic form, spondylocostal dysplasia is rarely associated with congenital heart defects, central nervous system or renal malformations, has a milder course compared to the recessive type (Jarcho-Levin syndrome, lethal) but is still associated with increased risk for respiratory failure due to ventilatory restrictions (23). Only one case associating spondylocostal dysplasia - with absent, fused, and bifid ribs, scoliosis, and hemivertebrae - in an IDM was reported in the literature (14). Maternal exposure to carbon oxide, boric acid, valproic acid, phenitoin, and hyperthermia - cited etiology of spondylocostal dysplasia - were excluded by maternal anamnesis in our case.

Macrosomia, defined either as birth weight > 90th percentile or > 4000 g, occurs in 15-60% of infants born by diabetic mothers (8, 24) as a result of fetal hyperinsulinism secondary to intermittent maternal hyperglycemia, as originally proposed by Pedersen (15). Typically, accelerated fetal growth occurs after the 24 weeks of pregnancy and the effect is more pronounced in insulin sensible fetal tissues - liver, muscles, myocardium, fat tissue (8). Macrosomic IDM have a disproportionate general appearance, with increased abdominal circumference (due to excessive fat tissue and visceromegaly) discordant with apparently reduced cranial circumference (25). The presented infant (4650 g birth weight), despite the fluffy, plethoric, and stuffed aspect, had also an increased cranial circumference (due to hydrocephaly), in accordance with the other anthropometric parameters (all above the 90th percentile). Macrosomia increases the risks for birth trauma during vaginal delivery, for cesarean section delivery, and metabolic disturbances. Correctly appreciating birth weight before birth, in the present case, cesarean delivery was chosen to avoid birth trauma.

Hypertrophic cardiomyopathy, restricting filling and obstructing outflow, occurs secondary to fetal chronic hypoxemia due to increased metabolic

rate and oxygen consumption. Chronic fetal hypoxemia exerts its effect on the myocardium *via* an increased catecholamine production and arterial hypertension (16). Another possible cause is increased deposition of glycogen and fat in myocardium cells (26). The risk is increased in poorly controlled maternal diabetes (8). Severe cases are evolving with cardiac failure but in most of the cases resolution of cardiomyopathy occurs spontaneously after correction of metabolic and electrolytic disturbances seen in the first days of life, usually in a few weeks (27). In many infants, hypertrophy is limited to interventricular septum as it was in the reported case, and disappears in months (27). In our case the hypertrophy of the ventricular septum was mild (thickness of 7.7-8 mm) and it was not seen any more at 4 months age.

Hypoglycemia, defined by serum glucose < 40 mg/dL, typically with onset in the first day of life and lasting 2-4 days, is the most frequently reported metabolic disturbance in IDMs, occurring in up to 74% of the cases (8, 28). The risk and severity of hypoglycemia is increased if maternal diabetes is poorly controlled (8) and in macrosomic IDMs (29). According to Pedersen (15), abrupt interruption of placental glucose transfer at birth and fetal hyperinsulinism are responsible for neonatal hypoglycemia. A depressed response of the counterregulatory hormones (glucagon and catecholamines) may also contribute to hypoglycemia in IDMs (30). In our case, hypoglycemia was transient, noted only during first hours of life, with prompt response to enteral and parenteral nutrition.

Fetal hyperinsulinism delays maturation of surfactant system (13) contributing to increased incidence of respiratory distress syndrome in preterm infants delivered by diabetic mothers with poor glycemic control (8). Also, transient tachypnea of the newborn, due to delayed resorption of fetal pulmonary fluid occurs 2-3 times more often in IDMs compared to infants born by mother without diabetes (31). In the presented case, elective cesarean delivery was an important contributing factor for neonatal transient tachypnea, as reported by others (32). In our case, respiratory distress was mild, transient requiring only short time free flow oxygen administration but the course of transient tachypnea of the newborn is frequently complicated with persistent pulmonary hypertension or hypertrophic cardiomyopathy, leading to acute cardiorespiratory failure.

Transient hypocalcemia is reported in up to 60% of the IDMs in the first 3 days of life (8, 18, 33) and is associated with poor maternal glycemic

control. Prematurity, birth asphyxia, hypomagnesemia, and advanced maternal diabetes are risk factors for neonatal hypocalcemia (33). Increased magnesium losses in pregnancy leading to fetal hypomagnesemia and hypoparathyroidism (8), inadequate response of parathormone in fetal hypothyroidism (33, 34), maternal hyperparathyroidism inhibiting the functioning of fetal parathyroids and leading to transient functional hypoparathyroidism, increased calcitonin concentrations, and low levels of maternal vitamin D (35) were all suggested as etiologic factors of hypocalcemia in IDMs. In IDM, hypocalcemia is usually asymptomatic, limited to the first 72 hours of life and treatment is not needed (16). In our case, the infant had no symptoms that could be linked to hypocalcemia, but hypocalcemia persisted, despite treatment with high doses of calcium, until the ventriculoperitoneal shunting was performed. Persistent hypoparathyroidism in our case was suggested by increased serum phosphate levels, low serum phosphatase concentrations, normal renal function, and reduced serum parathormone concentration (36). Prematurity, asphyxia, intrauterine growth restriction, maternal diabetes, maternal use of anticonvulsants, and neonatal hypoparathyroidism are the reported causes of early neonatal hypocalcemia (37), but in our case only maternal diabetes and neonatal hypoparathyroidism could be incriminated. Maternal hyperparathyroidism could not be excluded since mother left hospital before more investigations could have been done on this track. Maternal hyperparathyroidism may induce transient fetal and neonatal hypoparathyroidism with secondary hypocalcemia that usually disappears after 3 weeks, as happened in our case. We speculate that hydrocephaly and secondary increased intracranial pressure may have contributed to persistent hypoparathyroidism and hypocalcemia in our case, despite the fact that we were not able to find such references in the literature. An abnormal congenital development of the parathyroid glands, primary or secondary to a teratogen effect of maternal diabetes, occurring as isolated defect or in association with various congenital syndromes (as di George syndrome, velo-cardio-facial syndrome, Spitz syndrome, Sanjat Sakati syndrome, mitochondrial myopathy, etc.) could be excluded since hypocalcemia resolved after ventriculoperitoneal shunting. Familial history, lacking any chronic conditions except maternal diabetes, allowed exclusion of isolated familial hypoparathyroidism. Hypoparathyroidism is rarely diagnosed in infants less than 1 year old (30, 36). Familial, maternal, and neonatal history, the

onset and course of neonatal hypocalcemia allowed us to exclude other causes of hypoparathyroidism: secondary to radiation or cytostatic drug exposure, infiltrative conditions, magnesium deficit or excess, or autoimmunity.

Hyperbilirubinemia, defined by venous hematocrit > 65%, occurs in 11-29% of IDMs (11, 26, 31) and is also associated with poor maternal glycemic control, macrosomia, prematurity, and polycythemia (38). Increased carboxyhemoglobin concentrations and pulmonary elimination of carbon oxide are suggesting that hyperbilirubinemia of IDMs could be determined by increased hemolysis (39). Two risk factors for hyperbilirubinemia were identified in the presented case: poor maternal glycemic control and macrosomia.

As clearly demonstrated by data in the literature, poorly controlled pregestational diabetes has a significant impact on neonatal morbidity and mortality (11). Primary prevention strategies are important because the pathogenesis of defects induced by maternal diabetes has origins in early stages of embryogenesis. Prospective studies have demonstrated that pre-conception counseling and early pregnancy care with optimization of glycemic control can significantly lower the occurrence of major congenital anomalies (40). Also, diabetic pregnancy should be investigated as a high-risk pregnancy and efficient secondary prevention is needed, by fetal ultrasound scan, as early as possible. First trimester ultrasound examination is useful for monitoring fetal growth later in pregnancy and early prenatal screening for fetal major malformations (41). Multiple fetal and neonatal complications - hydrocephaly, schizencephaly, macrosomia, hypoglycemia, transient tachypnea of the newborn, hypocalcemia, hypoparathyroidism, hyperbilirubinemia, hypertrophy of the interventricular septum, spondylocostal dysplasia - were diagnosed in the presented case imposing a multidisciplinary approach immediately after birth. Respiratory, cardiac, and metabolic complications were managed rapidly and without significant complications. Persistent hypocalcemia imposed extended investigations that revealed hypoparathyroidism and it was controlled with unusually high doses of calcium. Evolving hydrocephaly with increased intracranial pressure needed early neurosurgical intervention. Spondylocostal dysplasia predisposed to frequent respiratory tract infections that finally led to readmission of the infant. Seizures reoccurred and significantly contributed to the unfavorable outcome of severe ventilatory problems associated to recurrent pneumonia, all leading to the death of the child at 5 months after birth.

In conclusion, the presented case illustrates the importance of preventive measures aimed to maintain a good maternal glycemic control in pregnant mothers with diabetes mellitus as this may lower the incidence and severity of fetal and neonatal complications in IDMs. The reported case had a complicated course due to a sum of unusual associations of complications - hydrocephaly, schizencephaly, spondylocostal dysplasia, prolonged transient hypocalcemia and hypoparathyroidism. These complications imposed a multidisciplinary approach and treatment but finally they had a significant negative impact on the outcome, leading to infant's death. Thus, the case also illustrates how multiple conditions with different severity are influencing the mortality risk of IDM.

Conflict of interest

The authors declare that they have no conflict of interest.

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