

Adverse perinatal outcomes complicated with gestational diabetes mellitus in preterm mothers and preterm infants

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Abstract. The incidence rate of gestational diabetes mellitus (GDM) in pregnancy is currently on the increase. GDM is associated with short and long-term adverse outcomes for mothers, fetuses and newborns. The aim of the present study was to compare the incidence of adverse perinatal outcomes in women with and without GDM, in addition to comparing the morbidity and mortality rates of preterm infants born to women with and without GDM. A retrospective analysis of 640 preterm infants admitted to the Neonatal Intensive Care Unit of Qilu Hospital of Shandong University (Qingdao, China) between January 2019 and December 2020 was undertaken in the present study. According to mothers with or without GDM, the preterm infants were divided into the GDM group (n=217) and non-GDM group (n=423). Women with GDM were older ($P<0.01$) and more of advanced maternal age (≥ 35 years) or multipara ($P<0.001$), tended to have an increased risk of gestational hypertension ($P<0.05$), placenta previa ($P<0.005$) and polycystic ovarian syndrome ($P<0.05$). In infants born preterm, those born from mothers with GDM were associated with an increased risk of respiratory distress syndrome ($P<0.001$) and sepsis ($P<0.05$). In addition, very low birth weight infants born to mothers with GDM were found to have an increased risk of hypoglycemia ($P<0.05$) and sepsis ($P<0.05$). In the logistic regression analysis, RDS was the only condition independently associated with GDM [adjusted odds ratio: 1.699 (95% confidence interval: 1.699-1.699)]. However, there was no significant difference in the risk of mortality among the two groups. In conclusion, data from the present study suggested that GDM is associated with a higher risk of adverse perinatal outcomes in pregnant women and a higher risk of adverse neonatal outcomes in infants born preterm.

Introduction

The incidence rate of diabetes during pregnancy is increasing annually; most of which are gestational diabetes mellitus (GDM) (1). GDM is a common complication of pregnancy, in which any degree of glucose intolerance is first recognized during pregnancy (2). According to the estimation made by the International Diabetes Federation (IDF) in 2021, GDM affected ~16.7% of all pregnancies worldwide and ~21 million newborns per year (3).

GDM is associated with short- and long-term adverse outcomes for mothers, fetuses and newborns (4). Preterm birth is a potential contributor to diabetes-associated morbidity. Previous studies have demonstrated that GDM by itself is a risk factor for premature birth (5-8).

Although the effect of various perinatal risk factors on the outcome of preterm infants have been studied previously, to the best of the authors' knowledge, an insufficient number of studies have focused on the outcome of preterm infants born to GDM mothers. In addition, the overall risk of morbidity and mortality of preterm infants born to GDM mothers remains to be elucidated.

Therefore, the present study aimed to compare the incidence of adverse perinatal outcomes in women with and without GDM and the rate of morbidity and mortality in preterm infants born to women with and without GDM. This was performed retrospectively in a cohort over a 2-year period.

Patients and methods

Study design. This study was approved by the Ethics Committee of Qilu Hospital of Shandong University (Qingdao, China). Patients who participated in this research had complete clinical data. Written informed consent was obtained from the parents of the pediatric patients. The present study is a retrospective cohort study of all preterm infants who were admitted to the Neonatal Intensive Care Unit (NICU) of Qilu Hospital, Shandong University (Qingdao, China) after obstetric delivery between January 2019 and December of 2020. The medical records of the mothers and preterm infants were provided by the Information Systems Department of Qilu Hospital of Shandong University (Qingdao, China).

The inclusion criteria were as follows: i) Consistency with the American Diabetes Association diagnostic criteria for

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GDM in 2015 (1); ii) singleton pregnancy; and iii) complete clinical data.

The exclusion criteria were: i) *In vitro* pregnancy embryo transfer (IVF-ET); ii) multiple pregnancy; iii) mothers with associated pathologies, such as type 1 diabetes, type 2 diabetes, chronic respiratory diseases, neoplasms, gastrointestinal, hepatic, infectious tract diseases and heart disease; and iv) neonates born with congenital anomalies or metabolic disorders.

Outcome measures. Diagnosis of GDM was made if results from the 75-g oral glucose tolerance test revealed abnormalities. Fasting venous blood was first collected, before the patient was fed 75 g glucose dissolved in water orally. The fasting venous blood was then collected 1 and 2 h after the consumption of glucose. Screening and diagnosis of GDM were universally performed at 24-28 weeks of gestation, when GDM diagnosis would be made if the fasting blood glucose level was found to be ≥ 5.1 mmol/l (92 mg/dl) and/or the 1-h blood glucose level was found to be ≥ 10.0 mmol/l (180 mg/dl) and/or the 2-h blood glucose level was found to be ≥ 8.5 mmol/l (153 mg/dl).

Hypertension occurring during pregnancy for ≤ 20 weeks was classified as chronic hypertension if it did not progress into preeclampsia toxemia. Only after >20 weeks of gestation could pregnancy-induced hypertensive diseases be diagnosed. This was performed according to the standards of the international community's research guidelines on pregnancy-induced hypertension (9).

The attending pediatrician determined the neonatal outcomes according to both international and national definitions. The neonatal adverse outcomes assessed in the present study included ≥ 1 of the following: i) Pneumonia; ii) sepsis; iii) hyperbilirubinemia; iv) hypoglycemia (blood glucose level <40 mg/dl); v) hypoxic-ischemic encephalopathy (HIE); vi) intraventricular hemorrhage (IVH); vii) respiratory distress syndrome (RDS); viii) bronchopulmonary dysplasia (BPD); and ix) necrotizing enterocolitis (NEC). Pneumonia, RDS, BPD and NEC were diagnosed according to the clinical and radiological criteria (10). IVH was diagnosed using cranial ultrasonography, whereas sepsis was diagnosed by positive blood culture.

Statistical analysis. Statistical analysis was performed using SPSS (version 25; IBM Corp.). The measurement data of normal distribution was expressed as the mean \pm standard deviation. Comparison between continuous variables was performed using Student's t-test. Categorical data were presented as n (%), which were compared using the χ^2 test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient summary. There were a total of 739 preterm infants admitted to the NICU between January 2019 and December 2020. According to the established criteria, 99 medical records were excluded due to the birth of twins (n=44), mothers taken ill (n=47), IVF-ET (n=3) and congenital anomalies or metabolic disorders (n=5). This resulted in the final sample containing 640 medical records in total. Of the eligible

preterm infants that remained for analysis, 217 (33.9%) were to mothers with GDM. By contrast, the non-GDM group (n=423; 66.1%) consisted of mothers without diabetes.

Comparison of parameters between mothers with GDM and mothers without GDM. Compared with women without diabetes, women with GDM were older ($P < 0.01$) and more of advanced maternal age (≥ 35 years) or multipara ($P < 0.001$), tended to have a higher rate of gestational hypertension ($P < 0.05$), placenta previa ($P < 0.005$) and polycystic ovarian syndrome (PCOS; $P < 0.05$). There was no significant difference between the two groups in terms of the occurrence of cesarean delivery, premature rupture of membranes or fetal distress (Table I).

Compared with preterm infants born to mothers without diabetes, preterm infants born to mothers with GDM had longer anti-infection times (duration of antimicrobial use) ($P < 0.05$), but there were no significant differences between the two groups in the incidence of newborn sex, gestational age, birth weight, Apgar score or hospitalization time. It showed that there was comparability among comparison of complications between the two groups of preterm infants (Table II).

Comparing the incidence of major neonatal complications and mortality rates between the two groups, preterm infants born from mothers with GDM had a higher rate of RDS ($P < 0.001$) and sepsis ($P < 0.05$). However, the mortality rate was not significantly different between the two groups (Table III).

Logistic regression analysis adjusted for RDS, hypoglycemia, and sepsis with the lowest P-value. The adjustment ratio for RDS caused by GDM diagnosis was 1.699 [95% confidence interval (CI): 1.699-1.699, $P = 0.002$]. This meant that GDM led to a higher risk of RDS compared with hypoglycemia (OR: 0.706, 95% CI: 0.442-1.121, $P = 0.360$) and sepsis (OR: 1.185, 95% CI: 0.571-2.459, $P = 0.90$). Hence, RDS was the only condition independently associated with GDM group (Table VI).

Very low birth weight infants (VLBWI) born from mothers with GDM had a higher rate of hypoglycemia ($P < 0.05$) and sepsis ($P < 0.05$). The percentages of VLBWI born to mothers with GDM in BPD (24.3 vs. 11.5%) and NEC (8.1 vs. 3.3%) were greater compared with those born to mothers without GDM, though the differences did not achieve statistical significance. VLBWI born to mothers without GDM had a higher rate of HIE (14.8 vs. 5.4%), though the differences did not reach statistical significance. The mortality rate was not significant between the two groups (Table V).

Discussion

The incidence rate of GDM in pregnancy has been increasing in women of reproductive age, against the backdrop of the worldwide prevalence of obesity and sedentary lifestyles. It was previously shown that the incidence rate of perinatal complications in diabetic women is considerably higher compared with those in the general population (11). These perinatal complications include preterm birth, macrosomia, preeclampsia and cesarean section.

In the present study, 640 hospitalized preterm infants were analyzed, of whom 217 (33.9%) were born from mothers diagnosed with GDM. The incidence of short-term pregnancy

Table I. Pregnancy outcome for women with or without GDM.

Characteristic	GDM (n=217)	NonGDM (n=423)	χ^2/t value	P-value
Maternal age, years	32.8±4.6	30.2±4.5	6.867	0.008
≥35	85 (39.2)	91 (21.5)	22.429	2.181
Primipara	101 (46.5)	260 (61.5)	12.987	<0.001
Multipara	116 (53.5)	163 (38.5)	12.987	<0.001
Cesarean delivery	181 (83.4)	348 (82.3)	0.130	0.718
Vaginal delivery	36 (16.6)	75 (17.7)	0.130	0.718
PROM	90 (41.5)	175 (41.4)	0.001	0.975
Hypertensive disorders				
Chronic hypertension	6 (2.8)	17 (4.0)	0.651	0.420
Gestational hypertension	9 (4.1)	6 (1.4)	4.667	0.031
Mild preeclampsia	15 (6.9)	18 (4.3)	2.071	0.150
Severe preeclampsia	16 (7.4)	38 (9.0)	0.481	0.488
HELLP syndrome	0 (0)	3 (0.7)	0.400	0.527
Placental abnormality				
Placenta previa	19 (8.8)	13 (3.1)	9.750	0.002
Placental abruption	6 (2.8)	17 (4.0)	0.651	0.420
Fetal distress	11 (5.1)	32 (7.6)	1.426	0.232
PCOS	8 (3.7)	5 (1.2)	4.521	0.033

Data are presented as n (%) or mean ± standard deviation. P, Student's t-test or χ^2 test between GDM and non GDM mothers. GDM, gestational diabetes mellitus; PROM, premature rupture of membrane; HELLP, hemolysis, elevated liver enzymes and low platelets; PCOS, polycystic ovarian syndrome.

Table II. Characteristics for preterm infants born to women with or without GDM.

Characteristic	GDM (n=217)	NonGDM (n=423)	χ^2/t value	P-value
Male neonates	113 (52.1)	238 (56.3)	1.017	0.313
Gestational age, weeks	33.5±2.2	33.6±2.2	0.544	0.461
<32	69 (31.8)	121 (28.6)	0.700	0.403
32-34	68 (31.3)	125 (29.6)	0.217	0.641
34-37	80 (36.9)	177 (41.8)	1.479	0.224
Birth weight, g	2140.18±542.33	2163.81±498.66	0.551	0.458
<1,500	37 (17.1)	61 (14.4)	0.765	0.382
1,500-2,500	125 (57.6)	255 (60.3)	0.427	0.513
2,500-4,000	53 (24.4)	107 (25.3)	0.058	0.810
>4,000	2 (0.9)	0 (0)	1.512	0.219
Apgar score				
0-3	6 (2.8)	9 (2.1)	0.255	0.614
4-7	19 (8.8)	47 (11.1)	0.860	0.354
Anti-infective treatment time, days	8.91±6.06	7.71±6.24	2.326	0.127
Hospitalization time (days)	17.67±12.03	16.38±13.30	1.199	0.274

Data are presented as n (%) or mean ± standard deviation. P, Student's t-test or χ^2 test between GDM and non GDM preterm infants. GDM, gestational diabetes mellitus.

outcomes among those with and without GDM were then compared, which revealed that women with GDM tended to be older, of advanced maternal age or multipara. Women with GDM were also found to be associated with an increased risk

of gestational hypertension, placenta previa and PCOS. These results are consistent with those from previous studies (12-14). However, the incidence rate of macrosomia and cesarean section was inconsistent with that previously reported (15-21).

Table III. Mortality and morbidities among preterm infants born to women with or without GDM.

A, 25-37 weeks' gestation				
Mortality and morbidities	GDM (n=217)	NonGDM (n=423)	χ^2 -value	P-value
Pneumonia	178 (82.0)	337 (79.7)	0.508	0.476
RDS	96 (44.2)	131 (31.0)	11.035	<0.001
Hypoglycemia	35 (16.1)	53 (12.5)	1.567	0.211
Hyperbilirubinemia	77 (35.5)	139 (32.9)	0.441	0.507
Sepsis	21 (9.7)	23 (5.4)	4.027	0.045
IVH	15 (6.9)	30 (7.1)	0.007	0.933
HIE	20 (9.2)	33 (7.8)	0.378	0.539
BPD	9 (4.1)	10 (2.4)	1.584	0.208
NEC	3 (1.4)	5 (1.2)	0.026	0.872
Mortality	7 (3.2)	8 (1.9)	1.116	0.291
B, <32 weeks' gestation				
Mortality and morbidities	GDM (n=69)	NonGDM (n=121)	χ^2 -value	P-value
Pneumonia	67 (97.1)	110 (90.9)	2.644	0.104
RDS	61 (88.4)	92 (76.0)	4.290	0.038
Hypoglycemia	11 (15.9)	14 (11.6)	0.735	0.391
Hyperbilirubinemia	23 (33.3)	44 (36.4)	0.177	0.674
Sepsis	12 (17.4)	10 (8.3)	3.575	0.059
IVH	5 (7.2)	11 (9.1)	0.194	0.660
HIE	5 (7.2)	14 (11.6)	0.913	0.339
BPD	9 (13.0)	10 (8.3)	1.115	0.291
NEC	3 (4.3)	4 (3.3)	0.001	0.975
Mortality	7 (10.1)	7 (5.8)	1.224	0.269
C, 32-34 weeks' gestation				
Mortality and morbidities	GDM (n=68)	NonGDM (n=125)	χ^2 -value	P-value
Pneumonia	53 (77.9)	100 (80)	0.114	0.736
RDS	26 (38.2)	21 (16.8)	10.985	<0.001
Hypoglycemia	8 (11.8)	13 (10.4)	0.085	0.771
Hyperbilirubinemia	31 (45.6)	46 (36.8)	1.419	0.234
Sepsis	3 (4.4)	5 (4.0)	0.058	0.810
IVH	7 (10.3)	7 (5.6)	1.442	0.230
HIE	10 (14.7)	11 (8.8)	1.584	0.208
BPD	0 (0)	0 (0)		
NEC	0 (0)	1 (0.8)	0.096	0.757
Mortality	0 (0)	0 (0)		
D, 34-37 weeks' gestation				
Mortality and morbidities	GDM (n=80)	NonGDM (n=179)	χ^2 -value	P-value
Pneumonia	58 (72.5)	127 (70.9)	0.065	0.799
RDS	9 (11.3)	18 (10.1)	0.084	0.772
Hypoglycemia	16 (20)	26 (14.5)	1.220	0.269
Hyperbilirubinemia	23 (28.8)	49 (27.4)	0.052	0.820
Sepsis	6 (7.5)	8 (4.5)	0.993	0.319
IVH	3 (3.8)	12 (6.7)	0.426	0.514

Table III. Continued.

D, 34-37 weeks' gestation				
Mortality and morbidities	GDM (n=80)	NonGDM (n=179)	χ^2 -value	P-value
HIE	5 (6.3)	8 (4.5)	0.368	0.544
BPD	0 (0)	0 (0)		
NEC	0 (0)	0 (0)		
Mortality	0 (0)	1 (0.6)	0.172	0.678

Data are presented as n (%). GDM, gestational diabetes mellitus; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; HIE, hypoxic-ischemic encephalopathy; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis.

Table IV. Logistic regression analysis on morbidities among preterm infants born to women with or without GDM.

Variable	P-value	OR (95% CI)
RDS	0.003	1.699 (1.699-1.699)
Hypoglycemia	0.360	0.706 (0.442-1.121)
Sepsis	0.904	1.185 (0.571-2.459)

GDM, gestational diabetes mellitus; RDS, respiratory distress syndrome; OR, odds ratio; CI, confidence interval.

This may be associated with the target of preterm births who were hospitalized. When pregnant women experience premature rupture of membranes, placental abruption, severe preeclampsia or eclampsia and fetal distress occurs, termination of pregnancy must be performed at the first opportunity in consideration of the safety of both the mother and fetus. This procedure must also be performed regardless of whether the fetus is full term. This can not only increase the incidence rate of preterm delivery, but can also increase the rate of cesarean section whilst reducing the rate of macrosomia. In the present study, the incidence rate of severe preeclampsia, placental abruption and fetal distress was found to be increased in the non-GDM group compared with that in the GDM group. By contrast, the rate of cesarean sections was found to be increased in the non-GDM group, but there was no significant difference compared with that in the GDM group.

A previous study reported that the incidence of neonatal complications in mothers with diabetes is 3-4 times higher compared with that in mothers without diabetes (22). In the present study, no significant differences were observed between the two groups in terms of newborn sex, gestational age, birth weight, Apgar score and hospitalization time. The results from the present study suggested that GDM was associated with an increased risk of RDS morbidity in preterm infants, which is consistent with the findings of Robert *et al* (23). Further analysis found that among the different gestational ages of preterm infants born to mothers with and without GDM, the most significant difference in incidence rate of RDS was in the 32-34-week-old group ($P<0.001$), followed by the <32 -week-old group ($P<0.05$). However, in the VLBWI group, there was no

significant difference in the incidence rate of RDS between the GDM and non-GDM groups, which may be associated with the gestational age being mostly <32 weeks in the non-GDM group. This suggested that lung immaturity remains a major risk factor for respiratory distress when the infant is premature, regardless of whether the mother was suffering from diabetes during pregnancy. With the increase in gestational age, GDM aggravates this lung immaturity further, because maternal hyperglycemia can lead to fetal hyperglycemia and hyperinsulinemia. The pathological mechanism of impairments in fetal lung maturity is considered to be a secondary effect of insulin on cortisol. The production of phospholipids necessary for fetal lung maturation is ultimately the product of a cascade of reactions triggered by cortisol on lung fibroblasts. Since insulin can block the effect of cortisol on fibroblasts, the synthesis of pulmonary surfactant will then be reduced (24).

The present study also found that the incidence rate of sepsis in the GDM group was significantly higher compared with that in the non-GDM group ($P<0.05$) and this was also observed in the VLBWI group. In addition, preterm infants born to mothers with GDM had longer anti-infection times compared with those in preterm infants born to mothers without diabetes ($P<0.05$). This may be due to fetal hyperglycemia. Maternal hyperglycemia leads to subsequent fetal hyperglycemia, which can then induce disorders in glucose metabolism in leukocytes and reduce glycolytic ability while also reducing the chemotactic, phagocytic and bactericidal abilities of neutrophils. In addition, hyperglycemia is conducive to the growth and reproduction of pathogenic microorganisms, causing respiratory tract, urinary tract and skin infections. Pathogenic microorganisms can then invade the blood circulation, grow, reproduce and produce toxins to induce sepsis (25).

In the present study, preterm infants of mothers with GDM had a higher rate of hypoglycemia, especially in VLBWI ($P<0.05$). This may be due to fetal dependence on maternal hyperglycemia (fetal hyperinsulinemia), such that following delivery, the mother's blood sugar supply becomes suddenly interrupted, these babies are then at an increased risk of hypoglycemic shock, which can contribute to brain injury if not managed carefully (26). Severe hypoglycemia occurs continuously or repeatedly and can not only cause damage to the central nervous system, but also lead to mortality. In the present study, the mortality rate in preterm infants had a higher rate of hypoglycemia in the GDM group compared

Table V. Mortality and morbidities among very low birth weight infants (birth weight, <1,500 g) born to women with or without GDM.

Characteristic	GDM (n=37)	NonGDM (n=61)	χ^2 -value	P-value
Gestational age, weeks				
<32	31 (83.8)	57 (93.4)	2.345	0.126
32-34	6 (16.2)	4 (6.6)	1.409	0.235
Pneumonia	35 (94.6)	53 (86.9)	1.494	0.222
RDS	32 (86.5)	51 (83.6)	0.147	0.701
Hyperbilirubinemia	13 (35.1)	21 (34.4)	0.005	0.944
Hypoglycemia	9 (24.3)	5 (8.2)	4.892	0.027
Sepsis	10 (27.0)	7 (11.5)	3.885	0.049
BPD	9 (24.3)	7 (11.5)	2.783	0.095
HIE	2 (5.4)	9 (14.8)	1.191	0.275
IVH	2 (5.4)	4 (6.6)	0.042	0.838
NEC	3 (8.1)	2 (3.3)	0.336	0.562
Mortality	3 (8.1)	6 (9.8)	0.005	0.944

Data are presented as n (%). GDM, gestational diabetes mellitus; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

with that in the non-GDM group (57.1 vs. 25%). However, this difference did not reach statistical significance, which may be due to the small sample size.

Also in the present study, NEC and BPD among VLBWI born from mothers with GDM was found to be 2.5 and 2.1 times higher, respectively, compared with those born from mothers without GDM, but the difference was not statistically significant. This may be because the sample size was relatively small. A Latin American study involving 11,991 mothers with diabetes previously reported the association between diabetes and an increased risk of NEC in VLBWI (27). Therefore, it is possible that GDM may be associated with an increased risk of NEC and BPD among VLBWI from mothers with GDM in larger sample sizes. This needs to be tested in the future by increasing the sample size. NEC and BPD are both diseases that can not only threaten the life of preterm infants, but can also significantly affect the prognosis and quality of life of the preterm infants. A number of studies have shown that a controlled diet, reasonable exercise and lifestyle improvements can effectively reduce the risk of GDM during the first or second trimester of pregnancy (28-30). This therefore suggests that altering the lifestyle can serve an important role in the management of pregnant women with GDM, which can then reduce the risk of complications in preterm infants.

A limitation of the present study is its retrospective nature with a relatively small cohort and the lack of data on the initial management of GDM, glycemic control and maternal body-mass index (BMI) of the mothers of preterm infants. These may have affected the results. Therefore, future studies should be performed prospectively in larger cohorts with the implementation of intervention strategies, such as glycemic control, maternal BMI and the prevention of complications in the mothers. It is only in this manner can the etiology of neonatal complications reported in the present study be truly

explored, with the ultimate aim of effectively reducing the risk of GDM-associated complications in mothers and preterm infants.

In conclusion, the present study revealed the effect of GDM on the incidence of short-term adverse perinatal outcomes of pregnant women and preterm infants. These adverse perinatal outcomes can have long-term adverse health consequences, such as increasing the risk of type 2 diabetes and cardiovascular disease in mothers, while also increasing the risk of obesity, hypertension and type 2 diabetes in the offspring later in life (31,32). Therefore, pregnant women with GDM should be diagnosed and treated early to improve both short- and long-term infant outcome. Achieving the term delivery of a healthy baby from women with GDM should be the ultimate goal.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CHZ and PLZ confirm the authenticity of all the raw data. CHZ wrote the manuscript. CHZ and PLZ conceived and designed the study, worked on total efficiency evaluation and

collected the data. CHZ analyzed and interpreted the patient data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by The Ethics Committee of Qilu Hospital of Shandong University (approval no. KYLL-KS-2023144; Qingdao, China). Patients who participated in this research had complete clinical data.

Patient consent for publication

Written informed consent was obtained from the parents of the pediatric patients.

Competing interests

The authors declare that they have no competing interests.

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