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Does gestational diabetes mellitus affect respiratory outcome in late-preterm infants?

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ABSTRACT

Background: Both gestational diabetes mellitus (GDM) and late-preterm delivery at 34–36 weeks' gestation are independently associated with neonatal respiratory complications, but it is unknown whether their combination increases further its risk. We therefore appraised the independent effect of GDM on the respiratory outcome of late-preterm infants.

Methods: In a retrospective cohort study, respiratory outcome of 911 infants delivered at 34–36 weeks' gestation between 1 January 2009 and 30 August 2012 from mothers with GDM (study group, n = 130) was compared with infants delivered at the same gestation by mothers without GDM (control group, n = 781).

Results: The study group had significantly higher incidence of transient tachypnoea of newborn (TTN, p = 0.02) and air leak (p = 0.012), and required more respiratory support, including oxygen, continuous positive airway pressure (CPAP), mechanical ventilation and neonatal intensive care, with a longer length of hospital stay, but not duration on respiratory support. On logistic regression analysis, GDM is an independent risk factor for TTN (aOR = 1.5, 95% C.I.1.0–2.4), CPAP (aOR = 2.37, 95% C.I. 1.05–4.89), mechanical ventilation (aOR = 4.02 95% C.I. 1.57–10.32) and neonatal intensive care (aOR 1.83, 95% C.I. 1.05–3.87).

Conclusions: Our results demonstrated an independent effect of GDM on the risk of severe respiratory complications in late-preterm infants. Additional close monitoring and timely intervention are necessary in the management of these infants.

1. Introduction

Of all the perinatal complications associated with gestational diabetes mellitus (GDM), neonatal respiratory complications are one of the commonest and potentially the most serious and life-threatening morbidity that may be encountered [1,2]. Globally, the incidence of respiratory complications in infants of mothers with GDM is as high as 34%, with a 4–6% incidence of respiratory distress syndrome (RDS) [3]. The risk of transient tachypnoea of newborn (TTN) is also increased 2–3 times compared to infants delivered from non-diabetic pregnancies [3,4]. In the Chinese population in Hong Kong, there is a 3.4-fold overall increased risk of neonatal respiratory complications for infants from diabetic pregnancies compared to controls [5]. GDM is also associated with increased late-preterm delivery [6–8], with up to 22% infants from mothers with GDM delivering between $34^0/_7$–$36^6/_7$ weeks' gestation [1,3]. There is now abundant evidence that neonates delivered at 34–36 weeks are at increased risk of neonatal complications, leading to significant morbidity and mortality [9–14]. One large epidemiological study has shown that compared to term infants at 39 weeks, the adjusted odds ratio (aOR) for RDS at 34 weeks was 40.1 and that for TTN was 14.7; at 35 weeks, 21.9 and 11.1; and at 36 weeks, 9.1 and 6.1; respectively [15]. Therefore, an increase in late-preterm births could also have contributed to the higher rate of neonatal respiratory complications associated with GDM.

Although it is well-established that both GDM and late-prematurity are risk factors for respiratory morbidity, no reported studies have targeted neonatal outcome of GDM in late-preterm deliveries. It is not known whether GDM confers any independent and additional risk for respiratory morbidity in late-preterm infants. A recent study [16] showed that maternal GDM and late-prematurity are independent risk factors for severe neonatal respiratory morbidities requiring neonatal intensive unit (NICU) care. However, the effect of GDM together with late-prematurity, and the risk of less severe morbidities which nevertheless required interventions, were not investigated. This retrospective cohort study was therefore conducted to examine the additional impact of GDM on respiratory outcome of late-preterm infants. Our results will provide information from the neonatal perspective to facilitate obstetric decision-making in pregnancies complicated by GDM, and to enhance

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neonatal management for infants from GDM pregnancies delivered at the 34–36 week period.

2. Materials and methods

Our hospital is a tertiary referral centre with an annual delivery rate of >5000. Gestational age was determined by the last menstrual period and verified by first trimester dating ultrasonography, with further confirmation by Ballad score assessment [17] by neonatologist after delivery. Universal screening for GDM has been adopted in our centre. Women with known risk factors for GDM would undergo the oral glucose tolerance test (OGTT) at 24 weeks and repeated 8 weeks later if the first test was normal. For normal risk women, a random venous blood glucose testing is performed at 24 weeks. Women with random glucose level of 6 mmol/L or above, irrespective of the time of last meal, would be further assessed by the WHO 75 g OGTT [18]. Those with results falling into either impaired glucose tolerance (IGT), or diabetes mellitus, are all managed as GDM. Monitoring of glycaemic control and subsequent management of these mothers conforms to internationally accepted guidelines. Paediatricians are called to standby at delivery for resuscitation of high risk infants. All late-preterm infants, irrespective of maternal diagnosis, are admitted to the neonatal unit for monitoring of vital signs and blood glucose. Appropriate treatment is given where necessary. The maternal and neonatal diagnoses are coded under the ICD system and entered into a computer database. Both obstetric and neonatal data such as maternal and neonatal demographics, maternal illnesses, pregnancy and intrapartum complications; neonatal diagnoses and procedures, neonatal unit admission, and length of hospital stay are captured and entered by obstetricians and neonatologists.

This is a retrospective cohort study covering the period 1 January 2009 to 30 August 2012 and included all liveborn infants delivered at the gestation of $34^0/_7$ to $36^6/_7$ weeks. Infants born to mothers with a diagnosis of GDM or pre-existing DM constituted the study group. The control group consists of the late-preterm infants from all non-diabetic pregnancies. Infants with major congenital malformations, chromosomal abnormalities, anatomical defects affecting lung development, and stillbirths were excluded from the analysis. Both obstetric and neonatal data retrieved from the aforementioned electronic database, including the neonatal diagnoses coding (ICD-9), and electronic inpatient discharge summaries for each infant were reviewed by the principal investigator. Where there was discrepancy between coding and electronic discharge summary, or missing data, hard copies of the case notes were retrieved for verification to ensure accurate data collection. Ethics approval for the study was obtained from the local Ethics Committee. The period reviewed for each case was from the time of delivery until discharge from hospital or death.

For analysis, respiratory complications were compared between the two groups. RDS, TTN and pneumonia are defined by characteristic chest radiographic changes together with typical clinical course for the condition. Air leak was defined as pneumothorax or pneumomediastinum on chest radiograph. Persistent pulmonary hypertension of newborn (PPHN) was defined as intrapulmonary shunting as evidenced by significant pre/post-ductal SpO2 difference and confirmed by echocardiogram. Apnoea was defined by cessation of respiration for >20 s associated with desaturation and/or bradycardia. Infants were also compared according to the intervention or treatment required, including oxygen therapy, defined as need for oxygen supplement for over 4 h; continuous positive airway pressure (CPAP); and mechanical ventilation, defined as need for intubation and any form of mechanical ventilation for over 4 h. Another measure of intervention included admission to neonatal intensive care unit (NICU) for over 12 h. The duration of each intervention as well as the length of stay was also examined.

Statistical analysis was performed using the SPSS 20.0 software (SPSS Inc, Chicago, IL). Categorical data were compared using the Chi-square test or Fisher Exact test (for cells less than 5), and odds ratio (OR) with 95% confidence interval (C.I.) was calculated. Continuous variables were compared using the independent t test or Mann–Whitney U test. Multivariate logistic regression was used to determine the effect of maternal GDM on neonatal outcome parameters. A two-sided p-value of ≤ 0.05 is considered significant.

3. Results

During the study period, there were a total of 929 livebirths delivered between $34^0/_7$ to $36^6/_7$ weeks, giving an overall incidence of late preterm birth of 4.78%. Of the 929 infants, 18(1.9%) were excluded because of major congenital anomalies, chromosomal abnormalities, and incomplete data, including 3 neonatal deaths related to major congenital anomalies (one with diaphragmatic hernia, one with omphalocoele and one with pulmonary hypoplasia). Among the remaining 911 infants in the final cohort, 130 (14.3%) were in the study group. There was a significantly higher maternal age (33.8 ± 4.2 vs 30.4 ± 5.4 years, $p < 0.001$), and total Caesarean section rate (43.3% vs 32.7%, $p = 0.02$) as well as elective Caesarean rate (10.7% vs 4.8%, $p = 0.006$) in the study group (Table 1). It was not the hospital protocol to give antenatal steroids routinely after 34 weeks' gestation, but a significantly higher percentage of the mothers in the study group had received antenatal steroids (10% vs 4.6%, $p = 0.001$).

As for respiratory complications, only TTN (OR 1.46, 95% C.I. 1.09–1.97) and air leak (OR 18.3, 95% C.I. 1.89–177.1) were significantly increased in the study group, while the incidences of RDS, apnoea, pneumonia and PPHN were similar between the two groups (Table 2). Admission to NICU was increased in the study group (OR 2.11, 95% CI 1.28–3.49), together with a longer length of stay (4 days vs 2 days, $p = 0.047$). Significantly more infants in the study group required respiratory support in terms of oxygen therapy (OR 1.81, 95% CI 1.11–2.25), CPAP (OR 2.18, 95% CI 1.45–3.29), and mechanical ventilation (OR 3.11, 95% CI 1.30–7.42), but the duration of intervention was similar between the two groups (Table 3).

To determine the independent effect of maternal GDM on respiratory complications, multivariate logistic regression analysis was performed after adjustment for gender, advanced maternal age, SGA,

Table 1
Maternal and neonatal demographic features of late-preterm infants with and without GDM.

	GDM (n = 130)	Non-GDM (n = 781)	p-Value
Maternal age (yrs)*	33.8 ± 4.2	30.4 ± 5.4	<0.005
Nulliparas (%)	45.4	53.1	0.11
Hypertensive diseases (%)[a]	12.3	9.9	0.43
Antepartum haemorrhage (%)	5.4	9.1	0.18
Other diseases (%)[b]	7.7	3.7	0.06
Antenatal steroids (%)	10	4.6	0.01
Tocolytics (%)	0.8	1.0	NS
Labour induction (%)	6.2	9.0	0.32
Caesarean delivery (%)	43.0	32.7	0.02
Elective Caesarean (%)	10.7	4.6	0.006
Gestation (wks)*	35.3 ± 0.8	35.4 ± 0.8	0.36
Male (%)	47.7	56.2	0.09
Birth weight (g)*	2470 ± 524	2525 ± 429	0.25
LGA (%)	4.6	3.8	0.81
SGA (%)	10	9.2	0.87
Congenital anomalies (%)[c]	5.4	4.5	0.32

Analysis by chi square test or t-test as indicated *.
Key: LGA = large for gestation, defined as birth weight > 2 s.d. above mean for gestation. SGA = small for gestation, defined as birth weight < 2 s.d. below mean for gestation. APH = antepartum haemorrhage.
[a] Includes maternal hypertensive disorders in pregnancy (pre-exisiting hypertension, pregnancy induced hypertension, PET and eclampsia).
[b] Includes maternal co-existing diseases other than hypertension (eg cardiac, thyroid, autoimmune diseases).
[c] Includes all minor congenital anomalies. Major congenital anomalies and chromosomal disorders are already excluded from the study.