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Effects of Maternal Diabetes on Respiratory Outcomes of Moderately Preterm Infants: Have We Made Progress?

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Abstract

Infants of diabetic mothers (IDMs) are at increased risk of respiratory distress syndrome (RDS) due to inhibitory effects on surfactant production.

Objective: To compare respiratory outcomes of 29 0/7–32 6/7 weeks IDM vs non-IDM in the current era of improved diabetes management

Methods: Retrospective data collected from neonates admitted to Rainbow Babies and Children's Hospital NICU (n = 387) in 2019–2022.

Results: Among the 387, 15.8% were IDM. Mean GA was 31.1 weeks. RDS occurred in 67.5%, with no difference between groups. Surfactant use was higher in IDMs (47%) vs. non-IDMs (36%). Peak FiO2 at 4–24 hours of age and time to wean to 21% were both significantly increased in IDMs ($p \leq 0.03$).

Conclusion: Despite improvements in maternal diabetes management, IDMs still have greater need for supplemental oxygen and positive pressure. Further work is needed to fully understand the effects of MDM on respiratory morbidity in moderately preterm infants.

Introduction

Rates of type 1 diabetes mellitus (T1DM), type 2 DM (T2DM), and gestational DM (GDM) during pregnancy are increasing globally[1]. The increased prevalence of T2DM and GDM correlates with an increased incidence of obesity and an increased average maternal age at conception[2–5]. Conversely, the factors contributing to the increasing incidence of T1DM are not currently well-understood[6]. The International Diabetes Federation estimated that in 2024 roughly 1 in 5 live births worldwide were affected by hyperglycemia in pregnancy[7]. Infants of diabetic mothers (IDMs) are more likely to develop congenital anomalies, macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, and neonatal respiratory distress syndrome, among other morbidities [8–11].

Neonatal respiratory distress syndrome (RDS) is one of the most common causes of morbidity and mortality in preterm infants, due to primary surfactant deficiency related to lung immaturity[12, 13]. It is characterized by increased work of breathing, a supplemental oxygen requirement, and characteristic chest X-ray findings shortly after birth[14]. In a 1976 study, Robert et al. found that IDMs are 5.6 times more likely to develop RDS after controlling for confounding factors such as gestational age and delivery method[15]. In the decades since, molecular research has revealed that maternal hyperglycemia and the resulting fetal hyperinsulinism have an inhibitory effect on fetal surfactant synthesis and maturation[16].

Since the 1970s, when the relationship between MDM and neonatal RDS was established, medical management of diabetes prior to and during pregnancy has significantly improved with valuable tools for achieving better glycemic control to improve both maternal and neonatal outcomes[17–20]. Standards for frequent fetal surveillance have been established, and the technology used for said surveillance has

advanced over time. Given these advances, our study aimed to evaluate the effect of MDM on respiratory outcomes among moderately preterm infants in the modern era of MDM management.

Our primary goal was to evaluate if there would be differences in respiratory outcomes among this subset of moderately preterm infants with MDM as the primary exposure. We hypothesized that infants exposed to MDM would have poorer respiratory outcomes compared with infants of non-diabetic mothers.

Methods

This is a retrospective population-based observational study. Institutional review board approval via University Hospitals was obtained prior to initiation of the study (IRB STUDY20210971). All infants admitted to the Rainbow Babies and Children's Neonatal Intensive Care Unit from 2019 to 2022 were eligible for inclusion. Inclusion criteria consisted of gestational age (GA) 29 0/7 weeks to 32 6/7 weeks. This GA range was chosen based on a prior pilot data collection to minimize the confounding effects of GA on the development of RDS at both very low GA when nearly all would have RDS, and at higher GA when very few would have RDS. We included both inborn and outborn infants. Infants without maternal information available were excluded.

All data were collected retrospectively from the electronic medical record of all mother-infant dyads and stored in a REDCap database. Maternal information collected included diabetic status and type of DM (T1DM, T2DM, GDM), first trimester hemoglobin A1c (A1c), pre-pregnancy weight and body mass index, delivery method, and any antenatal steroid administration. Infant data included birth weight and birth weight percentile, degree and duration of respiratory support, diagnosis of RDS, fraction of inspired oxygen (FiO_2) need, and need for surfactant administration. Finding a universally accepted diagnostic criteria for RDS was challenging. We used the Vermont Oxford Network (VON) definition of RDS, defined as; "*when infant has … a necessity for additional oxygen to maintain a PaO2 greater than 50mmHg, or a blood oxygenation level over 85% within the first 24 hours of life and …if he or she has "a chest radiograph consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life*[14],"

The statistical software used was STATA 15.1 (StataCorp, College Station, TX, USA). Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using Student's *t*-test or Wilcoxon rank sum test, based on normality. A P value < 0.05 was considered significant.

Results

A total of 387 mother-infant dyads were included. Among the 387 infants, 15.8% (n = 61) of mothers had diabetes. Of those 61 pregnancies complicated by MDM, 44% had pre-gestational diabetes (T1DM and

T2DM), and 56% had GDM (Fig. 1). Of all 387 infants, 7% (n = 27) were exposed to pre-gestational diabetes (3% T1DM, 4%T2DM) and 9% (N = 34) were exposed to GDM.

By design, the mean (SD) GA was 31.1(1.1) weeks (Table 1). The IDM and non-IDM groups did not differ by birthweight, GA, or male-female distribution. However, there were differences in birthweight across the individual DM groups of infants (T1DM, T2DM, GDM, no IDM, p = 0.004, by ANOVA) with T1DM infants having higher birthweight compared to non-IDMs in post-hoc analysis (p = 0.012, by *post-hoc* Sidak test). There was no significant difference among groups in antenatal steroid administration (at least one dose), delivery modality (vaginal versus cesarean-section), or maternal early pregnancy A1c. There was an overall high caesarean-section (C/S) rate in both groups, though we did note that those with pregestational DM (combined T1DM & T2DM) had a significantly increased C/S rate (84.6%) compared to those without DM (62.2%) (P = 0.032, by Fisher's exact test). Additionally, mothers with DM were more likely to have obesity (P < 0.01, chi square test) with rates varying with type of DM.

We assessed several respiratory outcomes related to RDS since it was known previously that IDMs are at increased risk for developing RDS. Using the VON RDS definition, 67.5% of infants had RDS (Table 2), and there was no difference between the IDM and non-IDM groups. There was a trend in surfactant administration with IDMs receiving more surfactant (47%) vs non-IDM (34%) (p < 0.1, by Fisher's exact test). IDMs also tended to have more days on positive pressure respiratory support, 5 days versus 3 days for non-IDMs (p < 0.1, by Wilcoxon rank sum test) and there was a trend toward higher respiratory support for IDMs (Table 2, Fig. 2). Significant differences include the peak oxygen need during the first 4–24 hours of age and time to wean to 21% FiO2 in IDMs (p < 0.05, by Wilcoxon rank sum test).

Discussion

The impact of MDM on the neonate is variable, and RDS is not consistently observed in all IDMs. Based on current evidence, it remains unclear whether glycemic control during pregnancy, mode of delivery, antenatal corticosteroid administration, or other maternal and neonatal factors directly influence the clinical diagnosis of RDS in moderate to late preterm IDMs. Another challenge is standardizing the diagnosis of RDS. As we encountered during the design of our study, objectively diagnosing RDS was difficult; a prospective cohort would have been preferable for more accurate assessment. Population studies have examined the relationship between MDM and RDS, as well as its impact on neonatal outcomes; however, few studies in the last decade have specifically evaluated surfactant use and oxygen requirements in moderately preterm IDMs and non-IDM infants.

Strengths of our study include a focus on moderately preterm infants and the reporting of detailed respiratory outcomes, including supplemental oxygen requirement, duration of positive pressure support (defined as > 2 L nasal cannula), and peak FiO_2 in the early postnatal period.

Looking at similar studies, a large cohort of 15,874 infants from 28 centers (born between 1995–2007, 24–33 weeks GA) found that maternal diabetes was not a significant risk factor for RDS, and this finding did not change when comparing pregestational diabetes (type 1 or type 2) with gestational diabetes[21].

The wide gestational age range in this study may have influenced the results; additionally, VON's broad definition of RDS used in this study posed similar challenges to those we encountered. In contrast to our study, evaluating respiratory causes of NICU admissions, MDM was found to be a risk factor for RDS in infants with a mean GA of 34.49 ± 3.31 weeks, however the definition of RDS was not clearly specified [22]. Supporting this, Vignoles et al. demonstrated that GDM was an independent risk factor for respiratory failure in neonates born at > 34 weeks[23]. Similarly, although RDS was not statistically significant in some studies, late preterm infants born to mothers with GDM had higher rates of transient tachypnea of the newborn (TTN), air leak syndrome, and increased use of CPAP and mechanical ventilation[24].

Several studies have examined respiratory outcomes in relation to maternal glycemic control. Infants of mothers requiring insulin treatment had higher rates of respiratory disease compared to those managed with lifestyle modifications[25]. A recent prospective study of term infants found that even with optimal glycemic control, IDMs had significantly higher rates of respiratory disorders compared to controls (19.5% vs. 3%)[26]. This raises the possibility of clinical bias, in which providers may be more likely to initiate respiratory support in IDMs based on perceived risk—a potential "self-fulfilling prophecy."

A randomized controlled trial (TOBOGM) evaluating early screening and treatment of GDM in patient at high risk of dysglycemia demonstrated lower rates of RDS in the early treatment group [27]. RDS in that study was defined as "*respiratory distress warranting ≥ 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation [or combinations thereof] during the 24 hours after birth*". However, gestational ages of affected infants were not specified, and prematurity may have confounded the findings. Furthermore, that study evaluated screening and treatment of "early onset" GDM < 20 weeks, which the American College of Obstetricians Gynecologists currently recommends against [28].

In the above studies, as well as ours, MDM has been consistently shown to increase respiratory morbidities across different gestational ages. One of the strengths in our study is that in addition to a "yes/no RDS" outcome we collected detailed respiratory data and found that IDMs had a significantly longer period of supplemental oxygen support as well as a longer duration of positive pressure. Although surfactant administration was not statistically significantly different, there was a trend toward higher usage in IDMs, which aligns with other studies clinically and with the concept of impaired surfactant synthesis at the molecular level, but also may be confounded by the previously stated bias. Our study has limitations including the retrospective nature of chart review, maternal glycemic control during pregnancy and labor, length of stay, and data on maternal preeclampsia or pregnancy related hypertension disorders were not collected. The distribution of gestational diabetes in our population was similar to the national average as about 8% of women in the United States had gestational diabetes in 2023[29] compared to 8.8% in our population.

Conclusion

Our study addresses a clinical knowledge gap regarding the moderately preterm infant's respiratory outcomes in the setting of MDM. Findings are consistent with other studies demonstrating that IDMs remain at increased risk for higher respiratory support needs in the immediate neonatal period even in the modern MDM management era. However, our study suggests fewer differences in RDS specific outcomes than previously thought. Despite advances in diabetes management, IDMs continue to require prolonged respiratory support, which not only affects the short-term respiratory outcome but may have a negative impact on maternal-fetal bonding, oral feeding - including delayed breastfeeding, and contribute to increased length of hospital stay. The long-term impact of this early respiratory morbidity remains unclear. Further research is needed to better classify RDS as a clinical research outcome, and to understand the complex effects of maternal diabetes on respiratory outcomes in moderately preterm infants.

Declarations

Conflict of Interest

Authors have no conflict of interest to report.

Author Contributions

RMR and CTN provided leadership and supervision in designing the study. HYA designed the study, built the REDCap data base, and collected data. NSA, SK, RH and MP all collected data. RMR performed the statistical analyses. SK created figures. All authors significantly contributed to major revisions of the manuscript. All authors read and agreed to the last version of the manuscript.

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Tables

Tables are available in the Supplementary Files section.

Figures

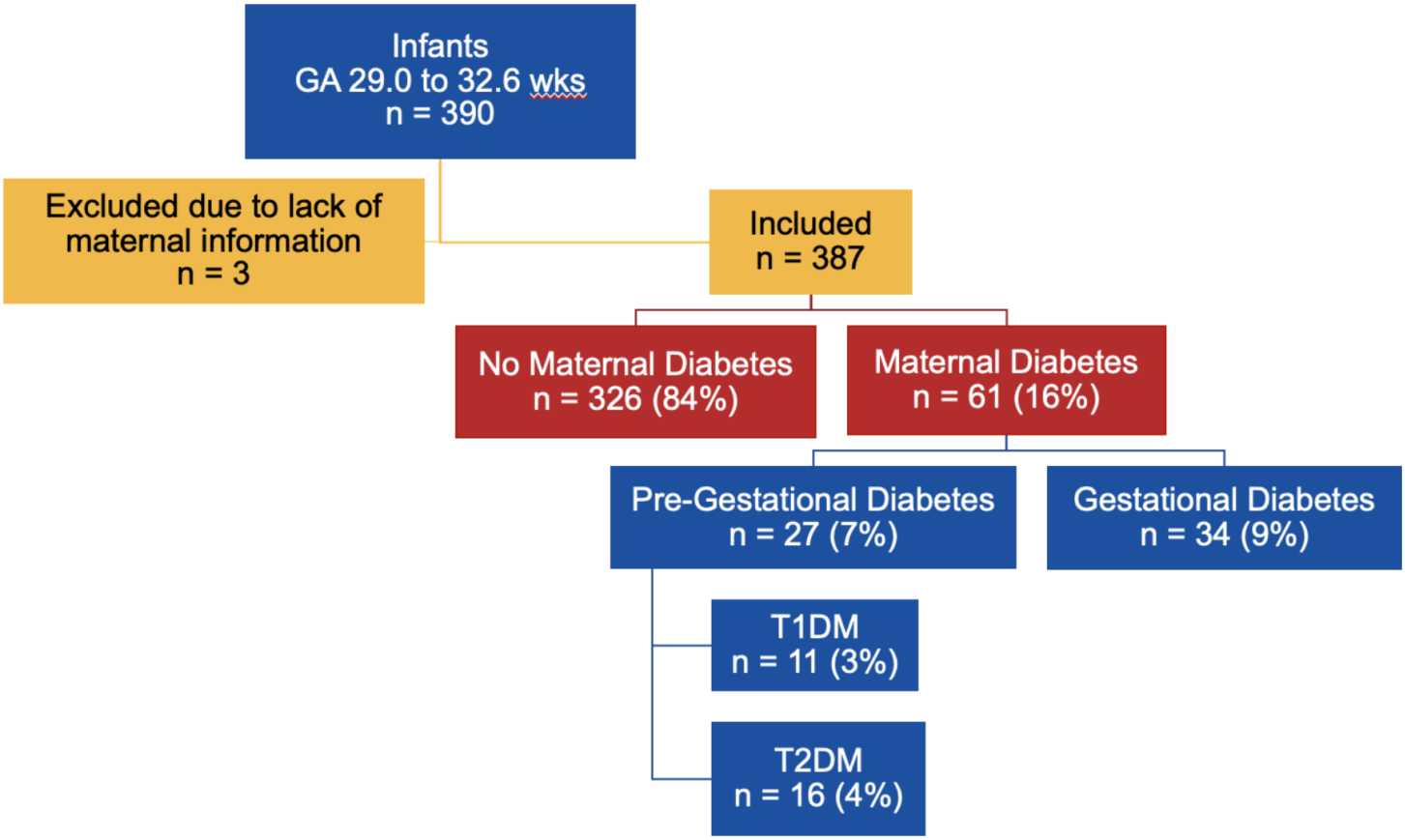


Figure 1: CONSORT Diagram
GA: Gestational Age, T1DM: Type1 Diabetes Mellitus, T2DM: Type2 Diabetes Mellitus

Figure 1

See image above for figure legend

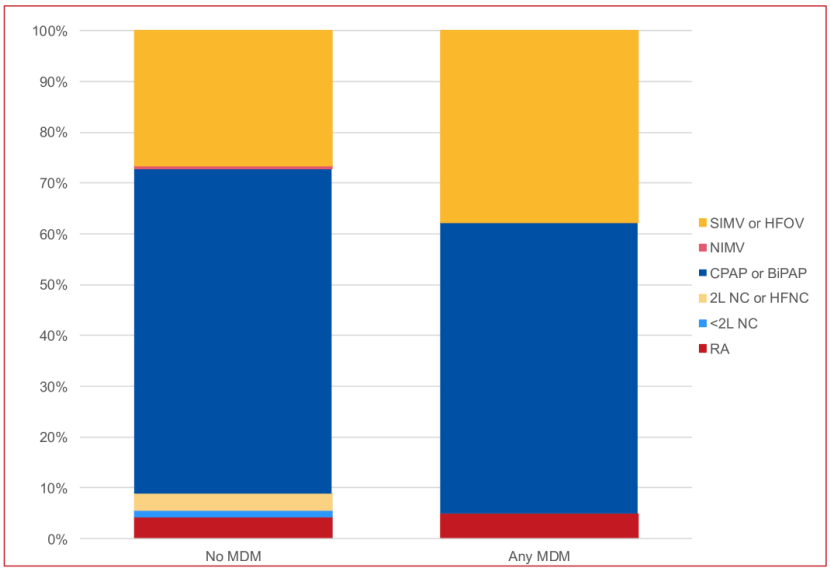


Figure2: Respiratory support between 4-24 hours.

MDM: Maternal Diabetes Mellitus, SIMV: Synchronized Invasive Mechanical Ventilation, HFOV: High Frequency Oscillator Ventilation, NIMV: Non-Invasive Mechanical Ventilation, CPAP, continuous positive pressure, BiPAP: Bi-level CPAP, NC: Nasal Cannula, HFNC: High Flow Nasal Cannula, RA: Room Air

Figure 2

See image above for figure legend

Supplementary Files

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- Table1.docx
- Table2.docx