

Fellows Column: Neonatal Respiratory Distress Syndrome in Near-Term to Full-Term Infants of Diabetic Mothers

Mona Singh, OSM IV, Mitchell Goldstein, MD, MBA, CML

Key Terms: *IDM, NRDS, term, surfactant, DM, hyperinsulinemia Abstract*

Neonatal Respiratory Distress Syndrome (NRDS) in infants of diabetic mothers (IDMs) is significantly influenced by maternal hyperglycemia and hyperinsulinemia, which impair surfactant production necessary for lung function. It is known that NRDS occurs in preterm infants, but research is limited on whether this occurs in near-term to full-term IDMs, which is what we discuss further in this paper. Studies indicate that maternal diabetes, both type 1 and type 2, increases the risk of NRDS, with hyperinsulinemia in the fetus inhibiting surfactant synthesis and contributing to respiratory complications. Furthermore, while insulin therapy manages maternal glucose levels, it can also be a risk factor for NRDS. Effective prenatal care, proper glycemic control, and further research into maternal HbA1C levels and insulin's role in surfactant production are essential for reducing NRDS incidence. Improved diagnostic criteria for gestational diabetes and enhanced management strategies can potentially prevent NRDS, benefiting neonatal outcomes globally.

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Introduction:

Neonatal Respiratory Distress Syndrome (NRDS) occurs secondary to either insufficient surfactant production or surfactant inactivation in the context of immature lungs. (Yadav, Lee, Kamity 2023). In respiratory distress syndrome (RDS), inadequate surfactant production decreases pulmonary compliance and increases surface tension. This increases the risk of alveoli collapse at expiration, followed by a reduction in total surface area for gaseous exchange and alveolar-capillary diffusion capacity. Hypoxia and hypercapnia develop due to the reduced surface area and alveolar-capillary diffusion capacity (Ma CC and Ma S 2012). Formerly, RDS was known as Hyaline Membrane Disease, and Avery and Mead first discovered the link between surfactant deficiency and clinical RDS in the 1950s.

When applied to a neonate, this is characterized as NRDS. NRDS is known to be a result of a preterm neonate being born before the age of 37 weeks, whether or not they are infants of diabetic mothers (IDMs). In 1959, Gellis and Hsia first described that IDMs had

increased mortality and morbidity due to RDS (Yildiz Atar, Baatz, Ryan 2021).

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There is a strong association between impaired glucose tolerance and diabetes during pregnancy with multiple fetal congenital anomalies, indicating that maternal hyperglycemia may be a significant teratogen to the growing fetus. Maternal HbA_{1c} correlation with congenital malformations was found in seven cohort studies from 1997 pregnancies. These pregnancies resulted in 117 live births with congenital anomalies. Maternal HbA_{1c} ≥14% resulted in a 20% congenital malformation rate, while an HbA_{1c} of 7.6% had a congenital malformation rate of approximately 4%. The other most common problems in IDMs include but are not limited to, hypoglycemia, hyperinsulinism, macrosomia, and RDS. (Yildiz Atar, Baatz, Ryan 2021). This shows that the higher the maternal HbA_{1c}, the greater the risk of the neonate developing congenital anomalies. Notably, glucose may be a teratogen to the growing fetus and could be a reason for its involvement in other disease processes such as NRDS.

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Insulin has also been shown to contribute to the development of NRDS as it can potentially inhibit fetal lung maturation. It also affects components of surfactant. Surfactant is made of various surfactant proteins, mainly A and B. Surfactant Protein A (SP-A) has also been shown to regulate surfactant phospholipid synthesis, secretion, and reuptake.

Surfactant Protein B (SP-B) is a low molecular weight, hydropho-

bic protein that significantly increases surfactant phospholipid absorption. SP-B enhances the uptake of phospholipids by type II cells in vitro and, therefore, like SP-A, may play a role in surfactant recycling. Insulin has been shown to inhibit the accumulation of mRNA for SPs A, and B. Insulin can potentially decrease surfactant proteins at the molecular level, further contributing to the development of NRDS because this would affect surfactant and lung maturation.

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Etiology of NRDS in IDMs of both type 1 and type 2 diabetes:

Infants of Diabetic Mothers (IDMs) have about a six-fold increased risk of RDS when compared to infants of the same gestational age born to nondiabetic mothers (Shattuck and Huff UTMB).

This is independent of the route of delivery (vaginal vs. c-section). Another retrospective analysis by Robert et al. showed that after controlling for other confounder factors, including gestational age (GA) and delivery route, IDMs have a 5.6 times greater risk of developing RDS than infants of nondiabetic gestation. In a recent prospective study of late preterm infants born to a mother with Gestational Diabetes Mellitus (GDM), GDM was found to be a significant risk factor for severe RDS. Severe RDS in this study was defined as clinical signs of early respiratory distress occurring within the first two hours following birth, with consistent radiologic features and oxygen dependence requiring invasive and/or non-invasive mechanical ventilation with a fraction of inspired oxygen (FIO_2) >0.25 for a minimum of 24 h and admission to a neonatal intensive care unit (NICU).

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UK's Confidential Enquiry into Maternal and Child Health (CEMACH) study between 2002 and 2007 was the most extensive study to date to investigate outcomes of pregnant women with type 1 and type 2 Diabetes Mellitus (DM) (Yildiz Atar, Baatz, Ryan 2021). In this study, macrosomia, NRDS, and shoulder dystocia neonatal outcomes were not significantly different between

maternal type 1 and type 2 DM. A systematic meta-analysis of studies performed throughout 1987–2008 compared fetal outcomes between type 1 and type 2 DM (total of 3781 and 7966 pregnancies, respectively) and did not reveal any statistically significant difference in NRDS. These results suggest that the type of diabetes does not influence NRDS outcome.

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Pathophysiology of NRDS in IDM:

Glucose homeostasis affects fetal growth and development throughout pregnancy. Insulin resistance in the mother increases physiologically during pregnancy, especially in the last trimester. Increased insulin resistance results in maternal energy coming more from fat metabolism, sparing carbohydrate usage by the rapidly growing fetus. This leads to both fetal hyperglycemia and hyperinsulinemia secondary to maternal diabetes (Yildiz Atar, Baatz, Ryan 2021). In order to compensate for the high levels of glucose in the mother, which transfer to the fetus through the placenta, the infant produces high levels of glucose as well as insulin as a result. Glucose is also an essential substrate for surfactant lipid synthesis. Insulin not only regulates glucose uptake to cells but also regulates surfactant synthesis. If insulin is high, it can inhibit components of surfactant synthesis. The fetal hyperinsulinemia secondary to maternal diabetes leads to decreased surfactant production and NRDS as a result (Yildiz Atar, Baatz, Ryan 2021). In IDMs, this compensation is exacerbated and, therefore, leads to hyperinsulinemia and NRDS as a result. Delayed lung maturation and increased risk of respiratory distress syndrome have been consistently observed among infants born to mothers with diabetes, and these findings are also observed in some rodent models of diabetes in pregnancy. (Azad et al., 2017).

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Accumulating evidence has proved that the placenta, as a selec-

tive barrier, makes adaptive changes to environmental and maternal factors and is involved in programming offspring health. It has been reported that pro-inflammatory responses and increased apoptotic rates in trophoblasts, increased trophoblast oxidative/nitritative stress, and reduced trophoblast mitochondrial respiration are related to the pathogenesis of GDM, which would lead to trophoblast dysfunction, impaired placenta development, restricted fetal growth, stillbirth, and neonatal respiratory distress syndrome (Chen et al., 2023).

“The study isolated and characterized the placenta-derived exosomes in normal and GDM umbilical cord blood plasma (NUB-exos and GDMUB-exos) and provided fresh evidence that the placenta-derived exosomes in GDM umbilical cord blood plasma can adversely affect the normal development of fetal lung by establishing in vitro, ex vivo and in vivo exosome exposure models.”

The study isolated and characterized the placenta-derived exosomes in normal and GDM umbilical cord blood plasma (NUB-exos and GDMUB-exos) and provided fresh evidence that the placenta-derived exosomes in GDM umbilical cord blood plasma can adversely affect the normal development of fetal lung by establishing *in vitro*, *ex vivo* and *in vivo* exosome exposure models. Placenta-derived exosomes are a heterogeneous group of exosomes secreted by various placental cells, and most of them are released by the syncytiotrophoblastic layer. They cultured human trophoblast HTR-8/SVneo cells with D-glucose (5 mM or 25 mM) for 48 h and isolated the exosomes (NC-exos and HG-exos) in conditioned media to further confirm the adverse effects of trophoblasts on lung development. Our study indicated that GDMUB-exos and

HG-exos significantly inhibited lung cell proliferation and promoted apoptosis, disturbing the imbalance between lung cell proliferation and apoptosis and impairing fetal lung development (Chen et al., 2023).

Various signaling pathways and transcription factors are known to play roles in branching morphogenesis. Sox9 is a marker of distal epithelial progenitor cells. Briana E. Rockich et al. demonstrated that epithelial-specific loss and gain of Sox9 caused severe branching defects in the lung, which developed large, cyst-like structures at the distal epithelial branch tips at all developmental times examined. Moreover, with lung bud growth, Sox9+ progenitor cells gradually extended to distal portions stimulated by FGF10 secreted by mesenchymal cells. The *ex vivo* study also found that after exposure to GDMUB-exos or HG-exos, the terminal buds and superficial areas of lung explants decreased, and the terminal buds developed large, cyst-like structures (Chen et al., 2023). In addition, in their *in vivo* assays, they found that at 18 months and five days post coitum (E18.5), fetal lungs exposed to GDMUB-exos or HG-exos showed lung morphology more comparable to that at E14.5–15.5, suggesting that GDMUB-exos or HG-exos result in delayed structural lung development. This shows that GDM can adversely affect trophoblasts and alter exosome contents, causing crosstalk disorder between trophoblasts and fetal lung

epithelial cells and leading to FLUD.

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Insulin Effect on Surfactant:

Increased insulin contributes to the development of NRDS by affecting surfactant components. Pulmonary surfactant is a complex molecule with a mixture of lipids (90%) and protein (10%) produced by type II alveolar epithelial cells (AEC2). Significant components of fetal lung maturation are the lecithin (PC)/sphingomyelin (L/S) ratio, presence of phosphatidylglycerol (PG), de-saturated phosphatidylcholine (DSPC), and lamellar body count. The effect of different insulin and glucose concentrations on glucose uptake, glucose metabolism, and surfactant synthesis were examined in AEC2 cultures by Engle et al. AEC2s derived from fetal rat lungs at 19 days of gestation (term = 21) were cultured in different insulin and glucose concentrations. Adding 10 units/mL of insulin caused a 35% increase in surfactant PC synthesis. However, 100 units/mL of insulin reduced PC synthesis to below control levels. The exposure to insulin (3 h vs. 24 h) did not change the result. These results indicate that a physiological level of insulin is a stimulatory hormone in surfactant synthesis, but a high insulin level can inhibit surfactant PC synthesis.

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Insulin Effect on Surface Proteins:

Increased systemic glucose and serum insulin concentrations in the fetus are potential inhibitors of fetal lung maturation and may contribute to the pathogenesis of NRDS in infants of DM mothers. Notably, it has been shown that increased insulin affects surfactant proteins A and B (Miakotina, Dekowski, Snyder 1998). Surfactant protein A (SP-A) is the major surfactant-associated protein and

may have a significant role in surfactant function and reutilization by type II cells. In addition to the developmental induction of surfactant glycerophospholipid synthesis, SP-A synthesis, and gene expression are initiated in fetal lung tissue (Mendelson, Acarregui, Odom, Boggaram 1991). SP-A has also been shown to regulate surfactant phospholipid synthesis, secretion, and reuptake. Surfactant Protein B (SP-B) is a low molecular weight, hydrophobic protein that significantly increases surfactant phospholipid absorption. SP-B enhances the uptake of phospholipids by type II cells in vitro and, therefore, like SP-A, may play a role in surfactant recycling. Insulin has been shown to inhibit mRNA accumulation for SPs A and B, although it has no effect on SP-C mRNA levels in human fetal lung tissue in vitro. Insulin can potentially decrease surfactant proteins at the molecular level, further contributing to the development of NRDS.

“NRDS due to surfactant deficiency can also occur in term or near-term infants in IDM. Eldeen et al. did a study where 1547 neonates were admitted to the NICU with a diagnosis of increased work of breathing for further management. One hundred seventeen cases of term and near-term neonates (mean GA = 36.8 wks) had a confirmed diagnosis of Surfactant deficiency respiratory distress syndrome (SRDS).”

NRDS in IDM: term vs preterm infants:

NRDS due to surfactant deficiency can also occur in term or near-term infants in IDM. Eldeen et al. did a study where 1547 neonates were admitted to the NICU with a diagnosis of increased work of breathing for further management. One hundred seventeen cases of term and near-term neonates (mean GA = 36.8 wks) had a confirmed diagnosis of Surfactant deficiency respiratory distress syndrome (SRDS). Who compared 60 preterm neonates with NRDS less than 35 weeks gestation (mean GA 27.5 weeks) as a control. The mean birth weight was 2.8 kg vs 1.1 kg in the preterm group. SRDS occurs more among the male gender (58%), with CS in 78.6% of all diagnosed cases. No apparent cause was found in 28.2%. 37.6% of all cases of NRDS in neonates born full-term were born to mothers with diabetes mellitus. Surfactant deficiency leading to NRDS is not uncommon among full-term and near-term neonates (10/1000 live births). By far, the most common associated risk factors are maternal diabetes mellitus and cesarean section. Gestational glucose intolerance or diabetes is one of the main risk factors of NRDS in full-term neonates, as confirmed by a study in the Bayi Children's Hospital in China (Liu J, Yang N, Liu Y 2014). This is notable as it shows there are cases of NRDS of IDM not only nationally but globally. Since gestational glucose intolerance or diabetes is one of the main risk factors of NRDS in full-term neonates, if diagnosed late and not managed properly, infants can be at risk of IDM and NRDS. Managing with respiratory support and surfactant are treatments, but prevention is possible through adequate prenatal care with the OBGYN (Liu J, Yang N, Liu Y 2014).

A small prospective study with 18 type 1 DM pregnant women was designed to show improvement in maternal euglycemia

with continuous subcutaneous glucose monitoring and continuous insulin administration. Glucose monitoring was performed on two different occasions where diabetic women are prone to be hyperglycemic: 72 h after betamethasone administration and during labor. Infants were observed for hypoglycemia and RDS as primary outcomes; none of them had hypoglycemia or RDS. Even though preterm infants <34 weeks GA are more at risk of having NRDS, preterm infants in this study did not show NRDS after being managed with insulin administration, suggesting better glycemic control in diabetic pregnancies can improve neonatal outcomes. Therefore, managing glucose levels is beneficial to prevent NRDS. This shows that NRDS can be prevented in pregnant women diagnosed with DM if appropriately managed with insulin in preterm and possibly full-term neonates. Further research may show that this most likely would occur in both full-term and preterm neonates in type 1 and 2 DM.

Additionally, a prospectively collected (1995–2007) Israel National Very Low Birth Weight Infant Database was used to observe pregestational or gestational Maternal DM multivariable logistic regression analysis was used to assess the independent effect of maternal DM status on infant mortality, RDS, and other complications of prematurity. Mothers with DM were more likely to have received a complete course of prenatal steroids than control mothers. Infants of diabetic mothers (IDM) had a slightly higher gestational age and birth weight than non-IDMs (Bental et al., 2011). The distribution of birthweight percentiles and the mean birthweight z scores were similar. The study showed no significant differences between the two groups regarding delivery room mortality, RDS, and other significant complications of prematurity (Bental et al., 2011). Total mortality and bronchopulmonary dysplasia rates were significantly higher in the nondiabetic group. The adjusted odds ratios for mortality, RDS, bronchopulmonary dysplasia, etc., did not significantly increase in the IDM group (Bental et al., 2011). This is significant because it shows that with modern management and adequate prenatal care, IDM born with a very low birth weight do not seem to be at an excessive risk of developing RDS or other significant complications of prematurity compared with non-IDM.

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Furthermore, a prospective study demonstrated that gestational diabetes is particularly an independent risk factor of NRDS in the near term to term infants after 34 weeks of gestation (Mortier

et al., 2017). Women with singleton pregnancy in labor after 34 weeks of gestation or admitted for planned cesarean section and who had been systematically screened for GDM were eligible to participate in this prospective cohort study. Diagnosis of SRDS was defined by the association of clinical signs of early neonatal respiratory distress with consistent radiologic features and requiring mechanical ventilation with a fraction of inspired oxygen (FiO₂) >0.25 for a minimum of 24 hours and admission to the neonatal intensive care unit. A total of 444 women were included. GD was diagnosed in 60 patients. A neonatal SRDS was diagnosed in 32 cases.

“Compared to others, neonatal SRDS was significantly more often seen in neonates from women diagnosed with GDM: 12 vs. 20, respectively ($p < 0.001$). Women who delivered neonates with SRDS were significantly more likely to be obese ($p = 0.002$), to have undergone a cesarean section ($p < 0.001$), and to have received corticosteroid therapy before 34 weeks ($p = 0.013$). In multivariate analysis, GD was identified as an independent risk factor of neonatal SRDS (aOR 3.6; 95% CI 1.5–8.6; $p = 0.005$).”

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Insulin as a risk factor:

While insulin can be used to manage glucose levels, as mentioned above, studies show it can also be a risk factor. A retrospective study studied in a large retrospective cohort the relationship between maternal DM status (non-DM, insulin-treated DM (IT-DM), and non-insulin-treated DM (NIT-DM) and respiratory distress in term and near-term inborn singletons. Results: Among 18 095 singletons delivered at 34 weeks of gestation or later, 412 (2.3%) were admitted to the neonatal intensive care unit (NICU) for respiratory distress within the first hours of life (Becquet et al., 2015). The incidence of NICU admission due to respiratory distress groups was 2.2%, 5.7%, and 2.1% in the nonDM, IT-DM, and NIT-DM groups, respectively (Becquet et al., 2015). Insulin treatment of DM, together with several other perinatal factors, was associated with a significantly increased risk for respiratory distress in this

study, which is crucial to consider since insulin is a treatment of DM. Several markers of the severity of respiratory illness, including durations of mechanical ventilation and supplemental oxygen and hypertrophic cardiomyopathy, were also found to increase following IT-DM compared to NIT-DM (Becquet et al., 2015). In a multivariate model, we found that IT-DM, but not NIT-DM, was significantly associated with respiratory distress independent of gestational age and cesarean section, with an incidence rate ratio of 1.44 (1.00–2.08) (Becquet et al., 2015). This study shows that the treatment of maternal DM with insulin during pregnancy is an independent risk factor for respiratory distress in term and near-term newborns. (Becquet et al., 2015). It is essential for Mothers who are diagnosed with diabetes to control their glucose levels before they begin insulin therapy.

“Using HbA1c may lack specificity and sensitivity. Establishing diagnostic criteria for HbA1C during pregnancy might reduce the need for an oral glucose tolerance test (OGTT) among pregnant women and perhaps be more straightforward to test as it can be a one-step test, requiring less time than oral OGTT. Not relying on OGTT might encourage more women to test and not be lost to follow-up.”

Discussion and Future Prospects:

Using HbA1c may lack specificity and sensitivity. Establishing diagnostic criteria for HbA_{1c} during pregnancy might reduce the need for an oral glucose tolerance test (OGTT) among pregnant women and perhaps be more straightforward to test as it can be a one-step test, requiring less time than oral OGTT. Not relying on OGTT might encourage more women to test and not be lost to follow-up. Randomized controlled trials in larger populations could improve our understanding of the role of HbA_{1c} during pregnancy. As we do not have a clear answer on how to use HbA_{1c} during pregnancy, OGTT remains the preferred diagnostic test for GDM. If more research is done on the topic, GDM can be diagnosed and better managed, and neonates would not be at risk of being an IDM and have less of a risk of developing NRDS. (Yildiz Atar H, Baatz JE, Ryan RM). Overall, more research needs to be done on this topic as it is crucial to understand how diabetes plays a role in developing NRDS.

Determining the blood glucose concentration that defines hypoglycemia in newborns remains a topic of debate. At birth, the mother's glucose levels influence an infant's blood glucose levels. The decline in blood glucose after birth is more rapid and pronounced in infants of diabetic mothers (IDM). Historically, hypoglycemia has been defined as blood glucose levels below 40 mg/dL, a threshold recently endorsed by the American Academy of Pediatrics (AAP). If hypoglycemia is suspected, blood glucose screening in asymptomatic IDM typically begins around one hour of life or sooner. Early oral feedings, whether breastfeeding or formula, prevent or correct neonatal hypoglycemia, though high rates of cesarean deliveries and other complications can hinder breastfeeding.

Data from a different study show that hypoglycemic episodes in the well baby nursery (WBN) occurred between one to four hours of life, most corrected through early breastfeeding or formula feeding (Cordero et al., 2014). The low recurrence of hypoglycemia suggests a potential benefit from early feedings. The preliminary data indicating a low incidence of hypoglycemia in exclusively breastfed IDM is encouraging. Higher breastfeeding initiation rates in the WBN compared to the Neonatal Intensive Care Unit (NICU) likely reflect more frequent maternal-infant interactions.

Over a decade, our institution saw a decline in NICU admissions for IDM from 47% to 25%, possibly due to improved maternal glucose control and efforts to promote maternal-infant contact and breastfeeding. NICU admissions often cite respiratory distress, prematurity, and hypoglycemia prevention. The high rate of transient tachypnea may be linked to cesarean deliveries, while the decrease in respiratory distress syndrome (RDS) indicates better delivery timing. Quick resolution of respiratory distress and successful initiation of oral feedings in late preterm infants may lead to shorter NICU stays and earlier returns to the WBN. (Cordero et al., 2014).

“In conclusion, we have demonstrated through a review that there is a risk of NRDS in IDM, which can occur in both near-term and full-term neonates. This is due in part to hyperinsulinemia in infants secondary to maternal diabetes. Hyperinsulinemia decreases surfactant production, further decreasing the L/S ratio, and the development of NRDS occurs as a result.”

Conclusion:

In conclusion, we have demonstrated through a review that there is a risk of NRDS in IDM, which can occur in both near-term and full-term neonates. This is due in part to hyperinsulinemia in infants secondary to maternal diabetes. Hyperinsulinemia decreases surfactant production, further decreasing the L/S ratio, and the development of NRDS occurs as a result. Prenatal care to check for DM is essential for Mothers, and if diagnosed with DM type 1 or 2, adequate glycemic control would be beneficial and possibly preventative in developing NRDS in neonates. As there have been cases in the United States and China, this can have global impacts if further research is conducted on the topic since the current literature is limited on in-depth reasoning behind the estimated gestational age of IDM who develop NRDS. Insulin and GDM may impose a risk on the development of fetal lung development through a variety of molecular mechanisms. This demonstrates the cruciality of determining ways to manage NRDS, as treatment is typically done with respiratory support. Doing so will have positive health impacts on the medical community, families, and beyond.

Works Cited:

1. Azad, M. B., Moyce, B. L., Guillemette, L., Pascoe, C. D., Wicklow, B., McGavock, J. M., Halayko, A. J., & Dolin-

sky, V. W. (2017). Diabetes in pregnancy and lung health in offspring: Developmental origins of respiratory disease. *Paediatric Respiratory Reviews*, 21, 19–26. <https://doi.org/10.1016/j.prrv.2016.08.007>

2. Becquet, O., El Khabbaz, F., Alberti, C., Mohamed, D., Blachier, A., Biran, V., Sibony, O., & Baud, O. (2015). Insulin treatment of maternal diabetes mellitus and respiratory outcome in late-preterm and term singletons. *BMJ Open*, 5(6). <https://doi.org/10.1136/bmjopen-2015-008192>
3. Bental, Y., Reichman, B., Shiff, Y., Weisbrod, M., Boyko, V., Lerner-Geva, L., & Mimouni, F. B. (2011). Impact of maternal diabetes mellitus on mortality and morbidity of preterm infants (24–33 weeks' gestation). *Pediatrics*, 128(4), 848–855. <https://doi.org/10.1542/peds.2010-3443>
4. Chen, P., Gu, M., Wan, S., Jiang, X., Zhang, F., Li, Y., Zhou, Q., Lu, Y., Li, L., & Wang, X. (2023). Gestational diabetes mellitus impedes fetal lung development through exosome-dependent crosstalk between trophoblasts and lung epithelial cells. *International Journal of Nanomedicine, Volume 18*, 641–657. <https://doi.org/10.2147/ijn.s396194>
5. Cheng-Hwa Ma, C. (2012). The role of surfactant in respiratory distress syndrome. *The Open Respiratory Medicine Journal*, 6(1), 44–53. <https://doi.org/10.2174/1874306401206010044>
6. Cordero, L., Ramesh, S., Hillier, K., Giannone, P. J., & Nankervis, C. A. (2013). Early feeding and neonatal hypoglycemia in infants of diabetic mothers. *SAGE Open Medicine*, 1. <https://doi.org/10.1177/2050312113516613>
7. Eldeen, S. M., Ali, S., & Salama, H. (2022). Clinical characteristics, diagnosis, and management outcome of surfactant deficiency respiratory distress syndrome in term and near-term neonates. A retrospective observational study. *Acta Biomedica*, 93(6), e2022337. <https://doi.org/10.23750/abm.v93i6.13794>
8. Liu, J., Yang, N., & Liu, Y. (2014). High-risk factors of respiratory distress syndrome in term neonates: A retrospective case-control study. *Balkan Medical Journal*, 33(1), 64–68. <https://doi.org/10.5152/balkanmedj.2014.8733>
9. Mendelson, C., Acarregui, M., Odom, M., & Boggaram, V. (1991). Developmental and hormonal regulation of surfactant protein A (SP-A) gene expression in fetal lung. *Journal of Developmental Physiology*, 15(1), 61–69.
10. Miakotina, O. L., Dekowski, S. A., & Snyder, J. M. (1998). Insulin inhibits surfactant protein A and B gene expression in the H441 cell line. *Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression*, 1442(1), 60–70. [https://doi.org/10.1016/s0167-4781\(98\)00121-3](https://doi.org/10.1016/s0167-4781(98)00121-3)
11. Mortier, I., Blanc, J., Tosello, B., Gire, C., Bretelle, F., & Carcopino, X. (2017). Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study. *Archives of Gynecology and Obstetrics*, 296(6), 1071–1077. <https://doi.org/10.1007/s00404-017-4505-7>
12. Robert, M. F., Neff, R. K., Hubbell, J. P., Taeusch, H. W., & Avery, M. E. (1976). Association between maternal diabetes and the respiratory-distress syndrome in the newborn. *New England Journal of Medicine*, 294(7), 357–360. <https://doi.org/10.1056/nejm197602122940702>
13. Shattuck and Huff. “UTMB Neonatology Manual-Babies with Special Challenges.” *Infant of Diabetic Mother*, 2014,

www.utmb.edu/pedi_ed/NeonatologyManual/SpecialChallenges/SpecialChallenges.html#:~:text=Respiratory%20Distress%20Syndrome, is%20delayed%20pulmonary%20biochemical%20maturation.

14. Yadav S, Lee B, Kamity R. (2023). Neonatal Respiratory Distress Syndrome. 2023 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. PMID: 32809614.
15. Yildiz Atar, H., Baatz, J. E., & Ryan, R. M. (2021). Molecular mechanisms of maternal diabetes effects on fetal and neonatal surfactant. *Children*, 8(4), 281. <https://doi.org/10.3390/children8040281>

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Corresponding Author



*Mitchell Goldstein, MD, MBA, CML
Professor of Pediatrics
Loma Linda University School of Medicine
Division of Neonatology
Department of Pediatrics
Loma Linda University Childrens Hospital
Loma Linda, CA
Email: mgoldstein@llu.edu*



*Mona Singh, OSM IV
Western University of Health Sciences
Pomona, CA
Email: mona.singh@westernu.edu*

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