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# The effect of maternal diabetes on the formation of fetal surfactant



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## ABSTRACT

Elevated maternal blood glucose levels in pregnancy correlate with increased risk of pregnancy complications, labor, and pregnancy outcomes. Type II alveolus cells produce a combination of fat and protein called pulmonary surfactant. To assist in preserving lung stability, pulmonary surfactant plays a crucial function in lowering the propensity of the alveolus to recoil and preventing alveolus collapse. The hallmark of maternal diabetes is the malfunctioning of pancreatic  $\beta$ -cells, which results in insufficient insulin production to sustain proper blood glucose levels. Respiratory distress syndrome (RDS) in newborns is caused by surfactant lack of sufficiency, which is caused by fetal hyperglycemia and hyperinsulinism brought on by maternal diabetes. Appropriate treatments are required to improve glycemic management since maternal diabetes raises the risk of RDS in term newborns. These therapies include a deeper comprehension of the molecular mechanisms behind gestational diabetes mellitus that impact the surfactant system. Phosphatidylglycerol levels are either nonexistent or extremely low in infants with RDS. Phosphatidylglycerol synthesis during pregnancy in diabetics is known to be delayed in comparison to the non-diabetic control group. For this reason, proper care is essential to enhancing long-term health and neonatal outcomes. These findings underscore the need for early detection and management of maternal diabetes to mitigate the risk of RDS and improve neonatal health.

**Keywords:** maternal diabetes, respiratory distress syndrome, surfactant

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## INTRODUCTION

Elevated maternal blood glucose levels in pregnancy are correlated with an increased risk of complications of pregnancy, childbirth, and pregnancy outcomes in both the mother and the child. In cases of maternal diabetes, the growing fetus experiences hyperglycemia and other metabolic abnormalities due to the unrestricted passage of glucose across the placenta into fetal circulation, which is caused by pancreatic  $\beta$ -cell malfunction that results in insufficient insulin production.<sup>1</sup>

Studies conducted throughout the globe indicate that the prevalence of gestational diabetes mellitus (GDM), which affects more than 10% of pregnant women, is on the rise. The prevalence of GDM is 11% among Asian pregnant women, according to a 2018 meta-analysis study. In Indonesia, GDM prevalence is relatively low. Using the Sullivan and Mahan criteria, research done before 2000 found that the frequency of GDM in Indonesia

ranged from 1.9 to 3.6%. Still, it did not explain the difference in gestational age.<sup>1</sup> Surfactant insufficiency in neonates can be significantly affected by maternal diabetes, especially in children whose mothers have diabetes. Because these newborns are more likely to experience respiratory distress syndrome (RDS), this influence is critical. Maternal diabetes and RDS have long been known to be associated. During the past several decades, the prevalence of both illnesses has grown as a result of the growth in obesity and diabetes among women who are of reproductive age.<sup>2</sup> Compared to newborns without maternal diabetes, the prevalence of RDS in infants induced by maternal diabetes is much greater. The link between maternal diabetes and the risk of newborn RDS was shown to have a pooled odds ratio of 1.47 (95% CI 1.24-1.74), according to a meta-analysis. Higher risk was observed for both GDM and pre-gestational diabetic mellitus (PGDM).<sup>3</sup>

A history of delivering children with macrosomia or congenital malformations,

advanced age at conception, a high body mass index (BMI) before conception, a particular race or ethnicity, hypertension, a family history of diabetes mellitus, a high range of weight gain throughout pregnancy, and smoking are risk factors for gestational diabetes mellitus.<sup>3</sup> Pregestational diabetes mellitus is linked to higher infant death rates, poor 5-minute APGAR scores, extended ventilatory support, higher surfactant requirements, and higher neonatal intensive care unit utilization in preterm newborns.<sup>4</sup> This literature review further discussed the impact of maternal diabetes on surfactants specifically. To know the risk factors, pathogenesis, diagnosis, and appropriate treatment steps to prevent morbidity and mortality in the mother and fetus.

## ALVEOLAR ANATOMY

The ductus alveolaris, saccus alveolaris, and expiratory bronchioles all have bag-shaped evaginations called alveoli. The canaliculi are between 16 and 26 weeks

along in their lung development. The respiratory epithelium differentiates at this time, and the initial gas exchange zones of the peripheral lung develop. The surfactant system's constituent parts also start to emerge. Alveolarization, which takes place between 36 weeks preterm and 36 months postnatally, is characterized by a rise in the alveolar number and a gradual reduction in the size of the alveolar air gaps. Alveoli are responsible for the formation of hollow structures in the lung (**Figure 1**).<sup>5,6</sup>

### Type I Alveolar Cells

The thin cells that line the surface of the alveolus are known as type I alveolus cells, often referred to as type I pneumocytes or squamous alveolar cells. 97% of the alveolus surface comprises type I cells; type II cells comprise the remaining space. Numerous pinocytotic cysts are present in the cytoplasm of the thin section, and they may be involved in the turnover of surfactants and the elimination of tiny contaminant particles from the outer surface. All type I epithelial cells include impermeable connections and desmosomes, which stop tissue fluid from leaking into the alveolus's air gaps.<sup>6</sup>

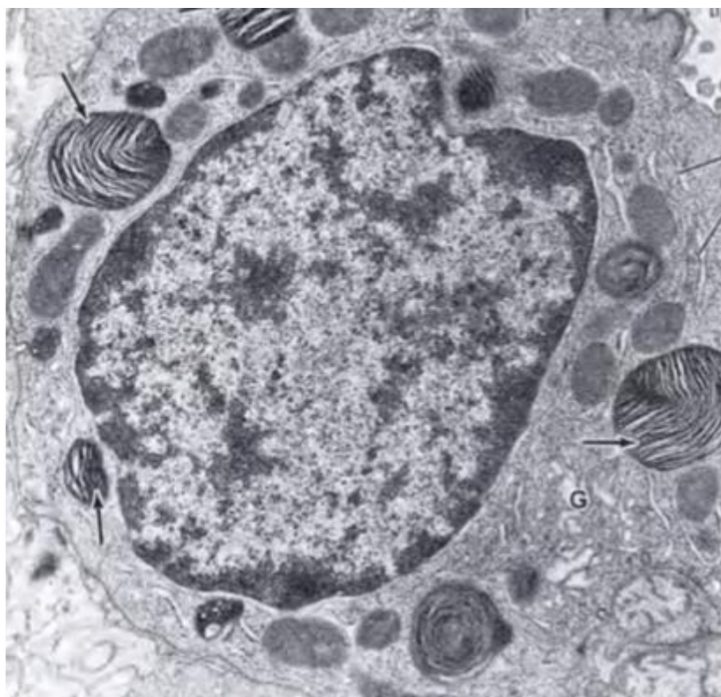
### Type II Alveolar Cells

With impermeable membranes and desmosomes linking them to type I alveolar cells, type II alveolar cells (also known as type II pneumocytes) are distributed throughout these cells. In histology preparations, type II cells exhibit a distinct cytoplasmic vesicle. The cause of these vesicles is lamellar bodies, composed of parallel or concentric lamellae surrounded by a single membrane. Surface tension is lowered by an extracellular layer formed by material produced by the lamellar bodies and spreading across the alveolus' surface as a surfactant.<sup>6</sup>

The surfactant layer consists of a proteinaceous aqueous hypophase covered by a thin layer of monomolecular phospholipids. The surfactant also contains several specific proteins. Pulmonary surfactant has several vital functions in lung efficiency, mainly working to reduce surface tension in the alveolus. The surfactant layer is not static but is replaced continuously. Lipoproteins are gradually removed from the surface by



**Figure 1.** Alveolar wall. The walls between the alveoli (A) contain several cell types. Capillaries (C) contain erythrocytes and leukocytes. The alveoli are mainly lined by type I (I) squamous alveolar cells, which line almost the entire surface of the alveolus and are where gas exchange occurs. Type II alveolar cells line each alveolus and are round cells that often protrude into the alveolus (II). Type II cells have many of the functions of Clara cells, including surfactant production. Alveolar macrophages (A) are also found in this image, sometimes called dust cells in the alveoli and intravascular septa.<sup>6</sup>



**Figure 2.** Ultrastructure of type II alveolar cells. TEM of type II alveolar cells protruding into the lumen of the alveolus reveals an unusual cytoplasmic appearance. Arrows indicate lamellar bodies that store newly deposited lung surfactant after processing its components in the Rough Endoplasmic Reticulum (RER) and Golgi Apparatus (G). Smaller multivesicular bodies with intraluminal vesicles are also frequently encountered. Short microvilli are also present, and type II cells are attached via junctional complexes (JCs) to very thin type I cells. The extracellular matrix contains prominent reticular fibers (RF).<sup>6</sup>

pinocytosis in both alveolus cell types and by macrophages (Figure 2).<sup>6</sup>

### Alveolar Macrophages

The alveolus and interalveolar septum contain alveolar macrophages, sometimes called dust cells. Filled macrophages can exit the lung in a few different ways: the majority migrate into the bronchioles, where they activate the mucociliary escalator to be expelled in the pharynx; others persist in the connective tissue of the interalveolar septum for years, and yet others exit the lung via the lymph stream.<sup>6</sup>

## SURFACTANT

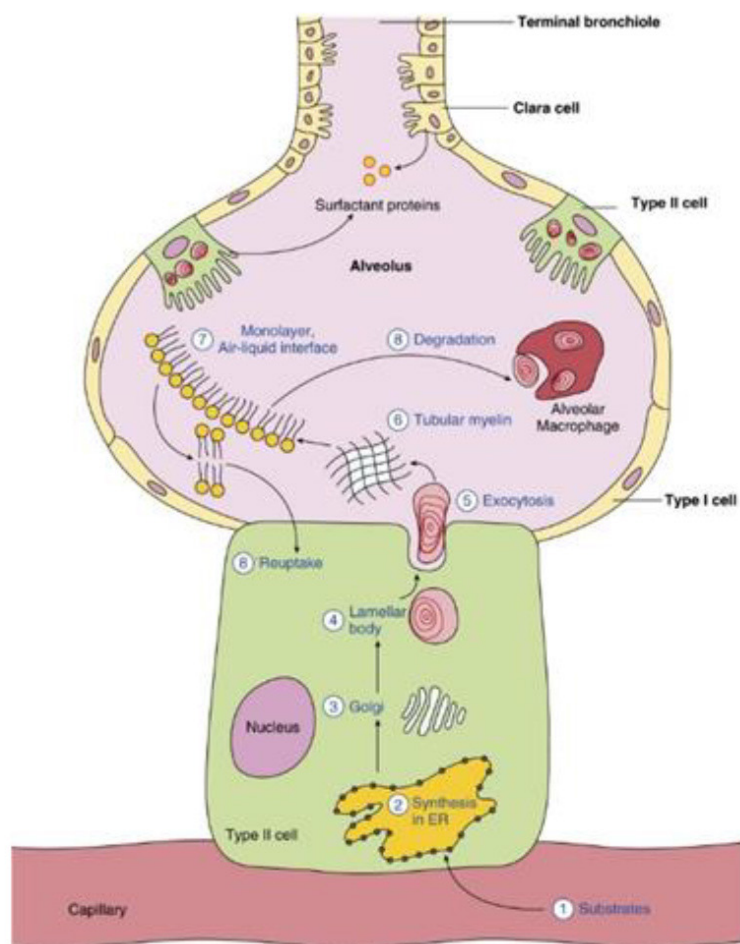
Type II alveolus cells release a mixture of lipids and proteins known as pulmonary surfactants. It lowers the surface tension between the alveolus's air fluid, preventing it from collapsing during end-expiration. Additionally, surfactant contributes to the host's natural defensive mechanism against inhaled infections. Phospholipids and dipalmitoylphosphatidylcholine (DPPC) are surface-active substances found in surfactants; surfactant proteins are SP-A, SP-B, SP-C, and SP-D. Pulmonary surfactant increases lung compliance and minimizes the lung's tendency to rebound, preventing the lung from collapsing readily by lowering the surface tension of the alveolus (Figure 3).<sup>7</sup>

### Role of Surfactant

Pulmonary surfactant decreases surface tension to a greater degree in the small alveolus. The presence of surfactant causes the pressure causing the small alveolus to collapse to be equivalent to that in the large alveolus. It minimizes the tendency of the small alveolus to collapse and channel its contents into the large alveolus. Thus, pulmonary surfactant helps stabilize the size of the alveolus and helps the alveolus stay open and participate in gas exchange.<sup>8</sup>

### Protein Components

The four recognized surfactant proteins are SP-A, SP-B, SP-C, and SP-D. The hydrophobic polypeptides (PP) SP-B and SP-C enhance lipid absorption to the alveolar surface, whereas the hydrophilic SP-A and SP-D contribute to the host defense mechanism of the innate immune system.<sup>9</sup>



**Figure 3.** Surfactant life cycle. Synthesis, secretion, and recycling. Type II alveolar cells, which cover approximately 7% of the surface of the alveolar epithelium, are primarily responsible for surfactant production using food substrates (1). Surfactant is synthesized in the endoplasmic reticulum (ER) (2) of type II alveolar cells and transported to the Golgi (3) for further modification. Most surfactant components are stored in lamellar bodies (4) until secreted into the fluid hypophase in the alveoli via exocytosis (5). Surfactant forms a lattice-like structure called tubular myelin (6), which is transported to the air-liquid interface to form a monolayer of surfactant film (7). Phospholipids are internalized and degraded by macrophages (8') or recycled back to type II cells for reuse (8''). Note that surfactant proteins (SP)-A, SP-B, and SP-D are also synthesized in club cells in terminal bronchioles.<sup>8</sup>

### Surfactant Metabolism

The alveolus is the site of pulmonary surfactant degradation after it has been generated, assembled, transported, and secreted there. After that, the surfactant is recycled using a highly intricate and well-organized system. Because type II cells have beta-adrenergic receptors, they secrete more surfactant when exposed to beta-agonists. Surfactant secretion has also been reported to be stimulated by mechanical stretching, such as hyperventilation and pulmonary distension. Alveolar macrophages and

Type II cells absorb surfactant components and remove them from the airspace; Type II cells do most of the work. Sporadic phospholipids are recycled and re-secreted into Type II cells by endocytosis, whereas SPs are recycled back to their flat bodies and re-secreted together with surfactant.<sup>9</sup>

### Impact of Surfactant Metabolism Defects

#### Respiratory distress syndrome

Among premature newborns, respiratory distress syndrome (RDS) is one of the leading causes of morbidity. Pathological

or biochemical evidence of a surfactant deficit can validate the diagnosis. Infants with respiratory distress syndrome (RDS) have lungs that exhibit extensive hyaline membranes in narrow, deformed airways, alveolar atelectasis, and alveolar and interstitial edema. The incidence was considerably decreased by postnatal surfactant replacement treatment and prenatal corticosteroids. The accepted practice for treating preterm newborns with RDS is surfactant treatment.<sup>10</sup>

### ***Meconium aspiration syndrome***

Meconium aspiration syndrome (MAS) is a significant contributor to prenatal respiratory distress, morbidity, and death. It has been demonstrated that meconium breaks down the fibrillary structure of surfactant and reduces its surface adsorption rate, albeit the exact processes driving this inactivation remain unclear. Restoring hypoxic conditions, reducing meconium aspiration-related pneumothorax, reducing the need for extracorporeal membrane oxygenation (ECMO), and shortening the duration of oxygen therapy and mechanical ventilation have all been demonstrated by replacing exogenous surfactant either as bolus therapy or by lung lavage of diluted surfactant.<sup>11</sup>

### ***Pulmonary hemorrhage***

Additionally, linked to RDS, pulmonary hemorrhage is complicated to diagnose on radiographs. It happens when pulmonary capillary pressure rises as a result of congestive heart failure, hypoxia, volume overload, or trauma from mechanical suction of the baby's airway. Another uncommon adverse effect of surfactant replacement treatment is pulmonary hemorrhage.<sup>12</sup>

### ***Pulmonary alveolar proteinosis***

An uncommon lung condition known as pulmonary alveolar proteinosis (PAP) causes the alveoli to fill with proteinaceous material high in PL. These discoveries in genetically changed mice have led to conjecture that the etiology of PAP is a total lack of alveolar cells or alveolar cell hyporesponsiveness to granulocyte-macrophage colony-stimulating factor (GM-CSF), even if the precise cellular

pathophysiology is unclear. To relieve symptoms, full lung lavage is the mainstay of therapy. Even with the most aggressive medical care, newborns with congenital PAP have a very bad prognosis.<sup>13,14</sup>

## **THE ROLE OF ULTRASOUND IN ASSESSING LUNG MATURITY**

The fetal lung maturity ultrasound measurements exhibit a range of sensitivity and specificity. Fetal lung maturity can also be assessed using fetal biometry. Research revealed a correlation between fetal lung maturity and the following measurements: femur length (FL) (62.7–72.1 mm), abdominal circumference (AC) between 295 and 322 mm, and biparietal diameter (BPD) between 82.8 and 93.5 mm. The evaluation of fetal lung maturity did not yield any noteworthy results from the analysis of colonic assessment or fetal lung echogenicity about the liver.<sup>15</sup>

## **MATERNAL DIABETES**

Fetal hyperglycemia is brought on by high maternal glucose levels that cross the placenta. Hyperglycemia triggers the stimulation of the fetal pancreas. Insulin's anabolic qualities cause the growth of embryonic tissues to accelerate. In pregnancy, blood glucose levels should be below 95 mg/dL during fasting plasma glucose, 130–140 mg/dL during one hour postprandial, and 120 mg/dL during two hours postprandial, according to the American College of Obstetricians and Gynecologists (ACOG). Human placental lactogen is the primary hormone linked to increased insulin resistance in GDM.<sup>16</sup>

## **RELATIONSHIP BETWEEN IDIOPATHIC MATERNAL DIABETES AND RESPIRATORY DISTRESS SYNDROME**

Insufficient synthesis of surfactants leads to a deficit of surfactants, which in turn causes respiratory distress syndrome (RDS). Avery and Mead discovered the link between surfactant deficit and clinical RDS. Gellis and Hsia initially reported in 1959 that idiopathic maternal diabetes was associated with higher rates of morbidity and death because of RDS. Ever since a great deal of study has been

done on the impact of maternal diabetes on the developing fetus.<sup>17</sup>

Pregnant women with type 1 and type 2 diabetes are the subject of the most extensive research to date, the UK Confidential Enquiry into Maternal and Child Health (CEMACH) project, which ran from 2002 to 2007. According to this study, there was no significant difference in newborn outcomes between type 1 and type 2 maternal diabetes in terms of macrosomia, RDS, or shoulder dystocia. High maternal glucose concentrations have been identified as the primary cause of harmful consequences in newborns.<sup>18</sup>

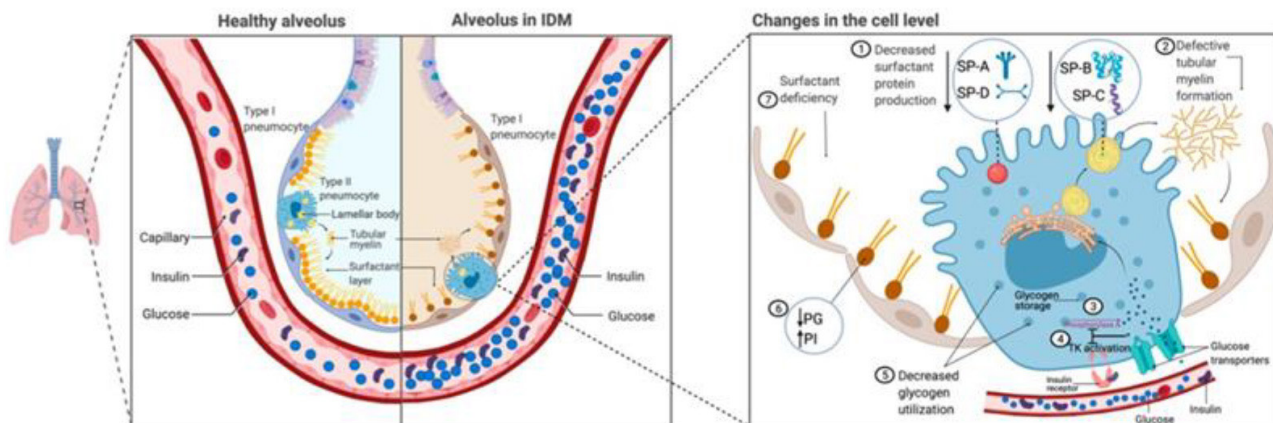
## **MOLECULAR MECHANISMS OF DELAYED LUNG MATURATION IN MATERNAL DIABETES**

### **Surfactant Phospholipid Composition**

The complex substance known as pulmonary surfactant comprises 10% proteins and 90% lipids and is generated by type II alveolar epithelial cells (AEC2s). About 70% of the lipid part of the surfactant is made up of phosphatidylcholine (PC), primarily found in the unsaturated form known as dipalmitoylphosphatidylcholine (DPPC).<sup>17</sup> At 24 weeks of gestation, AEC2s start to produce surfactant. Phosphatidylglycerol (PG), phosphatidylinositol (PI), and the L/S ratio all rise as pregnancy progresses. A delay in the surfactant's phospholipid composition's transition from PI to PG is linked to maternal diabetes.<sup>19</sup>

Glycogen storage in AEC2 is crucial, and glucose is a necessary substrate for surfactant lipid production. AEC2 glycogen corresponds with increased PC and surfactant production and rises with increasing gestational age, declining rapidly in late pregnancy. There are two types of glycogen phosphorylase—"A" is the active, phosphorylated form, and "B" is the inactive, unphosphorylated form—that breaks down glycogen. Elevated activity of glycogen phosphorylase A is linked to heightened breakdown of glycogen reserves. Moreover, there was no rise in glycogen phosphorylase A activity, which was considerably reduced compared to the non-diabetic control group. By raising phosphorylate phosphatase, which lowers glycogen phosphorylase A activity, glucose suppresses phosphorylase A

Alveolar Changes in IDM



**Figure 4.** Alveoli from newborns born to moms with diabetes and those from healthy parents are compared. On the right, changes in the alveolar epithelial cell level of infants born to type II diabetes moms are enlarged. Different processes are involved in the effects of fetal hyperglycemia and hyperinsulinemia resulting from maternal hyperglycemia on surfactant synthesis. Hyperinsulinism and hyperglycemia are seen in the capillaries. (1) Reduced SP-A, SP-B, SP-C, and SP-D surfactant proteins. Reduced levels of SP-B cause aberrant tubular myelin development. (2) Phosphorylase A activity is inhibited by excess glucose. (3) Insulin receptor tyrosine kinase (TK) activity is decreased by glucose. (4) A decrease in glycogen phosphorylase A activity results in a decrease in glycogen storage. (5) Insufficient glucose affects changes in surfactant phospholipid production, causing a rise in phosphatidylinositol (PI) and a reduction in glycerol phosphatidyl (PG). (6) As a result of surfactant insufficiency, these alterations exacerbate the incidence of respiratory distress syndrome in infants born to diabetes mothers.<sup>20</sup>

activity. Additionally, the activity of glycogen phosphorylase A is decreased by hyperglycemia. The kind of DM does not seem to have a significant impact on the altered surfactant lipid synthesis in the fetus, and maternal DM is a significant risk factor for this (Figure 5).<sup>20</sup>

**Surfactant Protein Composition**

Surfactant proteins significantly influence the production and function of surfactants. Reduction of all four SPs is expected to increase the risk of RDS in babies from diabetic mothers by impairing the surfactant’s capacity to reduce alveolar surface tension and facilitate a seamless transition to extrauterine life. The fetus is hyperglycemic with low to normal insulin levels, according to studies using animal models, so these data explicitly point to the inhibitory effect of hyperglycemia on protein and mRNA rather than the effects of hyperinsulinemia.<sup>20</sup>

Ex vivo studies were conducted to investigate the effects of hyperglycemia on the production of SP-A, -B, and -C. Fetal lungs from STZ-DB mice were taken on day 20 of embryonic development and cultured in 10, 25, 50, and 100 mM glucose. At varying glucose concentrations, SP-A mRNA was not significantly affected; however, the synthesis of SP-B and SP-C

Maternal diabetes effect		
	Hyperglycemia	Hyperinsulinemia
<b>Surfactant phospholipid composition</b>	Delayed PG production with ↓PG and ↑PI [38-40] Decreased PC and DSPC [51]	Normal insulin level insulin ↑PC synthesis High insulin levels ↓PC synthesis [50]
<b>Surfactant protein composition</b>	↓SP-A, B, C, D protein and mRNA [42-45]	↓SP-A protein [52] and ↓SP-A and B mRNA [46]
<b>Receptors and Enzyme effects</b>	High phosphorylated FOXA2 [53] High nitrolyogenic FOXA2 [54]	Depressed Glycogen phosphorylase A activity [47] Depressed IGF-1R mRNA [42] Downregulated insulin receptor TK activity [48]

**Figure 5.** Changes in metabolism. Enzymes, receptors, and surfactant composition are all impacted by metabolic alterations brought on by maternal diabetes. TK (tyrosine kinase), IGF-1R (insulin-like growth factor 1 receptor), PC (phosphatidylcholine), DSPC (desaturated phosphatidylcholine), PG (phosphatidyl glycerol), and PI (phosphatidyl inositol).<sup>20</sup>

mRNA was significantly reduced at 100 mM (<10%) in comparison to that at 10 mM.<sup>21</sup>

**Receptors**

The insulin receptor controls glucose absorption by cells, and glucose is a crucial substrate for surfactant phospholipids. The

complicated signaling cascade mechanism of the insulin receptor involves the activation of tyrosine kinase (TK). In rat fetal lungs, high glucose and high insulin both significantly reduced insulin receptor TK activity and insulin receptor mRNA. The notably poor glucose absorption from culture due to the decreased receptor and

TK activity suggests a clinically relevant role for these receptors and TK activity in glucose metabolism. Surfactant deficit might arise from insufficient glucose being supplied to AEC2 by the reduced insulin receptor TK activity.<sup>22</sup>

Other intracellular signaling pathways, such as FOXA2, are involved in surfactant formation in addition to the insulin receptor. The expression of FOXA2 is limited to AEC2 during the third trimester of pregnancy, when lung growth and surfactant production reach their peak in fetal life, even though FOXA2 is involved in other organogenesis, such as in the pancreas, liver, and adipose tissue.<sup>23</sup>

The Akt/mammalian target of the rapamycin (mTOR) pathway represents an additional insulin signaling route. At the molecular level, mTOR regulates insulin signaling. A transgenic mouse model was used to investigate the significance of the Akt/mTOR pathway. In lung epithelial cells, activation of Akt resulted in decreased lung epithelial maturation, downregulation of SP-B, and increased glycogen storage. The mTOR signaling downregulation pathway may significantly impact lung maturation and epithelial differentiation. These results highlight the significance of normal insulin levels and euglycemia for controlling the absorption of glucose and the production of surfactants.<sup>24</sup>

## SURFACTANT REPLACEMENT THERAPY

Since it increases survival and lowers respiratory morbidity, surfactant replacement therapy, or SRT, is crucial to the care of newborns with RDS. In clinical practice, surfactant administration and extubation techniques are well recognized in addition to intubation techniques. One systematic study compared the timing of early (within the first two hours of age) and late (delayed until RDS is established, generally 2 hours or more) surfactant administration for preterm newborns intubated for RDS. A substantial decrease in mortality was linked to early surfactant use, according to a meta-analysis of six randomized studies.<sup>25</sup>

Pneumothorax rates were more significant in two sizable randomized trials where surfactant was not administered

to newborns initially treated with CPAP until a FiO<sub>2</sub> threshold 0.6 was met. The infants who received surfactant sooner were intubated, and their pneumothorax rates were lower. As preterm babies are transported between facilities, the surfactant administration before the transfer is linked to reduced oxygen demand and shorter ventilatory support times compared to controls.<sup>25</sup>

## Types of Surfactants

### *Synthetic surfactant*

Regarding lowering ventilatory support, pneumothorax, and mortality, first-generation synthetic surfactants—which included DPPC without surfactant proteins—were less successful than surfactants drawn from animals. Lucinactant (also known as Surfaxin) is the first second-generation synthetic surfactant that has ever been tested on newborns. Current phase II studies use DPPC and its analogs SP-B and SP-C (CHF5633), part of a third-generation synthetic surfactant complex.<sup>25</sup>

### *Surfactants from animal*

Many clinical investigations have been carried out to test the effectiveness of different preparations, and an extensive range of natural or animal-derived surfactants are available for usage. A comprehensive analysis was conducted on 13 RCTs that compared animal-derived surfactants with placebo in infants with stable RDS. The results showed significant improvements in oxygenation, ventilation needs, and the rate of air leaks, deaths before hospital discharge, and bronchopulmonary dysplasia at 28 days. Emerging data compares various animal-derived surfactants and indicates that pig extract surfactant, particularly at higher dosages, may be more effective than bovine surfactant in treating RDS and lowering babies' mortality or bronchopulmonary dysplasia.<sup>26</sup>

### **Surfactant Dosing and Re-dosing**

Repeating the surfactant dosage is currently considered standard procedure, but only in cases where ventilation and oxygen requirements demonstrate persistent respiratory distress syndrome (RDS). Researchers Kattwinkel et al.

investigated the impact of re-dosing at two different thresholds: low (FiO<sub>2</sub>>0.3 and still needing intubation) and high (FiO<sub>2</sub>>0.4 and requiring mean airway pressure >7 cm H<sub>2</sub>O). As a result of the findings, it is reasonable to wait to reduce surfactant until the baby needs more respiratory assistance, except in situations in which sepsis or prenatal hypoxic-ischemic damage aggravates RDS.<sup>27</sup>

A greater beginning dosage (200 mg/kg) successfully lowered oxygen demand, re-dosing requirement, and death at 36 weeks gestation, according to one trial utilizing protectants. The only substance that is sufficiently concentrated to provide intratracheal volumes of large dosages is poractan.<sup>27</sup>

## Surfactant Administration Technique

### *Bolus*

Single-dose administration is where the complete dose is given in a single period. Multiple dose administration is where the total dose is divided into two or more doses and administered separately over time. Continuous infusion is slow administration of surfactant preparations.<sup>28</sup>

### *Less invasive surfactant administration and minimally invasive surfactant treatment*

Less Invasive Surfactant Administration (LISA) is similar to direct laryngoscopy with a tiny catheter placed in the trachea and Magill forceps used while the infant still receives CPAP assistance. LISA is one component of a plan that also excludes the use of positive pressure ventilation, the use of prenatal steroids, the use of CPAP at an early age, and the giving of coffee in the delivery room. Six studies involving preterm babies between 23 and <34 weeks GA with RDS were included in a systematic review comparing LISA vs intubate surfactant extubate (INSURE). According to this study, LISA led to a decrease in the requirement for mechanical ventilation, a reduction in BPD at 36 weeks, and a reduction in mortality.<sup>29</sup>

By employing a more rigid adult vascular catheter—also referred to as the Hobart method or Minimally Invasive Surfactant Treatment (MIST)—Dargaville et al. modified the LISA approach and avoided the need for Magill forceps.

A more extensive investigation is now underway, and two observational trials of the MIST approach yielded results comparable to those of LISA.<sup>29</sup>

### **Laryngeal mask airway**

Numerous studies have documented using LMA for surfactant administration in preterm infants with higher gestational ages (29 to 35 weeks). These studies have demonstrated the feasibility of this approach and the fact that LMA can achieve better oxygenation and less invasive ventilation requirements than surfactants administered via ETT. It has been reported that a novel method of guiding the catheter for LISA or MIST with LMA is viable and appears to have no negative consequences.<sup>29</sup>

### **Pharyngeal**

Pharyngeal surfactant administration enables surfactant to be distributed at the air-fluid interface during spontaneous breathing. One randomized controlled trial compared pharyngeal surfactant with saline placebo showed significant decreases in mortality, RDS severity, and breathing needs. Nevertheless, reaching firm conclusions on the advantages of this surfactant administration strategy is challenging because other research has shown inconsistent findings.<sup>29</sup>

### **Nebulization**

Nebulization is the only non-invasive technique for SRT. Nebulization's impact is contingent upon many crucial elements, such as the ideal particle size range of 0.5 to 2.0  $\mu\text{m}$ , the material's capacity to withstand nebulization, and the amount of particles lost relative to the effective dosage. In a recent trial, the use of CPAP with or without aerosolized protectants decreased the requirement for greater GA intubation in preterm babies with moderate RDS.<sup>29</sup>

## **MANAGEMENT OF GESTATIONAL DIABETES**

Multidisciplinary care is necessary for individuals with GDM to receive the best possible therapy. This involves educating patients on how to check their blood sugar levels independently, managing maternal weight gain, dietary adjustments, and

nutritional monitoring. Modest dietary and lifestyle changes combined with appropriate physical exercise can help treat up to 70–85% of people diagnosed with gestational diabetes. Maternal glycemic management is the main factor driving fetal evaluation's necessity. Fetal testing before 40 weeks of gestation is not recommended unless there are other signs in women who can regulate their blood sugar levels well with diet alone. Medication therapy, glycemic management, and other risk factors are the foundation of antepartum fetal monitoring.<sup>30</sup>

Based on glucose control, ACOG established guidelines for when to induce delivery in women with gestational diabetes. Thirty-nine weeks of gestation should be taken into consideration for delivery when GDM is effectively managed with diet and exercise. Premature birth is not advised in women with inadequate glycemic control but positive fetal test results. The date of birth will vary if there are hypertensive issues, other comorbidities, or a bad fetal evaluation.<sup>30</sup>

Insulin and oral medications should be stopped after delivery. Persistent hyperglycemia is confirmed by plasma glucose values of 126 mg/dL or 200 mg/dL after meals. It is recommended that these patients persist with their dietary and lifestyle adjustments, and they could require pharmaceutical medicines for treatment. It is not necessary to consider the adverse effects on newborns while prescribing glyburide or insulin during the postpartum period, even for nursing moms.<sup>30</sup>

After ten years of follow-up, the risk of type II diabetes mellitus in women with GDM is predicted to be ten times higher than that of the control group, which is 16.15%. According to specific research, the risk might reach 60%. Patients with type 2 diabetes mellitus and those with poor glucose tolerance are frequently missed by postpartum fasting blood glucose testing.<sup>28</sup> This literature review still has several limitations. Literature reviews still focus on qualitative discussion methods without systematically searching for inclusion studies. This literature review is still limited to a general discussion of aspects related to the topic discussed, so it is recommended that an in-depth discussion

be carried out by systematically searching for included studies in a systematic review and meta-analysis design.

## **CONCLUSION**

There is a positive correlation between higher maternal blood glucose levels during pregnancy and a higher risk of labor, pregnancy problems, and pregnancy outcomes. Type II alveolus cells release a combination of fat and protein known as pulmonary surfactant. Surfactant insufficiency and RDS in newborns are caused by fetal hyperglycemia and hyperinsulinism brought on by maternal diabetes, which interferes with surfactant production and function. Improving newborn outcomes and long-term health requires appropriate care.

## **DISCLOSURES**

### **Conflict of Interest**

All authors have no conflicts of interest.

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### **Ethical Statement**

Not applicable.

### **Author Contribution**

All authors contributed equally to this study.

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