LITERATURE REVIEW

Pregnancy-Related Disorders and Intrauterine Impaired Lung Development

Harry Agustio Zulhadji[1*], Faisal Yunus[1], Menaldi Rasmin[1], Yudianto Budi Saroyo[2], Bagus Radityo Amien[3]

[1]Department of Pulmonology and Respiratory Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2]Department of Obstetrics and Gynecology, Universitas Indonesia, Jakarta, Indonesia.
[3]Department of Respiratory Medicine, Juntendo University, Tokyo, Japan.

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ABSTRACT

Various pregnancy-related disorders are known to affect fetal lung development negatively. During pregnancy, chronic nutrition and/or oxygen limitation is known to impede lung maturation and induce airway and lung abnormalities. Structural abnormalities and reduced lung function may be evident immediately after birth, persist, or develop with age. The expansion of the fetal lung, fetal breath movements, fetal lung growth, alveolarization, blood-air barrier, extracellular matrix (ECM), airways, surfactant system, and lung immune function are all affected by nutritional limitations during pregnancy. Gestational hypoxia disrupts fetal lung development, which manifests as morphological and functional pulmonary abnormalities. Additionally, intrauterine growth restriction (IUGR), preeclampsia (PE), exposure to air pollution, and smoking are known to interfere with embryonic lung development. Birth defects, such as bronchopulmonary dysplasia, as well as chronic obstructive pulmonary disease (COPD), can be caused by abnormalities in pregnancy. Adequate nutrition, avoidance of smoking, and watchful monitoring and intervention during pregnancy should be promoted to prevent chronic lung disease of the newborn, child, and adult.

INTRODUCTION

The process of human development from a single cell to a newborn baby involves a number of sequential processes. The study of these processes is known as embryology, and it involves a variety of investigations into the molecular, cellular, and structural factors that contribute to the process of organism formation. Through embryogenesis and the fetal period, a single cell will develop. Embryogenesis occurs during the first eight weeks of pregnancy, after which the fetal period lasts until the birthing process. Good prenatal care is crucial not only for improved birth outcomes but also for long-term effects following birth.[1]

Various pregnancy-related conditions are known to affect fetal lung development negatively. These conditions are intrauterine growth restriction (IUGR),[2,3] nutritional deficiency,[4,5] gestational hypoxia,[6] smoking,[7,8] preeclampsia (PE),[9,10] and air pollution exposure.[11,12] Various prenatal conditions can interact with postnatal factors to cause chronic lung diseases that can occur at birth, such as bronchopulmonary dysplasia,[13,14] as well as later in life, such as chronic obstructive pulmonary disease (COPD).[15-17]

IUGR and low birth weight affect lung development and contribute to the impairment of lung function and the development of respiratory-related morbidity among infants that persist or develop throughout childhood and adulthood. Chronic malnutrition and/or decreased oxygen supply during late pregnancy could result in impairment of the airways and lung development of the fetus. The abnormalities of the airways and lungs could exist immediately after birth or progress with age. These alterations tend to cause lifelong pulmonary symptoms and accelerate lung aging.[18,19]

*Corresponding author: harryagustio@gmail.com

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CONDITIONS THAT MAY AFFECT THE DEVELOPMENT OF THE FETAL LUNGS DURING PREGNANCY

IUGR

According to epidemiological and experimental evidence, multiple organs may be negatively impacted by prenatal conditions that result in IUGR. The lung is an organ that can be negatively affected by various pregnancy-related conditions, resulting in structural changes and functional disturbances that can persist into postnatal life. Early developmental disorders of the lung can persist in later life since the lung has a limited ability to recover.[18,19]

IUGR causes an increased incidence of perinatal morbidity and mortality and carries a high risk of hypoxic-ischemic encephalopathy, intraventricular hemorrhage, and necrotizing enterocolitis. Asphyxia, hypothermia, uncontrolled blood glucose, polycythemia, persistent pulmonary hypertension, and meconium aspiration pose an immediate risk for infants with IUGR. These complications increase the risk of premature death for infants with IUGR, and this risk is even greater in developing nations.[2]

IUGR is caused by factors that derive from the mother, placenta, fetus, environment, or combination of these factors.[2] Hypertension brought on by pregnancy and abnormal uteroplacental circulation are the single most important factors in the development of IUGR. About 40% of IUGR cases in developed nations are associated with maternal smoking. Low placental nutrient supply during fetal development will induce fetal adaptation to reduced nutritional needs but will result in structural and functional changes with negative long-term effects on the lung.[19]

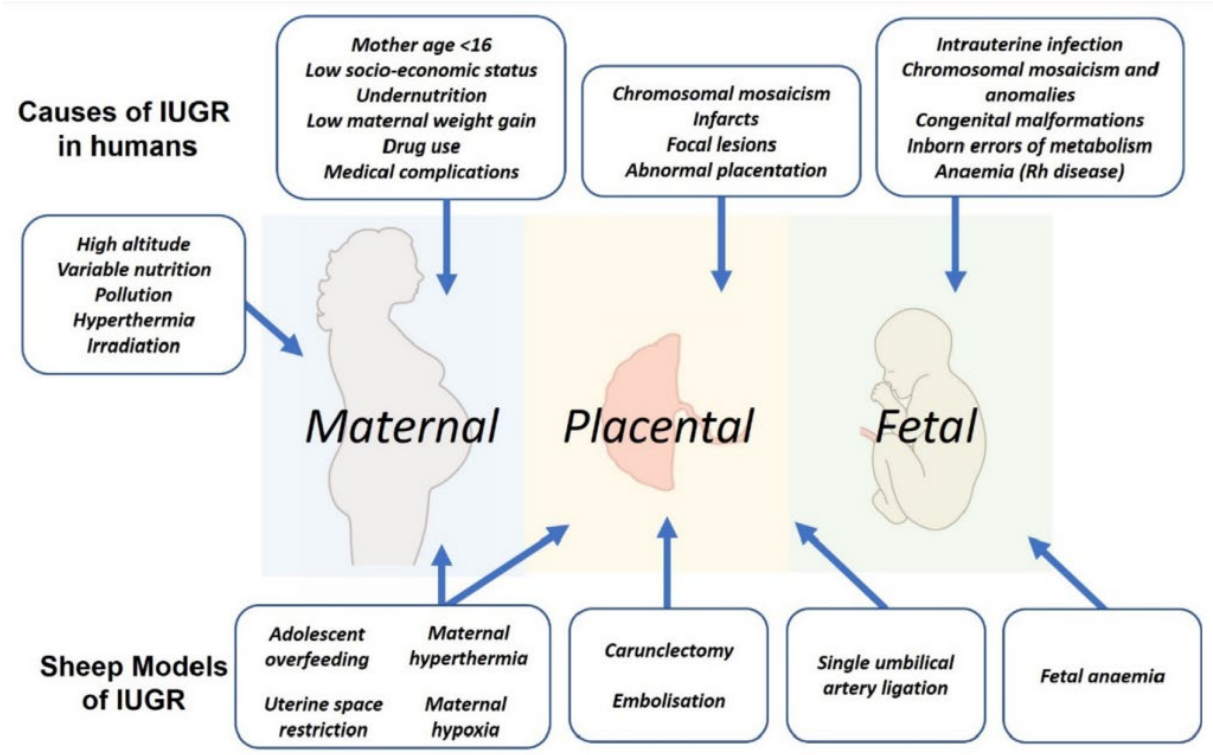

Figure 1. Factors associated with IGUR: maternal, fetal, placental, and environmental[2]

There are various stages of lung development, including the embryonic period, the pseudoglandular period, the canalicular period, the saccular period, and the alveolar stage.[16] Inadequate fetal nutrition and oxygen supply can have an effect on these phases, potentially influencing long-term lung function and respiratory-related morbidity. Placental insufficiency typically takes place in late pregnancy, which coincides with the development of acini and alveoli of the lung. Therefore, IUGR is likely to impact the structure and function of the distal lungs. Epidemiological evidence suggests that changes in lung formation have effects on lung function and disease both in early age and late adulthood.[1]

The majority of information on the impacts of IUGR on lung growth and maturation comes from animal studies.[2] Most of the studied animals have fetal development limitations due to nutritional approaches (limited maternal energy and/or protein intake), impaired placental function and uterine blood flow (embolectomy), or placental insufficiency caused by preconception carunclectomy, arterial ligation, or

chronic hypoxia. Cigarette smoke exposure and late pregnancy ischemia/reperfusion have been the subject of additional research. Numerous studies have confirmed that normal lung maturation is contingent on oxygen tension and a sufficient nutrient supply.[18,19]

Nutritional Disorder During Pregnancy

Nutrition has a vital role in fetal lung development, not only regulating lung growth processes directly but also impacting development through epigenetic modifications. IUGR is the most prevalent cause of inadequate prenatal nutrition, with the majority (80-90%) referring to a decreased delivery of nutrients and oxygen to the baby via the placenta as a result of placental insufficiency or maternal nutritional inadequacy. Placental insufficiency often develops in the second part of pregnancy, with the formation of acinar and alveolar cells. Therefore, IUGR most often affects the distal portion of the lung. Nutritional restriction has many impacts on the fetal lung, including expansion of the fetal lung, fetal breath movements, fetal lung development, alveolarization, the blood-air barrier, extracellular matrix (ECM), airways, and lung immune function.[5]

Micronutrients, a collective name for vitamins and minerals, are widely acknowledged as essential for fetal and newborn development. Vitamins A, D, E, and selenium are substances that contribute to lung growth. Other significant chemicals include zinc and docosahexaenoic acid (DHA). During lung development, the airways and air gaps do not collapse and retain fetal lung fluid, which is believed to be released by pulmonary epithelial cells. This fluid is crucial to fetal lung development because it keeps the lungs in an inflated state. Due to the dependence of this lung fluid on the metabolic activity of the airway epithelium, this process is affected by nutritional and oxygen limits. According to a previous study, chronic hypoxia and hypoglycemia limit the release of lung fluid.[5]

Numerous experimental investigations have shown that restricting fetal nutrition (including oxygen) may affect lung development, although the impact varies depending on the type and gestational age of the intervention at the time it is administered. Several species' studies have shown that dietary deficits during this phase of lung development might impede alveolarization. The majority of studies were performed on postnatally generated alveoli mice. The effects of malnutrition during the first postnatal week included alveolar expansion, septal thickness, and decreased elastin deposition at two weeks of age.[5]

The blood-air-lung barrier is composed of endothelial cells, type I alveolar cells, and fused basement membrane. It is a very thin layer of tissue connecting the alveolar lumen and alveolar capillaries. Its physical qualities control the rate of oxygen and carbon dioxide exchange between the blood and alveoli. The ECM of the lung, which supplies the alveolar framework and conducting airways, has a significant impact on the lung's mechanical characteristics and function. Elastin, collagen, proteoglycans, and basement membrane proteins make up the majority of the lung's ECM. Elastogenesis is a crucial step in lung tissue alveolarization and elastic characteristics. The foundation membrane and conducting airways are composed mostly of collagen. Proteoglycans have a significant impact on lung compliance and fluid balance.[5]

During embryogenesis, vitamin A (retinol) and retinoic acid play important roles in lung formation. Numerous aspects of lung development, including branching morphogenesis and structural remodeling during alveolarization, are influenced by retinoic acid. In rats with vitamin A shortage during pregnancy, the expression of surfactant proteins A, B, and C in the fetal lung is reduced. This suggests that vitamin A may contribute to surfactant production. Several studies imply a link between vitamin E deficiency and alterations in prenatal and newborn lung development. Vitamin E is absorbed by type II alveolar cells and may have a significant role in respiratory distress and chronic lung disease in preterm newborns.[5]

Selenium is required for the activity of glutathione peroxidase, an essential antioxidant enzyme that lowers organic and inorganic hydroperoxidases, which is essential for lung development. Selenium and vitamin E work synergistically to reduce peroxide production. In animal studies involving rats, zinc deficiency during pregnancy is associated with poor fetal lung development.[5]

Gestational Hypoxia

Gestational hypoxia is a substantial risk factor for pulmonary hypertension and other difficulties in newborns despite the fact that the disease's underlying causes remain unknown. This disorder results in less-than-ideal fetal development. Extreme exposure to prenatal hypoxia or other intrauterine stress may result in malformations or fetal mortality. Prenatal exposure to hypoxia causes severe stress on the fetus, which, depending on the degree of exposure, may result in growth limitation. The risk of newborn morbidity and death is increased by fetal growth restriction, as is the possibility of acquiring illness later in life.[6]

Gestational hypoxia may be caused by placental insufficiency, placental infarction, residing at high elevations, smoking during pregnancy, congestive heart

failure, valvular heart disease, pulmonary illness, acute or chronic respiratory infections, anemia, PE, and other diseases. Various animals, including humans, are especially vulnerable to lung injury induced by hypoxia throughout the prenatal and neonatal stages. As a result of low oxygen levels disrupting lung development, a fetus exposed to prenatal hypoxia is incapable of adapting to breathing air. This issue may show structural and functional abnormalities that increase lifelong vulnerability to illness.[6]

Pulmonary vascular disease caused by hypoxia and affecting human fetuses may be researched by observing fetuses and newborn lambs delivered to mothers living at high elevations. Resistant pulmonary artery thickening was seen in a lamb fetus whose mother was at an altitude of 3,801 meters, comparable to the delivery of a human infant. Fetuses and lambs born in highland regions exhibited abnormalities similar to the hypoxic state of the fetus in pulmonary hypertension, such as increased pulmonary pressure, hypoxic exacerbations triggered by pulmonary vasoconstriction, impaired vasodilation, arterial remodeling, and right ventricular hypertrophy.[6]

PE

PE is one of the most prevalent pregnancy problems and is linked with a significant risk of morbidity and death. In pregnant women, PE presents as hypertension with or without multisystem diseases and cardiovascular consequences. In addition, PE has also been linked to IUGR, placental abruption, and preterm delivery. The pathophysiology of PE is still not entirely known. However, it is presently believed to be the result of a failure in the physiologic transition of the spiral arteries, resulting in a reduction in uteroplacental perfusion.[9]

In PE, proangiogenic and antiangiogenic elements are out of balance. Given that airway and alveolar development tracks vascular expansion, it is probable that the antiangiogenic condition of PE influences fetal lung development. A cohort study of children born very preterm revealed a link between PE and respiratory distress syndrome (RDS).[10] There is experimental evidence that antiangiogenic factors in PE may disrupt prenatal and neonatal pulmonary vascular development.[9] Vascular alterations cause hypoperfusion of the placenta, which may generate persistent pulmonary problems such as bronchopulmonary dysplasia with pulmonary hypertension.[10]

In newborn blood from moms with PE, vascular endothelial growth factor (VEGF) levels are relatively low, although antiangiogenic factors such as VEGF receptor-1 and soluble endoglin (s-ENG) are elevated. It is recognized that these variables affect pulmonary alveolarization and vascular development. Animal studies have shown a correlation between appropriate VEGF exposure and enhanced surfactant synthesis in the intrauterine environment.[9] Although there is no published human data, it is probable that anti-VEGF exposure to PE impairs surfactant function.[9]

Inhalation of Air Pollutants

Air pollution exposure has long-term effects on respiratory health. It is recognized that exposures during pregnancy impact the fetus and postnatal life. Germ cells and fetal cells are more vulnerable to external exposure than adult cells owing to their greater replication and differentiation rates and increased sensitivity to adjacent signals. Exposure to air pollution during pregnancy also has a significant impact on fetal lung development and has been proven to have diverse effects on respiratory health.[20]

Lung morphogenesis and airway development occur between 4 and 7 weeks of gestation and continue to the alveolar phase at around 36 weeks. Exposures to the environment, such as air pollution, may affect the proliferation of cells, differentiation of epithelial cells, and alveolarization. In addition, the repair process of growing lung tissue is less effective than that of the mature lung, making the immature lung more vulnerable to various diseases.[16,20]

Although there have been fewer investigations on the impact of air pollutant exposure on postnatal lung function, a number of studies have shown the detrimental effects of prenatal air pollution on lung development and respiratory health. In a cohort study, exposure to particulate matter (PM) 10 from traffic during pregnancy causes decreased lung function at 8 years old.[21] Chronic exposure to high PM during pregnancy increases birth complications including low birth weight, pre-term delivery, and IUGR.[22]

The pathogenesis of birth complications due to chronic PM exposure involves the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These ROS and RNS trigger oxidative stress which results in deoxyribonucleic acid (DNA) damage and generation of placental DNA adduct. Polycyclic aromatic hydrocarbons (PAH) can interfere with placental growth factor receptors and inhibit nutrient and oxygen delivery through the placenta. Inorganic metals contained in PM consisting of chromium, silicon, aluminum, copper, iron, and titanium can increase the concentration of pro-inflammatory mediators and lead to pulmonary inflammation.[22]

Increased ROS can cause mitochondrial dysfunction and promote oxidative stress. Increased ROS leads to the dysfunction of essential proteins including succinate-ubiquinone reductase and

nicotinamide adenine dinucleotide reduced form (NADH)-ubiquinone reductase and results in tissue damage. Endoplasmic reticulum stress due to ROS can increase the activity of inflammatory genes and autophagic mechanisms which lead to pulmonary and placental inflammation. Placental inflammation inhibits the delivery of nutrients and oxygen. Pulmonary inflammation could impair lung growth in the fetus and eventually cause airway disease in children.[22] Previous cohort studies showed that exposure to fine PM during the prenatal period and early life could decrease lung function measured as forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in children aged 6-9 years old. Exposure to increased fine PM above 5th percentile average exposure (7.55 µg/m^3) during the second half of pregnancy could decrease 0.42 L of FVC and 0.38 L of FEV1 among children aged 6-9 years old.[23]

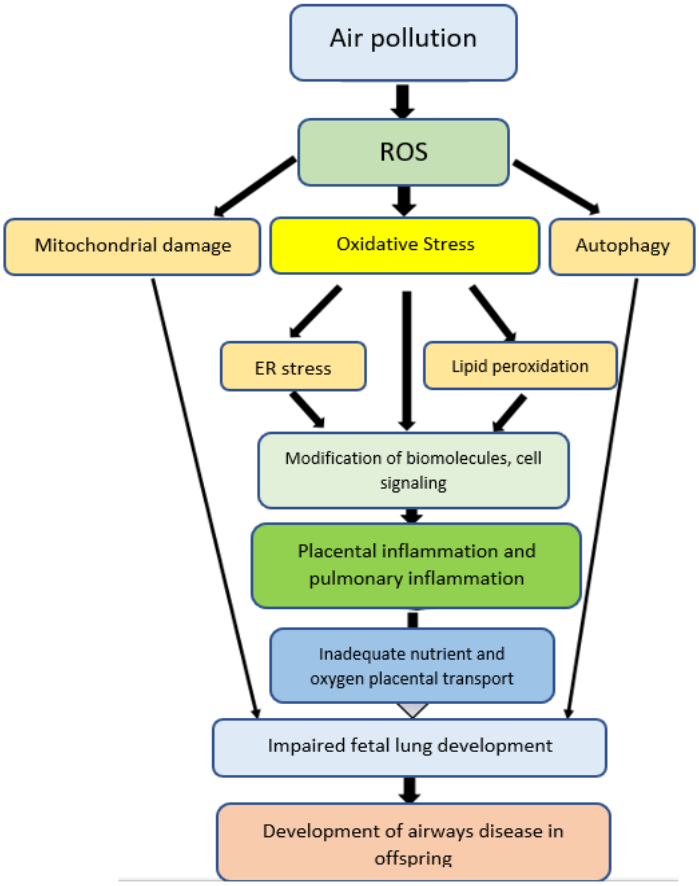

Figure 2. Impact of air pollution in pregnancy on lung development[22]

Smoke

Intrauterine smoking exposure could potentially lead to impaired lung development and decreased lung function during childhood. Maternal smoking exposure during delivery is associated with a reduction of the FEV1/FVC ratio. There are several mechanisms underlying the abnormality of lung development due to smoke exposure including shortening telomere length, DNA methylation, decreased expression of genes related to lung maturation, and damage of respiratory mucosa. These changes in lung development are mediated by nicotine inside tobacco.[16]

Inhaled nicotine reaches its peak concentration in the mother's blood within 15-30 minutes. Nicotine then circulates through the human placenta. A small portion of nicotine is eliminated through fetal urine in the amniotic fluid. Nicotine inside the amniotic fluid can cross through fetal skin and cause an increase in nicotine concentration in fetal circulation. Nicotine concentration in fetal blood can exceed more than 15% compared with nicotine concentration in maternal blood. Since the half-life of nicotine in the fetal circulation is longer due to slow metabolism in the fetal liver, fetal tissue contains a higher concentration of nicotine than maternal blood.[24]

An in vitro study stated that nicotine directly affects pulmonary alveolar type II cells and fibroblasts.[24] Nicotine can also impact airway smooth muscle and increase the deposition of collagen, thicken alveolar walls, and cause hyper-responsive airways based on studies in animals (rats, mice, sheep, and nonhuman primate models).[24]

Structural changes such as fewer saccules, larger saccules, decreased parenchymal tissue, and decreased surface area of alveoli were noted in the fetal lungs of

rats exposed to smoke. Nicotine also affects pulmonary function by reducing passive respiratory compliance, reducing forced expiratory volume (FEV), and decreasing tidal volume.[24]

CHRONIC LUNG DISEASES CAUSE DISORDERS IN PREGNANCY

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that mostly affects preterm newborns and is caused by an imbalance between damage and repair mechanisms in the growing immature lung. The pathophysiology of BPD is complex and complicated. Prenatal, birth, and postnatal factors are known to interfere with the development of pulmonary blood vessels and alveoli, hence contributing to BPD. Classic BPD is distinguished by abnormality of alveolarization heterogeneity of severe airway epithelial lesions, including squamous metaplasia, airway smooth muscle hyperplasia, mucus gland hyperplasia, swelling of epithelial, significant alveolar septal fibrosis, dysmorphic pulmonary microvessel growth, and remodeling of pulmonary artery hypertension. Minimal heterogeneity, increased alveolar structures, decreased vascular netting, few epithelial lesions, and minor thickening of airway smooth muscle are characteristics of BPD.[16]

BPD development is affected by the process of alveolarization starting from intrauterine fetal development, birth, to adulthood. Abnormal alveolarization could lead to BPD. There are several factors that influence alveolarization including gestational age, low birth weight, oxygen toxicity during ventilation, mechanical trauma, maternal smoking, PE, prenatal infections, IUGR, malnutrition, and genetics.[16]

Other prenatal risk factors that affect the development of BPD include tobacco smoking, chorioamnionitis, pregnancy-induced hypertension, and genetics. Tobacco smoking causes adverse effects on lung development mediated by nicotine. A recent meta-analysis also stated that intrauterine tobacco smoking exposure is associated with the increased prevalence of moderate to severe BPD.[25] Chorioamnionitis could cause inflammation in the preterm lung. Pregnancy-induced hypertension causes abnormal vasculature, reduced expression of placental growth factors, and vascular endothelial growth factors that can result in placental insufficiency. Genes that are involved in the expression of VEGF, tumor necrosis factor, toll-like receptors, matrix metalloproteinases, and interleukins could contribute to the development of BPD.[26]

Chronic Obstructive Pulmonary Disease (COPD)

COPD is well-recognized as a smoking-related condition that affects millions of individuals worldwide. Currently, COPD is the third biggest cause of mortality worldwide. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, COPD is a non-reversible obstructive airway disease with a FEV1/FVC ratio of less than 70% after bronchodilator treatment.[27] Genetic and environmental variables, as well as prenatal and postnatal lung growth factors, impact the incidence of COPD.[16]

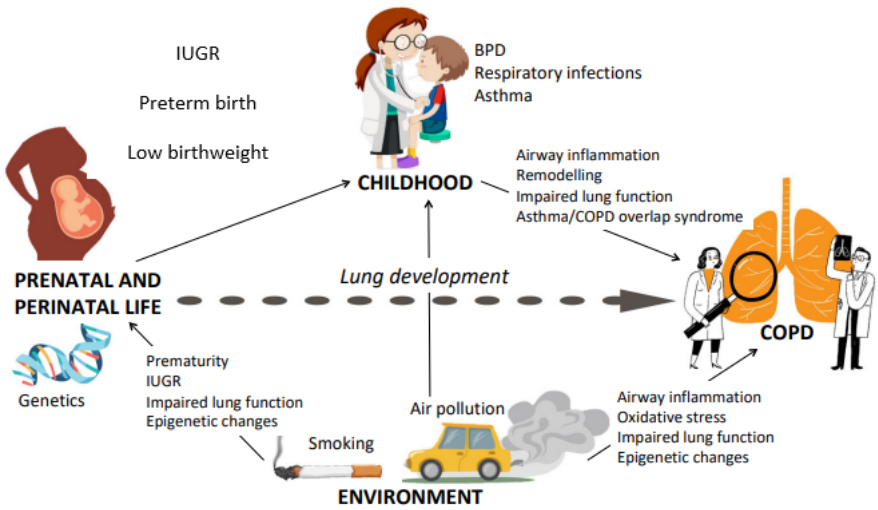

Figure 3. Prenatal and perinatal risk factors contributing to the development of COPD[16]

Low birth weight is a prenatal risk factor that affects the likelihood of COPD. The relationship between low birth weight, airway function, and morbidity in children, adolescents, and adults is supported by solid data. Most epidemiological research has shown a correlation between low birth weight and cardiovascular and pulmonary illness in adulthood. The primary causes of low birth weight include preterm delivery and IUGR. The primary cause of IUGR is transplacental disruption, which disrupts the fetus's

supply of oxygen and/or nutrients. This oxygen and food deprivation has wide-ranging impacts on fetal lung development, including lower alveolar surface area, thickening of the air-blood barrier, and decreased lung mass. According to animal studies, these alterations continue until maturity.[15-17]

Low birth weight positively correlates with lung function in adults measured as FEV1 and FVC. Every kilogram of birth weight is associated with a 48 ml increase in FEV1. Lower birth weight is a risk factor for lower FEV1. Preterm newborns or newborns with low birthweight (girls with a weight lower than 2,000 g and boys with a weight lower than 2,100 g) had a higher risk of developing COPD. Children with a history of IUGR showed decreased lung function including a decrease of 50 ml FEV1 and 40 ml FVC.[16]

There are also several genes that are involved in the development of COPD including CHRNA3/4/5/7, CHRNB3/4, HHIP, FAM13A, ADAM33, and HIP. CHRNA3/4/5/7, CHRNB3/4, HHIP, and FAM13A are correlated with the severity of airway obstruction in COPD. HIP gene is associated with early lung maturation and responses to injuries. Polymorphism of the ADAM33 gene can increase the risk of airway obstruction in children and COPD in adulthood.[16]

SUMMARY

Chronic nutrition and/or oxygen limitation in late pregnancy contributes to anomalies in the airways and lung development. Structural abnormalities and impaired lung function may be evident immediately after birth, persist, or develop with age. Various pregnancy-related disorders are known to affect fetal lung development negatively. These conditions include IUGR, dietary inadequacy, gestational hypoxia, smoking, PE, and air pollution exposure. Various disorders during pregnancy may be linked to postnatal variables that can lead to chronic lung illness that can arise at birth, such as BPD, or later in life, such as COPD.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Principal manuscript writer and data collector: HAZ. Concept writers: HAZ, MR, and YBS. Manuscript reviewers: FY, MR, YBS, and BRA. All authors contributed and approved the final version of the manuscript.

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