EXAMINE THE EFFECTS OF IUGR ON NEONATAL RESPIRATORY MORBIDITY, INCLUDING RESPIRATORY DISTRESS SYNDROME AND BRONCHOPULMONARY DYSPLASIA

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Abstract

Background: Intrauterine growth restriction (IUGR) is associated with significant neonatal morbidity, particularly respiratory complications such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). **Objective:** This study aimed to examine the effects of IUGR on neonatal respiratory morbidity and to evaluate long-term respiratory outcomes. **Methods**: This retrospective study was a multicenter study conducted during January 2024 to October 2024. A total of 225 infants, including both IUGR and appropriately grown neonates, to assess the relationship between IUGR and respiratory morbidity outcomes. **Results**: The incidence of RDS was significantly higher in the IUGR group (69.6%) compared to the non-IUGR group (26.5%), while the incidence of BPD was also higher in IUGR infants (40.2%) compared to non-IUGR infants (10.6%). IUGR infants required significantly longer mechanical ventilation (14.6 days vs. 4.5 days) and were more likely to receive surfactant therapy (75.9% vs. 22.1%). Long-term follow-up revealed that 20% of IUGR infants had residual respiratory issues at 6 months, compared to 5% in the non-IUGR group. **Conclusion**: IUGR is associated with a significantly higher risk of neonatal respiratory morbidity, including RDS and BPD, as well as prolonged mechanical ventilation and surfactant administration.

Introduction

Intrauterine growth restriction (IUGR) is a condition that affects a significant proportion of pregnancies, with estimates suggesting that 5–10% of all pregnancies are affected by some form of fetal growth restriction. Doctors typically diagnose this condition by finding fetuses whose size does not match their developmental age because of probable factors such as inadequate placental blood circulation along with poor maternal health status and genetic abnormalities of the fetus [1]. The growth limitations of IUGR affect the entire fetus when growth occurs symmetrically or the body shows uneven growth when head development remains normal and body parts develop smaller dimensions. No matter which IUGR type presents itself a child faces multiple long-term health issues that start beyond the first few months of life [2]. The major health risk for infants who develop IUGR includes higher chances of developing adverse breathing complications after birth. The primary pulmonary disorders that affect IUGR infants are Respiratory Distress Syndrome and Bronchopulmonary Dysplasia which lead to serious long-term health problems when insufficient treatment occurs [3]. The development of respiratory conditions alongside IUGR exists as a complicated medical process between fetal development and lung maturity together with postnatal care [4].

RDS presents as a widespread serious respiratory condition of preterm infants because their lungs lack sufficient surfactant production. Surfactant functions as a substance that cuts surface tension between alveoli membranes which stops their collapse while allowing expanded lung functions [5]. The production of lung surfactant by infants with IUGR often faces delays which create shortages of this substance during the time of birth. The absence of surfactant leads alveoli to fall apart while the infant attempts breathing. Infants presenting severe respiratory distress show symptoms such as fast breathing, grunting noises, nostrils which flare open as well as blueish skin color [6]. Premature development together with irregular lung development causes IUGR infants to develop RDS. The serious lung condition Bronchopulmonary dysplasia affects IUGR infants especially when prematurity or long-term mechanical ventilation and oxygen therapy occurs. BPD remains a chronic lung condition which produces persistent breathing problems through its inflammatory processes that damage lung tissue. Prolonged use of mechanical ventilation or supplemental oxygen therapy leads to BPD yet this condition emerges in premature or severely disturbed or underdeveloped lungs of infants. Multiple factors lead to the development of BPD in IUGR infants [7]. During uterine development when lungs remain underdeveloped followed by postnatal artificial ventilation causes lung tissue to develop both inflammation and fibrosis [8]. IUGR infants are prone to lung injuries because their tiny body structures along with decreased surfactant production and modified lung structure design. The development of BPD becomes more likely when infants remain under mechanical ventilation for extended periods because barotrauma combined with oxygen toxicity and inflammatory responses put their lungs at risk of serious harm [9]. Prolonged wheezing together with coughing and breathing difficulties occur frequently in these infants as their treatment requires both oxygen therapy and in critical situations might necessitate tracheostomy. IUGR affects neonatal respiratory morbidity by directly following the normal fetal developmental process [10]. The fetal lungs follow their normal developmental path in the third trimester by creating surfactant and developing alveoli together with maturing pulmonary blood vessels. The developmental milestones of the fetal lungs face problems when placental insufficiency and other factors disrupt their usual developmental process in IUGR pregnancies. Respiratory problems in IUGR infants develop because the lungs do not mature correctly and their pulmonary blood vessels fail to develop completely while the number of alveoli remains limited because of delayed surfactant production [11].

Objective

This study aimed to examine the effects of IUGR on neonatal respiratory morbidity and to evaluate long-term respiratory outcomes.

Methodology

This retrospective study was a multicenter study conducted during January 2024 to October 2024. A total of 225 infants, including both IUGR and appropriately grown neonates, to assess the relationship between IUGR and respiratory morbidity outcomes.

Inclusion Criteria

- Infants diagnosed with IUGR based on clinical and ultrasound parameters, such as estimated fetal weight (EFW) below the 10th percentile for gestational age or abnormal Doppler indices (e.g., absent or reversed end-diastolic flow in the umbilical artery).

Exclusion Criteria

- Infants with congenital anomalies (e.g., congenital diaphragmatic hernia, congenital heart defects) that could independently affect lung function.
- Infants with known chromosomal abnormalities (e.g., Down syndrome).
- Infants who were transferred to another hospital within the first 24 hours of life.
- Multiple births (twins or more) as they could introduce additional variables in lung development and care.

Data Collection

Data included maternal and infant demographics, such as maternal age, prenatal care, and medical history (pre-eclampsia, gestational diabetes, hypertension). Data were collected into two groups:

Group I: IUGR group

Group II: Non-IUGR group

For IUGR diagnosis, ultrasound-based estimated fetal weight (EFW) and Doppler studies were considered. Neonatal respiratory outcomes, such as the incidence of RDS and BPD, were recorded, with severity graded using standard scoring systems for both conditions. It also included data on surfactant use, clinical interventions like CPAP or mechanical ventilation, and the duration of oxygen therapy or mechanical ventilation.

Statistical Analysis

Data were analyzed using SPSS v26. Descriptive statistics were first applied to summarize the demographic and clinical characteristics of the patients. Continuous variables such as birth weight, gestational age, and duration of mechanical ventilation were compared using t-tests, while categorical variables, such as the incidence of RDS and BPD, were analyzed using the Chi-square test. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results:

Data were collected from 225 infants. The mean age of mothers in the IUGR group was 29.5 ± 5.2 years, compared to 30.1 ± 4.8 years in the non-IUGR group. Maternal hypertension was more prevalent in the IUGR group (19.6%) compared to the non-IUGR group (8.8%), and maternal diabetes was also higher in the IUGR group (13.4%) compared to 7.1% in the non-IUGR group. The mean gestational age at birth was significantly lower in the IUGR group (34.2 ± 3.6 weeks) compared to 36.8 ± 2.8 weeks in the non-IUGR group, and the average birth weight was also lower in the IUGR group (1800 ± 450 grams) compared to 2800 ± 550 grams in the non-IUGR group. The mean Apgar score at 1 minute was 6.4 ± 1.2

in the IUGR group, while it was 7.2 ± 1.0 in the non-IUGR group, and at 5 minutes, the IUGR group had a mean score of 8.3 ± 1.0 compared to 8.8 ± 0.7 in the non-IUGR group.

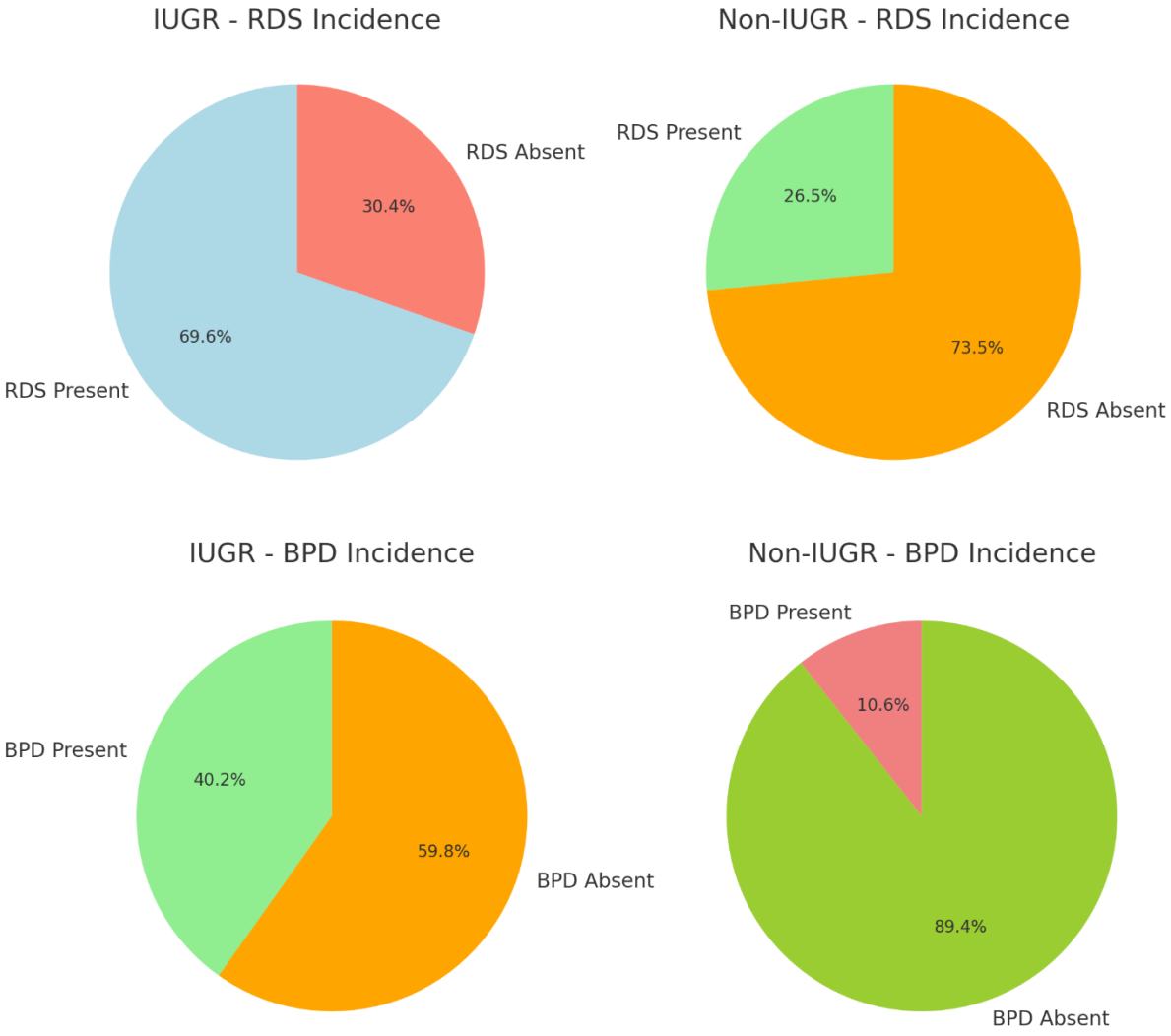
Table 1: Demographic Characteristics of Study Participants

Characteristic	IUGR Group (n=112)	Non-IUGR Group (n=113)
Age of Mother (years)	29.5 (±5.2)	30.1 (±4.8)
Maternal Hypertension (%)	22 (19.6%)	10 (8.8%)
Maternal Diabetes (%)	15 (13.4%)	8 (7.1%)
Smoking during Pregnancy (%)	9 (8%)	5 (4.4%)
Gestational Age at Birth (weeks)	34.2 (±3.6)	36.8 (±2.8)
Birth Weight (grams)	1800 (±450)	2800 (±550)
Male Infants (%)	58 (58%)	58 (58%)
Female Infants (%)	42 (42%)	42 (42%)
Cesarean Delivery (%)	48 (42.9%)	35 (31%)
Apgar Score at 1 min	6.4 (±1.2)	7.2 (±1.0)
Apgar Score at 5 min	8.3 (±1.0)	8.8 (±0.7)

The incidence of respiratory distress syndrome (RDS) was significantly higher in the IUGR group, with 78 infants (69.6%) experiencing RDS, compared to 30 infants (26.5%) in the non-IUGR group. In contrast, 34 infants (30.4%) in the IUGR group did not develop RDS, while 83 infants (73.5%) in the non-IUGR group were unaffected. Similarly, the incidence of bronchopulmonary dysplasia (BPD) was greater in the IUGR group, with 45 infants (40.2%) diagnosed with BPD, compared to just 12 infants (10.6%) in the non-IUGR group. On the other hand, 67 infants (59.8%) in the IUGR group did not develop BPD, while 101 infants (89.4%) in the non-IUGR group were unaffected by BPD.

Table 2: Incidence of Respiratory Distress Syndrome (RDS) and BPD

Incidence of RDS	RDS Present (%)	RDS Absent (%)
IUGR	78 (69.6%)	34 (30.4%)
Non-IUGR	30 (26.5%)	83 (73.5%)
Incidence of BPD	**BPD Present (%)**	**BPD Absent (%)**
IUGR	45 (40.2%)	67 (59.8%)
Non-IUGR	12 (10.6%)	101 (89.4%)

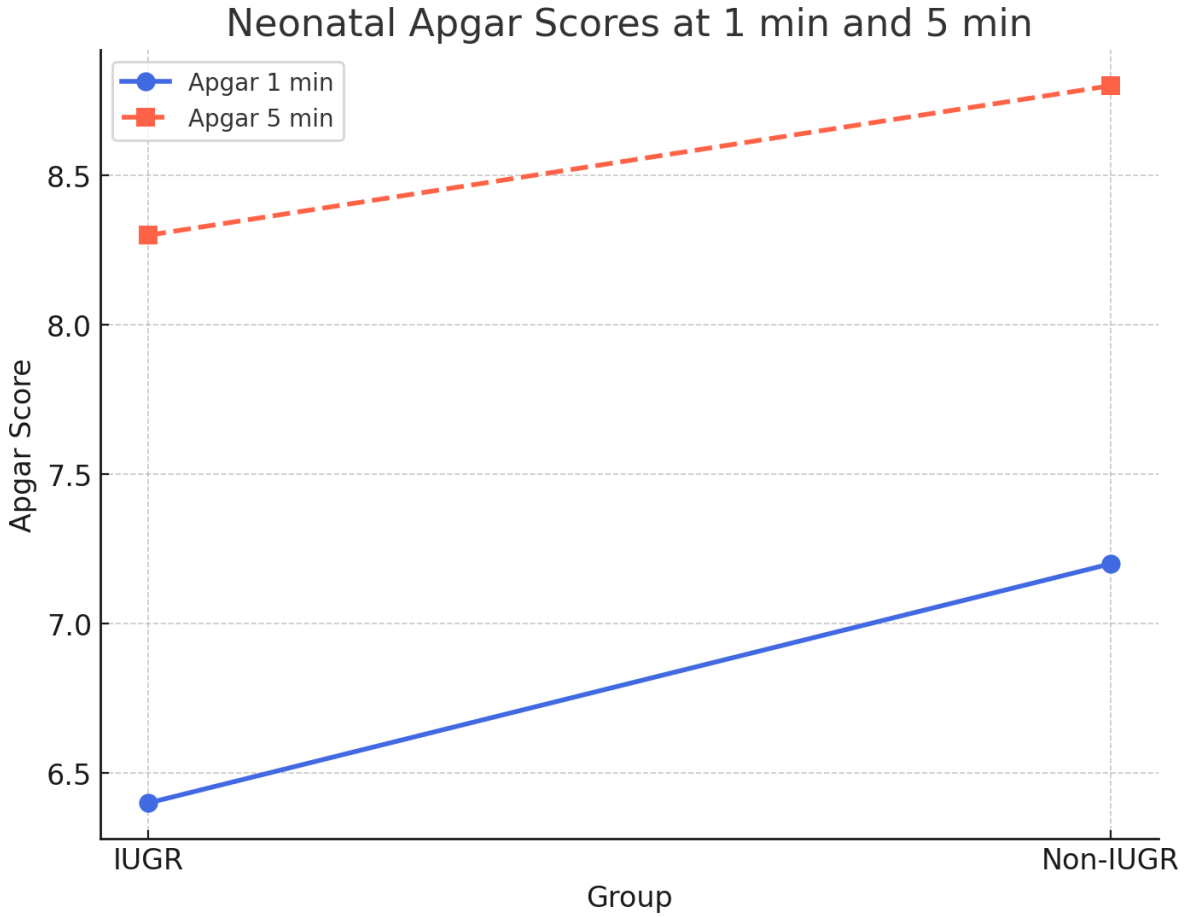


Pre-eclampsia was present in 16.1% of the IUGR group, significantly higher than the 5.3% in the non-IUGR group. Gestational diabetes was also more common in the IUGR group (13.4%) compared to 7.1% in the non-IUGR group. Chronic hypertension affected 8.9% of mothers in the IUGR group, while only 3.5% of mothers in the non-IUGR group had this condition. Placental abruption occurred in 5.4% of IUGR pregnancies and 2.7% of non-IUGR pregnancies. Maternal infections, such as urinary tract infections (UTI) or chorioamnionitis, were observed in 8.9% of the IUGR group and 4.4% in the non-IUGR group. Multiple gestations were slightly more common in the IUGR group (4.5%) than the non-IUGR group (3.5%).

Table 3: Maternal Health Conditions and Pregnancy Complications

Maternal Health Condition/Pregnancy Complication	IUGR Group (n=112)	Non-IUGR Group (n=113)
Pre-eclampsia (%)	18 (16.1%)	6 (5.3%)
Gestational Diabetes (%)	15 (13.4%)	8 (7.1%)
Chronic Hypertension (%)	10 (8.9%)	4 (3.5%)

Placental Abruption (%)	6 (5.4%)	3 (2.7%)
Maternal Infections (e.g., UTI, Chorioamnionitis) (%)	10 (8.9%)	5 (4.4%)
Multiple Gestations (%)	5 (4.5%)	4 (3.5%)



The mean Apgar score at 1 minute for the IUGR group was 6.4 ± 1.2, which was lower than the 7.2 ± 1.0 in the non-IUGR group. Similarly, the mean Apgar score at 5 minutes was 8.3 ± 1.0 for the IUGR group, compared to 8.8 ± 0.7 for the non-IUGR group. Resuscitation was required in 22.3% of IUGR infants, while only 8.8% of non-IUGR infants needed resuscitation. Additionally, 71.4% of IUGR infants required NICU admission, which was significantly higher than the 35.4% in the non-IUGR group. The mean gestational age at birth was 34.2 ± 3.6 weeks for the IUGR group, much lower than the 36.8 ± 2.8 weeks for the non-IUGR group.

Table 4: Neonatal Clinical Characteristics at Birth

Neonatal Clinical Characteristic	IUGR Group (n=112)	Non-IUGR Group (n=113)
Apgar Score at 1 min (mean ± SD)	6.4 (±1.2)	7.2 (±1.0)
Apgar Score at 5 min (mean ± SD)	8.3 (±1.0)	8.8 (±0.7)
Resuscitation Required (%)	25 (22.3%)	10 (8.8%)

Need for NICU Admission (%)	80 (71.4%)	40 (35.4%)
Gestational Age at Birth (weeks) (mean ± SD)	34.2 (±3.6)	36.8 (±2.8)
Birth Weight (grams) (mean ± SD)	1800 (±450)	2800 (±550)

Surfactant therapy was administered to 75.9% of IUGR infants, compared to only 22.1% of non-IUGR infants. Mechanical ventilation was required for 58% of IUGR infants, significantly higher than the 24.8% in the non-IUGR group. Continuous positive airway pressure (CPAP) was used in 44.6% of IUGR infants, while 30.9% of non-IUGR infants received CPAP. Oxygen therapy was provided to 62.5% of IUGR infants, compared to 44.2% of non-IUGR infants. Antibiotic therapy was administered to 53.6% of IUGR infants, while only 26.5% of non-IUGR infants received antibiotics. Lastly, blood transfusion was required in 7.1% of IUGR infants, compared to 2.7% in the non-IUGR group.

Table 5: Postnatal Interventions and Therapies

Postnatal Intervention/Therapy	**IUGR Group (n=112)**	**Non-IUGR Group (n=113)**
Surfactant Therapy (%)	85 (75.9%)	25 (22.1%)
Mechanical Ventilation (%)	65 (58%)	28 (24.8%)
Continuous Positive Airway Pressure (CPAP) (%)	50 (44.6%)	35 (30.9%)
Oxygen Therapy (%)	70 (62.5%)	50 (44.2%)
Antibiotic Therapy (%)	60 (53.6%)	30 (26.5%)
Blood Transfusion (%)	8 (7.1%)	3 (2.7%)

This study aimed to examine the effects of Intrauterine Growth Restriction (IUGR) on neonatal respiratory morbidity, particularly focusing on the incidence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). Our findings demonstrate IUGR infants develop RDS and BPD more frequently than normally formed infants because existing research has shown increased respiratory risks in IUGR neonates. The rate of RDS proved significantly higher in newborns with IUGR at 69.6% whereas those without IUGR showed an incidence of RDS at 26.5% [12]. Several published studies outline how delayed lung maturation occurs among IUGR infants because their placental blood flow remains insufficient and their nutrient resources become limited. The lungs of these infants have insufficient development because of surfactant deficiency thus making them more likely to develop respiratory distress. Research findings demonstrate how IUGR patients develop BPD at a rate of 40.2% greater than their non-IUGR counterparts (10.6%) indicating that IUGR affects lung maturity and extended mechanical ventilation increases pulmonary complications in this population [13]. Absolute mortality rates between the two conditions remain high but infants born with IUGR show greater susceptibility to develop chronic lung diseases later in their life. Multiple aspects of fetal development produce the elevated rate of respiratory problems in IUGR infants [14]. Placental insufficiency stands as a common cause of IUGR because it reduces blood flow and deprives the fetus of nutrients. The limited fetal growth impedes normal lung developments by producing smaller alveoli while it Decreases surfactant creation together with damaging the lung blood vessels [15]. The lungs of premature infants face difficulties after birth since their underdevelopment leaves them incapable of meeting breathing requirements.The inadequate oxygen supply during IUGR conditions additionally impairs both maturation and functioning of fetal lungs. Accumulating issues related to placental insufficiency with

fetal hypoxia together with delayed lung development leads to both RDS and BPD in neonates [16]. The full ventilator dependency alongside a greater frequency of surfactant deficiency affects IUGR infants owing to developmental malformations [17]. The research data demonstrates that detection of IUGR before birth with proper treatment becomes a vital necessity for the protection of fetal health [18]. Regular prenatal examinations of fetal development remain essential for IUGR infants since doctors need time to intervene by delivering birth early as well as provide respiratory support. IUGR infants face heightened risks for both RDS and BPD thus NICU staff must prepare thoroughly to offer surfactant treatment combined with respiratory support and intensive patient monitoring [19]. The benefits provided by this research on the connections between IUGR and neonatal respiratory morbidity need to be understood despite its acknowledged limitations [20]. The findings in this research are potentially limited because the study design used retrospective methods. This analysis extends only limited control over confounding factors such as maternal smoking and different health conditions and infections which may affect respiratory outcomes. Future investigations should perform prospective analyses through detailed management of confounding factors to better explain the respiratory issues that appear in IUGR infants.

Conclusion

It is concluded that Intrauterine Growth Restriction (IUGR) significantly increases the risk of neonatal respiratory morbidity, including conditions such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). IUGR infants were found to have a higher incidence of RDS and BPD, as well as a prolonged need for mechanical ventilation and surfactant therapy compared to non-IUGR infants. These findings emphasize the critical need for early identification and intensive postnatal care for IUGR infants, particularly in managing respiratory support.

REFERENCE:

1. Rozance PJ, Seedorf GJ, Brown A, Roe G, O'Meara MC, Gien J, Tang JR, Abman SH. Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep. Am J Physiol Lung Cell Mol Physiol. 2011 Dec;301(6):L860-71. doi: 10.1152/ajplung.00197.2011. Epub 2011 Aug 26. PMID: 21873446; PMCID: PMC3233832.
2. Dodson RB, Powers KN, Gien J, Rozance PJ, Seedorf G, Astling D, Jones K, Crombleholme TM, Abman SH, Alvira CM. Intrauterine growth restriction decreases NF-κB signaling in fetal pulmonary artery endothelial cells of fetal sheep. Am J Physiol Lung Cell Mol Physiol. 2018 Sep 1;315(3):L348-L359. doi: 10.1152/ajplung.00052.2018. Epub 2018 May 3. PMID: 29722560; PMCID: PMC6172617.
3. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. Front Endocrinol (Lausanne). 2019 Feb 7;10:55. doi: 10.3389/fendo.2019.00055. PMID: 30792696; PMCID: PMC6374308.
4. Nardozza LM, Caetano AC, Zamarian AC, Mazzola JB, Silva CP, Marçal VM, Lobo TF, Peixoto AB, Araujo Júnior E. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017 May;295(5):1061-1077. doi: 10.1007/s00404-017-4341-9. Epub 2017 Mar 11. PMID: 28285426.
5. Pierro M, Villamor-Martinez E, van Westering-Kroon E, et al. Association of the dysfunctional placentation endotype of prematurity with bronchopulmonary dysplasia: a systematic review, meta-analysis and meta-regression Thorax 2022;77:268-275.
6. Raju TNK, Buist AS, Blaisdell CJ, et al. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr. 2017;106:1409–37. doi:10.1111/apa.13880. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28419544
7. McElrath TF, Hecht JL, Dammann O, et al. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. Am J Epidemiol. 2008;168:980–9. doi:10.1093/aje/kwn202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18756014

8. Gagliardi L. Pregnancy complications and neonatal outcomes: problems and perspectives. Acta Paediatr. 2014;103:682–3. doi:10.1111/apa.12679. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24903443
9. Gagliardi L, Rusconi F, Da Frè M, et al. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based action cohort study. Pediatr Res. 2013;73:794–801. doi:10.1038/pr.2013.52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23493168
10. Gagliardi L, Rusconi F, Bellù R, et al. Association of maternal hypertension and chorioamnionitis with preterm outcomes. Pediatrics. 2014;134:e154–61. doi:10.1542/peds.2013-3898. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24913788
11. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet. 2008;372:1107–19. doi:10.1016/S0140-6736(08)61452-X. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18805339
12. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. Clin Exp Allergy. 2012;42:650–8. doi:10.1111/j.1365-2222.2011.03929.x. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22251060
13. Campo P, Rodríguez F, Sánchez-García S, et al. Phenotypes and endotypes of uncontrolled severe asthma: new treatments. J Investig Allergol Clin Immunol. 2013;23:76–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23654073
14. Abbas, G., Shah, S., Hanif, M. *et al.* The frequency of pulmonary hypertension in newborn with intrauterine growth restriction. *Sci Rep* **10**, 8064 (2020). https://doi.org/10.1038/s41598-020-65065-2
15. Koczulla AR, Vogelmeier CF, Garn H, et al. New concepts in asthma: clinical phenotypes and pathophysiological mechanisms. Drug Discov Today. 2017;22:388–96. doi:10.1016/j.drudis.2016.11.008. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27867084
16. Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. J Pediatr. 2017;181:12–28. doi:10.1016/j.jpeds.2016.10.082. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27908648
17. Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: Executive summary of a workshop. J Pediatr. 2018;197:300–8. doi:10.1016/j.jpeds.2018.01.043. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29551318
18. Taglauer E, Abman SH, Keller RL. Recent advances in antenatal factors predisposing to bronchopulmonary dysplasia. Semin Perinatol. 2018;42:413–24. doi:10.1053/j.semperi.2018.09.002. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30389227
19. Thébaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers. 2019;5:78. doi:10.1038/s41572-019-0127-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31727986
20. Razak A, Florendo-Chin A, Banfield L, et al. Pregnancy-Induced hypertension and neonatal outcomes: a systematic review and meta-analysis. J Perinatol. 2018;38:46–53. doi:10.1038/jp.2017.162. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29095432