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Review Article

Maternal Adiposity Impairs Offspring's Lung Development through Th1/Th2 Imbalance, Leptin Signaling, and Oxidative Stress: A Narrative Review and Bioinformatics Analysis

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Abstract

Aim: To summarize and critically analyze the existing peer-reviewed evidence on the link between maternal body-mass index (BMI) or gestational weight gain (GWG) and lung health in the offspring.

Background: Maternal obesity could affect the lung maturation of the offspring resulting in asthma and wheezing in early childhood.

Objective: This study aims to find the relation between maternal obesity and neonatal lung disorders by finding the link between significant obesity-associated factors and lung disorders.

Materials and Methods: Electronic databased research was conducted. The online STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) software was adopted to analyze the inter-dependence and network of different pathways associated with specific proteins.

Results: Twenty-three articles were included in our analysis. Evidence from prospective and observational studies implies a meaningful correlation between maternal obesity and long-term risk of asthma, early/late, and persistent wheezing. The risk continued after the studies were controlled for exposure to allergens, lifestyle, child growth trajectory, and lung health in early childhood. Two studies focusing on susceptibility to respiratory illness showed that children born to mothers with high BMI had a raised risk of respiratory tract infections. Increased adiposity is linked with greater levels of serum leptin, which has the potential to remodel airways and downregulate adiponectin, an adipokine with anti-inflammatory properties. Notably, T helper (Th-1, Th-2) cells, signal transducer and activator of transcription-3 (STAT-3), suppressor of cytokine signaling-3 (SOCS3), and oxidative stress could additionally play critical roles in maternal obesity and weaken fetal lung maturation.

Conclusion: GWG and maternal BMI can increase the chance of asthma, early, late, and chronic wheezing during the growth phase. Larger observational and in-depth studies are expected to further validate current findings.

Keywords: *Body-Mass Index (BMI); Gestational Weight Gain (GWG); Maternal Obesity; Maternal Adiposity; Lung Development; Th1/Th2 Imbalance; Leptin Signaling; Oxidative Stress*

Introduction

The World Health Organization (WHO) estimates that 650 million people suffer from obesity, while over 1.9 billion people are estimated to be overweight according to the 2016 statistics [1]. Women of reproductive age are among the affected population. Studies in the United Kingdom and the United States show that the prevalence of maternal obesity at conception has risen between 6 to 12 percentage points between the years 1990 and the early-2000s [2]. It is estimated that the prevalence of maternal obesity is increasing, with current statistics suggesting that 30% of the women with obesity are pregnant [2]. Furthermore, a significant number of pregnant women exhibit excessive weight or gestational weight gain (GWG) based on their pre-pregnancy body mass index (BMI).

Accumulating evidence suggests that maternal obesity could contribute to adverse respiratory outcomes of their offspring. Obese women have raised their chances of giving birth to obese children. The reasons underlying this can be increased maternal insulin resistance, which accompanies hyperinsulinemia, oxidative stress, and chronic inflammatory status. These factors often result in placental dysfunction and fetal overgrowth [3]. Also, many observational studies have proven a strong correlation between maternal body weight status, obesity, and cardiometabolic risk factors in the offspring. Large for gestational age (LGA), a birth weight that is defined as greater than 90th centile for gestational age, at birth significantly increased the risk of obesity in adolescence and adulthood. Furthermore, childhood obesity and the combination of LGA status and maternal gestational diabetes mellitus (GDM) were associated with insulin resistance [73]. A meta-analysis study done by Yu Z revealed that high maternal BMI clearly is associated with LGA [74].

Elevated reactive oxygen species (ROS) in embryogenesis interferes important signaling pathways leading to untypical function, and structural abnormalities during organogenesis that may result in spontaneous fetal abortion [4]. For instance, fetuses with down syndrome are shown to have prooxidant status i.e., linked to reduced complex I activity in the respiratory electron transport chain in the mitochondria which in turn is associated with ROS production, that together may cause respiratory disorders in the newborn [5]. Oxidative stress (OS) may cause neural tube defect via unrepairable DNA damage in fetal cells [6]. Also, congenital diaphragmatic hernia (CDH), a condition in which the abdominal contents herniate into the thoracic cavity during the fetal period, results in lung hypoplasia and vascular abnormal growth that can lead to critical pulmonary hypertension. Additionally, the fetal CDH lungs are found to be affected by OS that influences nucleotide synthesis, amino acid, glycerophospholipid, and glucose metabolism [7]. Furthermore, fetal growth restriction (FGR) or preeclampsia, were found to be connected with antioxidant deficiency. Premature birth had increased lipid peroxidation products, showing a relationship between OS and preterm birth [8]. However, to date there is enough evidence to prove the

existence of a link between OS and abnormal fetal growth, but larger observational and in-depth studies are expected to further validate our results. Preterm birth may also be a reason of lungs malformation.

The current narrative review aims to examine the existing empirical peer-reviewed evidence on the effect of maternal obesity, before and during pregnancy on the offspring's respiratory outcomes.

Methods

Electronic database research

A web search was conducted to assess and summarize the existing peer-reviewed evidence on the respiratory outcomes of the offspring born to mothers with obesity. We examined the current studies on a specific phenomenon to evaluate the quality of the studies, and summarized the findings, with an emphasis placed on answering the pertinent research questions. A thematic approach to data analysis was used, where the research identifies themes in the reviewed studies and used the information regarding the study design, population, outcomes, and inferences to support the overall conclusion of the review.

Electronic database research was conducted to identify potential studies. Multiple search engines were utilized, including Science Direct, MEDLINE, EBSCO, PubMed, and Google Scholar. The terms used throughout the literature search included "maternal obesity", "offspring", "respiratory health", "lung health", "lung disease", and "infant outcomes". Boolean operators such as "AND" and "OR" were used for combining the search terms to narrow the research to generate productive and focused results. We included only studies published within the last ten years and a few old ones, peer-reviewed, focused on the clinical phenomenon of interest, and in whom full-text was available.

Bioinformatics analysis of possible interactions of leptin via leptin receptor (LEPR) with other proteins

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) is a web resource of the biological database for the known and predicted protein-protein interactions. STRING employs a database derived from the pre-computed experimental data, analysis of co-expressed genes, and literature mining. STRING also provides a unique scoring method as per the different types of associative interactions against a common reference set resulting in a single confidence score per prediction. An evidence-based pattern, which is interactive or inter-related, is deduced by this online analytical software (http://string-db.org/).

Results

Electronic database research

The electronic search yielded forty-three peer-reviewed articles, with only twenty-three meeting the inclusion criteria. The findings of the review are summarized in figure 1. After selecting the articles, a thematic qualitative analysis was conducted to identify themes. The process involved initial coding, identification of the themes, and then matching the themes to the information from the articles.

Bioinformatics analysis of leptin and LEPR

The present bioinformatics results suggest that LEPR, which is a leptin receptor, interacts with several proteins (As described in figure 2 and 3), showing the strongest interacting score with leptin itself followed by Janus Kinase 2 (JAK-2), signal transducer and activator of transcription-3 (STAT-3), and suppressor of cytokine signaling-3 (SOCS-3) genes and/or proteins. The LEPR also showed some interaction with protein tyrosine phosphatase non-receptor type-1 (PTPN-1), insulin (INS), protein kinase AMP-activated catalytic subunit alpha-2

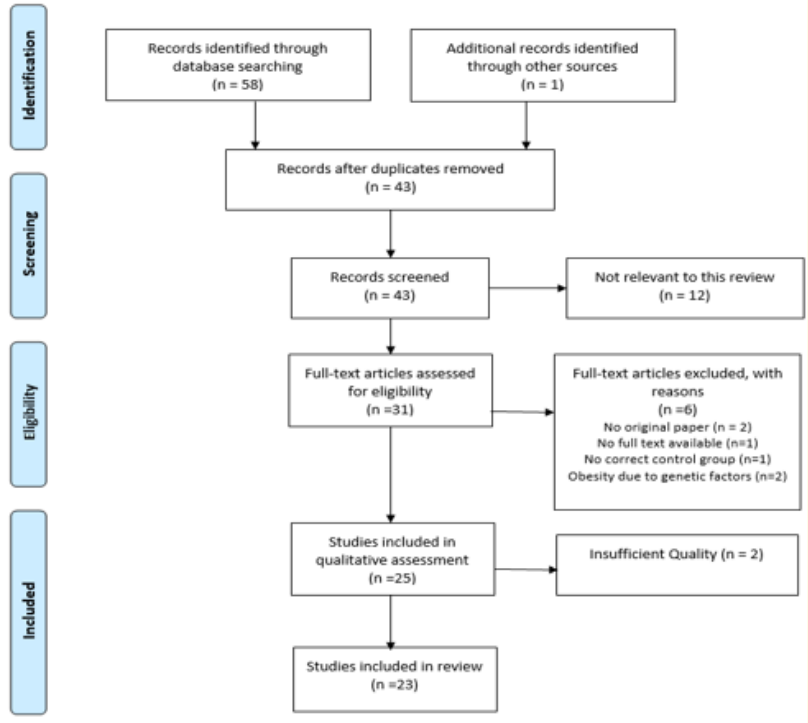

Figure 1: *PRISMA Flow diagram of literature search portraying different phases of quality search to upon maternal obesity and its effect on offspring's lung health. It contains the number of records identified, included and excluded and the reasons for exclusions.*

(PRKAA-2), protein kinase AMP-activated non-catalytic subunit beta-1 (PRKAB-1), protein kinase AMP-activated non-catalytic subunit gamma-2 (PRKAG-2), and protein kinase AMP-activated catalytic subunit alpha-1 (PRKAA-1). The search assumed that leptin via LEPR may represent a potential interacting protein participating in several key signaling pathways that may be associated with impaired fetal lung maturation resulting in asthma and wheezing. This hypothesis has been further discussed in-depth and detailed in the discussion section of this study.

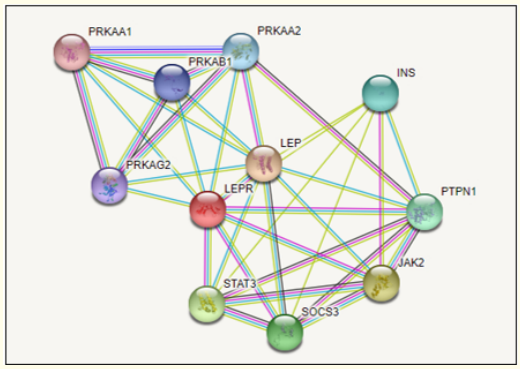

Figure 2: *String based study of Leptin and its receptor LEPR associated pathways.*

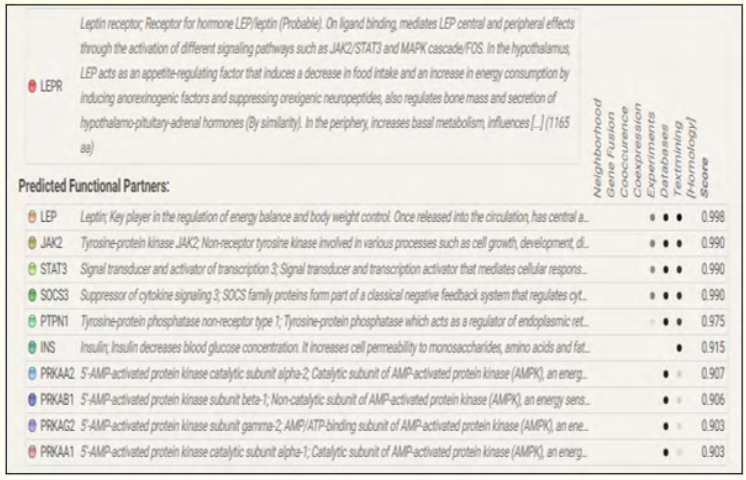

Figure 3: *Proteins and pathways associated with LEPR signaling.*

Discussion

High maternal pre-pregnancy BMI and GWG during pregnancy may increase the risk of wheezing and asthma in infants.

Indeed, a 2015 study of fourteen European birth cohorts by Zugna., *et al.* [9] analyzing overall 85,509 subjects, reported elevated rates of ever wheezing and recurrent wheezing in children born to mothers with either excessive GWG or pre-pregnancy high BMI. "Ever wheezing" or "persistent wheezing" was defined as at least one episode of wheezing, while "recurrent wheezing" was defined as at least 4 episodes of wheezing. The cohort-specific adjusted pooled risk ratios (RR) for persistent and recurrent wheezing were 1.08 (95% confidence interval [CI]: 1.05-1.11) and 1.19 (95% CI: 1.12-1.26) for overweight; 1.12 (95% CI: 1.08-1.17) and 1.16 (95% CI: 0.97-1.39) for obesity. The authors concluded that pre-pregnancy overweight and obesity are associated with an increased risk of developing wheezing disorders, mainly of recurrent wheezing.

A 2014 article conducted a meta-analysis of fourteen observational studies (n=108,321), twelve reported maternal obesity and 5 reported GWG, concluded that maternal obesity increased the probability of wheezing or physician-diagnosed asthma by 31% in the children aged between 14 months and 16 years (OR = 1.31; 95% CI, 1.16-1.49). The meta-analysis also found that a 3% raise in the risk arose from every 1-kg/m2 increment in the maternal BMI. Weight gain during pregnancy was associated with a 16% increase in the risk of developing persistent wheezing and asthma (OR = 1.16; 95% CI, 1.001- 1.34), but not recurrent wheeze or asthma [10].

These two studies [9,10] did not find any deviation in the outcomes when the researchers examined for birth conditions, socioeconomic status, lifestyle following birth, or the child's weight condition.

A 2015 prospective birth cohort study has determined from a sample of 2,606 children (age ≤ 5 years) of Netherlands that were born to women with obesity, reported more instances of physician consultations and wheezing rates as compared to the children born to healthy mothers with normal weight [11]. With each 1 kg·m−2 in maternal BMI, 3.3% (95% CI 1.001-1.065%) more consultations for wheezing illnesses were present after adjustment for potential confounders. The weight and height of the child at the age of 5 years explained the association with wheezing illnesses (incidence rate ratio [IRR] 1.002, 95% CI 0.962-1.044). The study provides further evidence that lung function in early life could partially explain the association with wheezing illnesses (IRR 1.022, 95% CI 0.986-1.059). Higher maternal BMI was also associated with more prescriptions of short-acting β2-agonists and inhaled corticosteroids in the offspring.

Based on these results, elevated maternal BMI may probably be connected with the remodeling of lung structure, resulting in a reduced pulmonary function in infants born to non-atopic mothers. These findings are also supported by another 2014 prospective-community based cohort study of Amsterdam (n = 2227), which observed a higher prevalence of infant wheezing in early life among the infants born to mothers suffering obesity (1 unit (kg/m^2) increase serum cortisol levels, OR: 1.03; 95% CI: 1.00-1.05) [12]. A total of 20.2% (n = 984) women were overweight or obese and 10.3% reported wheezing in their offspring. Notably, this study detailed that cortisol levels in overweight mothers were lower than those of women with a history of asthma, yet these lower levels did not mediate the increased offspring wheezing [12].

In allergic bronchial asthma, the airway remodeling is a result of a chronic inflammatory response entailing airway tissue destruction along with consequent chronic tissue repair [13]. As a result, the major determinant driving the processes of airway remodeling in chronic airways is inflammation. In fact, steroid treatment in asthmatic patients is determined to reduce airway inflammation and has positive effects on airway remodeling. Therefore, both endogenous and exogenous glucocorticoids are essential for fetal growth and development.

The very first randomized controlled trial on prenatal corticosteroids in humans was conducted in 1972, and several other similar researches has followed them [75]. The infusion of adrenocorticotropic hormone (ACTH), cortisol, or dexamethasone into the sheep preterm fetus provoked the delivery of lambs within 4-7 days [14] and accelerated adrenal growth and lung maturation in comparison to the term lambs [15].

Similarly, a 2018 Australian study showed that of the twelve hour betamethasone dose regimens, lambs in clinical course of 2 intramuscular low-dose of 0.25 mg/kg Celestone Chronodose (betamethasone phosphate plus betamethasone acetate) led to consistent amelioration in lung maturation (compliance, arterial pH, gas exchange), lower peak maternal and fetal plasma betamethasone levels than compared to the high-dose 20 ng/mL betamethasone in sheep with pregnancy [16]. In the 26-hour betamethasone dosing experiment, with approximately 2 ng/mL concentration of betamethasone, there was equivalent lung maturation noticed, approximately 70% less steroids used, and lower peak maternal and fetal plasma betamethasone concentrations were seen compared to the positive control group of Celestone Chronodose.

Human fetal lung explants incubated with dexamethasone stimulated fatty acid synthesis and fatty acid synthetase activity, resulting in the production of surfactant [17]. Betamethasone is proved to be effective in women at risk of preterm delivery by reducing the rate of neonatal respiratory complications [18]. These studies confirmed the effectiveness of glucocorticoids on fetal pulmonary maturation, which diminishes the neonatal respiratory distress syndrome and mortality. Another 2013 study, conducted in University Medical Center Hamburg-Eppendorf, Germany, showed that even minimal (0.01, 0.1 mg) doses of betamethasone can reduce the thymus volume affecting the developing cluster of differentiation CD4+ and CD8+ double-positive thymocytes [19]. Therefore, studies on the most efficacious steroid dosing must be emphasized [10].

In countries such as Europe and North America, 7-10% of pregnant women at risk of preterm delivery receive antenatal glucocorticoids, which significantly reduces the risk of neonatal morbidity and mortality in infants born before 34-week gestation by promoting lung maturation in the fetuses [20,76]. Such therapy is effective in reducing respiratory complications and is indicated by an increase in the ratio of lecithin to sphingomyelin in amniotic fluid.

However, the adverse effects of steroids like glucocorticoids, dexamethasone, and betamethasone cannot be neglected, which includes a reduction in the thymus size [19], gastroesophageal reflux [21,22], fetal heart modification, vasodilatory properties, and its relationship with a reduced birth weight in the preterm infants.

Multiple doses of prenatal steroids showed fewer reductions in fetal growth as compared to single doses [23,24]. A single dose of betamethasone reduced the head circumference by 4% and birth weight by 9% in preterm infants. Randomized, double blinded, placebo-

controlled trial evidence from 13 academic centers in the United States, which recruited pregnant women (n = 502) between 24 and 32 completed weeks' gestation and who were at high risk of preterm delivery. The participants were recruited from February 1996 through April 2000, and the trial suggests that there is no additional decrease in fetal growth or neonatal morbidity when repeated weekly courses (12 mg intramuscularly repeated once in 24 hours for 2 doses every week) of antenatal corticosteroids are utilized than single course (either betamethasone, 12 mg intramuscularly repeated once 24 hours for 2 doses, or dexamethasone, 6 mg intramuscularly repeated every 12 hours for 4 doses) [25,26].

Nevertheless, steroids prophylaxis used for respiratory distress syndrome (RDS), results in hypoglycemia and worse neurodevelopmental outcomes, especially in preterm infants. Neonatal hypoglycemia has been associated with antenatal betamethasone (24.0% relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001) but the rate of neonatal respiratory complications was significantly reduced in women with preterm delivery risk (8.1%; relative risk, 0.67; 95% CI, 0.53 to 0.84; P<0.001) [27].

Currently, prenatal steroids are administered only to preterm infants (< 34 weeks or <36 weeks or <37 weeks), in accordance to the European, English, and American guidelines respectively [28,29]. Moreover, long-term follow-up studies of the infants treated with antenatal corticosteroids during randomized trials have also failed to show negative effects of steroid treatment on blood pressure, both in childhood [30] or young adulthood [31,32]. The latest study concludes that earlier evidence about steroids reducing respiratory distress syndrome is defined [24].

Despite the reassurance of these randomized studies, future studies are required to overcome the contradictory results lying in the existing safety data. Long-term follow-up studies are needed to determine the impact of the steroids on the adverse outcomes since many pre-clinical (animal) studies have also reported the possibility of adverse effects related to the administration of steroids, including some human studies [77-83].

Maternal obesity-induced oxidative stress leads to abnormal lung development

Oxidative stress (OS) caused by reactive oxygen species (ROS) potentially jeopardizes both fetal and maternal health. Maternal obesity-induced OS is a risk factor to develop adverse outcomes during gestation such as fetal malformations, pre-eclampsia, intrauterine growth restriction, and teratogenesis, which play relevant roles in neonatology and is also the cause of various intellectual disabilities and permanent structural-functional abnormalities [33].

Teratogenesis may also be a cause of lung distress in early childhood [34]. The ROS comprises partially reduced, oxygen-containing metabolites and free radicals generated during normal cellular metabolisms also due to environmental factors. Specifically, the ROS are capable of oxidizing lipids, proteins, and DNA.

In obesity, adipose tissue has been proposed as the origin of the OS [35,36]. At the initial stages of obesity, antioxidant enzymes are upregulated to secure from the oxidative damage, but due to fat accumulations, the antioxidant defense is overruled, leading to the excessive OS. Balanced OS has been noticed in healthy gestation and also were in the second-trimester oxygen supply and metabolic rate spikes in the placenta [37]. If the ROS levels remain under control, they correctly regulate trophoblast proliferation, invasion, and proper angiogenesis, which are required for a healthy pregnancy.

Eventually, both obesity and gestation are characterized by the OS, but at different degrees. The OS has been proposed to involve many reproductive and pregnancy disorders via various mechanisms that result in adverse pregnancy outcomes [38].

Obesity affects reproduction function, mainly by endocrine and metabolic disturbances [39]. In detail, the defects in the endocrine program in women result from the mechanisms of metabolic dysregulation produced by hyperinsulinemia, pro-inflammatory cytokines, endoplasmic reticulum stress, and mitochondrial OS alterations.

These mechanisms may also influence the obesity-mediated teratogenesis which is still unrevealed. Traditionally, teratogenesis is hypothesized to occur due to the embryo's exposure to an excessive amount of nutrients, specifically ketone bodies and glucose, resulting in organ malformations leading to metabolic alterations in the youth [40].

During pregnancies with obesity, endometrial hyperoxidative state establishes soon, along with dysregulated immune cells, reduced anti-inflammatory T-regulatory (T-reg) lymphocytes and elevated natural killer (NK) lymphocytes [41]. These phenomena together promote early angiogenesis, which increases placental partial pressure of oxygen (pO2) before the maturity of the antioxidant system. This leads to depletion of non-enzymatic antioxidants, including glutathione (GSH), other non-protein thiols (NPSH), and vitamin E [35,36].

Another study in mice models demonstrated that chorioamnionitis can increase angiogenesis during the saccular stage, which may be mediated in part by chemokines, ultimately contributing to the altered vascularization, impaired intravascular gas exchange, and respiratory disease [42].

Studies performed by Rodney., *et al*. [43] described that increased angiogenesis impairs gas exchange and causes respiratory disease, though in their studies the cause of angiogenesis was chorioamnionitis OS, that also causes early and increased or defective angiogenesis, and thus may lead to the same respiratory disorders, and the burden of OS is very obvious among obese mothers. In hypoplastic fetal lungs, defective angiogenesis is also correlated with the nitric oxide synthase deficiency, though angiopoietin-2 and vascular endothelial growth factor (VEGF) remains high [43].

Ultimately, it seems that OS plays an essential role in maternal and neonatal respiratory diseases by remodeling fetal angiogenesis in obese mothers.

Existing evidence suggests that maternal pre-pregnancy obesity and excessive GWG may have a long-term effect on respiratory outcomes. A 2015 research study evaluated the offspring respiratory outcomes in 3,185 child-mother pairs cohort from Amsterdam found that 7-8 years of age children born to obese mothers were associated with the higher risk of asthma (adjusted RR 2.32 (95% CI: 1.49-3.61) and wheezing (adjusted RR 2.16 (95% CI: 1.28-3.64) [44]. There was no significant correlation by parental asthma in the association between maternal BMI and wheezing (p=0.34) or asthma (p=0.41). In a mediator model, the offspring of overweight and obese mothers showed a higher BMI z-score (a-coefficient = 0.48 and 0.63) and children with a higher BMI z-score had a higher risk of wheezing (b-coefficient = 0.26). Thus, the researchers found that the child's BMI could influence lung function and development later in life, especially within the first seven to eight years [44]. Harper., *et al.* [45] surveyed 38,874 Danish pairs of obese mothers and children between the years 1996 and 2002 and determined that 25.8% of the cases suffered from atopic eczema, while 10.4% cases had been diagnosed with asthma.

The risk of severe asthma correlated to the mother with obesity remained consistent for up to 7-years following the birth and was highest with a maternal BMI above the 95th percentile ([BMI ≥ 35 = adjusted OR, 1.87; 95% CI, 0.95-3.68] and [GWG ≥ 25 kg = adjusted OR, 1.97; 95% CI, 1.38-2.83]) [45]. Their result also suggested that the pathway to the onset of asthma may be non-allergic or extrinsic asthma [44,45]. This type of asthma is caused by non-allergic factors such as stress, cold or dry air, smoking, anxiety, virus, or other infection. Being non-allergic may be related to such factors as leptin and Th-2. In this 2013 population-based prospective cohort study, conducted by Leermakers., *et al.* in Netherlands, the authors further discussed these inter-relations [46].

The study collected data from a sample of 4,656 child-mother pairs aged between one and four-years long-term effects of being born to the mothers with high BMI or GWG, and unlike other studies, they evaluated how heritability affected the respiratory outcomes of the offspring. This study reported a meaningful correlation between the GWG (OR 1.09 (1.04, 1.14)), maternal obesity, and a higher risk of wheezing of pre-school children (OR 1.47 (1.12, 1.95)), and the strongest association was in children aged one year (OR 1.13 (1.05, 1.21), per SD increase of GWG) [46].

Conclusively, all the examined studies are consistent with the claims that maternal obesity elevates the risk of wheezing and asthma among the offspring during growth from infancy to adolescence.

The mechanism connecting maternal obesity, offspring asthma, and wheezing is not well studied and so understood; however, several possible mechanisms could potentially explain this possible association. In adults, adipokines, especially leptin, are a precursor to the development of asthma [51].

In healthy individuals, leptin plays a key role in stimulating metabolism and controlling appetite. In neonates, high levels of leptin could induce the production of inflammatory agents, which could play a pivotal role in the maternity obesity-asthma pathway. Indeed, high levels of leptin have been reported in overweight women [23,24]. Of interest, the level of leptin secretion is determined by the level of maternal adiposity that stimulates the secretion of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which are inflammatory mediators of adipose tissue [52,53]. There is a positive feedback mechanism between the production of leptin and TNF-α, which is seen as TNF-α promotes the expression and release of leptin from the adipose tissue. Distinctly, TNF-α, and other inflammatory factors, including interferon (IFN)-Y, are associated with asthma development [51,54]. However, leptin increases Th-1 cytokine production (IL-2, interferon-g and TNF-a) and decreases the production of Th-2 cytokine (IL-4, IL-5, and IL-10). These observations suggest that, if leptin plays a role in asthma, it is unlikely to be through a traditionally Th-2 phenotypes of asthma [51]. This inference made by the study is in contradiction with what is reported in the research below.

Role of Th-1 and Th-2 in maternal obesity derived neonatal asthma or lung disorder

The Th-2 cells are responsible for promoting the allergic inflammatory responses by releasing an array of cytokines, including IL-4, IL-5, IL-9, and IL-13. These cytokines prominently direct the production of IgE, which is specific to allergy reactions. The possibility of Th-2 cells effects on airway remodeling is still a matter of debate [57]. Among all the Th-2-type cytokines, only IL-13 has a deep impact on the structural cells of the airway capable of mucin secretion and can induce mucus metaplasia goblet cell hyper/metaplasia in humans by activating STAT-6 [58-60].

Decreased Th-2 cytokines by leptin may reduce the counteract towards the Th-1 cytokines, where Th-1 is pro-inflammatory and Th-2 is anti-inflammatory, which may lead to inflammation in the neonates and asthma disease. Excessive pro-inflammatory responses may lead to tissue damage, and so the Th-2 counterpart is highly essential to balance this process. Interestingly, the Th-2 activity includes the production of IL-10, which has more of an anti-inflammatory response. Thus, the decreased Th-2 activity in prenatal lungs may have an impact on the anti-inflammatory responses.

Interestingly, a fetus can switch the immune response early in the pregnancy and most babies tend to have Th-2 biased immune responses. The hypothesis claims that the babies who develop full-blown allergies are those with weaker Th-1 responses, although it is manifest from these studies that babies with allergies (or who produce weak Th-1 and non-allergic ones) can have weak Th-2 responses or both [61]. Thus, an equilibrium between the Th-1 and Th-2 cytokines and/or inflammatory responses can be one of the key determinants of well-developed lungs, with the least chances of future lung infection or excessive inflammatory response, ultimately playing a significant role in the neonatal maturation of healthy lungs.

Involvement of leptin in the maternal obesity derived neonatal lung disorder

Leptin has been shown to remodel airways via VEGF, while also promoting angiogenesis. Leptin also influences the maturation of lung tissue among infants and young children [11,20]. Overproduction of leptin in obese adults is thought to stimulate a cascade of mechanisms that lead to the development of lung inflammation, leading to asthma.

To analyze the function and networked pathways of leptin, we performed a bioinformatics study utilizing the STRING software. The STRING networking pathways of leptin and its receptor LEPR showed that they are associated with several pathway proteins with a score above 0.9, which indicates strong inter-relationships.

The associated pathways were JAK-2, STAT-3, SOCS-3, PTPN-1, INS, PRKAA-2, PRKAB-1, PRKAG-2, and PRKAA-1, with potential roles in mediating the leptin and its receptor signaling. Among these, we observed that JAK-2, STAT-3, and SOCS-3 exhibited some vital roles in fetal lung maturation or lung disease.

Specifically, the leptin binding to the LEPR leads to activation of JAK-2 [62], JAK-2-mediated phosphorylation, activation of epidermal growth factor receptor (EGFR), and STAT-3 [63]. The LEPR directly mediates STAT-3 activation, and it also intercedes the feedback inhibition of long-form of leptin receptor (LRb) signaling by binding to LRb-induced SOCS-3 (demonstrating the role of SOCS-3 in neonatal lung) [64].

A Portuguese laboratory Sprague-Dawley rats research by Piairo., *et al.* [65] proved that the fetal pulmonary tissue expresses all signal transducers and activators of transcription (STAT) proteins since the early development in fetal pulmonary tissue [65]. Hence, leptin might favor lung development via STAT-3 activation. Pathological conditions like congenital diaphragmatic hernia (CDH) show alteration in the expression, activation, and regulation in the fetal lung persistent over-expression of STAT-3 and STAT-6 and their early over activation combined with SOCS-3 over-expression in the diseased fetal lungs. Though inhibition of STAT-3 impacts the growth of fetal lung *in vitro* conditions, and over-expressed and over-activated STAT-3 signaling SOCS-3 is a characteristic of a diseased lung, and leptin via LEPR has an activating effect on STAT-3 as well as SOCS-3.

These studies suggest that a precise and controlled STAT signaling is required for normal lung development and leptin may interfere with this STAT signaling process. It is therefore suggested to further consider this associative protein while studying the effect of maternal obesity on fetal growth.

Since high serum levels of leptin have been found to influence lung development among youngsters and healthy individuals [53], leptin could also intervene in the mechanism or pathway through down-regulation of adiponectin levels [51]. Weight loss is associated with higher production of adiponectin, which has been known to alleviate inflammation signs in airways of animal models [51].

Besides, low production of adipokines has been shown to promote asthma risk in the general population [66,67]. Indeed, a study reported that intrauterine environmental factors of an over-nourished or obese mother had a significant impact on fetal lung development leading to complications and increased risk of respiratory disease at birth or even in postnatal life [68].

Clinical outcomes studies indicate that mothers with diabetes have an increased chance of delivering neonates with respiratory distress syndrome (RDS) than normal mothers [69]. 1996 research by Gewolb., *et al*. [69] on animal models in United States of America also indicates that the delay of fetal lung maturation is implicated by increased plasma glucose and/or insulin concentrations. It also causes abnormalities in lipid metabolism, and the mRNA expression of surfactant protein is decreased as well.

Hence, maternal obesity holds the risk of developing diabetes, it is therefore linked to persistent pulmonary hypertension, and it is associated with congenital diaphragmatic hernia, sepsis, birth asphyxia, meconium aspiration and respiratory distress syndrome in newborns [70].

Respiratory tract infections

While the majority of the researches has focused on asthma and wheezing, there are only a few studies that have evaluated the risk of other respiratory disorders among the offspring born to mothers with obesity. A United Kingdom study of 1998-2002 mother-child

pairs (n = 3158) Southampton Women's Survey cohort observed a higher prevalence of coughing (RR per 5 kg m^{-2}, 95%CI 1.10, (1.04-1.15)) and lower respiratory infections (RR 1.16, (1.09-1.22)) in 2,799 children in the first year of life [71]. An earlier study reported a relationship between weight gain, BMI, and asthma progression, and wheezing, but there was no association connecting these variables and the development of hay fever [45].

A 2019 single tertiary medical center population-based cohort analysis of 242,342 Israel deliveries, displayed a higher susceptibility of offspring (n = 3290) to respiratory infections who are born to obese mothers including pneumonia (4, 0.1%) and those diseases affecting the upper respiratory tract (114, 3.5%), as well as, higher susceptibility to various viral infections affecting the respiratory tract (the significance levels ranged from 0.05 - 0.84) [72]. Further research is essential to evaluate the role of maternal BMI in other lung health outcomes, including susceptibility to infections, lung function, and maturity.

Conclusion and Future Perspectives

The current evidence suggests that GWG and maternal BMI can raise the risk of asthma, as well as, early, late, and persistent wheezing from birth to adolescence. Confounding factors such as the lifestyle of the mother, environment, and diet could have influenced the outcomes of the reviewed studies and may have negatively impacted the robustness of the results.

However, despite further and extensive randomized and prospective studies are warranted, unfortunately, it is difficult to conduct randomized controlled studies in this line of research. Accordingly, the challenge of future research will be to ascertain the specific biochemical pathways on the relationship connecting maternal adiposity and offspring lung maturation.

While human research may not be viable, animal studies could provide some further evidence as to how a high maternal BMI can impact the prenatal offspring's lung health. Nonetheless, the existing evidence shows that the offspring born to mothers with obesity may have a high risk of poor lung health as compared to the offspring of healthy mothers, with an increase in BMI resulting in scanty health outcomes. Finally, the impairments in lung function may be attributed to the leptin signaling, Th1/Th2 imbalance, abnormal JAK, STAT-3, STAT-6, and SOCS-3 signaling.

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Author Contributions

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Bibliography

1. WHO. "Obesity and overweight". World Health Organization (2018).

2. Gaillard R., *et al*. "Childhood health consequences of maternal obesity during pregnancy: A narrative review". *Annals of Nutrition and Metabolism* 69.3-4 (2016): 171-180.

3. Catalano PM and Shankar K. "Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child". *British Medical Journal* 356 (2017): j1.

4. M Kemp., *et al*. "Nonequilibrium thermodynamics of thiol/disulfide redox systems: a perspective on redox systems biology". *Free Radical Biology and Medicine* 44.6 (2008): 921-937.

5. D Valenti., *et al*. "Deficit of complex I activity in human skin fibroblasts with chromosome 21 trisomy and overproduction of reactive oxygen species by mitochondria: involvement of the cAMP/PKA signalling pathway". *Biochemical Journal* 435.3 (2011): 679-688.

6. Laforgia N., *et al*. "The role of oxidative stress in the pathomechanism of congenital malformations". *Oxidative Medicine and Cellular Longevity* (2018): 7404082.

7. Romero-Lopez MDM., *et al*. "Lung metabolomics profiling of congenital diaphragmatic hernia in fetal rats". *Metabolites* 11.3 (2021): 177.

8. Kinga Toboła-Wróbel., *et al*. "Association of oxidative stress on pregnancy". *Oxidative Medicine and Cellular Longevity* (2020): 6398520.

9. Zugna D., *et al*. "Maternal complications in pregnancy and wheezing in early childhood: A pooled analysis of 14 birth cohorts". *International Journal of Epidemiology* 44.1 (2015): 199-208.

10. Forno E., *et al*. "Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma". *Pediatrics* 134.2 (2014): 535-546.

11. Eising J., *et al*. "Maternal body mass index, neonatal lung function and respiratory symptoms in childhood". *Pediatric Respiratory Medicine* 46.5 (2015): 1342-1349.

12. de Vries A., *et al*. "Increased maternal BMI is associated with infant wheezing in early life: A prospective cohort study". *Journal of Developmental Origins of Health and Disease* 5.5 (2014): 351-360.

13. Fehrenbach H., *et al*. "Airway remodeling in asthma: what really matters". *Cell and Tissue Research* 367.3 (2017): 551-569.

14. Liggins GC. "Premature parturition after infusion of corticotrophin or cortisol into foetal lambs". *Journal of Endocrinology* 42.2 (1968): 323-329.

15. Liggins GC. "Adrenocortical-related maturational events in the fetus". *American Journal of Obstetrics and Gynecology* 126.7 (1976): 931-941.

16. Kemp MW., *et al*. "The efficacy of antenatal steroid therapy is dependent on the duration of low-concentration fetal exposure: Evidence from a sheep model of pregnancy". *American Journal of Obstetrics and Gynecology* 219.3 (2018): 301.e1-301.e16.

17. Gonzales LW., *et al*. "Glucocorticoid stimulation of fatty acid synthesis in explants of human fetal lung". *Biochimica et Biophysica Acta* 1042.1 (1990): 1-12.

18. Gyamfi-Bannerman C., *et al*. "Antenatal corticosteroids for women at risk of late preterm delivery". *New England Journal of Medicine* 374.14 (2016): 1311-1320.

19. Diepenbruck I., *et al*. "Effect of prenatal steroid treatment on the developing immune system". *Journal of Molecular Medicine (Berl)* 91.11 (2013): 1293-1302.

20. McKinlay CJ., *et al*. "Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane Systematic Review". *American Journal of Obstetrics and Gynecology* 206.3 (2012): 187-194.

21. Chin SO., *et al*. "Antenatal steroid use is associated with increased gastroesophageal reflux in neonates". *American Journal of Perinatology* 20.4 (2003): 205-213.

22. Rotmensch S., *et al*. "The effect of betamethasone and dexamethasone on fetal heart rate patterns and biophysical activities: A prospective randomized trial". *Acta Obstetricia et Gynecologica Scandinavica* 78.6 (1999): 493-500.

23. Banks BA., *et al*. "Multiple courses of antenatal corticosteroids and outcome of premature neonates: North American Thyrotropin Releasing Hormone Study Group". *American Journal of Obstetrics and Gynecology* 181.3 (1999): 709-717.

24. White VA., *et al*. "Trials of antenatal corticosteroids for preterm fetal lung maturity: A review of the potential for selective outcome reporting". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 236 (2019): 58-68.

25. Guinn DA., *et al*. "Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial". *Journal of the American Medical Association* 286.13 (2001): 1581-1587.

26. Lee M-J., *et al*. "Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes". *Obstetrics and Gynecology* 103.2 (2004): 274-281.

27. Gyamfi-Bannerman C., *et al*. "Antenatal betamethasone for women at risk for late preterm delivery". *New England Journal of Medicine* 374.14 (2016): 1311-1320.

28. Sweet DG., *et al*. "European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update". *Neonatology* 115.4 (2019): 432-450.

29. ACOG. Antenatal Corticosteroid Therapy for Fetal Maturation.

30. Dalziel SR., *et al*. "Blood pressure at 6 years of age after prenatal exposure to betamethasone: Follow-up results of a randomized, controlled trial". *Pediatrics* 114.3 (2004): e373-e377.

31. Dessens AB., *et al*. "Twenty-year follow-up of antenatal corticosteroid treatment". *Pediatrics* 105.6 (2000): E77.

32. Dalziel SR., *et al*. "Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial". *Lancet* 365.9474 (2005): 1856-1862.

33. Laforgia N., *et al*. "The role of oxidative stress in the pathomechanism of congenital malformations". *Oxidative Medicine and Cellular Longevity* (2018): 7404082.

34. Alcala M., *et al*. "Antioxidants and oxidative stress: Focus in obese pregnancies". *Frontiers in Physiology* 9 (2018): 1569.

35. Alcala M., *et al*. "Short-term vitamin E treatment impairs reactive oxygen species signaling required for adipose tissue expansion, resulting in fatty liver and insulin resistance in obese mice". *PLoS One* 12.12 (2017): e0186579.

36. Alcala M., *et al*. "Vitamin E reduces adipose tissue fibrosis, inflammation, and oxidative stress and improves metabolic profile in obesity". *Obesity* 23.8 (2015): 1598-1606.

37. Wu F., *et al*. "Oxidative stress in placenta: health and diseases". *BioMed Research International* (2015): 293271.

38. Malti N., *et al*. "Oxidative stress and maternal obesity: Feto-placental unit interaction". *Placenta* 35.6 (2014): 411-416.

39. Silvestris E., *et al*. "Obesity as disruptor of the female fertility". *Reproductive Biology and Endocrinology* 16.1 (2018): 22.

40. Catalano PM. "Obesity, insulin resistance, and pregnancy outcome". *Reproduction* 140.3 (2010): 365-371.

41. Quenby S., *et al*. "Uterine natural killer cells and angiogenesis in recurrent reproductive failure". *Human Reproduction* 24.1 (2009): 45-54.

42. Britt RD Jr., *et al*. "Perinatal factors in neonatal and pediatric lung diseases". *Expert Review of Respiratory Medicine* 7.5 (2013): 515-531.

43. Boucherat O., *et al*. "Defective angiogenesis in hypoplastic human fetal lungs correlates with nitric oxide synthase deficiency that occurs despite enhanced angiopoietin-2 and VEGF". *American Journal of Physiology Lung Cellular and Molecular Physiology* 298.6 (2010): L849-L856.

44. Ginkel M., *et al*. "A study on mediation by offspring BMI in association between maternal obesity and child respiratory outcomes in the Amsterdam born and their development cohort". *PLoS One* 10.10 (2015): e0140641.

45. Harpsoe MC., *et al*. "Maternal obesity, gestational weight gain and risk of asthma and atopic disease in offspring: A study with the Danish National Birth Cohort". *Journal of Allergy and Clinical Immunology* 131.4 (2013): 1033-1040.

46. Leermakers E., *et al*. "Maternal weight, gestational weight gain and preschool wheezing: The Generation R Study". *European Respiratory Journal* 42.5 (2013): 1234-1243.

47. Scholtens S., *et al*. "Maternal overweight before pregnancy and asthma in offspring followed for 8 years". *International Journal of Obesity (London)* 34.4 (2010): 606-613.

48. Patel SP., *et al*. "Association between pre-pregnancy obesity and asthma symptoms in adolescents". *Journal of Epidemiology and Community Health* 66.9 (2012): 809-814.

49. Lowe A., *et al*. "Maternal obesity during pregnancy as a risk for early life asthma". *Journal of Allergy and Clinical Immunology* 128.5 (2011): 1107-1109.

50. Kumar R., *et al*. "Maternal pre-pregnancy obesity and recurrent wheezing in early childhood". *Pediatric Allergy Immunology and Pulmonology* 23.3 (2010): 183-190.

51. Ali Z and Ulrik S. "Obesity and asthma: A coincidence or a casual relationship? A systematic review". *Respiratory Medicine* 107.9 (2013): 1287-1300.

52. Brydon L. "Adiposity, leptin and stress reactivity in humans". *Biological Psychology* 86.2 (2011): 114-120.

53. Eising J., *et al*. "Relationship between leptin and lung function in young healthy children". *European Respiratory Journal* 43.4 (2014): 1189-1192.

54. Tessier D., *et al*. "Role of leptin in pregnancy: Consequences of maternal obesity". *Placenta* 34.3 (2013): 205-211.

55. Ott R., *et al*. "Maternal overweight is not an independent risk factor for increased birth weight, leptin and insulin in newborns of gestational diabetic women: observations from the prospective 'EaCH' cohort study". *BMC Pregnancy and Childbirth* 18.1 (2018): 250.

56. Briffa J., *et al*. "Leptin in pregnancy and development: A contributor to adulthood disease?" *American Journal of Physiology* 308.5 (2015): 335-350.

57. Fehrenbach Wagner C and Wegmann M. "Airway remodeling in asthma: What really matters". *Cell and Tissue Research* 367.3 (2017): 551-569.

58. Walter DM., *et al*. "Critical role for IL-13 in the development of allergen-induced airway hyperreactivity". *Journal of Immunology* 167.8 (2001): 4668-4675.

59. Atherton HC., *et al*. "IL-13-induced changes in the goblet cell density of human bronchial epithelial cell cultures: MAP kinase and phosphatidylinositol 3-kinase regulation". *American Journal of Physiology Lung Cellular and Molecular Physiology* 285.3 (2003): L730-L739.

60. Malavia NK., *et al*. "IL-13 induces a bronchial epithelial phenotype that is profibrotic". *Respiratory Research* 9.1 (2008): 27.

61. Berger A. "Th1 and Th2 responses: what are they?" *British Medical Journal* 321.7258 (2000): 424.

62. Yagi M., *et al*. "Phenethyl isothiocyanate activates leptin signaling and decreases food intake". *PLoS One.* 13.11 (2018): e0206748.

63. He K., *et al*. "Blockade of glioma proliferation through allosteric inhibition of JAK2". *Science Signaling* 6.283 (2013): ra55.

64. Bjorbak C., *et al*. "SOCS3 mediates feedback inhibition of the leptin receptor via Tyr985". *Journal of Biological Chemistry* 275.51 (2000): 40649-40657.

65. Piairo P., *et al*. "STATs in lung development: Distinct early and late expression, growth modulation and signaling dysregulation in congenital diaphragmatic hernia". *Cellular Physiology and Biochemistry* 45.1 (2018): 1-14.

66. Halonen M., *et al*. "Perinatal tumor necrosis factor-α production, influenced by maternal pregnancy weight gain, predicts childhood asthma". *American Journal of Respiratory and Critical Care Medicine* 188.1 (2013): 35-41.

67. Sood A and Shore S. "Adiponectin, leptin, and resistin in asthma: Basic mechanism through population studies". *Journal of Allergy* (2013): 785835.

68. Lock M., *et al*. "Regulation of fetal lung development in response to maternal overnutrition". *Clinical and Experimental Pharmacology and Physiology* 40.11 (2013): 803-816.

69. Gewolb IH. "Effect of high glucose on fetal lung maturation at different times in gestation". *Experimental Lung Research* 22.2 (1996): 201-211.

70. Storme L., *et al*. "Pathophysiology of persistent pulmonary hypertension of the newborn: Impact of the perinatal environment". *Archives of Cardiovascular Diseases* 106.3 (2013): 169-177.

71. Rajappan A., *et al*. "Maternal body mass index: Relation with infant respiratory symptoms and infections". *Pediatric Pulmonology* 52.10 (2017): 1291-1299.

72. Gutvirtz G., *et al*. "Maternal obesity and long-term infectious morbidity of the offspring". *American Journal of Obstetrics and Gynecology* 220.9 (2019): s557.

73. Boney CM., *et al*. "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus". *Pediatrics* 115.3 (2005): e290-e296.

74. Yu Z., *et al*. "Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis". *PLoS One* 8.4 (2013): e61627.

75. Liggins GC and Howie RN. "A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants". *Pediatrics* 50.4 (1972): 515-525.

76. Roberts D and Dalziel S. "Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth". *Cochrane Database of Systematic Reviews* 3 (2006): CD004454.

77. Dunlop S., *et al*. "Repeated prenatal corticosteroids delay myelination in the ovine central nervous system". *Journal of Maternal-Fetal and Neonatal Medicine* 6.6 (1997): 309-313.

78. Stewart J., *et al*. "Effects of multiple doses of betamethasone on the perinatal outcomes and growth of mice offspring". *American Journal of Obstetrics and Gynecology* 177.5 (1997): 1138-1144.

79. Howard E and Granoff D. "Increased voluntary running and decreased motor coordination in mice after neonatal corticosterone implantation". *Experimental Neurology* 22.4 (1968): 661-673.

80. Carlos R., *et al*. "Fetal dexamethasone exposure alters macromolecular characteristics of rat brain development: a critical period for regionally selective alterations?" *Teratology* 46.1 (1992): 45-59.

81. Uno H., *et al*. "Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques". *Brain Research. Developmental Brain Research* 53.2 (1990): 157-167.

82. Uno H., *et al*. "Neurotoxicity of glucocorticoids in the primate brain". *Hormones and Behavior* 28.4 (1994): 336-348.

83. Bohn M and Friedrich V. "Recovery of myelination in rat optic nerve after developmental retardation by cortisol". *Journal of Neuroscience* 2.9 (1982): 1292-1298.

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