Undernutrition/Hormones in Lung Development

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Maternal and perinatal undernutrition affects the lung development of litters and it may produce long-lasting alterations in respiratory health. This can be demonstrated using animal models and epidemiological studies. During pregnancy, maternal diet controls lung development by direct and indirect mechanisms. For sure, food intake and caloric restriction directly influence the whole body maturation and the lung. In addition, the maternal food intake during pregnancy controls mother, placenta, and fetal endocrine systems that regulate nutrient uptake and distribution to the fetus and pulmonary tissue development. There are several hormones involved in metabolic regulations, which may play an essential role in lung development during pregnancy.

Keywords: lung development ; undernutrition ; lung diseases ; ghrelin ; leptin ; GLP-1 ; retinoids ; cholecalciferol ; fetal growth restriction ; respiratory distress syndrome

1. Introduction

Maternal diet is an essential factor that controls fetal growth, both directly by providing nutrients to the embryo and indirectly by regulating the expression of endocrine mechanisms that control the uptake and use of nutrients by the fetus; it also contributes indirectly by changing epigenetic profile and so modulating the expression of genes. The reduction in caloric supply during pregnancy that usually comes accompanied by deficiency of macro and several oligonutrients is called maternal undernutrition. It is demonstrated that maternal undernutrition reduces fetal and placental growth in animals and humans [1]. The reduction in fetal growth is explained by the reduction in cell division [2], which is the result of the adaptation of the cells to the lack of nutrients and the alteration of growth factor and hormone supplies, especially insulin and growth hormone [3]. Fetal growth restriction (FGR) is defined as the fetal growth in lower rate than the normal growth potential, and is an important cause of fetal and neonatal morbidity and mortality [4].

Lung development is a complex process that initiates in utero and continues until early adulthood. In humans, lung development starts as soon as week 3 of gestation [5]. Lung organogenesis comprises five differentiated stages in humans [6]. In the embryonic stage (4 to 6 weeks of gestation, WG), the two lung buds and primary bronchi emerge from the primitive foregut. In the pseudoglandular stage (5 to 17 WG), there is an expansion of the conducting airways. Following this, in the canalicular stage (16 to 27 WG), the epithelia differentiates to separate conducting and respiratory airways and the pulmonary surfactant starts to be synthetized by alveolar type II cells (ATII). In the saccular stage (28 to 31 WG), there is a transition from branching morphogenesis to alveologenesis. In the final alveolar stage (32 WG until early postnatal life), alveoli form and grow.

2. Effect of Metabolic Hormones in Lung Development

Hormones and growth factors lead lung morphogenesis. Some key hormones for metabolic control such as insulin, glucocorticoids, and thyroid hormones are at the core of regulatory management of organ development. However, there is extensive literature about their role in lung development and organogenesis that the interested reader might easily find, and thus they are not included in our review, despite their undoubted relevance.

Instead, new hormones modulating metabolism have been recently shown to have a key role in the maturation of several organs, including the lung.

3. Effect of Undernutrition on Lung Development and Adult Lung Function

There are several different animal models for the study of FGR, including genetic manipulation models, but also mother food restriction during pregnancy [7]. The most frequently used animal species for modeling FGR are mice, rats, and lambs.

In a model of lamb FGR by the removal of endometrial caruncles, there is a reduction in fetal lung weight, lung liquid volume, and phospholipid concentration in liquid of alveolar lavage [8]. In this model, the lung weight is reduced by a similar rate to fetal body weight reduction, but carrying structural alterations that reveal a retarded maturation [9]. FGR reduces alveolar number and vascular density, but increases septal thickness [10][11]. These alterations become more pronounced during postnatal lung development [10], which leads to a smaller number of large alveoli, alveolar fenestrations, and increased number of mast cells in the lungs of adult animals, anticipating a premature lung aging [12]. At least part of these changes in lung architecture could be explained by a marked reduction in elastin synthesis and deposition [13]. FGR also promotes the reduction of the mRNA and protein expression of the SFTPs [14]. SFTP expression is higher after the delivery in FGR ewes due to the activation of the hypoxia-signaling pathway by increasing HIF-2α mRNA expression [15].

FGR alters normal structure of the lamellar bodies of ATII cells involved in surfactant synthesis and secretion, in the saccular stage before birth in rodents [16]. This alteration also reduces mRNA expression of SFTPs [17]. However, after birth, there is a reduction in lung surfactant lipid levels, just in the early postnatal period, without modifying the expression of surfactant-associated proteins in the remaining postnatal period [18]. As described in lambs, FGR also disrupts normal lung architecture in rodents, and it decreases alveolar number and increases septal thickness [19] from postnatal day 1 through adulthood. Moreover, this is accompanied by a decline in synthesis and secretion of elastin, and an increase in static lung compliance [20].

In humans, fetal undernutrition can be caused by at least five situations:

(1) Severe nausea and vomiting period that persists more than the first trimester [21];There are few studies linking FGR,
(2) The “Maternal Depletion Syndrome,” a product of a short inter-pregnancy interval, not allowing sufficient time to replenish energy reserves and recovery of mothers, which promotes a depletion of both macro- and micronutrients [22];
(3) Teenager pregnancy, where the mother, who may still be growing, competes with the fetus for resources [23];fetal lung
(4) Use and abuse of tobacco [24]; anddevelopment, and neonatal lung pathology in humans. In fact, there are some
(5) Alcohol/drugs [25], which may promote placenta under-function and reduced nutrient supply to fetus and/or maternal undernutrition.

conflicting results about the effect of FGR over respiratory distress syndrome (RDS). Several studies have concluded that FGR reduces the incidence of RDS and increases the ratio of lecithin/sphingomyelin in amniotic fluid, a marker of lung maturation [26][27]. They explain this accelerated lung maturation as a consequence of the chronic intrauterine stress that increases fetal glucocorticoid levels. Nevertheless, other studies have concluded that FGR increases the risk of developing RDS and the risk of respiratory failure and death [28], and yet others did not find this relation [29]. On the other hand, there is an association between perinatal growth restriction and an increased risk of developing bronchopulmonary dysplasia in preterm infants [30]. Moreover, low birth weight, but not prematurity, decreases lung size and bronchial airflow, and conversely increases bronchial hyperreactivity in children [31].

In the mature lung, there is a clear relationship between the early fetal nutritional environment and adult pulmonary diseases—despite the mechanistic basis of this relationship being unknown [32]. In the adult lung, there is a suggestive, not fully consistent, association between FGR and pulmonary function in adulthood [33]. There are some evidences that FGR can decrease adult lung function [34], whereas other studies did not find any effect over lung function [35]. Another study shows that prenatal exposure to famine did not modify the lung function, but increased the prevalence of COPD [36]. This risk is greater when severe famine exposure occurs during infancy [37]. Asthma is another lung pathology that is related with FGR. There are some studies that link FGR with an increased risk of developing adult asthma [38], whereas other studies conclude that environmental factors during childhood rather than fetal undernutrition are responsible for the increased risk of developing asthma in adult life [39].

4. Undernutrition and Hormones in Lung Development

Undernutrition in pregnancy promotes several changes in metabolic control and hormone levels, which are needed to adapt the energy demands to reduced supplies. It is easy to link a caloric deficit with reduced availability of precursor for hormones that are obtained in diet, such as retinoids and carotenoids [40][41]. However, these precursors may be stored in some amounts in the liver and fat depots. In such a way, nutritional deficits of these hormones must be set up likely before pregnancy, for reducing the reserves enough to affect fetus development during gestation. In developed countries, the follow-up of every pregnant women and nutritional advice should be enough to prevent this kind of deficit. A large part of the population is in the lower range or outside the normal range for cholecalciferols (VitD), which may be especially critical in some susceptible populations: Low sun exposure, low intake of fish and dairy products, obesity, or undernutrition.

The effect in the modulation on gene transcription by the activation of the retinoid hormone system is so important that it might be a source of teratogeny when in elevated levels during pregnancy. In addition, on the other hand, a deficit of retinoids promotes alterations in reproduction, placentation, and organ development. However, there is not a recommendation to supplement nutrition with retinoid precursors in pregnancy apart from in known deficient populations. In some African countries, this deficit may be present in the 21–48% of all pregnant women [41]. On the other hand, some hormones are involved in the short-term availability of energy resources, and may eventually be relevant in the case of reduced food intake during pregnancy. In this context, and as described above, leptin seems to be a relevant hormone in lung development. This hormone is mainly secreted by adipose tissue in proportion to total fat storage. During starving, even partial, fat depots and, consequently, leptin circulating levels are reduced [42]. Leptin is also produced by the placenta, where it plays a local role in protein synthesis and proliferation of placental cells. It has been also postulated that leptin is very important for maternal–fetal exchanges, regulating the growth and development of many organs, including the lung. In fact, dysregulation of leptin mechanisms is link to several disorders occurring in pregnancy, such as gestational diabetes and intrauterine growth restriction [43]. In FGR neonates, there is a reduction in circulating leptin levels, due to a reduction in fetal fat mass and placental production [44][45] The fetal reduction in leptin levels may compromise correct lung development. The reduction in fetal circulating leptin levels is usually compensated by a postnatal increase when enough energy supply is set up, which explains the catch-up lung growth in FGR offspring [46]; however, it may also be related to the augmented incidence of childhood asthma in FGR offspring [47].

Another hormone that has a relevant role in metabolic and food intake control is ghrelin. Ghrelin is a peptide with orexigenic, adipogenic, and GH-releasing properties [48]. Regarding all described effects for ghrelin, it is important in the regulation of metabolism and it has been suggested that it contributes to energy resource distribution, linking nutrients to growth and development of the organs. Ghrelin levels vary during pregnancy, reaching the highest peak at mid-gestation, and then declining up to term [49]. Ghrelin is present in the cord blood and inversely correlates with fetal growth. Moreover, intrauterine ghrelin levels have been linked to programming body weight in the postnatal period [50]. FGR fetuses present high ghrelin levels in response to intrauterine malnutrition, which might contribute to increase neonate appetite, which suggests a role of ghrelin in catch-up growth [51][52]. Nevertheless, more recently, others have shown that ghrelin levels are reduced in “small for gestational age” fetuses [52], and this is in accordance with increased levels of cortisol in FGR fetuses due to the stress in the intrauterine environment. It has been shown that there is a negative correlation between cortisol and ghrelin levels [53]. Despite there being few studies about ghrelin’s involvement in lung function and development, the reported results suggest it has a relevant role. The action mechanisms underlying the effects of ghrelin in the lungs will need some more studies to be revealed.

GLP-1 is the least studied metabolic hormone, here presented in relation with pregnancy. GLP-1 could compensate pregnancy-related alterations in metabolism, such as an increase in glycaemia and the development of insulin resistance, based on the increase of fasted active GLP-1 levels in the third trimester of gestation [54]. This increase in GLP-1 secretion is a product of gastrointestinal tissue expansion, rather than satiety [55]. GLP-1 circulating levels are reduced in pregnant mothers with gestational diabetes [56][57]. However, we have no data about changes in GLP-1 levels during normal pregnancy. It is important to emphasize that GLP-1 half-life is very short, lower than 2 min. Therefore, GLP-1 levels may change very fast after meals, and so to study GLP-1 variations will demand to do repeated short-interval blood sampling in every individual. In a recent study, it has been reported that GLP-1 and GIP circulating levels in mothers and cord blood negatively correlate with 25OHD, and, surprisingly, GLP-1, GIP, and ghrelin positively correlate with glycated albumin maternal/cord ratio, highlighting the relevance of these hormones and their interplay in the complex control of metabolism, especially in pregnancy.

Ghrelin and GLP-1 are secreted in relation to meals and, since they may serve as a link between maternal food intake and metabolism, may possibly modulate the exchange of nutrients through the placenta. However, and as described above, both hormones have direct and important effects in lung development. It must be highlighted that GLP-1 modulates many different functions of the lung, including key processes such as the production of surfactant components, or the modulation of vascular tone of pulmonary vessels by controlling the renin–angiotensin system local activation. In addition, it should of the greatest interest to study whether the placenta, as the maternal/fetal interchange organ, is a target for GLP-1 modulatory actions, as we have no data in this respect.

Finally, clinicians dedicated to pregnancy must be conscious of the delay in lung maturity in all of the five clinical situations mentioned above, which include: Persistent severe vomiting beyond first trimester; “Maternal Depletion Syndrome”, especially in susceptible populations; teenager pregnancy; use of tobacco and abuse of alcohol and drugs [25]; but also in obese and diabetic mothers. In all of these cases, a complete, well balanced, and eventually supplemented diet of mothers will guarantee normal lung development of fetuses and newborns, contributing to prevent lung pathology in infancy and adult life. This diet should provide enough, but not an excessive amount of, calories and calcitriol and retinoid

sources, in addition to other known nutrients needed for organogenesis, such as good quality protein, iodine, and iron. Although, correct attention to the diet of pregnant women is included in current gestational protocols in occidental medicine, it appears that this is not so general in many countries, and thus should be regarded as a priority objective of preventive health policies.

In conclusion, the reduction of food intake during pregnancy may not just directly affect tissue development because insufficient resources, but also undernutrition modifies the hormonal milieu, which is critical for many organs, including lung. Retinol and cholecalciferol are hormones synthetized from precursors obtained from diet; therefore, reductions in food intake limit the availability of these hormones. In fact, the deficit in cholecalciferol is one of the most frequent in pregnancy, especially in susceptible populations. Gestational undernutrition also reduces fat storage, as well as leptin circulating levels in the medium-term; and daily-reduced caloric intake may affect the levels of hormones regulated in the short-term, linked to meals such as ghrelin and GLP-1. The mentioned hormones have key roles in lung development and maturity, including morphogenesis and structure development, cell proliferation and apoptosis, and many functional processes such as production of surfactant components, activity of the local renin–angiotensin system, and vascular tone of pulmonary vessels (see **Table 1**). Moreover, undernutrition in pregnancy affects all of these hormonal systems at once, in addition to others also relevant such as insulin and IGFs, thyroid hormones, and glucocorticoids. Therefore, the correction of known specific deficits with diet supplementation during gestation is mandatory and should be included in clinical protocols. The disruption of the hormonal environment during pregnancy becomes especially important when the mothers present metabolic diseases such as diabetes and obesity, despite that caloric intake may be preserved. The dysregulation in hormonal control in altered metabolism in mothers may affect lung development and maturity of the fetus to different degrees, also conditioning higher risk to lung pathology in adult life. In this case, the correction during pregnancy of diet and food intake, in proper amounts and composition, is so important to lung development, like it might be in caloric restriction and undernutrition.

Table 1. Summary of the effects of the different hormones over lung development.

Hormone	Action in Lung Development	References
Ghrelin	Fetal lung branching	[58][59]
	Upregulating RA receptors/ sensitizing RA action	[60]
Leptin	Enhance lung maturity	[61][62][63][64][65]
	In vitro phosphatidylcholine secretion	[61]
	In vitro SFTPs expression	[61][63][64][65]
GLP-1	In vitro phosphatidylcholine secretion	[66][67]
	In vivo SFTPs expression	[68][69][70]
	Increase ACE2/Ang (1-7)/MasR branch of the renin-angiotensin system	[69][70]
Retinoic acid	Formation of bronchial tubules during pseudoglandular phase	[71]
	Lung maturation	[72][73][74][75][76][77][78]
	In vitro Proliferation of ATII cells and differentiation to ATI cells	[72][79]
	In vitro and in vivo SFTPs expression	[72][80]

Hormone	Action in Lung Development	References
Cholecalciferol	Branching morphogenesis	[81]
	In vitro proliferation of ATII cells	[82]
	In vitro surfactant phospholipids secretion	[82]
	In vitro SFTPs expression	[82]
	Lung maturation	[83][82]

Abbreviations: RA, retinoic acid; SFTPs, surfactant-associated proteins; ACE2, angiotensin-converting enzyme 2; Ang (1-7), angiotensin 1-7; MAS1, Mas proto-oncogene, G protein-coupled receptor; ATII cells, alveolar type II cells; ATI cells, alveolar type I cells.

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