Chapter 4

Hypercortisolaemia and Hyperinsulinaemia Interaction and their Impact upon Insulin Resistance/Sensitivity Markers at Birth

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Additional information is available at the end of the chapter

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Abstract

Information on insulin resistance/sensitivity in term-normoweight neonates is scarce. The hypothalamus-pituitary-adrenal cortex axis and pancreas are implicated in several aspects of foetal maturation and programming. This study aims to analyse the effects of a combination of hyperinsulinaemia *plus* hypercortisolaemia in such neonates together with their mothers℉ gestational glucose tolerance on growth hormone (GH), insulin-like growth factor-1 (IGF)-1, glucose, and insulin resistance/sensitivity markers [homeostatic model assessment-insulin resistance (HOMA-IR)/quantitative insulin sensitivity check index (QUICKI)] at birth. Furthermore, the importance of pregnancy diet quality on these markers is discussed. In a selected group of 187 term-normoweight non-distressed neonates, about 9% had increased insulin and cortisol cord-blood concentrations. In spite of normality criteria applied, the combination of hypercortisolaemia and hyperinsulinaemia at birth was associated with higher body weight, body length, glucose, HOMA-IR, GH, IGF-1 and glucose/insulin ratio values than those of neonates presenting low/normal concentrations of insulin and cortisol. Hyperinsulinaemia preferentially to hypercortisolaemia affected the markers studied. Impaired glucose tolerance prevalence was higher in mothers whose neonates were hyperinsulinaemic at birth. The hyperinsulinaemic plus hypercortisolaemic status was more prevalent in neonates whose mothers had poor Mediterranean diet adherence. Results show the importance of analysing insulin and cortisol in cord-blood even in term-normoweight neonates.

Keywords: neonates, term, normoweight, insulin, cortisol, growth, HOMA, insulin resistance/sensitivity, maternal impaired glucose tolerance

1. Introduction

Pregnancy is a very complex period where growth, development and maturity take place. The future body, in addition to increasing its cellular mass, progressively acquires functional capabilities that would permit it to live and grow out of the mother's womb [1, 2]. Two clear periods can be distinguished during pregnancy in the future mother. During the first period, a marked increase in insulin level and sensitivity occurs in the mother, with parallel increases in placenta size, amniotic volume, protein content and fat stores; however, the foetus weight gain is small in comparison with that of the mother [1–3]. During the second period, a physiological increase in insulin resistance and insulin degradation takes place in the mother, in parallel to the exponential foetal growth that partially or totally blocks the gain rhythm of maternal stores. This metabolic situation assures the availability of glucose for the maternal and foetal brains and mammary gland, reducing the uptake of glucose by other maternal tissues [1–3]. When glucose homeostasis is not physiologically balanced, changes and adaptation take place during pregnancy, predisposing the individual to degenerative diseases later in life [4–8]. In some non-diabetic women, an alteration in carbohydrate metabolism occurs during pregnancy; thus, although fasting glycaemia is normal, after a carbohydrate load, the glycaemia increases over normal values. This situation is rather more frequent at the end of pregnancy and is known as gestational diabetes (GD) [1, 9].

Several homeorhetic adjustments are required to assure adequate foetal anabolism, which in turn can also be affected by genetic and nutritional factors [1, 2, 10–15]. Maternal glucocorticoids, among others, clearly affect metabolites and foetal corticoids that compete with other anabolic and growth mediators as insulin and insulin-like growth factor-1 (IGF-1) [2, 16–18]. Thus, a hormonal balance seems to be of critical importance to guarantee suitable foetal and postnatal development [4, 5, 16–19]. Glucocorticoids are central hormones engaged in correct foetal growth and maturation [16, 17]; however, their excess induces intrauterine growth delay, clearly affecting glucose homeostasis and brain development and functions [20–22]. As discussed above, palliative mechanisms are available to reduce the negative effects of excess active corticoids [20–22].

2. Glucocorticoids: short metabolic review

Store capability of body steroid hormones is limited; thus, they are synthesized from cholesterol, mainly in liver and endocrine glands. The placenta, although it produces steroid hormones, is unable to synthesize cholesterol, being, thus obliged, to take it from maternal plasma low-density and high-density lipoprotein (LDL and HDL, respectively) particles [23].

Cholesterol (27 carbons, 27C), the common precursor of all steroid hormones, is converted in placenta to pregnenolone (27C) from which progesterone (21C) is derived. Progesterone is the precursor of several steroid hormones: (a) adrenal cortex hormones (mineralocorticoids and glucocorticoids); (b) male sex hormones (androgens) (19C); and (c) female sexual hormones (oestrogens) (18C).

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The adrenal cortex contains 11-, 17- and 21-hydroxylases. When hydroxylation takes place in C21, the 17-hydroxylase action is arrested and mineralocorticoids (e.g. aldosterone) are synthesized in the glomerular zone. When hydroxylation takes place in C17, glucocorticoids and sex hormones are formed in the fascicular and the reticular zones, respectively [16]. The final step production of glucocorticoids and mineralocorticoids is catalysed by two mitochondrial cytochromes P450, CYP11B1 (11b-hydroxylase or P45011b) and CYP11B2 (aldosterone synthase or P450aldo) [24]. The synthesis of steroid hormones is summarized in **Figure 1**.

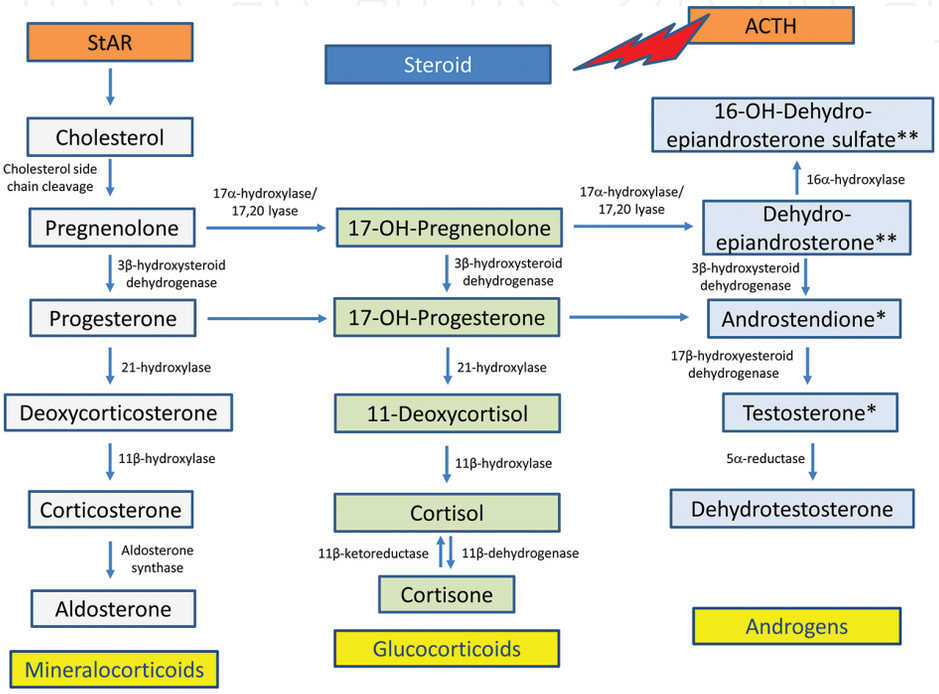

Figure 1. Steroid hormone synthesis. Notice that role of different hydroxylases. ACTH, adrenocorticotropic hormone; StAR, steroidogenic acute regulatory protein. *Androstenedione and *testosterone can be transformed in oestrone and oestradiol, respectively by the aromatase action. The **Dehydroepiandrosterone sulphate produces oestradiol, while the **17-OH-dehydroepiandrosterone, oestriol. Modified from Pascual-Leone Pascual and Goya Suárez [16] and Sibernagl and Despopoulos [25].

The fascicular zone produces cortisol (hydrocortisone) and, in much lower amounts, cortisone. Glucocorticoid synthesis and release is controlled by hypothalamus corticotropin-releasing hormone (CRH) and by the adrenocorticotropic hormone (ACTH) of the anterior hypophysis lobule [16, 25] (**Figures 1** and **2**). ACTH induces glucocorticoids releasing (and minor amounts of other cortical hormones), helping to maintain adrenal cortical structure and function and to assure cholesterol availability for hormonal synthesis. ACTH production and secretion are under negative feedback control but increased by adrenal medulla catecholamines [16, 21, 25].

Steroid hormones are fat soluble, and thus, they easily cross biological membranes, having crucial effects on cellular differentiation and organization. Cortisol binds amply to cortisol binding globulin (CBG), limiting the level and activity of free cortisol [16, 22, 26, 27].

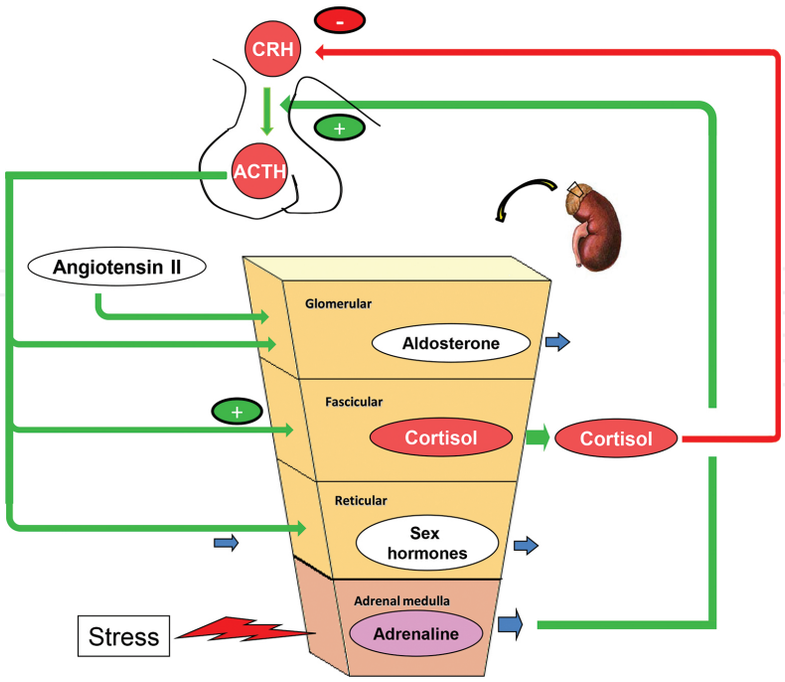

Figure 2. Steroid hormone and catecholamine location in the adrenal gland. The activating and negative feedback implicated mechanisms are shown. CRH, corticotropin-releasing hormone, ACTH, adrenocorticotropic hormone. Red lines, inhibition; Green lines, activation. Modified from Nelson and Cox [26].

System	Action	High concentrations
Metabolism	Increases glycaemia	
	Increases amino acids use	
	Increases urea	
Heart and circulation	Increases heart contraction strength	
	Increases peripheral vasoconstriction	
	Induce angiotensinogen formation	
Stomach	Increases gastric juices	Gastric ulcer
Kidneys	Maintains glomerular flux	Similar effects as aldosterone
	Delays water elimination	
Brain		Hypothalamus inhibition
Immune system		Anti-allergic and anti-inflammatory

Table 1. Effects of cortisol on different systems.

Glucocorticoids interact on receptors located on skeletal, smooth, and cardiac muscles, brain, stomach, kidney, liver, lung, adipose and lymphatic cells. Those hormones bind to both mineralocorticoid and glucocorticoid receptors (MR and GR, respectively), members of the nuclear receptor's superfamily. GR are expressed since the embryonic stage [28]. GR are expressed in pancreas, liver, visceral adipose tissue, skeletal muscle and in brain areas such as

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hippocampus and amygdaline nuclei, where they regulate memory and behaviour [17, 22]. There are GR and MR gene polymorphisms that could explain individual response to corticoids [29]. Optimum glucocorticoid concentrations in blood and tissues are needed to assure correct homeostasis. These levels are highly variable and affected by factors such as gender and circadian cycle, thus explaining difficulties on reference value establishment. Due to space limitations in this review, the particular effects of glucocorticoids on different systems and the effects of high cortisol actions are summarized in **Table 1**.

3. Glucocorticoids and stress: the *allostasis* concept

During alarm reaction, catecholamines stimulate hypothalamus, which releases hormones to guarantee adequate plasma glucose levels. These hormones become maximal 4 hours after alarm [16, 21]. Thus, glucocorticoids also help in the alarm reaction. Nowadays, stress response is accepted to be undoubtedly associated with *allostasis*, a term created by Sterling and Eyer [30] that textually means *maintaining stability through change*, in the idea that stress situation is a body adaptation to a unknown situation that must be transitory blocked or arrested. System failure would imply suppression of several anabolic processes with energy store diminution and immune system blocking, which can be highly deleterious to the body.

When stress becomes chronic, a high glucocorticoids release to plasma is kept. These high levels downregulate the GR expression in hippocampus. Thus, the correct feedback exerted by the hypophysis-pituitary axis (HPA) blocking is shunned, which results in lasting high glucocorticoids concentrations [26, 30, 31]. There exist three known mechanisms regulating the entrance of glucocorticoids to the brain [16]: (1) CBG, a molecule that determines the free cortisol levels in humans, and thus cortisol which is available to bind GR [16]. In response to very high free cortisol levels, the CBG transport capacity is saturated and the cortisol levels increased substantially. Thus, the situation is compatible with cortisol resistance or low response to cortisol [32]; (2) glycoprotein P carriers of blood–brain barrier limit, despite glucocorticoid fat solubility, the entrance of cortisol to the brain; and (3) isoenzymes (dehydrogenases or reductases) transform cortisone in active cortisol, which is available to bind GR. Conversely, the 11 β-hydroxysteroid dehydrogenase 2 (11 β-HSD 2) transforms in the kidneys cortisol into inactive cortisone (**Figure 1**). The presence of high renal levels avoid corticoids from interacting on MR. This enzyme is also available at high levels during development in the brain and placenta to protect the body against deleterious effects of high cortisol levels (e.g. cerebellar malformation [33], high HPA activity in adult life [34] and increased incidence of diseases related to corticoids hypersensitivity [22].

4. Human foetal adrenal gland

The human foetal adrenal gland has double weight than the foetal kidneys and after delivery its size decreases from 8 to 5 g in 5 weeks. It has three areas: foetal area, definitive area and

medulla. The foetal area is integrated by vast cells presenting steroid synthesis characteristics. This area occupies approximately the 80% of the total adrenal gland at the end of pregnancy. It secretes two main substances: dehydroepiandrosterone sulphate (DHAS), synthesized in the foetal area, and cortisol, synthesized in the definitive area [16, 21]. DHAS is synthesized from acetate or from cholesterol (**Figure 1**). It can be also formed by direct conversion from other steroid sulphates, beginning from cholesterol sulphate. The DHAS production increases as the pregnancy goes by. Its production is kept high during the first week after delivery, and then decreases, reflecting the foetal area's atrophy. After delivery, at the age of 1 year, total involution of the foetal area is observed [3, 35].

The step from DHAS to 16-α-hydroxydehydroepiandrosterone (16-α-OH-DHAS) is scarce in the foetal adrenal gland, but it can be observed in the foetal liver. Afterwards, both substances are used as substrates in the placenta for the oestrogens' synthesis: DHAS produces oestradiol and 16-α-OH-DHAS produces oestriol (see **Figure 1** footnote). In the definitive area, cortisol can be synthesized from maternal progesterone or de *novo* from LDL cholesterol. It is not known what of the two pathways is the most used. It seems that the foetal adrenal gland has small capability for progesterone secreting and there is a 3-OH steroid dehydrogenase–isomerase complex deficiency. The cortisol synthesis grows along pregnancy: 6.9 ng/mL in 13-week foetuses' cord blood and 70 ng/mL at the end of gestation [16, 21].

The definitive area secretes deoxycorticosterone and aldosterone. These secretions begin at 10–20 weeks and increase until the end of pregnancy. There is great cortisol transference from mother to foetus through the placenta. Most of this cortisol can be found in the foetus as corticosterone. Corticosterone levels in foetus are 5–10 times higher than in the mother's blood. Cortisol is also transferred from foetus to mother. Cortisol can be formed from cortisone in foetus, as some tissues as kidney, lung, amniotic membrane and liver have the 11-hydroxysteroid dehydrogenase (11-HSD) [16].

5. Regulation of the secretions of the definitive and foetal areas in the adrenal gland

Both the foetal and the definitive areas of the adrenal gland are stimulated by ACTH and α-melanocyte stimulating hormone (MSH). Both hormones are secreted by the foetal pituitary gland [16, 35]. As possible stimulators of the adrenal gland, angiotensin, prolactin, growth hormone (GH) and epidermal growth factor have also been suggested. Progesterone and deoxycorticosterone secretions decrease as pregnancy goes by, suggesting that the enzymatic systems for their transformation into aldosterone and cortisol become active, as these hormones levels increase at the end of pregnancy.

With respect to the medulla secretions, it is known that the corticosterone synthesized *in situ* by the foetus is required for negative feedback suppression of the hypothalamus-pituitary-adrenal axis and for catecholamine synthesis in adrenal medulla [36]. In addition, the maternal catecholamines can go across the placenta [16].

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6. Carbohydrate metabolism: pancreatic hormones

Glucose is recognized as the major energy porter of human metabolism [37–39]. Glycaemia is determined by carbohydrate intake and absorption, by the glycolysis and gluconeogenesis. **Figure 3** summarizes an integrated hormonal mechanism contributing to glycaemia balance. When glycaemia is reduced, mechanisms are produced to avoid hypoglycaemic shock, inducing appetite and compensatory mechanisms, as the lack of stimulation by β-cell to produce insulin and the stimulation of glucagon by α-2 pancreatic cells. When glycaemia increases, insulin promotes the intracellular cross of glucose through expression of receptors and carriers. In addition, a general enzyme activity occurs in liver, skeletal muscle, adipose tissue, etc., increasing the protein synthesis, lipogenesis and glycogenesis [25].

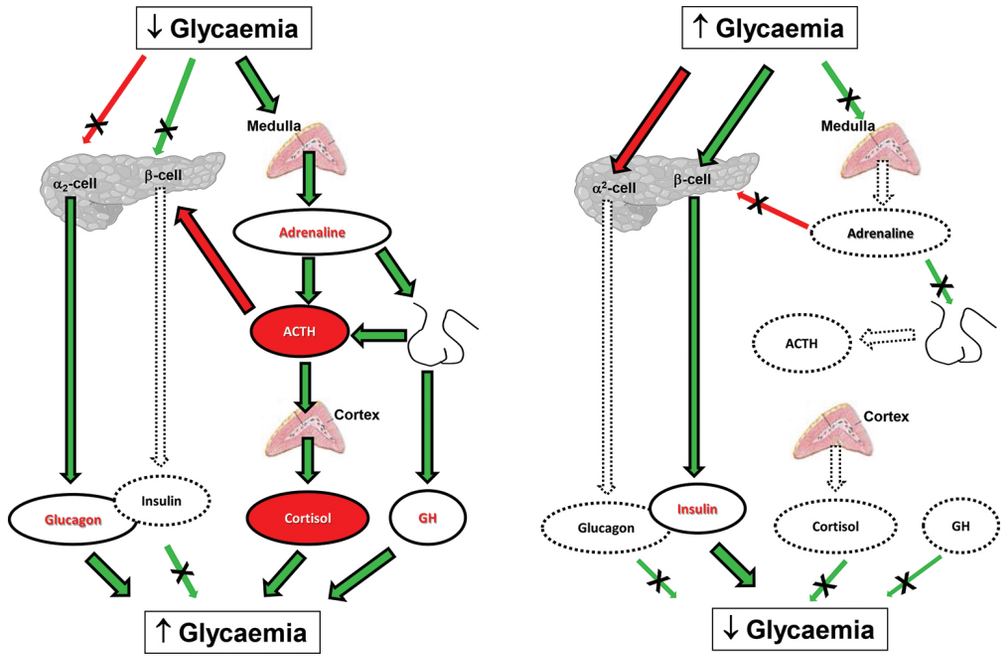

Figure 3. Integrative scheme of hormone response to hypoglycaemia and hyperglycaemia. ACTH, adrenocorticotropic hormone, GH, growth hormone. Red lines, inhibition; green lines, activation; Dot white lines, no effect. Red lines bearing a cross: missing the inhibitory mechanism; green lines bearing a cross: missing the stimulating mechanism. Modified from Sibernagl and Despopoulos [25] and Nelson and Cox [26].

Hypoglycaemia and a high level of amino acids are two major stimuli for glucagon release. However, fasting, general adrenergic excitation and a decrease in the fatty acid concentrations also lead to glucagon release. On the other hand, hyperglycaemia inhibits glucagon release. The main role of glucagon is raising the glycaemia [24] by increasing glycogenolysis (that is intensified by an increased lipolysis) and diminishing glycolysis. Somatostatin is secreted by the α-cells of the pancreas and inhibits GH, thyroid-stimulating hormone (TSH), gastrin, insulin and glucagon release. All these effects result in a hypoglycaemic action. Glycaemia is registered by glycoreceptors inducing compensation by modifying insulin and glucagon release. Nevertheless, this action is completed by cortisol action and the effect of catecholamines (**Figure 3**).

7. Foetal pancreas development

The pancreas is an endocrine and exocrine gland, which plays a major role in our economy. It contributes to the macronutrient digestion by producing enzymes while its endocrine function is critical to glucose homeostasis [1]. In humans, it appears first in gestation at 5–6 weeks, and at 11 weeks the islets can be observed. Insulin production is functional at week 20 [3, 40], and at this time, four cell types can be observed: α-cells producing glucagon, β-cells producing insulin, δ-cells producing somatostatin and PP-cells producing pancreatic polypeptide. As it occurs in adult life, at birth the most abundant cells are the β-cells and the least the PP-cells. The pancreas is an active organ at the end of the first trimester and plays a key role since the fourth month of pregnancy. IGF-1 is fundamental to pancreatic cell specialization, growth, islet maturation and thus to insulin production.

There is a pancreatic plasticity that allows pancreas response to high insulin-demand situations. β-Cell adaptation to different situations (nutrient lack or excess) depends on the equilibrium between cell division, growth and apoptosis death [7]. The foetal β-cell area increases during pregnancy without changing the cell size. However, there is an increase in the number of small islets, but not of the number of β-cells in each islet [41].

8. Growth hormones

IGF-1 is a low-molecular weight peptide hormone, expressed by all the adult and foetal tissues since early life stages. Similar to proinsulin, IGF-1 consists of one single polypeptide chain containing three disulphide bridges inside. Both IGF-1 and proinsulin have identical hydrophobic areas [42]. IGF-1 and its binding proteins (IGFBPs) are powerful stimulators of cellular division and have a very important role in the regulation of foetal growth [18]. After birth, the liver is the main source of IGF-1 and its IGFBPs. Nutritional factors such as protein intake, energy and micronutrients such as zinc regulate IGF-1 synthesis. Hormones such as GH, sexual steroids, thyroid hormones and insulin regulate the expression of IGF-1 and IGFBPs [43, 44].

Hormone	Placental GH	Human placental lactogen
Mother circulation	Liver IGF-1 production	Anti-insulinaemic effect acumulación de nutrientes
Foetal circulation	Without relevant effects	Stimulate liver IGF-1 and glycogenesis Stimulate fetal growth

GH, Growth hormone; IGF-1, insulin-like growth factor-1.

Table 2. Effects of placental GH and placental lactogen in both maternal and foetal circulations.

During gestation, pituitary GH production is scarce, while IGF-1 concentration increases, reaching the highest level at the end of pregnancy. This increment is associated with a high

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placental GH synthesis. Placental and pituitary GHs have similar structures, but different genes codify their production [45–47]. The main regulators of IGF-1 during pregnancy are both the placental GH and the human placental lactogen (hPL) [47]. Placental GH is secreted to maternal circulation, stimulating the synthesis of IGF-1 in the maternal liver. hPL is the most abundant peptide hormone secreted by the placenta. It circulates in both maternal and foetal blood, playing different roles. **Table 2** summarizes some of the major roles of both placental hormones.

9. Biological functions of IGF-1

IGF-1 stimulates cartilage growth, DNA, RNA and protein synthesis, and anabolic processes. IGF-1 is a key mediator of hippocampal neurogenesis. GH is expressed in the hippocampus where a high stress regulates it [48]. During pregnancy, IGF-1 stimulates cell division, maternal tissues' growth and anabolic processes resulting in increasing the adipose tissue, liver glycogen reservoir and mammary gland development. IGF-1 has effects that are similar to those of insulin on muscle and placenta, stimulating amino acid and glucose transport and inhibiting lipolysis in the adipose tissue. IGF-1 has also a main role in growth, as the correlation between its concentration and child growth speed shows [49]. In fact, it is the growth factor that best correlates with foetal growth during gestation. The protein-energetic malnutrition and preeclampsia associated with intrauterine growth retardation (IUGR) are two pathologic statuses where IUGR is associated with IGF-1 and IGFBP concentrations. Hypoglycaemia promotes adrenaline release, which stimulates hypothalamus GH release and inhibits insulin production by β-pancreatic cells (**Figure 3**). As indicated, placental GH induces liver IGF-1 production, palliating, at least in part, the negative effects of hypoglycaemia.

10. The Barker hypothesis: disputes and joint effects of insulin and cortisol

Hormonal equilibrium and adjustment are needed for an adequate anabolism and development [16, 17, 19, 37, 50]. This equilibrium is under nutritional and genetic regulation [7, 50]. Maternal glucocorticoids have relevant effects on the foetal metabolites and corticoid levels. They have opposite effects to those of other anabolic and growth mediators such as insulin or IGF-1 [38, 44]. Glucocorticoids are key hormones for adequate foetal development and maturation [16, 17], but at high concentrations they induce IUGR with a great affectation of glucose homeostasis, brain development and maturation and thus, all the processes regulated by this complex organ. Fortunately there are mechanisms regulating the concentration of active corticoids [7, 16], palliating, at least in part, the negative effects of the excess amount of these hormones.

Fifty years ago, it was assessed that children with marasmic malnutrition presented low insulinaemia and a high cortisol/insulin ratio [51]. However, these children kept a normal glucose tolerance [51] suggesting an increased insulin resistance. In animal models, the

tissue-insulin hypersensitivity induced by protein-energy malnutrition was confirmed [52, 53]. This disagrees with the thrifty phenotype theory [4–6], which supposes less glucose consumed by peripheral tissues because of an insulin resistance status, allowing an adequate glucose transfer to the brain even in nutritional restriction conditions.

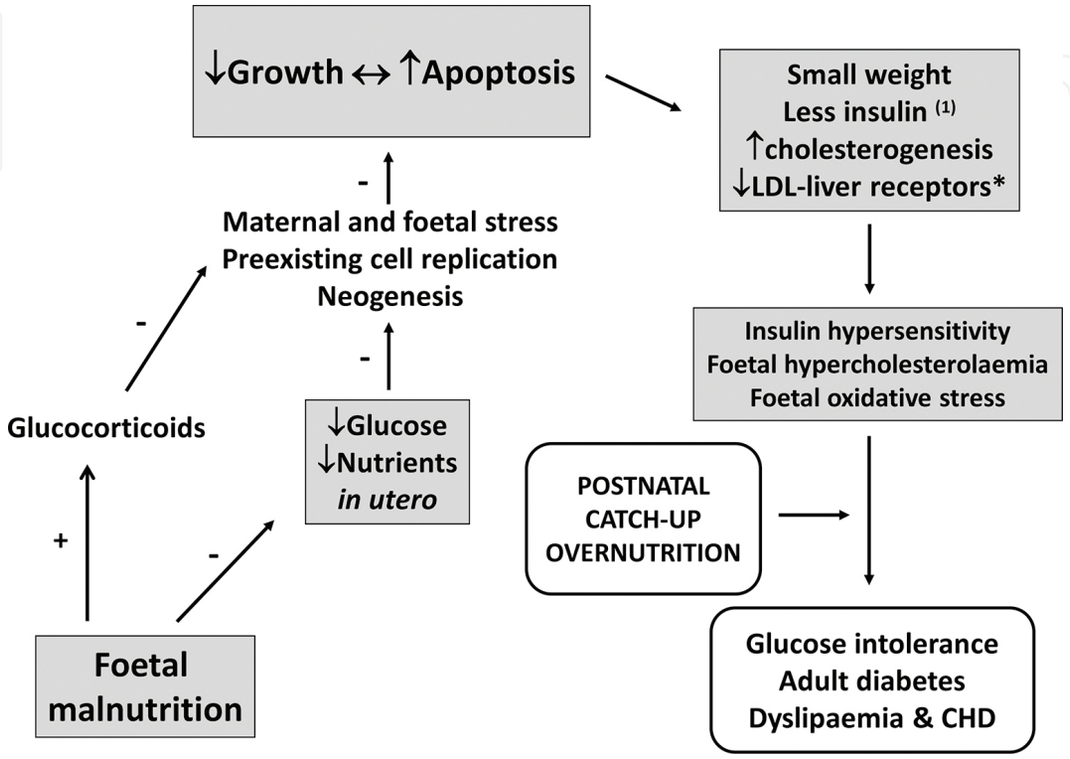

Figure 4. Insulin and lipoprotein programming during pregnancy. Foetal malnutrition influencing growth and pancreas capacities. Notice that the glucose and nutrient availability affect glucocorticoid concentrations and the flux of new cells originating lower pancreatic cell growth and less insulin production. This fact is counterbalanced by increasing insulin sensitivity and cholesterol synthesis. High food amount availabilities would induce adaptive mechanisms addressing glucose intolerance, diabetes mellitus, and/or dyslipidaemia and coronary heart disease (CHD) in this "programmed" body later in life. *Non-definitive evidence. Modified from Sánchez-Muniz et al. [1].

Inadequate nutrition in human foetuses negatively affects pancreatic development, leading to a smaller β-cell population [54] or a decreased ability for insulin production [55]. This situation makes pancreas unable to adequately respond to some metabolic and stress conditions in adult life. Foetal effects of this programming are less known, but it seems that malnutrition, placental insufficiency and GD alter the islets development in the perinatal period, increasing the risk of suffering diabetes in the future (**Figure 4**). There is no agreement on the results obtained as malnutrition effects on insulin secretion ability have been associated with alterations in the secretion mechanism or hormone biosynthesis, or other factors such as the amount of hormone in each islet and the insulin availability by modifying the expression of the insulin production and translation genes [56].

It is well known that pancreatic β-cells release adequate amounts of insulin as a response to nutrients, hormones and nervous stimuli in order to keep glucose levels in a narrow range and

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assure optimum tissue functioning [38, 39, 57]. Glycaemia is the main insulin-secretion regulator [38, 39, 57] (**Figure 3**). In the foetus, insulin synthesis is regulated by glucose, and it has been described a slight foetal β-cell immaturity in the face of glucose. This seems paradoxical as glucose is the main metabolic substrate in the foetus [38, 58]. The "thrifty phenotype" hypothesis proposed by Hales and Barker [5] suggests that type 2 diabetes is due to the action of unknown factors that reduce foetal growth, islet β cell ontogeny and insulin sensitivity during the prenatal period. This hypothesis supposes a foetal programming where the HPA axis is involved under hormonal and nutritional regulation. This programming is induced as an adaptation mechanism of the future being to its limited environment in order to guarantee its own survival and is more prevalent in low birthweight individuals [7].

However, there are different studies in neonates showing that even in adequate *intra utero* growth situations, there is a wide dispersion in the hormonal results [59], suggesting that more factors than malnutrition may be involved. Moreover, our group has found that normoweight neonates whose mothers had an adequate adherence to the Mediterranean diet (MDA) during pregnancy showed insulin resistance markers lower than those whose mothers followed a diet far from the Mediterranean pattern [12, 13].

The hormonal imbalance associated with hypercortisolaemia, hyperinsulinaemia and reduced levels of GH and testosterone is a typical fact of the metabolic syndrome [40, 60]. However, this association has never been suggested in neonates and thus studied by our research group.

11. Reference values in neonates: insulin resistance/sensitivity markers

Our group has defined reference values for insulin resistance/sensitivity markers in neonates [59]. These ranges were obtained considering strict criteria at birth, as only term, normoweight, appropriate for gestational age, and without foetal distress (Apgar test evaluation) neonates whose mothers had normal glucose tolerance (O'Sullivan test evaluation) were studied [61]. The insulin resistance/sensitivity was calculated by the following indexes: quantitative insulin sensitivity check index (QUICKI), using the formula: 1/[(log Insulin)(μUI/mL) + (log Glucose) (mg/dL)]; homeostatic model assessment-insulin resistance (HOMA-IR), calculated as: Glucose (mmol/L) × Insulin (μUI/mL)/22.5.

Taking these criteria into account, the following **hypothesis** was assessed: Term, normoweight, without foetal-distress neonates, presenting high cortisol and insulin levels have altered insulin sensitivity and other hormonal markers (GH, IGF-1). These effects can be modified by maternal glucose tolerance during gestation.

The following **aims** were established: (i) to define the anthropometric, hormonal and insulin sensitivity/resistance markers in a wide cohort of term, normoweight, without foetal-distress neonates; (ii) to know the normality of these parameters with respect to the reference ones; (iii) to define the prevalence of insulin resistance in these neonates; (iv) to know whether the association of high insulin and cortisol levels can explain the insulin resistance/sensitivity in these neonates; (v) to study the effect of maternal glucose tolerance during pregnancy on the

anthropometric and insulin resistance markers of those neonates; and (vi) to know how the maternal diet quality during gestation can affect the parameters studied in these neonates.

The main reason that led us to perform this study was the current increase in obesity and type 2 diabetes mellitus, especially in young populations. The early diagnosis of the insulin sensitivity affection will allow us to apply corrective and therapeutic measures in order to reduce the chronicity of the insulin resistance and its clinical posterior manifestations.

Taking into account the reference values for neonates [59], the cut-off point for high insulin concentrations (percentile 75, P75) was set up at 6.4 μUI/mL for females and at 4.8 μUI/mL for males. In the case of cortisol, the cut-off point for high levels (percentile 75, P75) was set up at 9.7 μg/dL for females and 9.4 μg/dL for males.

12. General data of neonates from Merida study

Table 3 shows the general characteristics of the studied population.

		Minimum	Maximum
Mothers			
Age (years)	30.33 ± 5.24	16	40
Glucose (mg/dL)	83.63 ± 6.72	64.0	101.0
Neonates			
Gestational age (weeks)	39.85 ± 1.10	37	42
Weight (g)	3301 ± 331	2520	3990
Length (cm)	50.0 ± 1.38	44.0	53.0
BMI (kg/m^2)	13.19 ± 1.12	10.08	15.80
Ponderal index (kg/m^3)	26.41 ± 2.39	20.16	33.22
Cephalic perimeter (cm)	34.19 ± 1.35	30.0	37.0
Thoracic perimeter (cm)	33.66 ± 1.43	30.0	39.0
Apgar 1	8.99 ± 0.72	7	10
Apgar 2	9.95 ± 0.29	9	10
Glucose (mg/dL)	78.23 ± 38.39	18	233
Insulin (μIU/mL)	6.57 ± 8.58	0.2	67.50
Cortisol (μg/dL)	7.54 ± 3.55	2.78	24.15
GH (ng/mL)	15.84 ± 10.19	0.6	73.1
IGF-1 (ng/mL)	57.7 ± 26.31	5.0	232.5
QUICKI	0.43 ± 0.12	0.26	1.18
HOMA-IR	1.53 ± 2.78	0.02	16.73
Glucose/insulin	29.26 ± 43.90	0.79	370.0
Insulin/cortisol	0.99 ± 1.40	0.02	11.05

Data are means ± standard deviations; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor 1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-insulin resistance.

Table 3. Characteristics of the studied population: term, normoweight neonates without foetal distress.

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Of the 178 neonates studied, 98 were females and 80 males. All of them were Caucasic, singleton, term, normoweight and without foetal distress. The study was performed in accordance with the Declaration of Helsinki and approved by the Management and Ethical Committee of the Merida Hospital. From the 178 mothers, 156 were screened for GD by the O'Sullivan test [61] between weeks 24 and 28 of pregnancy, and 33% had impaired glucose tolerance (IGT). There were 22 mothers who could not be screened.

	Insulin <P75 (N = 120)	**Insulin ≥P75 (N = 58)**	**Significance**
Mothers			
Age (years)	30.16 ± 5.25	31.14 ± 5.12	NS
Glucose (mg/dL)	83.20 ± 6.47	84.13 ± 7.10	NS
Neonates			
Gestational age (weeks)	39.47 ± 1.16	39.47 ± 1.17	NS
Birthweight (g)	3328 ± 290	3372 ± 297	NS
Length (cm)	50.09 ± 1.31	50.19 ± 1.35	NS
BMI (kg/m^2)	13.27 ± 1.06	13.38 ± 0.94	NS
Ponderal index (kg/m^3)	26.51 ± 2.37	26.67 ± 2.05	NS
Cephalic perimeter (cm)	34.47 ± 1.23	34.13 ± 1.21	NS
Thoracic perimeter (cm)	33.80 ± 1.32	33.69 ± 1.38	NS
Apgar 1	8.96 ± 0.83	9.03 ± 0.56	NS
Apgar 2	9.93 ± 0.35	9.97 ± 0.18	NS
Glucose (mg/dL)	68.40 ± 28.62	99.09 ± 48.50	<0.001
Insulin (μIU/mL)	2.84 ± 1.48	14.61 ± 11.62	ND
Cortisol (μg/dL)	7.39 ± 3.38	7.98 ± 3.91	NS
GH (ng/mL)	16.76 ± 10.41	13.28 ± 9.07	0.027
IGF-1 (ng/mL)	55.71 ± 22.85	63.64 ± 32.05	NS
QUICKI	0.47 ± 0.13	0.36 ± 0.08	<0.001
HOMA-IR	0.49 ± 0.33	3.99 ± 4.17	<0.001
Glucose/insulin	37.37 ± 37.02	8.61 ± 4.39	<0.001
Insulin/cortisol	0.47 ± 0.34	2.22 ± 2.08	<0.001

Data are means ± standard deviations; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-IR; P: percentile; NS, not significant; ND, not determined.

Table 4. Characteristics of the studied population according to the insulin concentration.

The general anthropometric data found were quite similar to those shown in previous studies [62, 63] with mean values of normality, clearly suggesting the absence of maternal-placental malnutrition. The mean values found in hormonal markers agree with those used as reference values in neonates [59]. Glycaemia in neonates is quite variable even in populations where distress and other factors are well controlled [59, 64]. HOMA-IR and QUICKI are usually

studied in adults [65, 66], but this occurred sparingly in neonates [59, 67] and more often in low birthweight populations [68]. The data obtained in this study show that HOMA-IR values are lower than those found in low birthweight neonates [68] suggesting less insulin resistance. In addition, QUICKI was much lower and HOMA-IR much higher than those found in youths suffering or not suffering from obesity and/or metabolic syndrome [66].

12.1. Anthropometric and insulin sensitivity/resistance markers in neonates classified according to insulin values at birth

Non-significant differences were found between anthropometric characteristics of neonates belonging to both insulin levels (**Table 4**).

	Cortisol <P75 (N = 137)	**Cortisol ≥P75 (N = 41)**	**Significance**
Mothers			
Age (years)	30.6 ± 5.24	30.10 ± 5.18	NS
Glucose (mg/dL)	83.74 ± 6.85	82.78 ± 6.12	NS
Neonates			
Gestational age (weeks)	39.4 ± 1.16	39.80 ± 1.12	0.067
Birthweight (g)	3338 ± 287	3358 ± 312	NS
Length (cm)	50.07 ± 1.37	50.28 ± 1.13	NS
BMI (kg/m^2)	13.31 ± 1.04	13.27 ± 0.97	NS
Ponderal index (kg/m^3)	26.62 ± 2.36	26.40 ± 1.93	NS
Cephalic perimeter (cm)	34.36 ± 1.15	34.31 ± 1.45	NS
Thoracic perimeter (cm)	33.75 ± 1.25	33.79 ± 1.55	NS
Apgar 1	8.99 ± 0.76	8.98 ± 0.76	NS
Apgar 2	9.94 ± 0.32	9.93 ± 0.26	NS
Glucose (mg/dL)	75.33 ± 36.69	88.66 ± 44.63	0.087
Insulin (μIU/mL)	6.39 ± 8.49	7.62 ± 9.38	NS
Cortisol (μg/dL)	6.04 ± 1.67	12.74 ± 3.33	ND
GH (ng/mL)	16.92 ± 10.26	11.43 ± 8.41	0.001
IGF-1 (ng/mL)	58.27 ± 24.32	58.24 ± 32.73	NS
QUICKI	0.44 ± 0.11	0.43 ± 0.15	NS
HOMA-IR	1.55 ± 2.87	1.89 ± 3.01	NS
Glucose/insulin	25.46 ± 26.58	36.49 ± 42.63	NS
Insulin/cortisol	1.16 ± 1.58	0.65 ± 0.91	0.011

Data are means ± standard deviations; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR,: homeostatic model assessment-insulin resistance; P, percentile; NS, not significant; ND, not determined.

Table 5. Characteristics of the studied population according to cortisol concentrations.

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Of the 178 neonates studied, 58 (30 females and 28 males) were hyperinsulinaemic (insulin concentrations >P75). From these 58 hyperinsulinaemic neonates, 86% showed HOMA-IR values ≥P75 taking in account the reference values for neonatal population [63]. As indicated by Gesteiro et al. [67], the increased neonatal insulinaemia was not able to normalize neonatal glycaemia in the >P75 neonates as those newborns presented significantly higher cord-blood insulin levels. Despite the fact that all studied infants were full-term normoweights, about one-third show very high insulin levels (≥15 μIU/mL). No clear reasons are available; however, foetal insulin levels increase under hyperglycaemia and GD [69]. Furthermore, of the 58 hyperinsulinaemic neonates, 25 (43%) were born from mothers presenting IGT and 28 (48%) from mothers without IGT. Thus, neonatal insulin sensitivity/resistance markers could be clearly affected by maternal IGT. This factor effect will be discussed later in this review.

12.2. Anthropometric and insulin sensitivity/resistance markers in neonates classified according to cortisol values at birth

Table 5 shows the characteristics of the studied population according to their cortisol levels. In the case of cortisol, from the 178 neonates studied, 20 females and 21 males were hypercortisolaemics as presented cortisol levels ≥ P75.

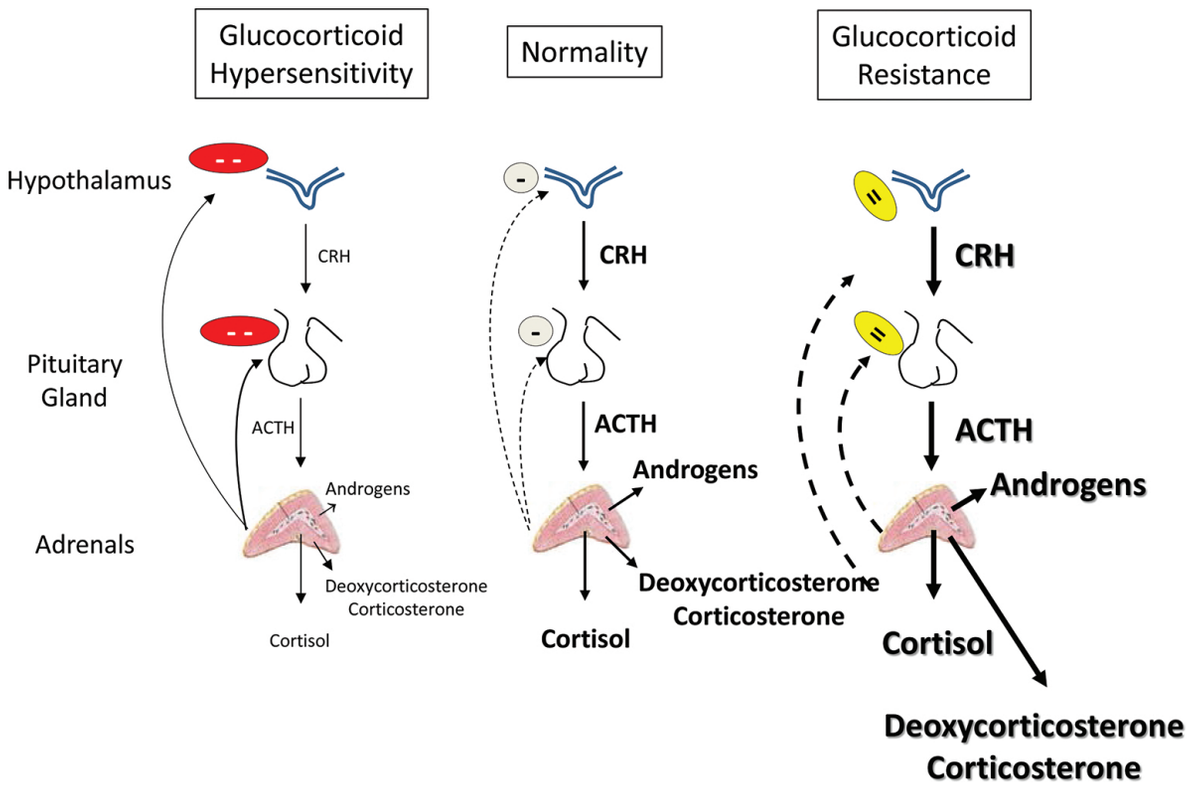

Figure 5. Potential mechanisms implicated in glucocorticoid hormone regulation. Three possibilities are suggested. Note that glucocorticoid sensitivity in the HPA axis and tissues can be independently regulated and the former determines the serum free cortisol levels. Combination of their directions influences net peripheral action of this hormone. The glucocorticoid resistance would be a consequence of glucocorticoid receptors saturation. Modified from Chrousos and Kino [32].

There is a lot of available information about foetal programming and glucocorticoids in low birthweight newborns [16, 17]. However, the present study was done in control neonates where scarce information is available. Cortisol levels at birth were not affected by foetal distress as all of them had a high score in the Apgar test (>7 at the first minute and >9 at the fifth minute). Cortisol levels are highly dependent on stress and type of delivery [70, 71]. As our neonates were strictly selected, other factors, such as low cortisol sensitivity which is different from these factors, should be considered. **Figure 5** shows a model comparison where cortisol and other hormone levels appear clearly related to cortisol resistance. Thus, it can be accepted that high cortisol level at birth would be also associated with low response control of cortisol.

We also find that neonates presenting high cortisolaemia had lower GH ($P = 0.001$) and an insulin/cortisol ratio ($P < 0.05$) than those neonates with low–normal cortisol levels.

12.3. Anthropometric and insulin sensitivity/resistance markers in neonates presenting high cortisol and high insulin levels at birth

This study finds for the first time in the bibliography that the conjunction of high levels of insulin and cortisol together was present in nearly 9% of term, normoweight without foetal-distress neonates, and was associated with low GH concentrations, impaired neonatal insulin sensitivity and high glycaemia at birth.

Table 6 resumes the anthropometric, hormonal and insulin resistance/sensitivity in neonates attending to their insulin and cortisol levels together. It can be observed that neonates presenting both high insulin and cortisol concentrations showed a slightly higher birthweight without differences in length, body mass index (BMI), ponderal index, cephalic or thoracic perimeters. Although fat was not analysed in these neonates, it can be speculated that as variation in length was lower than in weight, neonates presenting higher levels of both cortisol and insulin tended to accumulate more fat, as it is known that in adults, the troncular fat accumulation is associated with plasma lipids increase [72] and insulin resistance severity in adults [72, 73]. Nonetheless, data in adolescents are controversial and limited [74].

Values of GH (ANOVA, $P = 0.009$), glucose, insulin, cortisol, QUICKI, HOMA-IR and the glucose/insulin and insulin/cortisol ratios (all $P < 0.001$) were significantly different between the four groups. When insulin was elevated regardless of cortisol levels, neonates showed higher glucose, IGF-1, HOMA-IR and insulin/cortisol index, but lower QUICKI and glucose/insulin ratio (at least $P < 0.05$). Neonates with hypercortisolaemia but not hyperinsulinaemia showed lower values of GH (at least $P < 0.05$) than those with non-elevated levels of both hormones.

In agreement with our results, where higher IGF-1 correspond to higher birthweight, other groups have found that IGF-1 levels are related to higher birthweight, supporting the premise that IGF-1 plays a major role in promoting the foetal growth [75], but also in keeping the hormonal balance.

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	Insulin and cortisol <P75 (N = 95)	Insulin >P75 and cortisol <P75 (N = 42)	Insulin <P75 and cortisol ≥P75 (N = 24)	Insulin and cortisol ≥P75 (N = 17)	ANOVA
Mothers					
Age (years)	30.09 ± 5.13	31.71 ± 5.35	30.63 ± 5.77	29.35 ± 4.26	0.16
Glucose (mg/dL)	83.48 ± 6.61	84.32 ± 7.41	82.05 ± 6.09	83.75 ± 6.22	0.57
Neonates					
Gestational age (weeks)	39.41 ± 1.10	39.26 ± 1.29	39.79 ± 1.29	39.82 ± 0.88	0.15
Birthweight (g)	3332 ± 296	3350 ± 269	3303 ± 275	3437 ± 353	0.15
Length (cm)	50.07 ± 1.39	50.08 ± 1.37	50.15 ± 1.04	50.47 ± 1.27	0.35
BMI (kg/m^2)	13.29 ± 1.09	13.36 ± 0.93	13.13 ± 0.96	13.47 ± 0.99	0.56
Ponderal Index (kg/m^3)	26.59 ± 2.47	26.70 ± 2.13	26.20 ± 2.02	26.68 ± 1.83	0.89
Cephalic perimeter (cm)	34.45 ± 1.09	34.09 ± 1.26	34.39 ± 1.69	34.21 ± 1.18	0.88
Thoracic perimeter (cm)	33.80 ± 1.20	33.66 ± 1.38	33.82 ± 1.71	33.75 ± 1.42	0.93
Apgar 1	8.96 ± 0.87	9.05 ± 0.38	8.96 ± 0.69	9.00 ± 0.87	0.84
Apgar 2	9.93 ± 0.36	9.98 ± 0.15	9.92 ± 0.28	9.94 ± 0.24	0.88
Glucose (mg/dL)	64.06 ± 19.08^a	100.81 ± 51.81^b	85.67 ± 48.59^c	92.88 ± 39.42^{bc}	<0.001
Insulin (μIU/mL)	2.92 ± 1.45^a	14.26 ± 11.96^b	2.41 ± 1.45^a	14.98 ± 10.90^b	<0.001
Cortisol (<g/dL)	5.99 ± 1.66^a	6.15 ± 1.73^a	12.61 ± 2.95^b	12.92 ± 3.89^b	<0.001
GH (ng/mL)	17.61 ± 10.65^a	15.32 ± 9.23 ^{ab}	12.67 ± 7.89^b	9.56 ± 9.06^b	0.009
IGF-1 (ng/mL)	56.60 ± 24.19^a	62.10 ± 24.48^{ab}	50.41 ± 14.23^a	69.49 ± 46.77^b	0.083
QUICKI	0.46 ± 0.12^a	0.37 ± 0.08 ^{b}	0.48 ± 0.17 ^{a}	0.35 ± 0.06 ^{b}	<0.001
HOMA-IR	0.47 ± 0.29 ^{a}	4.00 ± 4.28^b	0.54 ± 0.46 ^{a}	3.80 ± 3.97^b	<0.001
Glucose/insulin	32.79 ± 41.83 ^{a}	8.87 ± 4.49^b	56.60 ± 61.54^c	8.10 ± 4.10 ^{b}	<0.001
Insulin/cortisol	0.54 ± 0.34^a	2.55 ± 2.26^b	0.19 ± 0.11^a	1.30 ± 1.13^c	<0.001

Data are means ± standard deviations; Different letters for the same parameter are significantly different. BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-insulin resistance.

Table 6. Comparison of the different groups of neonates according to their insulin and cortisol levels.

Pancreatic β-cells are very sensitive to substrate and hormone changes during the foetal stage. An inadequate environment *intra utero* would affect the expression of transcription factors and these in turn, the correct β-cell development [1, 7]. Álvarez Escolá and Escrivá Pons [7] observed that impaired intrauterine development due to maternal malnutrition, uterus-placental restriction or GD is related to low IGF-1 concentrations in term rat foetuses. Corticosteriods diminish IGF-2, IGF-1 receptor and transcription factors necessary for β-cell expression at the foetal stage [7, 76]. Although it seems that insulin and cortisol have opposite effects on IGF-1 levels, when hypercortisolaemia and hyperinsulinaemia occurred together, IGF-1 levels were not lower than those of neonates presenting only high insulin levels. Hypercortisolaemia has been related to insulin resistance in adults [17] and low levels of GH in girls aged 3–18 years

in increased insulin resistance and hypercortisolaemia situations [77, 78]. Neonates showing high concentrations of insulin and cortisol together showed the lowest concentration of GH and the highest of IGF-1. Although the precise mechanism is unknown, it can be speculated that the inverse relationship between GH and IGF-1 involved in insulin sensitivity [79] could be modulated by cortisol levels. In such a way, high cortisolaemia in neonates with previous impaired insulin sensitivity would tend to reduce GH and increase IGF-1 concentrations. In fact, the mean values of IGF-1 rise up over P75 and GH ones fall under P25 found in the reference population [59]. Thus, paradoxically, the hypercortisolaemia seems to diminish, at least partially, the negative effects ascribed to the hyperinsulinaemia. Circulating IGF-1 plays an important role in maintaining the hormonal balance between GH and insulin and controlling glucose homeostasis. GH antagonizes the action of insulin in liver and peripheral tissues and leads to insulin insensitivity (**Figure 6**).

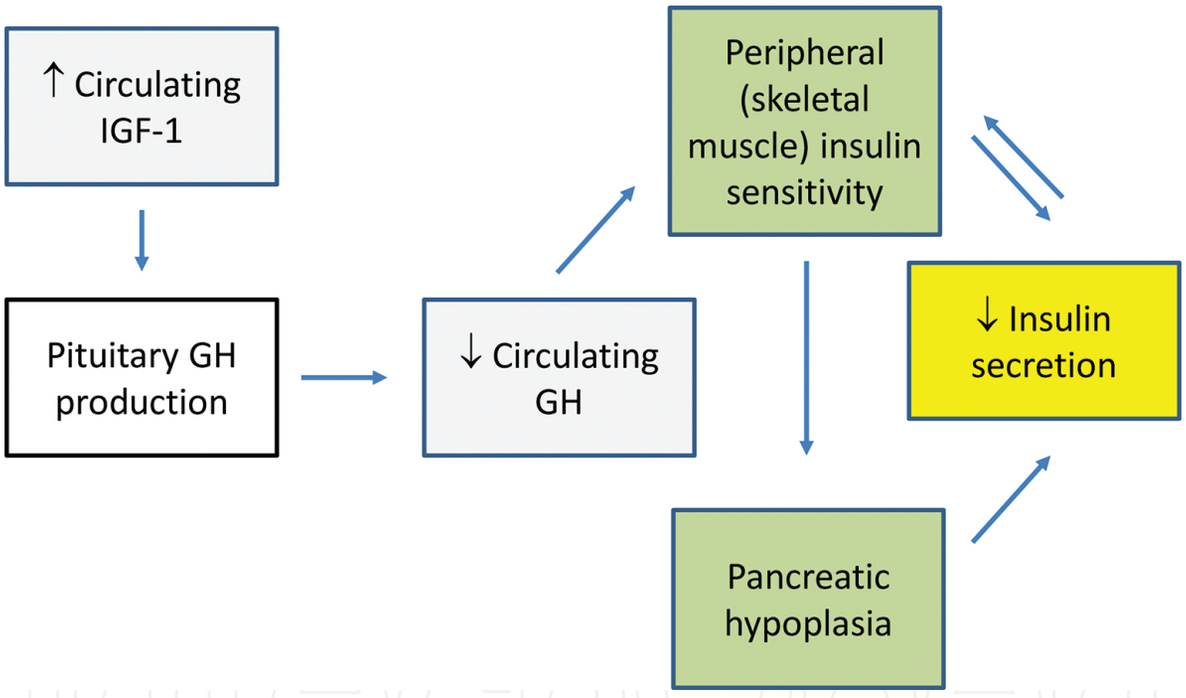

Figure 6. Regulation of insulin secretion by IGF-1 and GH. Notice the inverse relationship between IGF-1 and GH. IGF-1, insulin-like growth factor-1; GH, growth hormone. Modified from Yakar et al. [79].

Neonates presenting hyperinsulinaemia together with hypercortisolaemeia showed low insulin sensitivity and high insuline resistance according to their QUICKY and HOMA-IR values, while neonates with no elevation of both hormones showed QUICKI and HOMA-IR values >P50 and <P50 of the reference population, respectively [59]. Nevertheless, the conjunction of high levels of both hormones does not significantly affect QUICKI and HOMA-IR values with respect to those shown by the neonates presenting only high insulin concentrations. The ROC curve (**Figure 7**) shows that the conjunction of both high insulin and cortisol is a strong predictor for neonates presenting high HOMA-IR and low QUICKI values.

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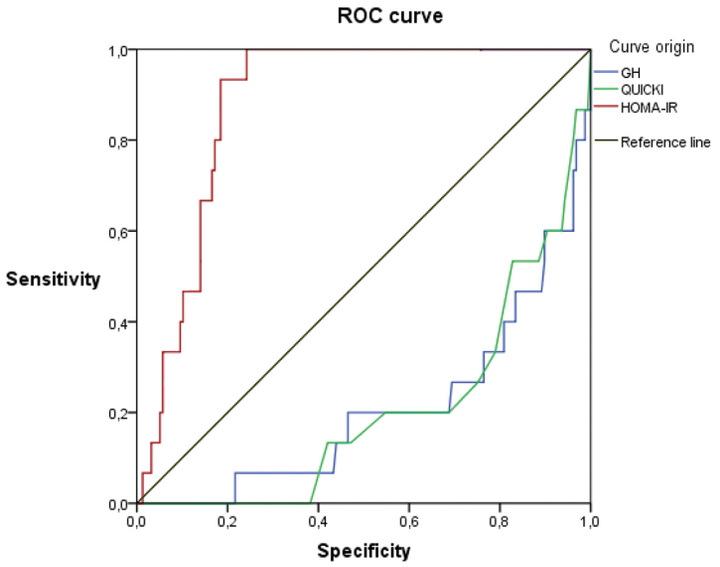

	Area under the Curve	95% CI Lower limit	95% CI Upper limit	Significance
GH	0.207	0.085	0.330	<0.001
QUICKI	0.205	0.097	0.313	<0.001
HOMA-IR	0.885	0.829	0.934	<0.001

Figure 7. ROC curves. Predictive value of both high insulin and cortisol concentrations. GH, growth hormone; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-insulin resistance; IGF-1, insulin-like growth factor-1. Area under curve: GH = 0.207, QUICKI = 0.205, HOMA-IR = 0.882 (all P < 0.001).

12.4. The effect of maternal impaired glucose tolerance on anthropometric and insulin sensitivity/resistance markers in neonates presenting high cortisol and high insulin levels at birth

Table 7 shows neonatal results after considering two factors: the association of high cortisol-high insulin levels and the presence of IGT during pregnancy. The gestational age did not differ in neonates with high cortisol-high insulin levels whose mother presented or not IGT with respect to those described in a neonatal control population [59].

Neonatal weight and length were significantly affected (P = 0.006 and 0.016, respectively) by the joint effect of high cortisol–high insulin levels but not by IGT. BMI, ponderal index, cephalic and thoracic perimeters, and the Apgar at 1 and 5 min did not change by any of the two studied factors or by their interaction. The maternal glycaemia appeared higher in IGT mothers (P < 0.001) (**Table 7**).

Neonatal cortisolaemia and insulinaemia were significantly affected by maternal IGT and by the interaction of IGT and high cortisol-high insulin levels (all P < 0.001). Neonatal glycaemia increased while GH decreased in children with high insulin–cortisol at birth (P < 0001), but was not affected by IGT presence. IGF-1 was affected by the cortisol–insulin joint (P = 0.031)

and by IGT (P = 0.037). The insulin/cortisol ratio was significantly modified by the joint effect of high cortisol–high insulin (P < 0.001), maternal IGT (P = 0.012), as well as the interaction of the two factors (P < 0.001) (**Table 7**).

	Insulin and cortisol <P75		**Insulin and cortisol ≥P75**		**Two-way ANOVA (significance)**		
	No IGT (N = 96)	**IGT (N = 45)**	**No IGT (N = 9)**	**IGT (N = 6)**	**Interaction**	**IGT**	**High insulin–high cortisol**
Mothers							
Age (years)	29.86 ± 4.95	32.22 ± 5.09	28.44 ± 3.09	30.33 ± 5.24	0.76	0.160	0.54
Glucose (mg/dL)	81.97 ± 6.04	86.84 ± 7.03	80.22 ± 4.44	88.83 ± 5.56	0.28	<0.001	0.80
Neonates							
Gestational age (weeks)	39.49 ± 1.14	39.24 ± 1.30	40.11 ± 0.60	40.00 ± 0.00	0.93	0.66	0.17
Birthweight (g)	3336 ± 286	3297 ± 272	3432 ± 402	3488 ± 329	0.26	0.88	0.006
Length (cm)	50.16 ± 1.37	49.82 ± 1.29	50.39 ± 0.99	50.83 ± 1.72	0.17	0.86	0.016
BMI (kg/m^2)	13.26 ± 1.02	13.29 ± 1.05	13.49 ± 1.26	13.47 ± 0.66	0.70	0.99	0.14
Ponderal index (kg/m^3)	26.47 ± 2.30	26.70 ± 2.40	26.77 ± 2.32	26.52 ± 1.35	0.98	0.97	0.54
Cephalic perimeter (cm)	34.30 ± 1.35	34.44 ± 1.13	34.42 ± 1.28	34.20 ± 1.15	0.39	0.51	0.51
Thoracic perimeter(cm)	33.75 ± 1.36	33.85 ± 1.25	34.00 ± 1.90	33.40 ± 0.89	0.78	0.33	0.77
Apgar1	8.84 ± 0.89	9.22 ± 0.42	8.78 ± 1.09	9.33 ± 0.52	0.76	0.082	0.93
Apgar2	9.90 ± 0.40	10.0 ± 0.0	9.89 ± 0.33	10.0 ± 0.0	0.99	0.29	0.99
Glucose (mg/dL)	73.92 ± 37.33	79.98 ± 37.77	100.89 ± 48.60	78.33 ± 18.01	0.20	0.065	<0.001
Insulin (μIU/mL)	4.62 ± 5.81	8.96 ± 11.82	18.03 ± 13.95	11.32 ± 4.19	0.012	0.029	<0.001
Cortisol (μg/dL)	7.03 ± 2.89	7.22 ± 3.49	10.35 ± 0.41	16.35 ± 4.62	<0.001	<0.001	<0.001
GH (ng/mL)	17.09 ± 9.40	14.89 ± 12.32	8.44 ± 6.81	8.20 ± 5.04	0.82	0.78	0.020
IGF-1 (ng/mL)	55.87 ± 23.49	58.76 ± 23.32	55.06 ± 16.31	88.58 ± 72.03	0.14	0.037	0.031
QUICKI	0.46 ± 0.14	0.40 ± 0.09	0.35 ± 0.07	0.36 ± 0.06	0.52	0.73	0.001
HOMA-IR	1.12 ± 2.44	2.17 ± 3.42	5.00 ± 5.08	2.10 ± 0.68	0.002	0.003	<0.001
Glucose/insulin	35.80 ± 42.38	18.39 ± 14.29	7.97 ± 4.81	7.93 ± 3.86	0.58	0.54	0.032
Insulin/cortisol	0.80 ± 1.19	1.57 ± 2.11	1.75 ± 1.37	0.76 ± 0.46	0.001	0.012	<0.001

Data are means ± standard deviations; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-insulin resistance.

Table 7. Effects of high insulin and cortisol levels in neonates and impaired glucose tolerance (IGT) in mothers on anthropometric, foetal distress and insulin sensitivity/resistance markers.

With respect to insulin resistance/sensitivity markers, the glucose/insulin ratio and the QUICKI were not affected by IGT but appeared lower in neonates with high cortisol-high insulin levels (P = 0.032 and <0.001, respectively). HOMA-IR was higher in neonates with high cortisol-high insulin (P < 0.001) and affected by maternal IGT (P = 0.003) and by the interaction of two factors (P = 0.002).

With respect to maternal IGT prevalence, we found that one of two mothers of hyperinsulinaemic children suffered from IGT, while one out of four mothers showed IGT in those groups with insulin below P75. According to Herrera and Ramos Álvarez [19] during the last third of gestation, maternal levels of hPL, oestrogens and progesterone, increase in parallel to the placental mass. These hormones show anti-insulinaemic action, which together with the placenta availability to degrade insulin increases the maternal insulin needs. In fact, during late gestation an increase in the pancreatic β-cell sensibility to the insulintropic stimuli, and also an accelerated insulin turnover have been described. Maternal insulin level effects were partially arrested by insulin resistance. The increased insulinaemia capacitates the future mother to efficiently balance the intense metabolite extraction by the foetus–placenta unity, despite the tendency of insulin resistance occurring in the mother [2, 19].

GD is responsible for very high glycaemia that can induce important alterations in foetus size, glucose and insulin production [1, 9]. These premises encouraged us to study whether maternal pregnancy IGT presence could affect the values of insulin resistance (HOMA-IR) or insulin sensitivity (QUICKI) markers in neonates already showing high insulin and high cortisol levels at birth.

Results suggest that neonatal insulin-cortisol levels influence the anthropometric parameters and the insulin resistance/sensitivity markers more than IGT presence. Nonetheless, the effect of IGT on insulin was different in the two study groups, as the level of this hormone decreased remarkably in neonates with high cortisol-high insulin levels. It can be hypothesized that mothers presenting IGT should have high glucose concentrations. This increase would induce, in turn, a neonatal insulin increase in order to avoid the negative effects of glucose excess [1, 9].

It seems interesting to notice that neonates presenting high cortisol-high insulin at birth, whose mothers were presenting IGT showed higher weight and length but the lowest GH and the highest IGF-1 values. Again, the inverse relationship between IGF-1 and GH seems a palliative mechanism against insulin resistance, a highly negative fact for the foetus physiology. Thus, in addition to its role in foetal growth [75], IGF-1 seems crucial in keeping hormonal balance [79]. It also seems relevant that the presence of maternal IGT and high insulin–high cortisol levels at birth reduced the negative effects on glucose, insulin and HOMA-IR but increased cortisol and IGF-1 levels with respect to their non-IGT but high insulin–high cortisol level counterparts. These findings seem paradoxical, as they suggest that the increased maternal glycaemic response to carbohydrate intake would allow the mitigation of the negative effects of reduced GH and increased cortisol levels in the neonates. More studies are needed to understand this interesting metabolic maternal-neonatal interaction.

13. Pregnancy diet influences on cortisol and insulin levels at birth

Unfortunatly complete information of the diet consumed through the whole pregnancy was available in only 31 mothers whose neonates fulfil the selection criteria. Nonetheless, some relevant results were observed when comparing results from neonates whose mothers followed an adequate or unadequate diet according to the MDA (**Table 8**).

	MDA <7 (N = 11)	MDA ≥7 (N = 20)	Significance
Mothers			
Age (years)	28.18 ± 5.42	31.90 ± 5.17	0.078
Glucose (mg/dL)	80.44 ± 6.46	84.24 ± 7.36	NS
Neonates			
Weight (g)	3140 ± 419	3309 ± 275	NS
Length (cm)	49.68 ± 0.46	50.20 ± 1.27	NS
BMI (kg/m^2)	12.72 ± 1.66	13.13 ± 1.02	NS
Ponderal index (kg/m^3)	25.61 ± 3.33	26.18 ± 2.26	NS
Glucose (mg/dL)	93.91 ± 31.28	70.70 ± 14.84	0.044
Insulin (μIU/mL)	12.46 ± 10.69	3.98 ± 3.24	0.040
Cortisol (μg/dL)	8.93 ± 3.46	7.14 ± 2.56	NS
GH (ng/mL)	17.20 ± 13.01	17.49 ± 9.25	NS
IGF-1 (ng/mL)	58.41 ± 32.02	57.55 ± 28.11	NS
HOMA-IR	3.69 ± 5.25	0.73 ± 0.67	0.038
QUICKI	0.39 ± 0.07	0.45 ± 0.14	NS
Glucose/insulin	17.49 ± 10.61	40.30 ± 41.71	NS
Insulin/cortisol	1.94 ± 2.98	0.60 ± 0.47	0.057

Data are means ± standard deviations; BMI, body mass index; GH, growth hormone; IGF-1: insulin-like growth factor-1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment-insulin resistance; NS, not significant.

Table 8. Effects of maternal adherence to mediterranean diet (MDA) during pregnancy on different neonatal parameters.

Thus, the conjoint presence of high cortisolaemia–high insulinaemia at birth was clearly associated with pregnancy diet characteristics. In no case, neonatal hyperinsulinaemia or neonatal hyperinsulinaemia *plus* hypercortisolaemia was found in children whose mothers' diets had a MDA ≥7 over 13. Thus, those findings suggest a clear relationship between pregnancy diet quality and high neonatal insulinaemia. Almost 50% of neonates, whose mothers' diets were inadequate, according to the MDA score, presented hyperinsulinaemia *plus* hypercortisolaemia at birth. Previously we reported that a relatively high pregnancy MDA was a guarantee for glucose, insulin, HOMA-IR and QUICKI normal values, while mothers with a poor MDA score delivered neonates whose plasma insulin sensitivity/resistance markers were conceptually those of prediabetes [12, 13].

Thus, in the absence of known factors (reduced gestational age, reduced neonatal body weight, foetal distress) that would suggest limited and stressed gestation, pregnancy diet characteristics (MDA) clearly affect glycaemic hormone balance, and thus insulin sensitivity/resistance at birth.

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14. Conclusion

The results of this chapter show the importance of analysing insulin and cortisol cord-blood concentrations even in term, normoweight neonates. Results show for the first time on the international bibliography that about 9% of term, normoweight, without foetal-distress neonates, showed increased values (≥P75 of reference values) for both cord-blood insulin and cortisol.

The insulinaemia affected the insulin sensitivity/resistance markers more than cortisolaemia in the different neonate groups classified according to cortisol and insulin levels. In those neonates, GH values appear decreased, a fact that in addition to the join presence of high cortisol-high insulin induces decreases in insulin sensitivity in those neonates without affecting body weight as they were normoweight. IGT was more prevalent in mothers whose neonates were hyperinsulinaemic at birth. In addition, a follow-up study of this neonatal population is needed in order to assess the importance of the present findings. Mothers with adequate MDA score diet delivered newborns presenting healthier insulin and cortisol profiles. This finding suggests the benefits of following an adequate diet through gestation. It will allow the design of future interventions aimed to decrease the metabolic syndrome risk later in life.

Abbreviations

ACTH, adrenocorticotropic hormone; BMI, body mass index; CBG, cortisol binding globulin; CRH, corticotropin-releasing hormone; DHAS, dehydroepiandrosterone sulphate; , GD, gestational diabetes; GH, growth hormone; GR, glucocorticoid receptor; HDL, high-density lipoproteins; HOMA-IR, homeostatic model assessment-insulin resistance; HPA, hypophysis-pituitary axis; hPL, human placental lactogen; HSD, hydroxysteroid dehydrogenase; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IGT, impaired glucose tolerance; IUGR, intrauterine growth retardation; LDL, low-density lipoproteins; MDA, Mediterranean diet adherence; MR, mineralocorticoid receptor; MSH, melanocyte stimulating hormone; QUICKI, quantitative insulin sensitivity check index; TSH, thyroid-stimulating hormone.

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