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Intrauterine Growth Retardation (IUGR) as a Novel Condition of Insulin-Like Growth Factor-1 (IGF-1) Deficiency

I. Martín-Estal, R.G. de la Garza, and I. Castilla-Cortázar

Abstract Insulin-like growth factor 1 (IGF-1) is an anabolic hormone with several biological activities, such as proliferation, mitochondrial protection, cell survival, tissue growth and development, anti-inflammatory, antioxidant, antifibrogenic and antiaging. This hormone plays an important role in embryological and postnatal states, being essential for normal foetal and placental growth and differentiation. During gestation, the placenta is one of the major sources of IGF-1, among other hormones. This intrauterine organ expresses IGF-1 receptors and IGF-1 binding proteins (IGFBPs), which control IGF-1 activities. Intrauterine growth restriction (IUGR) is the second most frequent cause of perinatal morbidity and mortality, defined as the inability to achieve the expected weight for gestational age. Different studies have revealed that IUGR infants have placental dysfunction and low circulating levels of insulin, IGF-1, IGF-2 and IGFBPs. Such data suggest that IGF-1 deficiency in gestational state may be one of the major causes of foetal growth retardation. The aim of this review is to study the epidemiology, physiopathology and possible causes of IUGR. Also, it intends to study the possible role of the placenta as an IGF-1 target organ. The purpose is to establish if IUGR could be

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considered as a novel condition of IGF-1 deficiency and if its treatment with low doses of IGF-1 could be a suitable therapeutic strategy.

Keywords Cell proliferation • Foetal/placental growth • GH • GH/IGF-1 axis • IGF-1 • IGF-1R • IGF-2 • IGFBP-rPs • IGFBPs • Intrauterine growth restriction • Placental lactogen • Somatostatinergic tone

Contents

Abbreviations

ALS	Acid-labile subunit
CG	Chorionic gonadotropin
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
CTGF	Connective tissue growth factor
Cyr61	Cysteine-rich protein 61
ESM-1	Endothelial cell-specific molecule
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHBP	Growth hormone binding protein
GHRH	Growth hormone-releasing hormone
GnRH	Gonadotropin-releasing hormone
HPA	Hypothalamus–pituitary–adrenal gland axis
IGF-1	Insulin-like growth factor 1
IGF-1R	IGF-1 receptor
IGF-2	Insulin-like growth factor 2
IGFBP-rPs	IGFBP-related proteins
IGFBPs	IGF binding proteins
IGFs	Insulin-like growth factors
IUGR	Intrauterine growth restriction

LDL	Low-density lipoprotein
LH	Luteinising hormone
MAP	Mitogen-activated protein
NGAS	Neonatal growth assessment score
NovH	Human nephroblastoma overexpression gene
PAPP-A	Pregnancy-associated plasma protein A
PGAS	Prenatal growth assessment score
PI3K	Phosphatidylinositol-3-kinase
PL	Placental lactogen
PLGF	Placental growth factor
PSF	Prostacyclin-stimulating factor
PSG	Pregnancy-specific β-glycoprotein
TAF	Tumour adhesion factor
TSC 1	Tuberous sclerosis protein 1
TSC 2	Tuberous sclerosis protein 2

1 Insulin-Like Growth Factor 1 (IGF-1)

1.1 Introduction

Insulin-like growth factor 1 (IGF-1) is an anabolic hormone produced in several tissues, specially in the liver (Laron 2001; Le Roith 1997). IGF-1 is synthesised by the endocrine growth hormone (GH) stimulation (Sara and Hall 1990). Although IGFs were first described by Salmon and Daughaday in 1957 (Salmon and Daughaday 1957), the discovery culminated two decades later, thanks to studies performed by Rinderknecht and Humbel (Rinderknecht and Humbel 1978a,b). Finally, all these findings allowed to identify a new family of proteins composed by proinsulin, IGF-1 and IGF-2 (Le Roith 1997).

IGF-1 shares >60% homology with IGF-2 and 50% homology with proinsulin structures (Le Roith 1997). Similar to proinsulin, both hormones, IGF-1 and IGF-2, are divided into A, B, C and D domains. A and B domains are similarly bridged by two inter-domain disulphide bonds and with one internal disulphide bond in the A domain. Both domains are connected by a C domain, which, unlike proinsulin, is not proteolytically cleaved during structural maturation. In IGF-1, positions 1 to 29 are homologous to insulin B chain and positions 42 to 62 are homologous to insulin A chain. The "connecting" peptide region (C domain) has 12 amino acids and shows no homology to proinsulin C peptide (Fig. 1). Such structural similarity to insulin explains the ability of IGF-1 to bind the insulin receptor (Laron 2001; Rinderknecht and Humbel 1978a). The primary difference between IGF-1 and IGF-2 resides in their biological activity. IGF-2 is expressed predominantly in early embryonic and foetal life and IGF-1 is expressed in the adult (Laron 2001; Rinderknecht and Humbel 1978a).

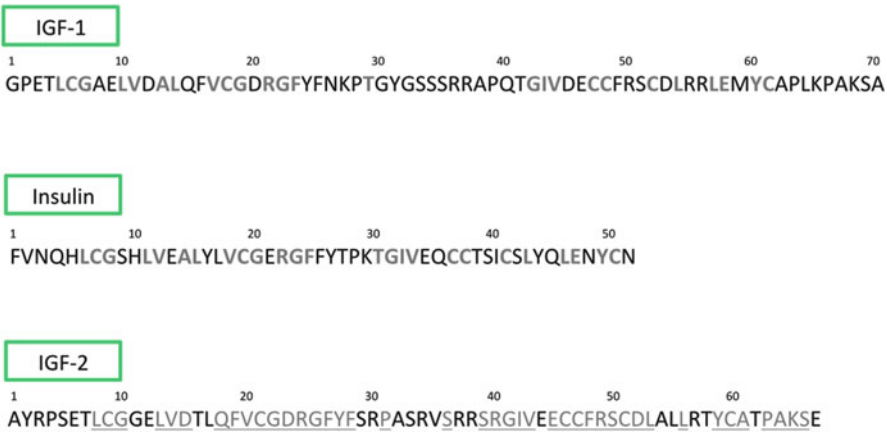

Fig. 1 Amino acid sequences of human IGF-1, IGF-2 and insulin. Homologous amino acids in IGF-1 (70 amino acids) and proinsulin and insulin (51 amino acids) are represented in *red*. Homologous amino acids in IGF-1 and IGF-2 (67 amino acids) are represented in *blue*

IGF-1, as a somatomedin, possesses insulin-like activity in the presence of insulin antibodies (Froesch et al. 1963; Zapf et al. 1978), and it is also a sulphation factor (Daughaday et al. 1972), is growth hormone dependent (Sara and Hall 1990; Daughaday et al. 1972) and acts as a mitogen (Zapf et al. 1978; Rinderknecht and Humbel 1976).

In the last decades, many evidences have provided us a wide list of IGF-1 activities, such as the following: proliferative, mitochondrial protection (Pérez et al. 2008), cell survival (Vincent and Feldman 2002), tissue growth and development (Powell-Braxton et al. 1993; Fowden and Forhead 2013), anti-inflammatory and antioxidant (García-Fernández et al. 2003, 2005), antifibrogenic (Muguerza et al. 2001) and antiaging (Puche et al. 2008; García-Fernández et al. 2008).

Because of its several physiological roles, IGF-1 activities must be strictly controlled by its association with six well-characterised binding proteins (IGFBPs 1 to 6) (Tables 1 and 2). These proteins have high affinity for IGF-1 and were identified, cloned and sequenced in the early 1990s (Jones and Clemmons 1995; Lamson et al. 1991), thanks to the development of the Western ligand blot techniques (Hossenlopp et al. 1986). IGFBPs share ≈35% sequence identity with each other, with apparent molecular mass of 24–45 kDa. They have a primary structure consisting of three different domains: the conserved N-terminal domain, the highly variable mid-region and the conserved C-terminal domain (Lamson et al. 1991; Hwa et al. 1999). The IGFBPs are produced by a variety of biological tissues and found in several biological fluids, such as follicular liquid, amniotic liquid, vitreous humour, lymph, plasma, seminal fluid, cerebrospinal fluid and gastrointestinal secretions (Rajaram et al. 1997; Binoux et al. 1991) (Tables 1 and 2). All these binding proteins are expressed by virtually all tissues, but the major source of serum IGFBPs is the liver. The IGFBPs function as carrier proteins for circulating IGFs, with higher affinity for them ($K_d \approx 10^{-10}$ M) than type I IGF receptors ($K_d \approx 10^{-8}$

Table 1 Characteristics of the IGFBP human superfamily. IGFBPs: high-affinity IGF binders

	Molecular mass (kDa)[a]	No. of amino acids[b]	IGF affinity	Modulation of IGF action	Source in biological fluids	Presence in placenta	References
IGFBP-1	25.3	234	1 = 2	Inhibition and/or potentiation	Amniotic fluid, serum, milk, urine, synovial fluid, interstitial fluid, seminal fluid, amniotic fluid	Labyrinth, uterine tissue, yolk sac placenta	Hills et al. (1996)
IGF BP-2	31.4	289	2 > 1	Inhibition	CSF, serum, milk, urine, synovial fluid, interstitial fluid, lymph follicular fluid, seminal fluid, amniotic fluid	Junctional zone, yolk sac placenta	Hills et al. (1996); Firth and Baxter (2002)
IGFBP-3	28.7	264	1 = 2	Inhibition and/or potentiation	Serum, follicular fluid, milk, urine, CSF, synovial fluid, interstitial fluid, seminal fluid, amniotic fluid	Junctional zone, uterine tissue	Hills et al. (1996); Firth and Baxter (2002)
IGF BP-4	26.0	237	1 = 2	Inhibition	Serum follicular fluid, seminal fluid, interstitial fluid, synovial fluid	Junctional zone, uterine tissue, yolk sac placenta	Hills et al. (1996)
IGFBP-5	28.6	252	2 > 1	Potentiation	Scrum, CSF	Junctional zone, uterine tissue	Hills et al. (1996); Firth and Baxter (2002)
IGF BP-6	22.8	216	2 > 1	Inhibition	CSF, serum, amniotic fluid	Uterine tissue	Hills et al. (1996); Firth and Baxter (2002)

High-affinity binder: involves greater intermolecular force between the ligand and its binder
CSF cerebrospinal fluid
[a]Predicted molecular mass (kDa) of nonglycosylated, mature protein
[b]Number of amino acids of mature protein

Table 2 Characteristics of the IGFBP human superfamily. IGFBP-rPs: low-affinity IGF binders

		Molecular mass (kDa)[a]	No. of amino acids[b]	Organ and/or tissue expression	References
IGFBP-7	IGFBP-rP1/Mac25	26.4	256	Leptomeninges	Bradham et al. (1991)
IGFBP-8	IGFBP-rP2/CTGF/CCN-2	35.5	323	Connective tissue, placenta	Myers et al. (2012); Hu et al. (1998)
IGFBP-9	IGFBP-rP3/NovH/CCN-3	36.0	329	Kidney	Holbourn et al. (2008)
IGFBP-10	IGFBP-rP4/Cyr61/CCN-1	39.5	358	Foetal and adult brain and liver; adult lung, kidney and thymus	Wang et al. (2012)
IGFBP-11	IGFBP-rP5/L56/HtrA	49.0	458	Osteoarthritic cartilage	Castilla-Cortázar et al. (2001)
IGFBP-12	IGFBP-rP6/ESM-1	18.1	165	Endothelial and epithelial cells, lung	Clemmons and Underwood (1991)
IGFBP-13	IGFBP-rP7/WISP-2/CCN-5	24.4	228	Smooth muscle, bone, uteri	Chitnis et al. (2008)
IGFBP-14	IGFBP-rP8/WISP-1/CCN-4	38.0	345	Heart, lung, smooth muscle, bone	Puche and Castilla-Cortázar (2012)
IGFBP-15	IGFBP-rP9/WISP-3/CCN-6	37.1	334	Cartilage, breast epithelium	Duan et al. (2000)

Low-affinity binder: involves less intermodular force between the ligand and its binder
[a]Predicted molecular mass (kDa) of nonglycosylated, mature protein
[b]Number of amino acids of mature protein

to 10^{-9} M), and by regulating IGF turnover, transport and tissue distribution, thus determining physiological concentrations of IGFs (Jones and Clemmons 1995; Hwa et al. 1999). For example, during normal pregnancies serum levels of IGF-1 and IGFBPs (mainly IGFBP-1) rise progressively through gestation, especially since the second trimester of pregnancy. An elevated level of IGFBP-1 in the foetal circulation is an indicator of IUGR, caused by placental insufficiency and utero hypoxia. Such binding protein is believed to restrict foetal growth by sequestering IGFs (Hills et al. 1996). Additionally they modulate IGF activities in target tissues, such as cell proliferation, differentiation, survival and migration (Jones and Clemmons 1995; Firth and Baxter 2002), being able to activate or inhibit IGF actions. Also they facilitate transport of IGFs from the vascular space to target tissues. Most IGFs in circulation are found forming complexes with IGFBPs,

especially in a ternary complex with IGFBP-3 and ALS (acid-labile subunit). The aforementioned complex serves as a reservoir for IGF and also increases the half-life of IGF-1 (Rajaram et al. 1997). In addition, IGFBPs can be associated with cell membranes or extracellular matrix, allowing them to maintain a local pool of IGF-1 (Firth and Baxter 2002).

Interestingly, another nine binding proteins arose as the so-called IGFBP-related proteins (IGFBP-rPs), which are cysteine-rich proteins with structural and functional similarities to the IGFBPs (Hwa et al. 1999). At present, there are four proteins/families that are related to the IGFBPs (Tables 1 and 2). Mac25 was originally identified as a cDNA derived from leptomeninges (Murphy et al. 1993) and was subsequently expressed in a baculovirus system. The synthesised protein was shown to bind IGFs and was renamed IGFBP-7 (Oh et al. 1996). Its expression is regulated by specific growth factors and IGFs, and it is involved in diverse biological functions, such as regulation of epithelial cell growth, stimulation of fibroblast cell growth and stimulation of prostacyclin production in endothelial cells (Hwa et al. 1999). The CCN family consists of several proteins, and it acquired its name from the first three proteins discovered: Cyr61 (cysteine-rich protein 61) (Saglam et al. 2014), connective tissue growth factor (CTGF) (Bradham et al. 1991) and the human nephroblastoma overexpression gene (NovH) (Burren et al. 1999). CTGF major function is to regulate the formation of connective tissue. This protein is also important in both physiological (tissue homeostasis) and pathological (fibrosis) conditions (Nguyen et al. 2008). Three new members of this family have been identified in Wnt-1 transformed cells: WISP-1 (Wang et al. 2012); WISP-2, which was designated CTGF-like because it was identified in primary human osteoblast cells (Myers et al. 2012); and WISP-3 (Baker et al. 2012). The CCN proteins are key signalling and regulatory molecules involved in several vital biological functions, including cell proliferation, angiogenesis, tumourigenesis and wound healing (Holbourn et al. 2008). Two other IGFBP-related proteins are L56, a potential serine protease of IGFBPs, also named HtrA (Hu et al. 1998), and endothelial cell-specific molecule (ESM-1) (Lassalle et al. 1996). The physiological role of the IGFBP-rPs in the IGF system remains undefined, but their structural relationship with IGFBP-1 to IGFBP-6 reveals the ability of some of these proteins to bind IGF-1, modulating its activity (Oh et al. 1996; Burren et al. 1999).

On the other hand, the majority of IGF-1 actions are mediated through the union of IGF-1 to its putative receptor, IGF-1R, a tyrosine kinase with an $\alpha_2\beta_2$ heterotetrameric structure that is one of the most potent natural activators of Akt pathway, closely related with cell survival, growth and proliferation (Puche and Castilla-Cortázar 2012; Annenkov 2009; Chitnis et al. 2008). Ligand binding induces phosphorylation of tyrosine residues in the intracellular domains of the β-subunits and activate the receptor. The activated IGF-1R in turn activates multiple signal transduction cascades, including the mitogen-activated protein (MAP) kinase pathway and phosphatidylinositol-3-kinase (PI3K)–Akt pathway (Duan et al. 2000). The IGF-activated pathways promote cell survival through regulation of multiple effectors (BCL-2, BAD, caspase-9, p53, etc.), cell proliferation, migration and/or differentiation (Jones and Clemmons 1995) (Fig. 2).

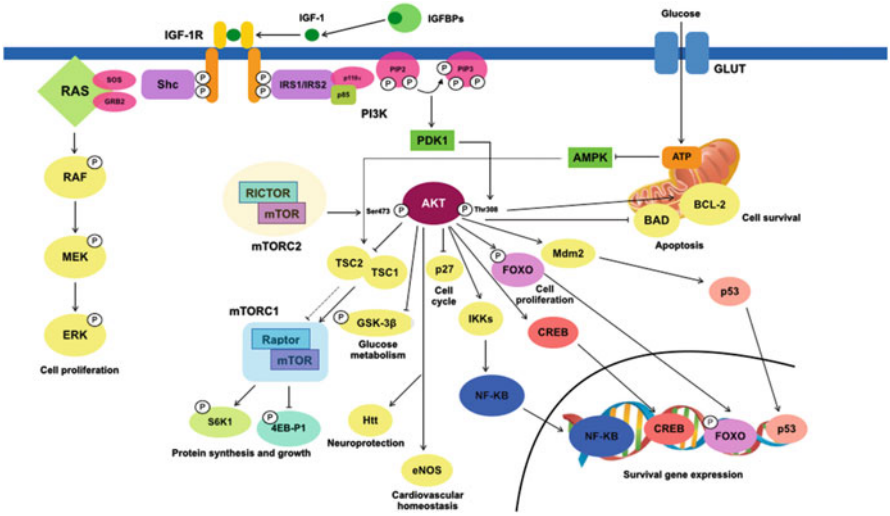

Fig. 2 The IGF-1 signalling pathway. IGF binding proteins (IGFBPs) modulate IGF-1 bioavailability. IGF-1 functions as a ligand to interact with IGF-1 receptor (IGF-1R) in the cellular membrane, which leads to autophosphorylation and recruitment of the adaptor proteins IRS-1, IRS-2 and Shc. The interaction of IRS-1 and IRS-2 with IGF-1R induces the activation of PI_3-kinase (phosphatidylinositol-3-kinase), which transforms PIP_2 in PIP_3. Akt family of kinases is activated by PDK1 and by mTOR-containing complex mTORC2 and regulates downstream signalling molecules such as TSC1 and 2 (tuberous sclerosis protein 1 and 2) and FOXO transcription factors, GSK-3β, p27, BAD and BCL-2. All these molecules are involved in several cellular processes including protein synthesis, cell proliferation, glucose metabolism, cell cycle and cell survival. In parallel, Shc activation induces the activation of the RAS/MAP kinase pathway, which increases cell proliferation. Low glucose levels activate AMPK, which activates TSC2 and inhibits mTORC1 action (*discontinue lines*)

In addition, the similarity in structure of IGF-1R and insulin receptor (≈60%) (Nissley and Lopaczynski 1991) explains that IGF-1 can also bind to the insulin receptor but with lower affinity. Ligand binding can be a secondary pathway by which IGF-1 mediates some of its metabolic functions (Rinderknecht and Humbel 1978a). Similarly, insulin can bind to the IGF-1R with a lower affinity than it does to the insulin receptor.

1.2 Physiological Activities of IGF-1

IGF-1 is an important hormone in embryological and postnatal states. Although it is mainly produced by the liver (approximately 75% of circulating IGF-1 is produced by this organ) (Ohlsson et al. 2009), virtually every tissue is able to secrete IGF-1 for autocrine and/or paracrine purposes.

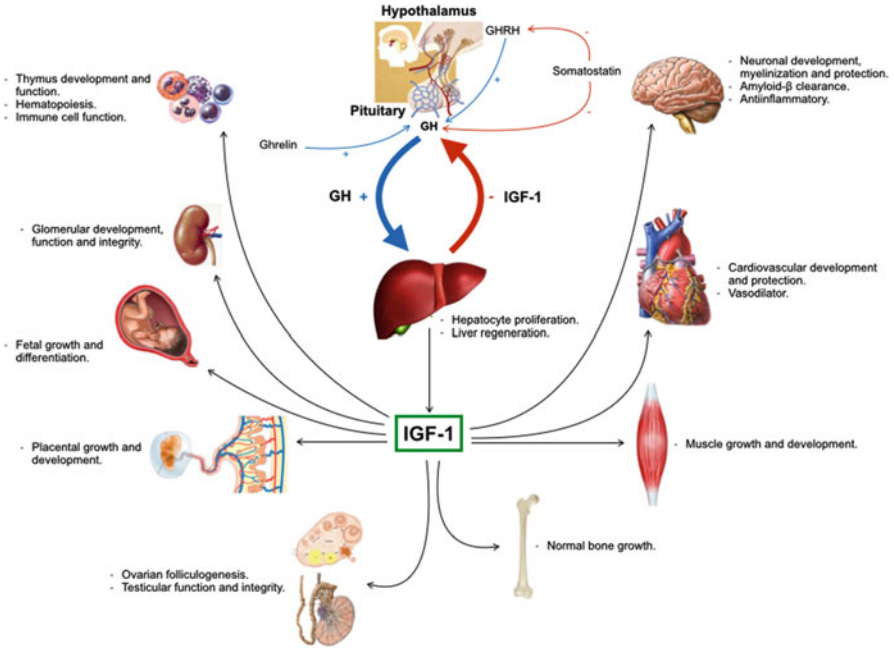

Fig. 3 Model of GH/IGF-1 axis and its target organs. Negative feedback mechanism induced by IGF-1 regulates GH/IGF-1 axis: IGF-1 inhibits GH gene expression by stimulating somatostatin secretion. GHRH (growth hormone-releasing hormone) stimulates GH secretion, which stimulates IGF-1 secretion

The secretion of IGF-1 is stimulated by growth hormone (GH), forming the GH/IGF-1 axis, where GH secretion is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin (Puche and Castilla-Cortázar 2012) (Fig. 3). Both hormones are generated in the hypothalamus as a result of neurogenic, metabolic and hormonal factors. This GH/IGF-1 axis is regulated by negative feedback mechanisms induced by IGF-1 itself: IGF-1 can inhibit GH gene expression by stimulating the secretion of somatostatin (Bertherat et al. 1995), which inhibits GH secretion. In various diseases, such as liver cirrhosis, this axis is altered: low IGF-1 serum levels and high GH levels, with the concomitant reduced somatostatinergic tone. Such disruption is reverted by the exogenous administration of IGF-1 at low doses (Castilla-Cortázar et al. 2001).

Circulating GH exist in both free and bound states by the GHBP (growth hormone binding protein – the secondary domain of the GH receptor). Hepatic GH receptor activation induces IGF-1 production, which is released in the circulation, where it is found in its free form (<1% bioactive component) and bound to IGFBPs. IGF-1 is specially bound to IGFBP-3, which binds ≈90% of the circulating hormone, increasing its half-life (Ohlsson et al. 2009).

In physiological conditions, IGF-1 activities are still being investigated, and it is being recognised as a GH-independent peptide. For example, it is known that GH and nutrition are the major factors that regulate hepatic IGF-1 expression, as well as in other organs (Clemmons and Underwood 1991). However, in some other tissues, IGF-1 expression appears to be regulated by tissue-specific trophic factors. For example, in uterus, oestrogens stimulate IGF-1 expression instead of the GH (Murphy and Friesen 1988).

IGF-1 has a wide variety of effects, but essentially, these can be divided into acute metabolic effects and long-term growth-promoting effects (Juul 2003). The acute actions of IGF-1 overlap with those of insulin on carbohydrate and protein metabolism to promote energy storage, including the stimulation of amino acid uptake into skeletal muscle, as well as the peripheral glucose uptake and regulation of insulin secretion and sensitivity (Juul 2003). On the other hand, its long-term effects are on cell proliferation, differentiation and anti-apoptosis (Jones and Clemmons 1995; Yu and Rohan 2000). Hence, IGF-1 plays a major and important role in several target organs (Fig. 3), as further described.

In the brain, IGF-1 is a potent neurotrophic and neuroprotective factor, promoting neuronal proliferation, survival and development (Gómez 2008), and it could be involved in the modulation of blood–brain barrier permeability (Carson et al. 1993). It is also one of the main factors regulating the clearance of brain amyloid-β levels with implications in Alzheimer's disease (Carro et al. 2002).

The liver is the main source of circulating IGF-1 (Ohlsson et al. 2009) and there is few data regarding local effects of this hormone in this organ (Skrtic et al. 1997). Nevertheless, it has been demonstrated that IGF-1 support hepatocyte proliferation and accelerate DNA synthesis, promoting liver regeneration (Desbois-Mouthon et al. 2006).

IGF-1 is also needed for an optimal fecundity during the reproductive period (Livingstone 2013). It increases granulose cell proliferation, steroidogenesis (Villalpando and López-Olmos 2003) and oocyte growth in most mammalian species (Silva et al. 2009; Giudice 1992; Giudice and Saleh 1995). And it also has a role on sperm number, as seen in IGF-1-deficient mice (Baker et al. 1996).

Moreover, IGF-1 has physiological roles in maintaining the normal function of the immune system, such as T lymphocytes development and function (Walsh et al. 2002), thymus development (Hadden et al. 1992) and B-cell differentiation (Landreth et al. 1992). IGF-1 regulates renal function (Bach 2012) and maintains glomerular integrity (Martin et al. 1991; Hirschberg 1996) and plays an important role in cardiovascular development and protection (Delafontaine et al. 2004), acting as a potent vasodilator (Delafontaine et al. 2004). It also controls muscle growth and development (Schiaffino and Mammucari 2011), stimulates protein synthesis in skeletal muscle (Velloso 2008), is essential for the attainment of peak bone mass during puberty, is necessary for normal bone growth (Yakar et al. 2010; Tahimic et al. 2013; Guntur and Rosen 2013) and plays a central role during muscle regeneration (Florini et al. 1996).

1.3 Role of IGF-1 During Pregnancy

Gestation can be divided into three well-defined periods. During the first period (pre-differentiation period), fertilisation, segmentation and gastrulation occur (Valsamakis et al. 2006). Once the gastrula is formed, the embryonic period begins, where proliferation and embryonic organogenesis occur. In this period, the embryo is more susceptible to damage, caused by external agents, such as alcohol, drugs, medicine, X-rays, radiation, etc. (Valsamakis et al. 2006). In the last period (foetal period), foetal organs develop both functionally and anatomically, leading to continuous foetal growth (Valsamakis et al. 2006).

All this process involves endocrine and metabolic changes in maternal pituitary gland and placental secretion (Kumar and Magon 2012). After involution of ovarian sex steroid production by the 6th week, placental oestrogen and progesterone production by the *corpus luteum* increases exponentially to term. Progesterone is important in suppressing the maternal immunologic response to foetal antigens, preparing and maintaining the endometrium to allow implantation of the embryo. Between the 8th and 10th weeks of gestation, placental production of chorionic gonadotropin (CG) rescues the *corpus luteum* from involution and maintains progesterone secretion (Kumar and Magon 2012; Freemark 2010).

During mid-gestation (13th to 28th weeks), there is a progressive increase in prolactin, secreted by the maternal pituitary gland, and placental growth hormone (pGH) levels. Several studies had found low maternal serum levels of both hormones in pregnancies associated to intrauterine growth retardation (Kumar and Magon 2012; Freemark 2010). During this period, placental lactogen (PL) is necessary for a normal production of progesterone, as seen in diverse mice strain models. Additionally, PL is responsible for the marked rise in maternal plasma IGF-1 concentration as the pregnancy approaches term (Kumar and Magon 2012).

Insulin is also an important factor for foetal metabolism, because it stimulates glucose and amino acid cellular capitation, necessary for tissue growth. Insulin deficiency in the uterus may lead to IUGR (Fowden and Forhead 2013). Inside the insulin family, IGF-1 and IGF-2 regulate cell cycle, proliferation and differentiation. Both hormones control transport capacity of the placenta and mediate stimulatory actions of insulin and thyroid hormones (Fowden and Forhead 2013). In the prenatal period, differences between GH and IGF-1 are clearly shown. During gestation, IGF-1 production is stimulated by placental GH. GH insensitivity, both in humans and in transgenic mice, has only mild retardation of growth at birth (Jameson 1999), whereas IGF-1 deficiency in gestational state reveals serious postnatal growth retardation, as has been reported both in humans and in transgenic animal models with IGF-1 gene deletion (Lupu et al. 2001; Baker et al. 1993; Liu et al. 1993; Woods et al. 1996). Interestingly, in contrast to growth hormone insensitivity, IGF-1-deficient animals are neurologically impaired, as was also reported in a single patient with a defect in the IGF-1 gene (Woods et al. 1996). Accordingly, all these data suggest that IGF-1 is necessary for normal brain development in the uterus (Randhawa and Cohen 2005).

Therefore, IGF-1 has a major role in foetal and placental growth and differentiation (Cohick and Clemmons 1993; Hiden et al. 2009; Forbes and Westwood 2010), being a major regulator of intrauterine and normal body growth (Lupu et al. 2001; Baker et al. 1993; Woods et al. 1996). IGF-1 enhances protein synthesis and inhibits proteolysis, having a key role in growth regulation both embryonically and postnatally (Fryburg et al. 1995; Clemmons 2009). It is essential for the attainment of normal body size during foetal development. Additionally, IGF-2 plays a key role in placental growth (Rajaram et al. 1997; Sferruzzi-Perri et al. 2006).

1.3.1 The Placenta as an IGF-1 Target Organ

The placenta is an intrauterine organ with central functions in pregnancy: it supplies nutrients and oxygen to the foetus and produces a range of hormones and growth factors that may affect mother, foetus or both (Hiden et al. 2009; Murphy et al. 2006). Moreover, hormones and growth factors present in maternal and foetal circulation may regulate foetal growth and placental development (Murphy et al. 2006).

Besides insulin, IGF-1 and IGF-2, several hormones (summarised in Table 3) are produced by the placenta during pregnancy, which are involved in the regulation of both foetal and placental development and growth (Hiden et al. 2009; Murphy et al. 2006). In addition to the aforementioned hormones, IGFBPs also participate in the regulation of both placental and foetal development and growth. The placenta has the ability to differentially express these proteins (Table 4). IGFBP-1 is the predominant binding protein synthesised by the placenta. It is expressed predominantly in trophoblast and decidua, where it regulates the biological activity of IGFs by modulating their interaction with IGF-1 receptor (Jones and Clemmons 1995; Rajaram et al. 1997; Gibson et al. 2001; Chard 1994; Crossey et al. 2002; Clemmons 1997; Lee et al. 1993). The other binding proteins (IGFBP-2, 3, 4, 5 and 6) are only expressed in some cells where they regulate placental development (Jones and Clemmons 1995; Rajaram et al. 1997; Clemmons 1997; Carter et al. 2006). In growth-restricted foetuses, serum and umbilical cord levels of IGFBP-1 and IGFBP-2 are increased compared to normal foetuses (Crossey et al. 2002; Street et al. 2006; Tzschoppe et al. 2015).

IGFs and insulin actions are mediated through binding to their receptors, which are expressed on distinct placental surfaces. Their expression varies with gestational age (Table 5). For example, cytotrophoblast and syncytiotrophoblast express receptors for progesterone. Such hormone is implicated in embryogenesis (Ziyan et al. 2010; Shanker and Rao 1999; Zachariades et al. 2012). These two areas of the placenta also express receptors for GnRH, which has a key role in implantation of the zygote and in endometrial, placental and foetal development (Fowden and Forhead 2013; Wolfahrt et al. 1998). They also express receptors for LH, CG and oestrogens such as oestradiol, important hormones in the development and maintenance of reproductive tissues (McCormack and Glasser 1978). Other regions of

Table 3 Placental hormones and its expression during pregnancy

Hormone	Expression in placenta	Period of gestation	Function	References
CG	Trophectoderm	Preimplantation embryo	Quality of placentation	Muyan and Boime (1997)
	Syncytiotrophoblast	1st to 12th weeks	Corpus luteum maintenance	
			Regulation of foetal testicular testosterone secretion	
PL	Syncytiotrophoblast	13th to 28th weeks	Stimulation of food intake	Handwerger and Freemark (2000)
			Regulation of growth and development	
Leptin	Syncytiotrophoblast, cytotrophoblast	1st to 40th weeks	Mother: accumulation of body fat	Ashworth et al. (2000)
			Foetus: mediate insulin's anabolic actions	
CRH	Syncytiotrophoblast, amnion, musculature of umbilical vessels, maternal decidua	Late pregnancy	Promote labour and initiation of parturition	Grammatopoulos (2008); Karteris et al. (2001)
			Vasodilation of placental vessels	
			Accelerate pulmonary maturation	
Neuropeptide Y	Cytotrophoblast	Early pregnancy until term	Stimulation of CRH from placental cells	Petraglia et al. (1989)
		Decreases after delivery	Contributes to uterine contractility	
Inhibin	Syncytiotrophoblast, cytotrophoblast	Increases during pregnancy	Control of steroidogenesis, peptide hormone and prostaglandin secretion	Petraglia (1997); Riley et al. (2000)
			Inhibition of FSH secretion	
Activin	Syncytiotrophoblast, cytotrophoblast	At term, labour	Stimulation of prostaglandins, oxytocin and FSH secretion	Petraglia (1997); Rabinovici et al. (1992)
			Modulation of cytotrophoblast proliferation and differentiation	

(continued)

Table 3 (continued)

Hormone	Expression in placenta	Period of gestation	Function	References
PSG	Syncytiotrophoblast, spongiotrophoblast	Preimplantation embryo	Prevents rejection of the foetus	Wu et al. (1999); Wynne et al. (2006)
PAPP-A	Syncytiotrophoblast, maternal decidua	Increases during pregnancy	Is the IGFBP-4 protease: increases IGF bioavailability	Lawrence et al. (1999); Sun et al. (2002)
PLGF	Trophoblast	During pregnancy	Stimulation of proliferation, migration and activation of endothelial cells	Vuorela et al. (1997)
		Increases in early stages of pregnancy	Coordinate vascularisation in the decidua and placenta	
Placental GH	Syncytiotrophoblast	13th to 28th weeks	Insulin resistance of pregnancy	Lacroix et al. (2002)
			Regulator of IGF-1	
Progesterone	Syncytiotrophoblast	6th to 8th weeks	Uterine quiescence	Shanker and Rao (1999); Freemark (2006); Iliodromiti et al. (2012)
		Increases during pregnancy and labour	Stimulation of weight gain and fat deposition	
Oestrogen	Placenta?	6th to 8th weeks	Initiation of labour	Freemark (2006); Kaludjerovic and Ward (2012); Albrecht and Pepe (2010)
			Biosynthesis of progesterone	
			Foetal adrenal maturation	
IGF-1	Syncytiotrophoblast	During pregnancy	Steroidogenesis	Hiden et al. (2009)
			Glucose and amino acid uptake	
			Foetal and placental growth, differentiation and development	
IGF-2	Trophoblast	1st to 12th weeks	Facilitates trophoblast invasion into the maternal decidua	Hiden et al. (2009)
			Key role in placental growth	

The question mark indicates that oestrogen placental expression is not yet well defined
CG chorionic gonadotropin, *PL* placental lactogen, *CRH* corticotropin-releasing hormone, PSG pregnancy-specific β-glycoproteins, *PAPP-A* pregnancy-associated plasma protein A, *PLGF* placental growth factor, *IGF-1* insulin-like growth factor-1, *IGF-2* insulin-like growth factor-2
Trimesters of pregnancy are described in weeks: 1st trimester, 1st to 12th weeks; 2nd trimester, 13th to 28th weeks; 3rd trimester, 29th to 40th weeks

Table 4 IGFBP expression in mouse placenta

Placenta	IGFBP-1	ICFRP-2	IGFBP-3	IGFBP-4	IGFBP-5	IGFBP-6
Labyrinth						
Trophoblast	✓		✓			
Syncytiotrophoblast		✓				
Junctional zone						
Spongiotrophoblast		✓				
Glycogen cells		✓				
Chorionic mesoderm				✓	✓	
Uterine tissue						
Decidua	✓		✓		✓	✓
Metrial gland stroma		✓			✓	✓
Maternal vessel endothelium			✓	✓	✓	
Stromal cells	✓					
Myometrium		✓		✓	✓	✓
Yolk sac placenta						
Endoderm	✓	✓				
Mesoderm				✓		
Blood vessels						
Amnion						
Function	Inhibits IGF action	Inhibits IGF action	Major carrier of IGFs in serum	Inhibits IGF action	Potentiates IGF-1 action	Inhibits IGF action
	Stimulates smooth muscle cell migration		Reduces its affinity for IGF-1		Stimulatory effect on a variety of cell types	Inhibits IGF-2 actions preferentially
			Stimulates proliferation		Fix IGFs to extracellular matrices (bone)	

Table 5 Hormone receptor expression in placenta

Placental tissue	Hormone receptor expression
Syncytiotrophoblast	Insulin (1st trimester)
	IGF-1 (1st trimester and term)
	IGF-2 (term)
	Progesterone
	GnRH
	LH
	CG
	Oestrogens
Cytotrophoblast	Progesterone
	GnRH
	LH
	CG
	Oestrogens
Trophoblast	IGF-1 (end of gestation)
	GH
	Thyroid hormones
	PL
	CRH
Myometrium	GH
	Thyroid hormones
	PL
	CRH
Placental endothelium	Insulin (term)

the placenta, such as villous and extravillous trophoblast, also express receptors for GH, an important hormone in the physiological adjustment of gestation and control of maternal IGF-1 levels (Lacroix et al. 2002). These regions also express receptors for thyroid hormones, PL and CRH. Such hormones, respectively, regulate oxidative metabolism and energy available for gestation (Fowden and Forhead 2013; Leonard et al. 2001) and are necessary for normal production of progesterone during pregnancy (Hill et al. 1988; Freemark and Comer 1989).

Insulin receptors are expressed on the microvillous membrane of the syncytiotrophoblast in the first trimester of pregnancy, directed to the maternal circulation and, hence, maternal insulin. These receptors, at term, are mainly expressed on the placental endothelium directed to the foetal blood (Hiden et al. 2009). Insulin receptor expression suggests that, in the first trimester of pregnancy, maternal insulin regulates insulin-dependent processes, whereas, at term, it must be foetal insulin, the one that mainly controls these processes (Desoye et al. 1997). However, the IGF-1Rs are expressed in almost all placental tissues in the first trimester of pregnancy and at term (Fang et al. 1997). Nevertheless, IGF-1R expression is higher in the trophoblast than in endothelial cells at the end of gestation (Hiden et al. 2009; Abu-Amero et al. 1998). Such expression suggests that both maternal and foetal IGF-1 will affect the trophoblast compartment. Both hormones act as an

autocrine/paracrine factor in regulating early placental growth and function (Abu-Amero et al. 1998; Maruo et al. 1995). IGF-2 receptors are expressed in trophoblast and syncytiotrophoblast in first trimester of pregnancy and at term, respectively (Fang et al. 1997; Abu-Amero et al. 1998; Harris et al. 2011; McKinnon et al. 2001). Additionally, insulin and IGF-1 receptors are also expressed in resident macrophages and endothelial cells (Hiden et al. 2009). Therefore, dysregulation of insulin and IGFs may have important effects on placenta and foetus (Hiden et al. 2009), resulting in placental insufficiency and inadequate substrate supply to the developing foetus. These effects could lead to the appearance of intrauterine growth restriction (IUGR) (De Vrijer et al. 2006).

1.4 IGF-1-Deficient Conditions in Humans

As mentioned before, IGF-1 possesses a wide number of own properties (anabolic, antioxidant, anti-inflammatory and cytoprotective actions). Actually, the best-characterised conditions of IGF-1 are Laron's syndrome in children; liver cirrhosis in adults; aging, including age-related cardiovascular and neurological diseases; and, as discussed in this review, intrauterine growth restriction (IUGR).

Laron's syndrome or primary growth hormone insensitivity (GHI) was first described in 1966 by Zvi Laron et al., as a new type of dwarfism indistinguishable from genetic isolated GH deficiency. Such syndrome is characterised with unexpected high serum GH levels and the inability to synthesise IGF-1 and its binding proteins (Jameson 1999; Laron et al. 1966). Laron's syndrome was the first condition of IGF-1 described. Epidemiologically, this syndrome is closely related to an ethnic origin (>90% of cases). Clinically, patients with Laron's syndrome have growth abnormalities in uterus and in childhood; osteopenia; retardation in the maturation of dentition, organs and tissues; and a puberty delay, among other clinical manifestations (Rosenbloom 1999; Laron 1984). Animal models of GHI are available since 1997 and help us to better understand the pathophysiological changes and possible therapeutic strategies for these patients (Zhou et al. 1997).

Cirrhosis, a chronic liver disease, is characterised by low serum levels of IGF-1 and the presence of liver fibrosis, necrosis and regenerative nodules, leading to a loss of functional liver mass. The main causes are alcoholism, hepatitis B and C and fatty liver disease (Conchillo et al. 2007). Liver cirrhosis has been considered a condition of IGF-1 deficiency during adulthood, and IGF-1 has been proposed as a good indicator for functional hepatocellular capability (Caufriez et al. 1991). Nowadays, several animal models of experimental liver cirrhosis have been developed in order to better elucidate the role of IGF-1 in this pathology (García-Fernández et al. 2003; Muguerza et al. 2001; Castilla-Cortazar et al. 1997; Cemborain et al. 1998; Castilla-Cortázar et al. 2011).

Aging is a progressive, irreversible, universal and heterogeneous process of involution, characterised by a gradual loss of physiological functions that increases the probability of death. The circulating GH and IGF-1 levels progressively decline

with age (Perry 1999). Reduced GH/IGF-1 secretion in the elderly is responsible for several symptoms of aging, such as loss of muscle mass, increased adiposity, reduced bone mineral density and lower energy levels (Puche and Castilla-Cortázar 2012). Several pathologies, such as cardiovascular diseases, metabolic syndrome and neurodegenerative diseases, are correlated with aging and low circulating levels of IGF-1. Our group has demonstrated that low doses of IGF-1 restored circulating IGF-1 levels. IGF-1 replacement therapy improves insulin resistance, lipid metabolism and mitochondrial protection in aging rats (Puche et al. 2008; García-Fernández et al. 2008). Thus, IGF-1 could become a potential beneficial therapeutic strategy by improving mitochondrial function, decreasing oxidative stress and preventing insulin resistance-related pathologies. Data from transgenic mice with liver-derived IGF-1 deficiency explains the possible role of IGF-1 in vasoprotection, cardioprotection, insulin resistance, angiogenesis and neurogenesis (Puche and Castilla-Cortázar 2012).

2 Intrauterine Growth Restriction (IUGR)

2.1 Introduction

Foetal growth is a complex process involving maternal, placental and foetal factors from genetic, environmental and nutritional nature. Intrauterine growth restriction (IUGR) is an important obstetric issue defined as the inability to achieve the expected weight for gestational age (Collins et al. 2013). To define this pathology, it is really important to establish standardised curves of birth weight during foetal period and at term (Fig. 4) (Gómez-Gómez 2012). Growth-restricted foetuses/newborns are those born below the 10th percentile (weighing less than 2,500 g) according to each population (Goldenberg and Cliver 1997) and those who have an abdominal circumference less than 2.5th percentile (Valsamakis et al. 2006; Sferruzzi-Perri et al. 2006; Maulik 2006). IUGR is associated to perinatal mortality and morbidity (Kramer et al. 1990). Thereby, growth-restricted foetuses/newborns are characterised by an increased risk of clinical disorders in adult life, such as cardiovascular disease, diabetes and obesity (Hattersley and Tooke 1999; Bamfo and Odibo 2011).

There are two types of IUGR: symmetric intrauterine growth restriction, where all body parts of the baby are similarly small, and asymmetric intrauterine growth restriction, where baby's head and brain are normal, but the remaining parts of the body are smaller (Valsamakis et al. 2006).

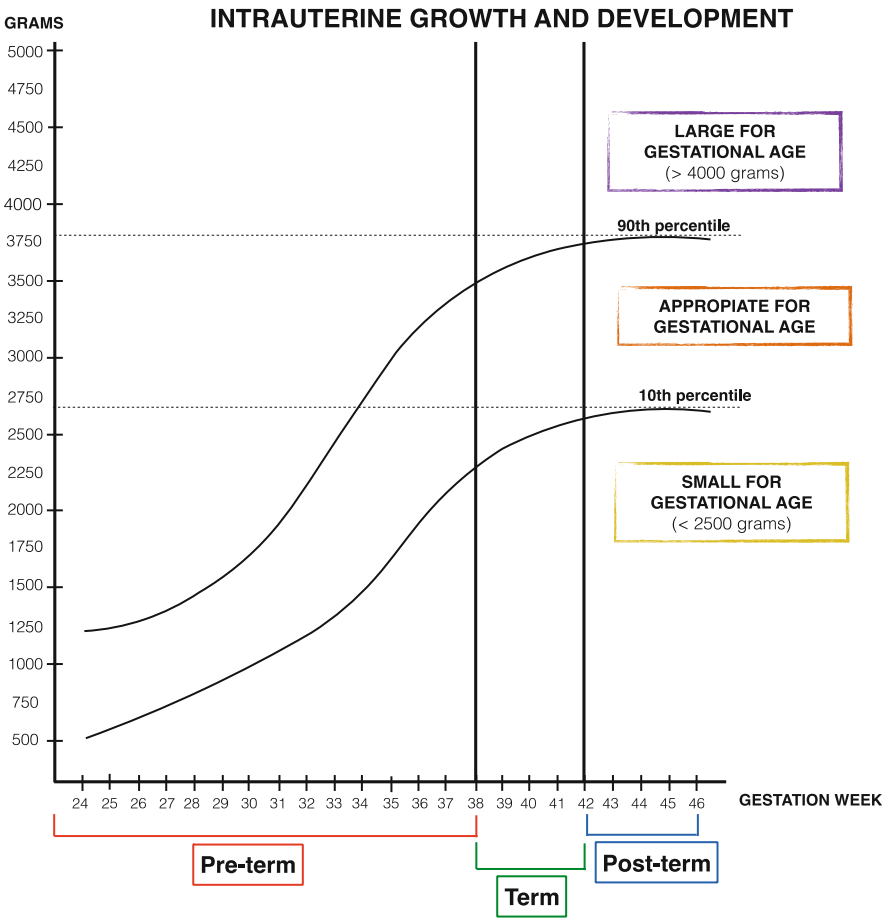

Fig. 4 Percentile curve to sort out newborns according to their weight for gestational age. Preterm babies born between 28th and 37th weeks of gestation. Term babies born between 37th and 42nd weeks of gestation. Post-term newborns born after 42nd week of gestation

2.2 Epidemiology

IUGR incidence varies according to the discrimination criteria adopted (Romo et al. 2009), but approximately 5–10% of newborns worldwide have intrauterine growth restriction (Resnik 2002). Moreover, it has been estimated that ≈20 million infants are born with low birth weight (<2,500 g) every year (WHO 2004; De Onis et al. 1998). There is a high variability depending on the geographic zone: in underdeveloped countries, IUGR affects ≈30% of pregnancies (Saleem et al. 2011), while in developed countries, it only affects ≈5% of pregnancies (Zepeda-Monreal et al. 2012; Baschat 2004; Hay et al. 2001). This variability could

Table 6 Worldwide distribution and prevalence of small for gestational age infants (shaded regions show the highest rate of small for gestational age infants)

Region		Prevalence (%)
Asia	Caucasus and Central Asia	12.9
	East Asia	5.3
	Southeast Asia	21.2
	South Asia	41.5
	West Asia	19.6
Oceania	Oceania	19.4
Africa	North Africa	8.5
	Sub-Saharan Africa	23.5
America	Latin America and the Caribbean	10.7
	Northern America	7.7
Europe	Eastern Europe	6.4
	Northern Europe	6.5
	Southern Europe	5.9
	Western Europe	6.7

be due to the higher prevalence of malnutrition and underweight at the beginning of gestation in the underdeveloped countries. In some studies, it was observed that the vast majority of small for gestational age (≈87%) and low-birth-weight babies (≈26%) were born in south Asia, southeast Asia and sub-Saharan Africa (Lee et al. 2013; Adair 1989; Isaranurug et al. 2007; Victora and Barros 2006; Victora et al. 2008; Santos et al. 2011; Gonzalez et al. 2006; Shah et al. 2008; Schmiegelow et al. 2012) (Table 6).

2.3 Physiopathology

IUGR has a multifactorial aetiology and is hard to define a specific cause. It is known that the pathology onset is due to factors of maternal, foetal and placental origin and an increase in oxidative stress (Bamfo and Odibo 2011). Moreover, different risk factors before and/or during pregnancy, as well as environmental and behavioural features, play a role in the development of the disease (Bamfo and Odibo 2011).

2.3.1 Maternal Factors

Maternal factors such as severe maternal malnutrition and underweight at the beginning of gestation and low weight gain during the gestation could be causes that promote IUGR (Mitchell et al. 2004). In addition, maternal characteristics such as age, height, nulliparity and multiparity and toxic habits (smoking, alcohol and

drug consumption, use of certain medicines, maternal stress) can increase the risk of IUGR. Alcohol crosses the placenta and could affect directly to foetal cell and tissue development and also can induce changes in mother–foetus hormonal interaction. Such changes can reschedule hypothalamus–pituitary–adrenal gland axis (HPA), leading to immunological, behavioural and cognitive deficits in the foetus (Zhang et al. 2005). The HPA axis has a key role in the implantation of the zygote and in endometrial, placental and foetal development, because it secretes several hormones such as GnRH (gonadotropin-releasing hormone), FSH (follicle-stimulating hormone) and LH (luteinising hormone) (Miller and Takahashi 2014).

Likewise, chronic maternal stress compromises normal regulation of hormonal activity during gestation, because it increases β-endorphin, glucocorticoids, catecholamines and CRH (corticotropin-releasing hormone) levels. An excess of the aforementioned hormones, in addition to an increase in cortisol levels, breaks through the placenta and can reduce foetal weight at birth. Catecholamines can also induce vasoconstriction of blood vessels causing placental hypoxia in the foetus. Hypoxia can activate HPA axis leading to an abnormal implantation of the zygote and an abnormal endometrial and placental development (Valsamakis et al. 2006; Weinstock 2005). Foetal responses to placental hypoxia include downregulation of insulin, IGF-1 and IGF-2 and increased expression of inhibitory IGFBPs (Han and Carter 2001), all of these leading to IUGR. Other risk factors that affect foetal growth could be inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematous and periodontal disease, as well as maternal vascular disease and thrombophilia. Such factors could lead to uteroplacental hypoperfusion, thus compromising foetal growth (Murphy et al. 2006; Bamfo and Odibo 2011).

Another important factor could be an increase of maternal oxidative stress. In studies with pregnant-IUGR women, an increase in oxidative stress has been observed (Biri et al. 2007). Also, these women are more susceptible to LDL (low-density lipoprotein) oxidation. LDL oxidation can lead to placental dysfunction and foetal growth retardation, as it decreases nutrient supply to the foetus (Sánchez-Vera et al. 2005). In the same way, it has been observed that in normal pregnancies, vitamin E levels (important for normal physiological function, because of its antioxidant actions) and prostacyclin levels (which have a vasodilatation action) increase progressively throughout pregnancy. On the other hand, thromboxane levels (implicated in vasoconstriction) decrease (Wang et al. 1991; Gagné et al. 2009).

Moreover, in animal models it has been observed that hypoxia induces a decrease of serum vitamin E levels and an increase in thromboxane production. These metabolic alterations would be responsible for an abnormal placental development and the decrease in steroid production. All these changes could lead to a foeto-placental vascular resistance and an increase of oxidative stress, which could be responsible for the appearance of IUGR (Parraguez et al. 2013; Majed and Khalil 2012; Sorem and Siler-Khodr 1997).

2.3.2 Foetal Factors

Foetal factors are less common. They include aneuploidies (trisomies of chromosomes 13, 18 and 21), which make up between 5 and 10% of IUGR cases; foetal malformations and congenital infections (rubella, cytomegalovirus, toxoplasmosis, etc.), which are responsible of 1.5% of IUGR cases; and inborn metabolic disorders (Bamfo and Odibo 2011).

2.3.3 Placental Factors

The placenta has two principal functions: it facilitates the exchange of nutrients, oxygen and waste products between mother and foetus and acts as an endocrine organ that integrates signals from the mother and foetus (Murphy et al. 2006). It has been estimated that the progenitor's genes account for only 20% of the variation of human birth weight. Nevertheless, the majority of the variation (62%) is due to the intrauterine environment. Thus, a suitable placental growth is essential for normal foetal development. For example, an adequate trophoblastic invasion is necessary. Trophoblastic tissue is metabolically active and produces hormones, absorbs nutrients and eliminates waste products (Bamfo and Odibo 2011). Therefore, anatomical abnormalities of the placenta, such as an abnormal insertion of the umbilical cord and placental thrombosis, decrease uteroplacental blood flow during pregnancy and consequently oxygen and nutrient transport (Murphy et al. 2006). Placentas from IUGR pregnancies have been shown to have poor invasion of the trophoblastic cells into the maternal decidual tissues, particularly the maternal spiral arteries (Setia and Sridhar 2009; Brosens et al. 2002). Studies looking into the pathological process of IUGR have pointed to an abnormal placental function as a common mechanism. However, it is known that the placental dysfunction is often gradual and it can occur much earlier than any demonstrable IUGR (Voigt and Becker 1992), making the resolution of this hypothesis difficult. Also, it was observed that approximately 20–30% of dichorionic twin pregnancies present IUGR, as they share placentas and such could lead to the appearance of stress in uteroplacental circulation, compromising development and growth of both foetuses (Bamfo and Odibo 2011).

The placenta, as a key organ for foetal growth, has a major role in amino acid transport, the most important nutrient for foetal life. During pregnancy, there is an active transport across the placenta from the maternal to the foetal circulation. The concentration of free amino acids in the placental tissue is higher than the concentration both in foetal and maternal plasma. In IUGR pregnancies, the concentrations of most essential amino acids (valine, leucine and isoleucine) decreased in foetal tissues but are significantly higher in maternal tissues. Such observation is a result of a maladaptation to pregnancy, suggesting the key role of amino acid transport. Several studies in animals showed a significantly reduced uptake of oxygen, glucose and essential amino acids in IUGR pregnancies. Also, studies in vitro in humans showed a reduced uptake of leucine and lysine, suggesting a reduced

activity of cationic amino acid transporters. Together, these data suggest the key role of amino acid transport in foetal development and its deficiency in IUGR pregnancies (Avagliano et al. 2012).

It is known that the placenta plays an important role in the production and transport of growth hormones that are critical for foetal growth and placental development (Murphy et al. 2006). It has been described that decreased levels of PL, which induces early embryonic growth and production of IGF-1 and insulin (Murphy et al. 2006), are associated with reduced foetal size. The same happens when oestradiol levels decrease, but in neither cases values are predictive, so the role of both hormones in the disease's pathophysiology is unknown (Markestad et al. 1997). In fact, detailed hormonal relationships of the mother–placenta–foetus unit are not known.

IGFs also control growth directly, where circulating IGF-1 appears to be virtually independent of foetal GH secretion (Randhawa and Cohen 2005). However, under this condition, placental GH may take this role as the prime regulator of maternal serum IGF-1 during pregnancy (Verhaeghe et al. 2000), being of particular interest the positive expression of IGF-1R in placenta (Reece et al. 1994) and the lower expression of placental-derived IGF-1 during IUGR (Koutsaki et al. 2011). In general, the endocrine milieu of the human foetus with growth retardation is also characterised by low circulating levels of insulin, IGF-1, IGF-2 and IGFBP-3 and high levels of GH and IGFBP-1 (Tzschoppe et al. 2015; Setia and Sridhar 2009; De Zegher et al. 1997). At this point, a study in zebrafish demonstrated that knockdown of IGFBP-1 significantly alleviated the hypoxia-induced growth retardation and developmental delay. Consistently, overexpression of IGFBP-1 caused growth and developmental retardation under normoxia conditions (Kajimura et al. 2005).

2.4 Clinic Course of IUGR

IUGR is the second most frequent cause of perinatal morbidity and mortality, only preceded by prematurity (Valsamakis et al. 2006). IUGR newborns could suffer numerous clinical disorders, such as hypoglycaemia, breathing difficulties that could cause neonatal asphyxia, hypothermia, ventricular haemorrhage and polycythaemia (Maulik 2006; Bamfo and Odibo 2011). All these clinical disorders can lead to consequences during early life, which could affect estatural and weight development and may also affect neurological development, resulting in behavioural anomalies, immature sleep patterns, diminution of visual fixation, decrease in overall activity, alteration of early mother–child interaction, alteration of motor skills and hyperactivity (Maulik 2006). It has been observed that children born small for gestational age had between 5 and 7 times increased risk to develop cerebral palsy, compared with those whose weight at birth was normal. It is still unknown whether this abnormal growth is the cause or the consequence of this disability (Jacobsson et al. 2008; Dahlseng et al. 2014).

In addition, newborns with IUGR had an increased risk during adulthood of suffering other clinical disorders, such as cardiovascular disease, insulin resistance, diabetes and hypertension, all of them related to metabolic syndrome (Valsamakis et al. 2006; Maulik 2006). As previously stated, kidney growth is under IGF-1 control; and a reduced IGF action, parallel to increased cortisol levels, results in a smaller number of glomeruli (Vehaskari et al. 2001). Alterations in the renin–angiotensin system are also frequent, probably downstream to activation of the HPA axis. These changes together with compensatory responses for the reduced kidney function probably account for the predisposition to adult hypertension (Vehaskari et al. 2001).

In the last years, a role for an altered GH/IGF axis in foetal programming in IUGR is being proposed, constituting the so-called thrifty phenotype hypothesis (Setia and Sridhar 2009), with an already proven inverse association between IGF-1 levels at 9 months and 17 years. Under this perspective, GH/IGF-1 axis may be programmed early in life. This foetal programming could be involved in, at least, two pathological conditions in later life, insulin resistance and hypertension. Firstly, children with IUGR show an impaired GH/IGF-1 axis, which might be contributing to reduced insulin sensitivity and IGF-1 resistance, as higher basal and GH-induced IGF-1 levels are required to achieve a growth velocity similar to that of other children. Secondarily, this alteration leads to a compensatory hyperinsulinemia to counteract insulin antagonistic effects of GH (Woods et al. 2002) and an impaired regulation of glucose transporter-4 expression by insulin in muscle and adipose tissue (Jaquet et al. 2001).

Moreover, some studies have shown that women who had given birth to newborns small for their gestational age (birth weight lower than 2,500 g) have an increased risk of mortality, due to cardiovascular alterations, such as ischaemic heart disease. This risk is 7 times higher than in women who had given birth to newborns normal for their gestational age (Smith et al. 2001).

2.5 Diagnosis

Diagnosis of IUGR is based upon clinical exploration and specific tests (Maulik 2006). When suspected, a complete medical history of the mother should be done, including the evaluation of risk factors such as medication use, recent infections, toxic exposure, smoking, alcoholism or drug consumption (Maulik 2006). The medical history must be completed with physical exploration of abdominal circumference size and uterine fundal height (Maulik 2006). If still suspected, an umbilical uterine arterial Doppler could be performed in order to establish the diagnosis, which allows to detect placenta insufficiency (Gheita et al. 2011). Ultrasound biometry allows to obtain parameters about foetal development such as foetal abdominal circumference, foetal head circumference and foetal femur length (Bamfo and Odibo 2011; Gheita et al. 2011).

However, at present, a suspected diagnosis of IUGR is made based on diverse criteria established by Gardosi, who defined personalised growth charts that improve detection of IUGR and help to distinguish slow growth foetuses (Chard et al. 1992). Deter et al. (1992) also established diverse criteria used to detect growth anomalies: prenatal growth assessment score (PGAS) and neonatal growth assessment score (NGAS) (Deter et al. 1992).

3 Conclusions and Perspectives

Intrauterine growth restriction (IUGR) is a relevant obstetric pathology. This disease is considered the second most frequent cause of perinatal morbidity and mortality, only preceded by prematurity, having a multifactorial aetiology. In recent years the understanding and characterisation of the pathophysiology and specific causes of the disease has become essential in order to reach a useful and successful therapeutic strategy.

Insulin-like growth factor 1 (IGF-1) is an anabolic hormone with a major role in foetal and placental growth and development. IGF-1 is produced by almost every tissue, including the placenta. The placenta is a metabolically active intrauterine organ. It secretes several hormones (IGF-1, IGF-2, GH, PL, etc.) and facilitates the exchange of nutrients, oxygen and waste products between mother and foetus. It is why the placenta plays an important role in foetal and embryonic development. Hence, suitable placental growth is essential for normal intrauterine development.

Several studies in IGF-1-deficient animals showed the key role of IGF-1 in foetal growth, liver cirrhosis, aging, vasoprotection, cardioprotection, insulin resistance, angiogenesis and neurogenesis. Also, several studies in humans have revealed that IUGR infants have low circulating levels of insulin, IGF-1 and IGF-2 and an abnormal placental function. Together, these data postulate that the mere IGF-1 deficiency in the gestational state may produce serious intrauterine growth retardation. Thus, it can be established that IGF-1 low levels could compromise oxygen and nutrient transport across the placenta, producing an abnormal placental growth and environment, leading to an abnormal foetal growth and development. Therefore, IUGR could be considered as a novel condition of IGF-1 deficiency, where replacement therapy at low doses with this hormone could be a beneficial and useful therapeutic strategy.

Our group has demonstrated that low doses of IGF-1 in IGF-1-deficient animals can restore physiological IGF-1 levels and improve insulin resistance, lipid metabolism and mitochondrial protection. Low doses of IGF-1 in these animals can have several beneficial hepatoprotective, neuroprotective, antioxidant and antifibrogenic effects. In consequence, treatment of IUGR, a novel condition of IGF-1, with low doses of IGF-1 prior to birth, where the foetus and placenta are growing and developing, could be beneficial, restoring circulating IGF-1 levels, and could improve the characteristics of the pathology.

Our perspective is to design and appropriate IGF-1-deficient mouse model to determine the pathophysiology of IUGR and to observe if low doses of IGF-1 during pregnancy could restore IGF-1 levels in both mother and foetus and if the administration of such hormone could improve foetal growth. Also, our perspective is to design a multicentric study between several hospitals in Monterrey (Nuevo Leon, Mexico) where we would try to administrate low doses of IGF-1 to pregnant mothers with possible IUGR and see how this treatment would affect both mother and foetus.

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Conflict of Interest The authors declare that they have no conflict of interest.

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