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Intrauterine Growth Restriction and Adult Disease: the Role of Adipocytokines

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ABSTRACT

Intrauterine growth restriction (IUGR) is the failure of the fetus to achieve his/her intrinsic growth potential, due to anatomical and/or functional disorders and diseases in the feto-placental-maternal unit. IUGR results in significant perinatal and long-term complications, including development of insulin resistance/metabolic syndrome in adulthood.

The thrifty phenotype hypothesis holds that intrauterine malnutrition leads to an adaptive response that alters the fetal metabolic and hormonal milieu designed for intrauterine survival. This fetal programming predisposes to an increased susceptibility for chronic diseases. Although the mechanisms controlling intrauterine growth are poorly understood, adipose tissue may play an important role in linking poor fetal growth to the subsequent development of adult diseases. Adipose tissue secretes a number of hormones, called adipocytokines, important in modulating metabolism and recently involved in intrauterine growth.

This review aims to summarize reported findings concerning the role of adipocytokines [leptin, adiponectin, ghrelin, tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), visfatin, resistin, apelin] in early life, while attempting to speculate mechanisms through which differential regulation of adipocytokines in IUGR may influence the risk for development of chronic diseases in later life.

Key words: intrauterine growth restriction, adipocytokines, adipose tissue, metabolic syndrome, adult disease

INTRAUTERINE GROWTH RESTRICTION

Intrauterine growth restriction (IUGR) is the failure of the fetus to achieve his/her intrinsic growth potential, due to anatomical and/or functional disorders and diseases in the feto-placental-maternal unit [1]. IUGR is characterized a) as symmetrical if weight, length and head circumference are low, usually indicative of a process originating early in pregnancy, b) as asymmetrical when brain sparing takes place and the head circumference is within normal limits, indicative of a process occurring as gestation advances [1].

Asymmetrical IUGR is usually related to impaired uteroplacental function or nutrient deficiency [1]. In these cases, fetal growth is normally evolving until growth rate exceeds substrate provision, generally during the third trimester [1]. Even a slight decrease in energy substrate limits fetal glycogen and fat formation, as well as muscle growth [2]. Bone growth -and thus fetal length- are less affected, whereas redistribution of cardiac output leads to preferential substrate delivery to the brain [1, 2]. Therefore, asymmetric IUGR represents an adaptation to an unfavorable intrauterine environment and results in significant perinatal and long-term complications [1, 3-5].

THE DEVELOPMENTAL ORIGINS OF ADULT DISEASE

Since the late 1980s numerous epidemiological studies demonstrated a strong association between IUGR and the later development of the metabolic syndrome, comprising arterial hypertension, coronary heart disease, dyslipidemia, visceral obesity, impaired glucose tolerance, type 2 diabetes mellitus and many other diseases, including osteoporosis [6]. This association, described in various populations, is

unrelated to age, sex and ethnic origin, and occurs independently of current weight and level of exercise [6, 7].

The *thrifty phenotype hypothesis* proposes that the association between poor fetal growth and subsequent development of type 2 diabetes/metabolic syndrome results from the effects of poor intrauterine nutrition, producing permanent changes in glucose-insulin metabolism [8]. These changes include reduced capacity for insulin secretion and insulin resistance [8].

In this respect, alterations in fetal nutrition may result in developmental adaptations that permanently change the physiology and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine and cardiovascular disorders [8, 9]. This phenomenon, termed “fetal programming”, has led to the “fetal origins of adult disease” theory [10, 11].

The fetus adapts to an adverse intrauterine milieu by optimizing the use of a reduced nutrient supply to ensure survival. Therefore, blood flow redistribution in favour of vital organs and changes in the production of fetal and placental hormones, controlling fetal growth, take place [10]. Although this topic has been controversial, recent epidemiological, clinical and animal studies support the theory of the “developmental origins of adult disease” [12-14].

On the other hand, the *fetal insulin hypothesis* proposes that genetically determined insulin resistance could result in low insulin-mediated fetal growth and insulin resistance in childhood and adulthood [15]. Insulin is one of the major growth factors in fetal life, and monogenic disorders that affect fetal insulin secretion and resistance also affect fetal growth [16, 17]. However, such mutations are rare, and no analogous common allelic variation has been discovered.

Mechanisms

Underlying molecular and cellular mechanisms of metabolic programming are not clear, but may include reprogramming of the hypothalamic-pituitary-adrenal axis and insulin-signaling pathways [18]. In many instances, the metabolic and other disorders associated with IUGR have an endocrine origin and are accompanied by changes in hormone bioavailability in adulthood [19]. Abnormalities in the circulating concentrations of insulin, catecholamines, cortisol, growth hormone (GH) and insulin-like growth factors (IGFs) have been observed in children and adults being born IUGR [18, 20]. These observations have led to the hypothesis that adult disease arises in utero, in part, as a result of changes in the development of key endocrine axes during suboptimal intrauterine conditions [19]. Thus, a thrifty phenotype results to increased sensitivity of the peripheral tissues to metabolic hormones, such as glucocorticoids and insulin, a condition that ensures survival and maximizes growth and fuel deposition, given that nutritional conditions improve after birth [19]. If postnatal nutrient availability is greater than prenatally predicted, enhanced postnatal growth and fat deposition will occur. In turn, this increased adiposity will lead to adult insulin resistance [21]. Certainly, the risk of developing adult metabolic syndrome is greatest, when poor prenatal growth is coupled with rapid catch-up growth during childhood [22].

In this respect, a study conducted in a Finish cohort in 1999 revealed a possible link between catch-up growth and insulin resistance, reporting that IUGR individuals experiencing rapid catch-up growth had the highest mortality from coronary heart disease [23]. Since then many researchers have illustrated this link in children and young adults born IUGR [24-26]. Furthermore, the work of Colle *et al.* first established that glucose-stimulated plasma insulin concentrations in infants and

children born small-for-gestational-age (SGA) were higher during catch-up growth [27]. This and other studies have emphasized that insulin resistance is an early manifestation of the mechanisms by which catch-up growth may predispose to adult disease [26, 28].

THE ROLE OF ADIPOSE TISSUE

A growing body of evidence recently suggests that the adipose tissue may also play a major role in linking poor fetal growth to subsequent development of adult diseases [29]. Insulin resistance, obesity-related diabetes and accompanying metabolic disorders are strongly associated with increased visceral fat mass [30].

IUGR is known to alter the development of fetal adipose tissue [31]. IUGR fetuses show a marked reduction in body fat mass, which mainly reflects a decreased accumulation of lipids in the adipocytes. However, although total body fat percentage is reduced, visceral adipose tissue is relatively increased [31]. In this respect, IUGR children with rapid catch-up growth in infancy present with increased and more centralized distributed fat mass [29], even if they are not overweight [32]. Moreover, their abdominal adipose tissue shows hyperresponsiveness to catecholamines [33] and early insulin resistance [21].

Interestingly, polymorphisms in the gene encoding the peroxisome-proliferator-activated receptor γ2 (PPARγ2), which is involved in the development and metabolic function of adipose tissue, modulate the susceptibility of IUGR subjects to develop insulin resistance in adulthood [34]. This polymorphism is responsible for higher risk of type 2 diabetes only in IUGR cases [34].

Since the discovery of adipocyte-derived hormones, collectively called adipocytokines, the adipose tissue is no longer considered an inactive fat store tissue,

but an endocrine organ, secreting a variety of bioactive molecules, which regulate body metabolism and energy homeostasis. Furthermore, adipocytokines have been recently implicated in fetal growth [35-40].

Given the importance of adipose tissue and its hormones in fetal growth and maturation for both survival at birth and overall health, it is of interest to explore the physiology of adipocytokines in early life, as well as those factors that may perturb the balance of these hormones in the IUGR state with pathological consequences in terms of confining an increased risk for adult disease.

Leptin in IUGR

Leptin, the product of the obesity (*ob*) gene, is a hormone of 16 kDa comprising 167 aminoacids [41]. The central source of leptin is the adipose tissue (white and brown), although it can also be produced in other sites, including the placenta [35, 36]. It mainly acts by binding to specific central and peripheral receptors in the hypothalamus, adipose tissue, liver and pancreatic β-cells [42]. Leptin stimulates a negative energy balance by increasing energy expenditure and reducing food intake [43]. Rodents and humans lacking leptin or functional leptin receptors develop severe obesity and hyperphagia [44]. However, endogenous hyperleptinemia fails to stimulate body weight loss in obese individuals, suggesting that a state of leptin resistance is linked to the development of obesity [45].

Leptin seems to be a critical factor for overall fetal development [46, 47]. The hormone is produced in both maternal and fetal adipose tissues and the placenta [46, 48], while its receptors are abundant in the uterine endometrium, trophoblast and the fetus [49]. Fetal adipose tissue is an important source of leptin and fetal leptin levels are strongly related to birth weight and fetal adiposity [37, 50-53]. Furthermore, a

strong association between neonatal leptin levels, bone mineral content and estimated bone density has been confirmed, supporting a role for leptin in the process of fetal bone remodeling [54].

Recent data suggest that prenatal undernutrition associated with IUGR can shape future susceptibility to obesity, obesity-related disorders and osteoporosis through alterations in the regulation of leptin secretion and sensitivity [45, 46, 54, 55]. Thus, leptin may play a role in the control of substrate utilization and in the maintenance and functional characteristics of fat mass before birth, producing permanent changes, concerning adiposity and body composition in adult life [55, 56]. Moreover, accumulating evidence indicates that the risk of osteoporosis may also be determined by factors acting on intrauterine bone development via alterations in leptin dynamics [54, 57].

Several studies demonstrated lower circulating leptin concentrations in IUGR neonates at birth, due to reduced fat mass [58-72] and/or decreased placental production [73-75]. In some of these studies, fetal leptin levels per kilogram of fetal weight, as well as fetal leptin levels before 34 weeks of gestation, were not significantly different in IUGR, indicating that leptin secretion is mainly associated with adipose tissue accumulation [61-64]. However, other investigators suggested that low fetal leptin levels in IUGR are associated with reduced placental production, since leptin levels dramatically decrease shortly after birth [73-75]. Nevertheless, these reduced fetal concentrations increase and become higher in IUGR infants, children and adults, compared to normal birth weight controls, regardless of body mass index (BMI) [76-78], suggesting either an adaptive leptin resistance beneficial for catch-up growth, or an adipocyte dysfunction associated with IUGR [76]. Therefore, leptin may represent one of the mechanisms whereby intrauterine factors,

which affect weight and adiposity at birth, could influence postnatal levels of satiety, metabolism and weight gain [46, 55, 79].

Although most studies suggest that fetal leptin levels are lower in IUGR [58-75], other investigators determined similar [80] and also higher [81] leptin concentrations. In this respect, a recent study from our group demonstrated lack of significant differences in fetal leptin concentrations between characteristic IUGR (birth-weight $<3^{rd}$ customized centile) cases and appropriate-for-gestational-age (AGA) controls, possibly due to a more active production of leptin by visceral fat in the former [80]. Furthermore, higher fetal leptin concentrations in IUGR in an older report [81] may be attributed to differences in the fetal oxygenation status, since leptin gene is highly sensitive to oxygen abundance [82] and IUGR fetuses exhibiting severe distress have significantly higher leptin concentrations per kilogram of weight [64]. The authors suggest that the persistence of such adaptation within the adipocyte may predispose to excess fat deposition in later life [81]. Nevertheless, more studies are needed to evaluate the role of fetal leptin secretion patterns in different types of IUGR.

In order to investigate the role of leptin in fetal programming, the maternal protein-restricted rat model of IUGR has been used [79, 83, 84]. In this respect, numerous studies indicated that prenatal exposure to maternal undernutrition lead to development of diet-induced obesity, hyperleptinemia, hyperinsulinism and hypertension in the rat offspring [85-90]. Suggested underlying mechanisms include pre-existing fetal leptin resistance [87], excessive fetal exposure to glucocorticoids associated with IUGR [88] and permanent dysregulation of the adipoinsular feedback system, leading to hyperinsulinism and compensatory leptin production by pancreatic delta-cells [89] or adipose tissue [90]. Desai *et al.* [91, 92] documented reduced leptin levels in IUGR neonates and impaired anorexigenic response to leptin in the central

satiety pathway, contributing to programmed obesity in the rat offspring, while Delahaye et al. [93] showed that IUGR drastically reduces the postnatal surge of plasma leptin, particularly disturbing the gene expression of the anorexigenic neurons. Moreover, leptin administration to low-protein dams reverses the reduction in fetal IGF-1 levels in the IUGR offspring and significantly elevates both IGF-2 and fetal leptin levels, which affect the fetal development of key endocrine organs, e.g. the pancreas [83, 84]. Thus, maternal leptin administration results in an increase of fetal pancreatic insulin content and provides long-term protection from type 2 diabetes and obesity [83, 84].

On the other hand, leptin levels were elevated in the IUGR ovine fetus and inversely related to uterine blood flow and fetal/placental weight, suggesting that fetal leptin may be involved in an adaptive response [94]. Interestingly, altered hypothalamic leptin receptor distribution has been very recently showed in IUGR piglets, while leptin supplementation partially reversed the IUGR phenotype, by correcting growth rate and body composition in the offspring [95]. Furthermore, in the sheep fetus, moderate maternal undernutrition does not seem to influence fetal plasma leptin levels, while severe maternal undernutrition leads to suppression of fetal leptin synthesis, secondary to profound fetal hypoglucemia or hypoinsulinemia [96, 97]. It is possible that IUGR may alter the expression of appetite-stimulating neuropeptides in the fetal brain, programming susceptibility to adult obesity [55].

Taken together, these data indicate that intrauterine exposure to either intrauterine hypo- or hyperleptinemia may programme central or peripheral energy-regulating systems, predisposing to postnatal obesity.

Adiponectin in IUGR

Adiponectin is one of the most abundant adipose tissue-specific proteins and is predominantly expressed and secreted from adipose tissue [98]. Adiponectin is postulated to play a role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues [99]. Circulating adiponectin concentrations decrease in insulin-resistant states, including type 2 diabetes [99, 100]. Unlike leptin, adiponectin concentrations are inversely correlated with body weight and the amount of fat mass [101]. Moreover, recent findings indicate that adiponectin has antiatherogenic and antiinflammatory properties [102].

In addition to regulating body metabolism, adiponectin is also produced within the intrauterine environment [52, 103-105]. The findings that adiponectin is present in cord blood [103], positively correlates with birth-weight [52, 104] and is highly produced by both the placenta and the fetus [52, 105], suggest that this adipocytokine may play a key role in fetal growth, probably enhancing the growth-promoting effect of insulin through its insulin-sensitizing action [52]. The high fetal adiponectin concentrations may be attributed to lack of negative feedback on adiponectin production, resulting from lack of adipocyte hypertrophy, low percentage of body fat, or a different distribution of neonatal fat depots [106, 107]. On the contrary, other investigators failed to demonstrate a relation between fetal adiponectin and birth weight [103].

Given the significance of glucose and insulin in fetal growth [108] and the fundamental role of adiponectin in insulin metabolism [99, 100], it is reasonable to assume that adiponectin may play a regulatory role in IUGR. A number of studies [71, 103, 106], including our published data [80], demonstrated lack of significant differences in fetal adiponectin concentrations between IUGR cases and AGA controls, probably due to lack of insulin resistance, present in early life. However,

SGA fetuses have been recently reported to shift their adiponectin pattern towards the high-molecular-weight isoform (which specifically correlates with insulin sensitivity), thus sensitizing their body to insulin and preparing for neonatal catch-up growth [109]. By contrast, two previous studies demonstrated lower adiponectin concentrations in IUGR and proposed that this down-regulation may be a predisposing factor for later development of insulin resistance/metabolic syndrome [110, 111]. Interestingly, in support of this view, adiponectin levels in IUGR children were particularly low in those who showed postnatal catch-up growth, compared to levels in IUGR children who remained small during childhood [112, 113]. This may indicate that the low adiponectin levels in IUGR infants may actually predict the subsequent development of visceral fat and insulin resistance [112]. On the contrary, limited number of human and animal studies has revealed normal adiponectin levels in SGA prepubertal children, despite the fact that they were more insulin resistant, probably responding to a mechanism aiming at improving insulin sensitivity [114-116]. On the other hand, normal or higher adiponectin concentrations in IUGR insulin-resistant children have been recently reported [117]. A possible explanation for these contradictory results may rely on the fact that all above studies have not consistently characterized IUGR. Alternatively, discrepancies could be, to a large extent, explained by differences in specific methodological aspects.

Taken together, these data imply that adiponectin deficiency may be a plausible and attractive explanation for the metabolic abnormalities observed in IUGR children and adults. However, the association between IUGR and postnatal circulating adiponectin is not constant, indicating that the modifying effects of early and late postnatal growth characteristics may not completely explain the variability in adiponectin concentrations [118].

Ghrelin in IUGR

Ghrelin, an endogenous ligand of the GH secretagogue receptor, is an acylated 28-amino acid peptide that is predominantly produced by the stomach [119], but also by many other tissues, including the pituitary and the placenta [120]. It has potent orexigenic, adipogenic and GH-releasing properties that facilitate food intake and increase fat storage [121, 122]. In this respect, ghrelin concentrations have been shown to increase with fasting and decrease following feeding in humans and rats [123]. These data suggest that ghrelin may be an important link between nutrition and growth. The presence of significant immunoreactive ghrelin concentrations in human cord blood and their inverse correlation with fetal growth-related parameters, including birth weight, have recently been demonstrated [39, 124]. A small number of studies documented higher fetal ghrelin concentrations in IUGR [39, 125, 126]. This finding was attributed to the state of undernutrition of these fetuses and a role for ghrelin in fetal adaptation to intrauterine malnutrition has been proposed [125, 126]. Furthermore, fasting is known to stimulate GH release in infants with IUGR, who characteristically show elevated basal levels of GH [127]. Therefore, the augmented ghrelin concentrations in IUGR may consequently lead to elevated GH concentrations, as ghrelin has a potent GH-releasing activity [122]. Eventually, the higher ghrelin concentrations may serve to stimulate appetite, resulting in higher nutritional intake by the IUGR neonate after birth [126]. In agreement, both higher ghrelin levels and hyperphagia have postnatally been demonstrated in human and animal IUGR subjects, suggesting a role for ghrelin in postnatal catch-up growth [91, 128, 129].

Tumor necrosis factor-alpha (TNF-a) and Interleukin-6 (IL-6) in IUGR

Adipose tissue monocytes and macrophages produce inflammatory cytokines, such as TNF-a and IL-6, which may eventually lead to insulin resistance [130]. TNF-a and IL-6 are also produced by the placenta during pregnancy [131], but very few and contradictory data exist in the literature, regarding the IUGR state. In this respect, reduced [132, 133] and also increased [134] fetal IL-6 levels have been documented in IUGR, possibly due to impaired trophoblast function and severe placental insufficiency in the former and to hypoxia and/or nutrient deficiency in the latter, supporting the hypothesis that IL-6 may be related to fetal growth in the fetomaternal interface. On the other hand, normal [132] and also decreased [135] fetal TNF-a levels have been demonstrated, proposing a role for TNF-a in the pathogenesis of IUGR. On the other hand, upregulation of TNF-a has been postulated to be a survival mechanism in the IUGR fetus, by inducing muscle insulin resistance, thus enabling glucose to be spared for brain metabolism [136]. It would be reasonable to suggest that perinatal stressors could lead to reprogramming of TNF-a regulation with overproduction that persists in postnatal life and causes insulin resistance. However, low TNF-a levels have been reported in SGA insulin-resistant children [137]. The authors speculate that down-regulation of TNF-a may be one of the mechanisms leading to insulin resistance in these subjects [137]. Furthermore, Casano-Sancho *et al.* reported that SGA children show increased frequency of the TNF-308G allele, that is associated with prenatal growth and postnatal insulin resistance [138]. This polymorphism may be implicated in the metabolic abnormalities that characterize SGA children [138].

Nevertheless, IUGR is a heterogeneous state, including cases of fetal malformations, infections or placental insufficiency due to preeclampsia [1]. This fact, as well as

differences in disease severity, might explain the contradictory results of the above studies.

Novel adipocytokines in IUGR

Given the documented importance of fetal adipose tissue and its hormones in fetal growth for both survival at birth and overall health, a number of very recent studies from our group [139-143] investigated the implication of newly discovered adipose-derived hormones in fetal growth and IUGR, in terms of confining their potential association with an increased risk for adult disease.

Specifically, resistin, a newly discovered metabolic hormone secreted by human adipocytes and mononuclear cells, has been postulated to play important roles in regulating energy homeostasis [144]. Resistin impairs glucose metabolism and opposes the action of insulin in peripheral tissues [144, 145]. Higher serum resistin concentrations have been documented in obese subjects and resistin has been suggested to link obesity to insulin resistance [144, 145]. Furthermore, resistin is expressed in the human placenta and has been postulated to play a role in regulating energy metabolism in pregnancy [146, 147]. Recent reports, including our data [40, 139, 148], have also demonstrated the presence of markedly high concentrations of resistin in umbilical plasma samples, indicating the potential role of this adipocytokine in controlling fetal energy homeostasis and affecting deposition of adipose tissue in utero.

Apelin is a novel bioactive peptide, identified as the endogenous ligand of the orphan G protein-coupled receptor, APJ [149]. It has a widespread pattern of expression in human tissues and it is produced in several organs, including brain, lung, lactating breast and gastrointestinal tract [150]. Embryonic expression studies indicated that apelin is an angiogenic factor required for normal blood vessel growth and endothelial

cell proliferation [151]. Moreover, the presence of apelin has been documented in human placental tissue, indicating an important role of this peptide in fetal development [152]. We recently demonstrated the presence of markedly high concentrations of apelin in umbilical plasma samples and suggested a potential role of this peptide in intrauterine growth [140]. Furthermore, apelin has been identified as a novel adipocytokine, secreted in substantial amounts by adipose tissue in a regulated manner [153]. In this respect, apelin is up-regulated by obesity and hyperinsulinemia in both humans and mice [153]. Thus, current research focuses on the potential link of apelin with obesity-associated insulin resistance [154].

Recent studies from our group, investigating resistin and apelin concentrations in the IUGR state, demonstrated lack of differences in resistin and apelin concentrations between IUGR cases and AGA controls and lack of correlation between resistin, as well as apelin with insulin concentrations, as well as customized centiles (adjusted birth-weights) of the studied infants [139, 140]. We speculate that resistin and apelin may not be directly involved in the regulation of insulin sensitivity and adipogenesis in the perinatal period [139, 140].

Visfatin, a 52-kD protein, has been recently identified as a visceral fat-specific adipocytokine [155], probably linking the expansion of adipose depot to insulin resistance [156]. Visfatin was initially thought to be upregulated in obesity and in states of insulin resistance, while exerting insulin mimetic effects in various tissues [155]. However, subsequent studies have generated disparate findings with regard to the role of visfatin in obesity and insulin resistance and the pathophysiological role of visfatin in humans remains controversial and largely unknown [157, 158].

Visfatin is identical to pre-B-cell colony enhancing factor (PBEF), a cytokine involved in B-cell precursor maturation [155]. The PBEF protein is immunolocalized

in both normal and infected human fetal membranes and is significantly up-regulated by labor [159]. Moreover, data of a recent study from our group indicate that visfatin is present in cord blood in substantial amounts, probably due to placental production [141, 142].

Of particular interest are our results regarding visfatin concentrations in the IUGR state [143]. In this respect, higher visfatin concentrations were found in IUGR neonates compared to AGA counterparts, probably due to increased visceral adiposity or altered fetal development of adiposity in IUGR subjects [29, 31], which may predispose to the later development of insulin resistance [143]. We hypothesize that higher visfatin concentrations in IUGR could probably serve as an early marker with prognostic value for the later development of the metabolic syndrome in this population [143]. By contrast, a recent study concluded that visfatin may not be involved in the disturbed glucose metabolism of the IUGR rat offspring and may only represent a marker of fat accumulation [86].

Table 1 summarizes the results of major articles investigating circulating concentrations of adipocytokines in IUGR versus AGA subjects.

CONCLUSIONS

Differential regulation of adipocytokines in the IUGR state may be predictive of adult disease occurrence. The inability to undertake longitudinal studies from early to adult life makes it difficult to directly evaluate the existence of such associations. Nevertheless, a role of leptin, adiponectin, ghrelin and visfatin appears likely, although at this stage, it is difficult to document whether this is a major regulating role or a reflection of other more critical endocrine and growth-related processes. Most studies indicated lower leptin, normal or lower adiponectin and higher ghrelin, as well

as visfatin fetal/neonatal concentrations in the IUGR state, probably holding implications for susceptibility to long-term development of obesity and insulin resistance. Further understanding of the changes in body fat distribution and adipocyte maturation during early postnatal development will surely help to explain the complex associations between IUGR, rapid postnatal weight gain and adult disease risk. In addition, a deeper understanding of how prenatal and postnatal nutrition interact and influence molecular pathways involved in the development of obesity, will support the development of more effective preventive strategies and therapeutic approaches to curb the worldwide epidemic of type 2 diabetes and obesity.

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Ariadne Malamitsi-Puchner: idea conception, writing, overall supervision.

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Table 1. Results of major articles investigating circulating concentrations of adipocytokines in intrauterine growth restricted (IUGR) versus (vs) appropriate for gestational age (AGA) subjects.

ADIPOCYTOKINE (concentrations)	**SPECIES**	**RESULTS (IUGR vs AGA)**	**REFERENCES**
Leptin	**Human fetus/neonate**	Lower	Koistinen *et al.* (1997) [63] Matsuda *et al.* (1997) [69] Tamura *et al.* (1998) [66] Jaquet *et al.* (1998) [61] Marchini *et al.* (1998) [67] Varvarigou *et al.* (1999) [60] Shaarawy *et al.* (1999) [70] Cetin *et al.* (2000) [64] Lea *et al.* (2000) [73] Lepercq *et al.* (2001) [65] Ben *et al.* (2001) [75] Yildiz *et al.* (2002) [59] Lepercq *et al.* (2003) [74] Pighetti *et al.* (2003) [58] Arslan *et al.* (2004) [62] Martinez-Cordero *et al.* (2006) [71] Koklu *et al.* (2007) [68] Valuniene *et al.* (2007) [72]
		Higher	Shekawat *et al.* (1998) [81]

		Similar	Kyriakakou *et al.* (2008) [80]
	Human infant/child	Higher	Ong *et al.* (1999) [77]
			Jaquet *et al.* (1999) [76]
	Rat newborn	Lower	Desai *et al.* (2005) [91]
			Desai et al. (2007) [92]
			Delahaye *et al.* (2008) [93]
	Rat offspring	Higher	Vickers *et al.* (2000) [85]
			Sudgen *et al.* (2001) [88]
			Vickers *et al.* (2001) [89]
			Holness *et al.* (2001) [90]
			Krechowec *et al.* (2006) [87]
			Nusken *et al.* (2008) [86]
	Ovine fetus	Higher	Buchbinder *et al.* (2001) [94]
Adiponectin	**Human fetus/neonate**	Similar	Lindsay *et al.* (2003) [103]
			Kotani *et al.* (2004) [106]
			Martinez-Cordero *et al.* (2006) [71]
			Kyriakakou *et al.* (2008) [80]
		Lower	Kamoda *et al.* (2004) [110]

			Takaya *et al.* (2007) [111]
	Human child	Lower	Cianfarani *et al.* (2004) [112]
			Sancakli *et al.* (2008) [113]
		Similar	Lopez-Bermejo *et al.* (2004) [114]
			Iniguez *et al.* (2004) [115]
		Similar or higher	Evagelidou *et al.* (2007) [117]
	Rats	Similar	Chen *et al.* (2003) [116]
Ghrelin	**Human fetus/neonate**	Higher	Kitamura *et al.* (2003) [39]
			Farquhar *et al.* (2003) [125]
			Medez-Ramirez *et al.* (2008) [128]
			Iniguez *et al.* (2002) [129]
			Onal *et al.* (2004) [126]
	Rat offspring	Higher	Desai *et al.* (2005) [91]
TNF-α	**Human fetus/neonate**	Similar	Opsjon *et al.* (1995) [132]
		Lower	Schiff *et al.* (1994) [135]
		Higher	Fernandez-Real *et al.* (1999) [136]
	Human child	Lower	Jefferies *et al.* (2004) [137]
IL-6	**Human fetus/neonate**	Lower	Opsjon *et al.* (1995) [132]
			Odegard *et al.* (2001) [133]
		Higher	Street *et al.* (2006) [134]
Resistin	**Human fetus/neonate**	Similar	Briana *et al.* (2008) [139]
Apelin	**Human fetus/neonate**	Similar	Malamitsi *et al.* (2008) [140]

Visfatin	**Human neonate**	Higher	Malamitsi *et al.* (2008) [143]
	Rat offspring	Similar	Nusken *et al.* (2008) [86]