The Influence of Growth Hormone on Bone and Adipose Programming

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Abstract

In utero growth hormone exposure is associated with distinct immediate growth responses and long term impacts on adult physiological parameters that include obesity, insulin resistance, and bone function. Growth hormone accelerates cellular proliferation in many tissues but is exemplified by increases in the number of cells within the cartilaginous growth plate of bone. In some cases growth hormone also potentiates differentiation as seen in the differentiation of adipocytes that rapidly fill upon withdrawal of growth hormone. Growth hormone provokes these changes either by direct action or through intermediaries such as insulin-like growth factor-I and other downstream effector molecules. The specific mechanism used by growth hormone in programming tissues is not yet fully characterized and likely represents a multipronged approach involving DNA modification, altered adult hormonal milieu, and the development of an augmented stem cell pool capable of future engagement as is seen in adipose accrual. This review summarizes findings of growth hormone's influence on in utero and neonatal cellular and metabolic profiles related to bone and adipose tissue.

Keywords

Growth hormone • Adipose tissue • Insulin-like growth factor • Bone growth • Small-for-gestational age

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1 Fetal Programming and Growth

It is well recognized that the hormonal and environmental milieu in which the fetus develops greatly impacts health and disease susceptibility in later life [1, 2]. Early intrauterine nutritional and environmental stressors or endocrine challenges may all program the fetus such that adult physiology is altered. For instance, metabolic bone diseases are purported to arise from prenatal undernourishment [3]. Evidence likewise exists for neonatal metabolic programming for obesity. Small for gestational age (SGA) offspring, often arising as a consequence of malnourished mothers, is also correlated with adult hypertension, glucose intolerance, insulin resistance, type 2 diabetes, dyslipidemia, reduced bone mass, and reduced bone strength. Differential fetal programming occurring at the gene level with methylation, gene silencing, and other epigenetic modifications permit adult onset disorders associated with SGA neonates (reviewed in [4]).

2 Role of GH-IGF in Normal Growth and Development

Postnatally, the growth hormone (GH) insulin-like growth factor (IGF) axis is the predominant endocrine pathway that modulates overall body growth [5, 6]. In utero, GH plays a much reduced role as compared to postnatal development with other hormones assuming more prominent fetal roles: insulin, IGF-I, IGF-II, glucocorticoids, and thyroid hormones being essential in normal fetal growth [1]. Yet it is known that GH influences fetal growth. For instance, when mice transgenic for a GH construct are exposed to the transgene stimulus, hence elevated GH, in utero, they exhibit a 12 % reduction in birth weight [7] and calves born to dams given exogenous bovine somatotropin (GH) have reduced birth weights [8, 9]. Insulin levels of calves born to GH treated dams also tended to be reduced at birth [9] reflecting additional influences due to GH.

In a cohort of infants having low birth weight, at 1 year of age IGF-I levels were not associated with being born SGA. Likewise, when 17 years of age, there were no associations between IGF-I levels and being born SGA [10]. There was however a trend in children born SGA to have lower circulating GH as young adults [10] indicating persistent effects by early developmental experiences on GH secretion.

Interestingly, despite the early growth compromise, approximately 90 % of SGA births have accelerated growth in the first two postnatal years and achieve a final height that is within the normal range [11, 12]. However the remaining 10 % of SGA births do not exhibit catch-up growth indicating sustained impairment of the GH-IGF endocrine axis suggesting fetal programming of the axis as a consequence of early growth dysfunction [13].

Evaluating early effects of GH on inflammation and immune competence also suggests a direct role of GH in fetal and early neonatal development. Treating SGA rat pups with exogenous GH during the pre-weaning growth stage reverses the persistent negative effects on immune function that accompanies SGA [14]. The ability of GH to reverse chronic inflammatory conditions suggests that GH can restore epigenetic changes evoked by uterine growth perturbations. The responsiveness of the neonate demonstrates the plasticity of postnatal development.

As noted above, postnatal development is highly regulated by GH. For instance, in GH transgenic mouse models, mouse pups born and nursed by dams exposed to elevated GH grow approximately 50 % faster than contemporary pups nursed by dams with normal circulating GH [15] and transgenic pups stimulated to express GH likewise show significant growth enhancement. In normal rodent development, the composition of gain is invariant such that each unit of gain is composed of the same proportions of water, lipid, protein and ash across the entire growth phase, despite the speed of accrual [16]; under conditions of elevated GH, composition of protein gain exceeds that of the other components [17] indicating GH repartitions nutrients preferentially.

3 Programming Linear Bone Growth by GH

In addition to protein accretion, another key growth parameter controlled by GH is linear bone elongation and bone remodeling. A consequence associated with SGA neonates is reduced bone mass and strength in adulthood reflecting programming of this axis [18]. As noted above, the vast majority of SGA births achieve normal height within the first 2 years [11, 12] demonstrating competence of the growth plate chondrocytes regulating linear growth. Early therapeutic provision of GH to SGA neonates having sufficient GH enhances the velocity of bone growth transiently but only for the duration of GH treatment [4]. Similar acceleration effects of GH on linear growth rates have been reported for rodents. As seen in children, transient high GH levels in mice increased growth rate but did not alter overall outcome on bone length [7]. Importantly, for rodents the developmental stage of exposure is critical to bone elongation more so than duration of exposure [19]. Specifically in the mouse, provision of GH between birth and 28 days is most influential on bone elongation and adult size. Initiating the elevated GH beyond 28 days of age increases growth but not to the extent realized with earlier exposure despite the presence of a functional growth plate. At the cellular level, GH accelerates bone growth by hyperplasia as opposed to growth plate chondrocyte hypertrophy [19].

Calves and rodents exposed to elevated GH in utero have reduced birth weights. In mice, bone lengths are reduced postnatally and catch-up growth is not detected by weaning (22 days postnatal) but if GH is provided after birth then the postnatal exposure to GH compensates for the in utero growth inhibition reversing the effect and overall bone length is restored [7]. In another model that altered fetal GH, treatment of pregnant sows with beta hydroxyl beta methylbutyrate significantly enhanced GH and IGF-I in the piglets [20]. In piglets from the treated dams, femur lengths remained significantly reduced at 6 months of age though measures of bone strength were improved. Taken together, these data indicate exposure of the fetus to elevated GH represses linear bone into adulthood.

4 Programming Adiposity by GH

Offspring from mothers who are undernourished during pregnancy exhibit SGA at birth and adult onset obesity, insulin resistance, hypertension, and metabolic dysfunction. These conditions can be ameliorated by providing exogenous GH at early postnatal stages with GH treatment improving cardiovascular function and reversing endothelial dysfunction [14, 21]. For example, in rats, the adiposity that typically accompanies adulthood in offspring of undernourished mothers can be reversed by provision of GH treatment preweaning ([22] and reviewed in [23]). Caution is warranted however as provision of GH to neonates can result in the development of insulin resistance [24].

Elevated GH in adult mice significantly increases circulating insulin with the levels remaining elevated even after reducing circulating GH levels demonstrating insulin resistance [25]. Insulin resistance is observed in SGA prepubertal children (reviewed in [4]) and Jensen et al. [13] suggest that those that do not experience catch-up growth may be even more at risk for type 2 diabetes. Concern surrounds therapeutic GH treatment of SGA children because GH reduces insulin sensitivity potentially exacerbating the risk of diabetes. Although insulin levels in children born SGA return to normal levels following cessation of GH treatment [4], the SGA children who have been treated with GH are not yet old enough to fully evaluate consequences of GH treatment on adult carbohydrate metabolism.

Insulin resistance promotes the retention of lipid stores thereby contributing to adult onset obesity reflecting. The elevated insulin, as a consequence of the elevated GH, may also induce lipoprotein lipase further promoting adipose storage. Prenatal adipocyte differentiation with enhanced lipogenic and adipogenic capacity also promotes adult obesity as seen in SGA offspring [26].

White adipose tissue in humans and rodents possess a reservoir of precursor cells that can continue to differentiate [27, 28]. In a GH transgenic mouse model in which the GH transgene can be directly and specifically regulated to increase circulating GH, elevated GH either in utero or postnatally results in increased adipose depot size and lipid stores [7]. The adiposity was due to both greater adipocyte numbers as a result of hyperplasia and differentiation driven by GH and enlarged cellular lipid content [25, 29].

A possible mechanism explaining GH contributions to the development of SGA, and thus future adiposity, is the impact of GH on maternal leptin levels. Elevated GH can drive adipocyte differentiation increasing maternal adipose storage potential thereby increasing overall level of leptin in circulation. Notably, concomitant with enhanced adipose content driven by elevated GH, in transgenic mice transiently exposed to elevated GH, associated with the elevated leptin levels is elevated NPY gene and protein expression suggesting leptin resistance [30]. However, maternal exposure to GH also drives the development of fetal adiposity as seen in sheep treated with GH. Although leptin levels were reduced in both the dam and the fetus as a response to treatment, adipose was significantly amplified [31] indicating the direct effect of GH on adipose metabolism.

An additional mechanism of potential GH programming lies in its effects on membrane lipids. Elevated GH alters cellular membrane characteristics to create a more unsaturated lipid profile [32]. Membrane desaturase pathways activated in response to GH cause a net flux through the lipid metabolism pathways to generate eicosanoids [33]; many of the changes are consistent with the inflammation conditions observed in chronic health disturbances associated with the obesity and other adult sequelae of SGA [24].

5 GH Programming of Leptin

Leptin, first identified in adults, has a clear role in postnatal and adult energy metabolism (reviewed in [34]). The fetus too is exposed, in varying degrees, to leptin derived from the maternal circulation, the placental, and the fetus itself. Leptin is known to effect pre- and postnatal development with autocrine/paracrine mechanisms preferred over the endocrine system [34]. Leptin regulates brain and bone development in the fetus [35], controls intrauterine and periuterine growth, and programs appetite drive in the neonate to facilitate rapid body weight accrual [36] indicating that in fetal metabolism, leptin has an analogous role as it does in the adult. Fetal exposure to leptin is also intimately involved in fetal programming of adult satiety including that of hunger-mediated ingestive behavior. Specifically, reduced neurotransmission of leptin signals of energy storage adequacy during neonatal life chronically alter adiposity and food intake regulation at later ages [36, 37].

Leptin levels correlate with birth weight: SGA infants have low leptin levels while large for gestational age babies born to mothers with diabetes have high leptin concentrations [38]. This association appears to be independent of the GH/IGF endocrine axis reviewed by [36] although GH can impact maternal and fetal leptin levels as detailed below.

Despite the knowledge of leptin's involvement, the specific mechanistic role of leptin in fetal life is less well defined especially in light of the varied sources of leptin. As an example, insulin and IGF-I concentrations are directly correlated with leptin in newborn [39] but the correlation does not answer the mechanistic question of whether leptin is directing fetal growth or the leptin is a mere reflection of adipose accrual in the growing fetus since fetal adipose is significant source of leptin [40]. It is also known that leptin in fetal circulation can be regulated by circulating insulin [41] and dams with elevated insulin influence the leptin levels in the fetus. Further, leptin derived from the placenta may influence fetal growth by influencing placental function.

Maternal leptin levels increase over the course of pregnancy while the fetus during the final trimester of gestation contributes ever increasing amounts of leptin as the fetal white adipose depots enlarge [36]. The placenta synthesizes leptin with the majority entering maternal circulation though the role of placental leptin in the

fetus varies by species (reviewed [34]) as does the placenta's permeability to leptin. In the sheep maternal and fetal leptin levels correlate with nutritional plane of the dam but that does not hold true for primates [40]; the rat placenta is more similar to the sheep with leptin permeable to the placenta [42].

Elevated maternal leptin in mice correlate with reduced placental and fetal weights of their offspring [43]. In contrast, human offspring born to mothers with gestational hyperleptinemia are born with higher leptin levels and are at risk of being large for gestational age [36]. These mothers also had elevated insulin that increases placental leptin synthesis leading to greater exposure of the fetus [44]. In a prospective human study designed to assess the impact of maternal weight gain during pregnancy on offspring body weight, it was found that cord leptin was positively associated with birth weight and excessive weight gain during pregnancy was directly associated with cord hyperleptinemia [45]. In a separate prospective human study, elevated maternal leptin levels accompanied SGA births [46] indicating that elevated maternal leptin reflected impaired fetal growth. Thus the influence of maternal leptin in human fetal development remains indeterminate.

Circulating neonatal leptin, for human infants, is associated with numerous fetal growth indicators including body weight, bone length as reflected in crown rump length, adiposity, and bone mineral density (reviewed in [34]). Low leptin in SGA neonates correlates with elevated leptin and leptin resistance at adulthood. The initial function of neonatal leptin resistance may be permissive for the catch-up growth seen in the majority of SGA offspring [47]. In neonatal pigs and humans exhibiting nutritionally induced SGA birth weights, nutritionally adequate diets during the postnatal period facilitates catch-up growth though there is a greater proportion of lipid accumulation than would accompany normal developmental growth [48].

In rats, restricting maternal dietary protein to induce intrauterine growth restriction and SGA pups, these SGA pups, when adults, have excess abdominal adipose depots [49]. Further, as adults, the fat depots exhibit altered gene profiles for genes associated with lipid metabolism and adipose accrual upregulated. Interestingly, neonatal provision of exogenous leptin to SGA piglets and rat pups reverses the adipocyte proliferation induced by intrauterine growth restriction [37, 48]. Excessive calories in the neonate creating "maternal diet-induced obesity", leads to leptin resistance in adulthood optimizing conditions favorable for adult onset metabolic disease [50]. McMillen et al. [51] reported that fetal leptin can modify adipocyte metabolism leading to disrupted appetite regulation of the neonate culminating in programmed leptin resistance, enhanced adiposity, and adult obesity. It is also known that leptin can drive adipocyte differentiation. The action of leptin and leptin resistance in the neonate clearly requires additional study.

Leptin resistance occurs when the receptors for leptin fail to transmit adequacy of energy stores. It is speculated that leptin resistance, programmed during fetal and neonatal life, represents impaired maturation of the neural circuits informing the body of energy stores [48]. The reduced leptin levels in SGA infants are suspected to disrupt normal neuronal programming and adult regulation of appetite. Supporting this concept is that provision of leptin to SGA rodent pups can normalize adult metabolism [37]. Increased expression of fetal neuropeptide-Y (NPY), leptin's receptor, may also contribute to the obesity that follows SGA [26, 51].

Dysregulation of GH early in life can increase adipocyte proliferative and differentiative potential thereby predisposing an individual to elevated leptin levels that would impact adult life. In GH transgenic mice with a regulated promoter enabling transient exposure to excessive GH, mice transiently exposed to elevated GH during early postnatal development rapidly become obese upon withdrawal of the elevated GH; accompanying the adiposity is an overall increase in circulating leptin [25]. In these animals, each adipocyte expresses less leptin such that on a per gram of adipose basis leptin secretion is reduced but the cumulative amount is greater due to the overall enhanced adipose storage. It is hypothesized that the reduced leptin expression at the

adipocyte level represents a GH induced insulin resistance and reduced adipocyte glucose utilization. At the hypothalamus, elevated leptin corresponds to enhanced transcript and protein expression of NPY [30]. Mice in which the GH remains elevated also exhibit reduced leptin expressed on per gram of lipid [29].

Whether GH directly alters leptin in utero or whether it is through a secondary mechanism remains unknown. However, GH can drive adipocyte differentiation enabling future adiposity, and potentiate insulin and leptin resistance. Enlarged adipose depots will synthesize more leptin further exacerbating the leptin resistance. Taken together, altered perinatal leptin levels can affect fetal programming and ultimately potentiate adult metabolic disorders.

6 Conclusion

Growth hormone directly impacts bone length and strength postnatally while substantive evidence exists to demonstrate a significant role of GH in utero with adult consequences. Similarly GH modulates adipose development pre- and postnatally at both the proliferation and differentiation stages, including adipose membrane involvement. Growth hormone may exert its programming influence through leptin and persistent effects on its action. Additional studies are necessary to characterize the contribution of GH and the mechanistic changes that mediate the fetal programming observed.

References

1. Fowden AL, Forhead AJ. Endocrine regulation of feto-placental growth. Horm Res. 2009;72:257–65.
2. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008; 359:61–73.
3. Cooper C, Javaid M, Taylor P, Walker-Bone K, Dennison E, Arden N. The fetal origins of osteoporotic fracture. Calcif Tissue Int. 2002;70:391–4.
4. Jung H, Rosilio M, Blum WF, Drop SL. Growth hormone treatment for short stature in children born small for gestational age. Adv Ther. 2008;25:951–78.
5. Oberbauer AM. The regulation of IGF-1 gene transcription and splicing during development and aging. Front Endocrinol. 2013;4:39.
6. Bartke A, Sun LY, Longo V. Somatotropic signaling: trade-offs between growth, reproductive development, and longevity. Physiol Rev. 2013;93:571–98.
7. Oberbauer AM, Cruickshank J, Thomas A, Stumbaugh A, Evans KD, Murray JD, et al. Effects of pre and antenatal elevated and chronic oMt1a-oGH transgene expression on adipose deposition and linear bone growth in mice. Growth Dev Aging. 2001; 65:3–13.
8. Oldenbroek JK, Garssen GJ, Jonker LJ, Wilkinson JI. Effects of treatment of dairy cows with recombinant bovine somatotropin over three or four lactations. J Dairy Sci. 1993;76:453–67.
9. Gallo GF, Block E. Effects of recombinant bovine somatotropin on nutritional status of dairy cows during pregnancy and of their calves. J Dairy Sci. 1990;73:3266–75.
10. Jensen RB, Vielwerth S, Frystyk J, Veldhuis J, Larsen T, Mølgaard C, et al. Fetal growth velocity, size in early life and adolescence, and prediction of bone mass: association to the GH–IGF axis. J Bone Miner Res. 2008;23:439–46.
11. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res. 1995;38:733–9.
12. Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL. Children born small for gestational age: do they catch up? Pediatr Res. 1995;38:267–71.
13. Jensen RB, Chellakooty M, Vielwerth S, Vaag A, Larsen T, Greisen G, et al. Intrauterine growth retardation and consequences for endocrine and cardiovascular diseases in adult life: does insulin-like growth factor-I play a role? Horm Res. 2003;60 Suppl 3:136–48.
14. Reynolds CM, Li M, Gray C, Vickers MH. Preweaning growth hormone treatment ameliorates bone marrow macrophage inflammation in adult male rat offspring following maternal undernutrition. PLoS One. 2013;8:e68262.
15. Pomp D, Geisert RD, Durham CM, Murray JD. Rescue of pregnancy and maintenance of corpora lutea in infertile transgenic mice expressing an ovine metallothionein 1a-ovine growth hormone fusion gene. Biol Reprod. 1995;52:170–8.
16. Thonney ML, Oberbauer AM, Duhaime DJ, Jenkins TC, Firth NL. Empty body component gain of rats grown at different rates to a range of final weights. J Nutr. 1984;114:1777–86.
17. Pomp D, Narcarrow CD, Ward KA, Murray JD. Growth, feed efficiency and body composition of transgenic mice expressing a sheep metallothionein 1a-sheep growth hormone fusion gene. Livest Prod Sci. 1992;31:335–50.
18. Sayer AA, Cooper C. Fetal programming of body composition and musculoskeletal development. Early Hum Dev. 2005;81:735–44.

19. Oberbauer AM, Pomp D, Murray JD. Dependence of increased linear bone growth on age at oMT1a-oGH transgene expression in mice. Growth Dev Aging. 1994;58:83–93.
20. Tatara MR, Śliwa E, Krupski W. Prenatal programming of skeletal development in the offspring: effects of maternal treatment with β-hydroxy-β-methylbutyrate (HMB) on femur properties in pigs at slaughter age. Bone. 2007;40:1615–22.
21. Gray C, Li M, Reynolds CM, Vickers MH. Preweaning growth hormone treatment reverses hypertension and endothelial dysfunction in adult male offspring of mothers undernourished during pregnancy. PLoS One. 2013;8:e53505.
22. Reynolds CM, Li M, Gray C, Vickers MH. Preweaning growth hormone treatment ameliorates adipose tissue insulin resistance and inflammation in adult male offspring following maternal undernutrition. Endocrinology. 2013;154:2676–86.
23. Vickers MH, Sloboda DM. Strategies for reversing the effects of metabolic disorders induced as a consequence of developmental programming. Front Physiol. 2012;3:242.
24. Takano A, Haruta T, Iwata M, Usui I, Uno T, Kawahara J, et al. Growth hormone induces cellular insulin resistance by uncoupling phosphatidylinositol 3-kinase and its downstream signals in 3T3-L1 adipocytes. Diabetes. 2001;50:1891–900.
25. Oberbauer AM, Stern JS, Johnson PR, Horwitz BA, German JB, Phinney SD, et al. Body composition of inactivated growth hormone (oMt1a-oGH) transgenic mice: generation of an obese phenotype. Growth Dev Aging. 1997;61:169–79.
26. Sarr O, Yang K, Regnault TR. In utero programming of later adiposity: the role of fetal growth restriction. J Pregnancy. 2012;2012:134758.
27. Hauner H, Entenmann G, Wabitsch M, Gaillard D, Ailhaud G, Negrel R, et al. Promoting effect of glucocorticoids on the differentiation of human adipocyte precursor cells cultured in a chemically defined medium. J Clin Invest. 1989;84:1663–70.
28. Maumus M, Sengenès C, Decaunes P, Zakaroff-Girard A, Bourlier V, Lafontan M, et al. Evidence of in situ proliferation of adult adipose tissue-derived progenitor cells: influence of fat mass microenvironment and growth. J Clin Endocrinol Metab. 2008; 93:4098–106.
29. Oberbauer AM, Runstadler JA, Murray JD, Havel PJ. Obesity and elevated plasma leptin concentration in oMT1A-o growth hormone transgenic mice. Obes Res. 2001;9:51–8.
30. Thomas AD, Murray JD, Oberbauer AM. Leptin modulates fertility under the influence of elevated growth hormone as modeled in oMt1a-oGH transgenic mice. J Endocrinol. 2004;182:421–32.
31. Wallace JM, Matsuzaki M, Milne J, Aitken R. Late but not early gestational maternal growth hormone treatment increases fetal adiposity in overnourished adolescent sheep. Biol Reprod. 2006;75:231–9.
32. Murray JD, Oberbauer AM, Sharp KR, German JB. Expression of an ovine growth hormone transgene in mice increases arachidonic acid in cellular membranes. Transgenic Res. 1994;3:241–8.
33. Oberbauer AM, German JB, Murray JD. Growth hormone enhances arachidonic acid metabolites in a growth hormone transgenic mouse. Lipids. 2011;46:495–504.
34. Forhead AJ, Fowden AL. The hungry fetus? Role of leptin as a nutritional signal before birth. J Physiol. 2009;587:1145–52.
35. Hoggard N, Haggarty P, Thomas L, Lea RG. Leptin expression in placental and fetal tissues: does leptin have a functional role? Biochem Soc Trans. 2001;29:57–63.
36. Alexe DM, Syridou G, Petridou ET. Determinants of early life leptin levels and later life degenerative outcomes. Clin Med Res. 2006;4:326–35.
37. Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, et al. Neonatal leptin treatment reverses developmental programming. Endocrinology. 2005;146:4211–6.
38. Lea RG, Howe D, Hannah LT, Bonneau O, Hunter L, Hoggard N. Placental leptin in normal, diabetic and fetal growth-retarded pregnancies. Mol Hum Reprod. 2000;6:763–9.
39. Maffeis C, Moghetti P, Vettor R, Lombardi AM, Vecchini S, Tato L. Leptin concentration in newborns' cord blood: relationship to gender and growth-regulating hormones. Int J Obes Relat Metab Disord. 1999;23:943–7.
40. Yuen BS, McMillen IC, Symonds ME, Owens PC. Abundance of leptin mRNA in fetal adipose tissue is related to fetal body weight. J Endocrinol. 1999; 163:R11–4.
41. Devaskar SU, Anthony R, Hay Jr W. Ontogeny and insulin regulation of fetal ovine white adipose tissue leptin expression. Am J Physiol Regul Integr Comp Physiol. 2002;282:R431–8.
42. Smith JT, Waddell BJ. Leptin receptor expression in the rat placenta: changes in ob-ra, ob-rb, and ob-re with gestational age and suppression by glucocorticoids. Biol Reprod. 2002;67:1204–10.
43. Yamashita H, Shao J, Ishizuka T, Klepcyk PJ, Muhlenkamp P, Qiao L, et al. Leptin administration prevents spontaneous gestational diabetes in heterozygous Lepr (db/+) mice: effects on placental leptin and fetal growth. Endocrinology. 2001;142:2888–97.
44. Lepercq J, Cauzac M, Lahlou N, Timsit J, Girard J, Auwerx J, et al. Overexpression of placental leptin in diabetic pregnancy: a critical role for insulin. Diabetes. 1998;47:847–50.
45. Karakosta P, Georgiou V, Fthenou E, Papadopoulou E, Roumeliotaki T, Margioris A, et al. Maternal weight status, cord blood leptin and fetal growth: a prospective mother–child cohort study (Rhea study). Paediatr Perinat Epidemiol. 2013;27:461–71.
46. Mise H, Yura S, Itoh H, Nuamah MA, Takemura M, Sagawa N, et al. The relationship between maternal plasma leptin levels and fetal growth restriction. Endocr J. 2007;54:945–51.

47. Jaquet D, Leger J, Levy-Marchal C, Oury JF, Czernichow P. Ontogeny of leptin in human fetuses and newborns: effect of intrauterine growth retardation on serum leptin concentrations. J Clin Endocrinol Metab. 1998;83:1243–6.
48. Attig L, Djiane J, Gertler A, Rampin O, Larcher T, Boukthir S, et al. Study of hypothalamic leptin receptor expression in low-birth-weight piglets and effects of leptin supplementation on neonatal growth and development. Am J Physiol Endocrinol Metab. 2008;295:E1117–25.
49. Guan H, Arany E, van Beek JP, Chamson-Reig A, Thyssen S, Hill DJ, et al. Adipose tissue gene expression profiling reveals distinct molecular pathways that define visceral adiposity in offspring of maternal protein-restricted rats. Am J Physiol Endocrinol Metab. 2005;288:E663–73.
50. Glavas MM, Kirigiti MA, Xiao XQ, Enriori PJ, Fisher SK, Evans AE, et al. Early overnutrition results in early-onset arcuate leptin resistance and increased sensitivity to high-fat diet. Endocrinology. 2010;151:1598–610.
51. McMillen IC, Edwards LJ, Duffield J, Muhlhausler BS. Regulation of leptin synthesis and secretion before birth: implications for the early programming of adult obesity. Reproduction. 2006;131:415–27.