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Minireview

Leptin in Pregnancy: An Update[1]

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ABSTRACT

Leptin influences satiety, adiposity, and metabolism and is associated with mechanisms regulating puberty onset, fertility, and pregnancy in various species. Maternal hyperleptinemia is a hallmark of mammalian pregnancy, although both the roles of leptin and the mechanisms regulating its synthesis appear to be taxa specific. In pregnant humans and nonhuman primates, leptin is produced by both maternal and fetal adipose tissues, as well as by the placental trophoblast. Specific receptors in the uterine endometrium, trophoblast, and fetus facilitate direct effects of the polypeptide on implantation, placental endocrine function, and conceptus development. A soluble isoform of the receptor may be responsible for inducing maternal leptin resistance during pregnancy and/or may facilitate the transplacental passage of leptin for the purpose of directly regulating fetal development. The steroid hormones are linked to the regulation of leptin and the leptin receptor and probably interact with other pregnancy-specific, serum-borne factors to regulate leptin dynamics during pregnancy. In addition to its effects on normal conceptus development, leptin is linked to mechanisms affecting a diverse array of pregnancy-specific pathologies that include preeclampsia, gestational diabetes, and intrauterine growth restriction. Association with these anomalies and with mechanisms pointing to a fetal origin for a range of conditions affecting the individual's health in adult life, such as obesity, diabetes mellitus, and cardiovascular disease, reiterate the need for continued research dedicated to elucidating leptin's roles and regulation throughout gestation.

conceptus, leptin, leptin receptor, placenta, pregnancy

INTRODUCTION

Leptin is the hormone product of the *LEP* gene and was originally thought to be produced only by adipocytes to aid in modulating satiety and energy homeostasis [1, 2]. However, the polypeptide is now known to be produced in many tissues and enhanced levels are associated with the advent of reproductive maturity and fertility [3, 4]. Regulatory mechanisms are linked to gender, as women of reproductive age exhibit higher serum concentrations than comparably aged men. Similarly, levels in female fetuses [5, 6] and neonates [7, 8] are higher than in their male counterparts and levels in premenopausal women may be greater than those following menopause [as reviewed, 9–11]. Leptin functions via a specific receptor that is a member of the class I cytokine receptor superfamily and is manifested in alternatively spliced isoforms that are distinguished by the relative lengths of their cytoplasmic regions. These include a long form ($LEPR_L$) that predominates in the hypothalamus, and a short form ($LEPR_S$) that is found in many organs and tissues. $LEPR_L$ exhibits consensus amino acid sequences involved in binding to Janus tyrosine kinases (JAK/STAT), while $LEPR_S$ has distinct signaling capabilities involving mitogen-activated protein kinase (MAPK) [12]. A soluble, circulating leptin receptor (solLEPR) is generated in humans by the proteolytic cleavage of membrane-bound receptors [13]. Mice [14] and rats [15] manifest their own version of the circulating receptor ($LEPR_E$), which is specifically expressed in copious amounts in the placenta. In pregnancy, as in some forms of obesity, "leptin resistance" may result from inhibited transport across the blood-brain barrier [16] or sequestration of bioactive leptin in the circulation by a soluble receptor [17, 18].

Leptin/Leptin Receptor Ontogeny in Pregnancy

Because of the wealth of research published over the last decade concerning its importance during pregnancy, we will focus primarily on the years following our last minireview of the subject [9]. As previously documented [9–11, 19–21], serum leptin concentrations are elevated throughout human pregnancy. Increases in the first trimester, before any perceptible increase in body weight due to progressive gestation, imply that factors other than increased adiposity modulate levels. Leptin concentrations rise along with estrogen and are correlated in early pregnancy with those of hCG. Fetal adipose tissue produces leptin [22], although the decline in neonatal levels following birth may denote the placenta's role as an important contributor to fetal concentrations [23]. The presence of leptin mRNA transcripts in the placental syncytiotrophoblast initially lead to the contention that the increase in maternal levels with advancing gestation might originate there [24]. In this regard, we have reported that transcripts for *LEP*, as well as for $LEPR_L$ and $LEPR_S$ leptin receptor isoforms, were expressed both early (7–14 wk) in gestation and at term, and in situ hybridization localized them in the endocrinologically active trophoblast [25]. The logical

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presumption of a placental contribution to maternal hyperleptinemia can also be traced to two other observations. The first is the postpartum decline in leptin levels typically observed after the placenta is delivered, although the decline in leptin is relatively prolonged for a hormone with such a short half-life. The second results from the findings of placental perfusion studies. In contrast, however, we have examined (unpublished results) the role of placental mass in the rat by adjusting the number of fetal-placental units shortly after implantation, so that pregnant rats had 1–2, 4–5, or >10 implantation sites. Maternal serum leptin levels were highest in animals with fewer implantations and, conversely, were least in those with the greatest number of implantations. we also compared maternal serum leptin concentrations in women (15–20 wk of gestation) with singleton or twin pregnancies, and mean leptin levels and leptin levels plotted against BMI were virtually identical for both groups. Serial samples from singleton, twin, and triplet pregnancies demonstrated that placental number was not related to maternal serum leptin levels but rather that maternal adiposity was the controlling factor. These ongoing studies, as well as our work in nonhuman primates [as reviewed, 10, 11], suggest that increases in maternal leptin levels are not directly related to increases in placental mass, implying rather that the hormonal milieu of pregnancy upregulates the synthesis of leptin by maternal adipose tissue.

Leptin/leptin-receptor regulation and function in rodent pregnancy [26–28] differ significantly from that during pregnancy in both humans [25] and nonhuman primates [29–31]. Thus, although maternal peripheral leptin concentrations increase with gestational age in the human, *LEP* mRNA in placental villous tissue is greater in the first trimester than at term [25]. In contrast, Amico et al. [32] reported that, in the rat, placental *Lep* mRNA increased 4- to 5-fold over the final one third of pregnancy, while Garcia et al. [33] observed that *Lep* mRNA in placenta increased in abundance throughout gestation. In the mouse, although leptin transcripts may be expressed in both the placenta and fetus [34], the polypeptide does not appear to exert any physiological effects in either. Indeed, there is some disagreement as to whether the mouse placenta produces any leptin at all [35]. Consequently, Zhao et al. [36] concluded that the regulation of leptin in pregnancy is taxa specific and, although representatives of three orders (Chiroptera, Rodentia, Primate) exhibit pregnancy-associated hyperleptinemia, they accomplish it by different mechanisms. The highly conserved nature of this trait indicates, however, that leptin plays fundamental physiological roles in mammalian pregnancy.

To better understand the mechanisms regulating leptin dynamics in human pregnancy, we have employed a well-characterized nonhuman primate model, the baboon (*Papio* sp.), an Old World primate [37–39] that differs in some respects from New World monkeys [30] with regard to leptin production. In this species, leptin concentrations in pregnant animals are much higher than in either cycling or postpartum baboons and increase approximately 2.5-fold between days 60 and 160 of gestation [29]. Normal term in the baboon is approximately 184 days. As in humans, leptin transcripts in placental villous tissue decline between early and late gestation, but maternal serum leptin levels increase almost 3-fold with pregnancy and are correlated with advancing gestational age. Because the presence of both leptin and its receptor in the placenta [24, 25], amnion, chorion, and umbilical vasculature [40] suggest important roles in human pregnancy, we assessed these tissues, as well as omental and subcutaneous fat at early (Day 60), mid (Day 100), and late (Day 160) baboon pregnancy [41]. A resurgent corpus luteum and decidual tissue were also collected on Day 160, as was fetal brain (hypothalamic region). Expression of $LEPR_L$ and $LEPR_S$ mRNA transcripts were detected by RT-PCR in all tissues, using human leptin receptor primers. Transcripts for both isoforms were constitutively expressed throughout gestation in placenta and adipose tissue, with the short form expressed in greater abundance than the long form in all tissues examined. This agrees with prior reports that $LEPR_L$ transcripts typically occur in lesser abundance in peripheral tissues than those encoding short intracellular domain forms [12]. As in humans [25], in situ hybridization localized transcripts for leptin and both receptor isoforms in baboon trophoblast. Expression intensity for leptin was greatest in early pregnancy, which mirrored the enhanced abundance of *LEP* transcripts at that time [29].

Increases in maternal serum leptin levels with advancing gestation has always presented a conceptual problem for those attempting to explain the rise in a perceived satiety factor during gestation, a period of increased nutritional demand. Although there is some disagreement as to whether soluble leptin receptor concentrations increase [42] or remain the same [43] with pregnancy in women, we have advocated that an increase in the amount of a soluble isoform of the leptin receptor and, hence, the level of bound/complexed leptin in the maternal circulation increases with advancing gestational age [9–11]. This increase would serve to reduce the availability of the hormone to hypothalamic receptors and prevent any inhibitory influence on food intake during this developmental period. In the human, at least two soluble leptin receptor isoforms bind leptin and perhaps potentiate leptin resistance [44, 45], with an increase in this protein having been proposed to explain the enhancement in maternal leptin typical during mammalian pregnancy [46]. A report by Schulz et al. [47] identified two isoforms of the leptin receptor in human placenta that are similar in size to those we have identified in the baboon [48]. Collectively, results associate pregnancy-specific tissues with the production of leptin receptor and suggest that increasing receptor concentrations could play a role in regulating leptin availability in primates.

Roles of Leptin in Pregnancy

Many physiological roles have been suggested for leptin in human pregnancy [9–11, 19–21]. As in the corpus luteum of luteal-dependent species [49, 50], both leptin and leptin receptors have been identified in the placental syncytiotrophoblast, which suggests the potential for autocrine and paracrine mechanisms in a tissue that produces hormones necessary for the maintenance of primate pregnancy [37, 51]. Cultured cytotrophoblast cells produced leptin and the addition of recombinant leptin enhanced hCG release [52]. Leptin also stimulated hCG secretion by human placental explants and was responsible for both the induction of hCG pulses and enhancement of their amplitude [53]. A recent report indicated that leptin also activated the release of proinflammatory cytokines and prostaglandins from human placental explants, further implicating leptin as a modulator of placental endocrine function [54]. Intriguingly, the expression of leptin and leptin receptor in human placenta [55] and uterine endometrium [56] and the observation that endometrial leptin secretion is enhanced in the presence of a viable blastocyst link the polypeptide to early conceptus development [57, 58] and suggest its place among the array of regulators active during the aposition and adhesion phases of implantation [59–62]. Recent work also suggests that leptin augments the oocyte's

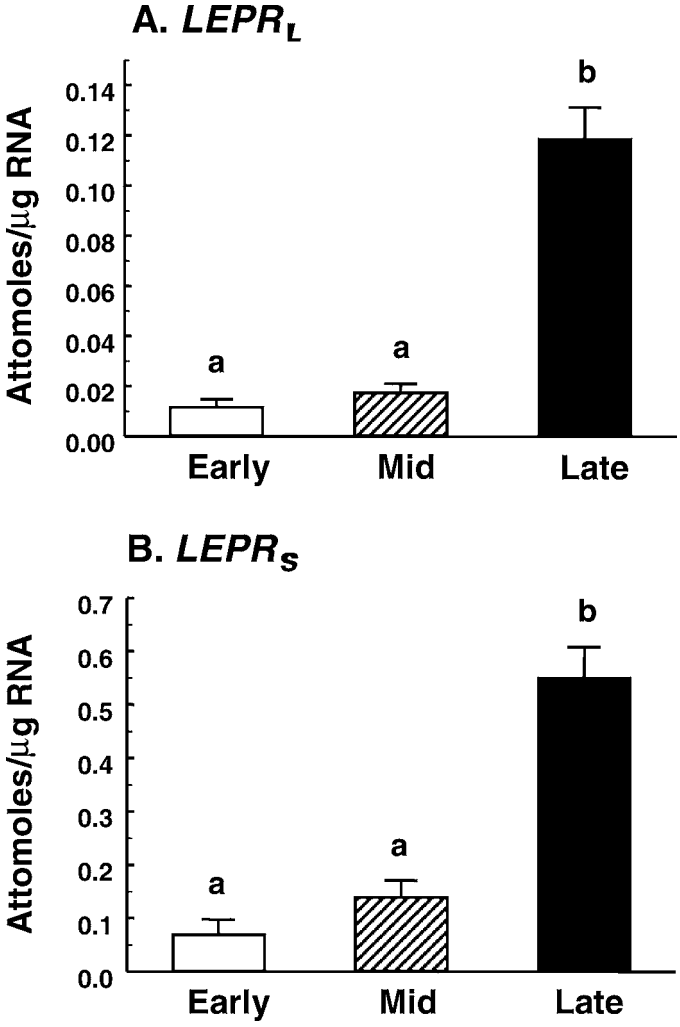

FIG. 1. $LEPR_L$ (**A**) and $LEPR_S$ (**B**) mRNA transcript abundance, as determined by competitive RT-PCR in fetal lung tissues collected in early (n = 4 fetuses), mid (n = 4 fetuses), and late (n = 4 fetuses) baboon pregnancy. Different lowercase letters indicate significant differences between means ± SEM (ab, $P < 0.01$). As adapted from Henson et al. [100] by permission of the Society for Reproduction and Fertility.

ability to sustain embryonic development and potentiates a downregulation of apoptosis in the early blastocyst [63]. Because leptin receptor is expressed in maternal decidua and the uterine endometrium is identified as a target for leptin action, a definitive role is suggested in the blastocyst-endometrial dialogue [64–67]. In this capacity, the obligatory nature of leptin signaling in mammalian implantation [68] was illustrated by experiments in the mouse that demonstrated that endometrial leptin receptor expression was pregnancy dependent and that intrauterine injection of a leptin peptide antagonist or a leptin antibody impaired implantation. To this end, leptin enhances the invasiveness of mouse trophoblast cells in vitro via the upregulation of matrix metalloproteinases and may thereby play its role in early placental development [69]. Because the expression of leptin mRNA was increased severalfold in bovine placentomes from conceptuses produced by nuclear transfer, it was proposed that this effect could account for the increased fetal/placental macrosomia noted in conceptuses produced by this technique and be owed to aberrations in cell migration and invasion [70].

In addition to its relationship with early embryonic development and implantation, leptin has been linked to the regulation of fetal growth, as concentrations of the polypeptide in umbilical cord blood were highly correlated with birth and placental weights [71, 72], an effect that was unrelated to the influences of other growth regulators [72–75]. Levels were also correlated with infant length [7, 75] and head circumference [75], and postnatal leptin administration restored the depressed brain weights of leptin-deficient Lep^{ob}/Lep^{ob} neonates [71, 76]. Interestingly, Smith and Waddell [77] proposed that, in the rat, a soluble form of the leptin receptor may actually serve as the physiological vehicle responsible for the transplacental movement of leptin into the fetal circulation for the purpose of modulating fetal growth. This same investigational team recently expanded its original observations in rodents to examine similar mechanisms in a human BeWo choriocarcinoma cell model [78]. The results of these experiments strongly suggested a potential for maternal-fetal leptin exchange across the human placenta, as well.

Because umbilical leptin concentrations have been associated with whole-body mineral content [79], the polypeptide has been proposed to directly stimulate fetal bone growth [80]. This effect could be potentiated via changes in the rates of osteoblast/osteoclast growth and differentiation [81, 82] or by the inhibition of bone resorption, resulting in a net increase in bone mass [83]. The ability of adipocyte-derived leptin to regulate osteogenic cells was also noted by Morroni et al. [84], who reported that growing rat bone expresses leptin in chondrocytes and stromal cells that may interact in a paracrine manner with specific receptors on osteogenic cells. Prior work had also suggested that leptin not only acted on human marrow stromal cells to enhance differentiation into osteoblasts and inhibit differentiation into adipocytes, but influenced endochondral ossification by regulating angiogenesis [85]. This angiogenic role has been demonstrated in various developmental models [86, 87]. With respect to the means by which it could facilitate angiogenesis in pregnancy, the polypeptide was reported to enhance vascular endothelial growth factor synthesis in cultured human cytotrophoblast cells [88].

Leptin may also be associated with pulmonary development in utero. In this capacity, insufficient maturation of the fetal lungs is a condition that can be characterized by inadequate production of pulmonary surfactant by epithelial type II cells. Increasing cortisol at term prompts the differentiation of type II cells and surfactant synthesis [89], although in preterm infants, surfactant levels are insufficient and pulmonary insults lead to acute lung injury and, potentially, chronic lung disease. Torday et al. [90] observed that leptin was expressed by fibroblasts and that leptin receptor was expressed in fetal rat lung type II cells. Subsequent experiments indicated that leptin plays a direct role in enhancing surfactant production in this species [91]. Recent investigations suggested the need to identify and characterize the array of growth factors potentially affecting pulmonary development [92]. Therefore, although it is well accepted that the maturation of type II cells is modulated by a number of soluble, low molecular-weight peptides, the identity of a specific fibroblast pneumocyte factor (FPF) remains elusive. This putative protein regulator promotes surfactant production and is downregulated by androgens [90], similarities that exist between it and leptin. In this respect, lung development in male fetuses is somewhat delayed when compared with females in many species, a phenomenon that reflects an inhibition by androgens [93]. This effect is mirrored by the inhibition of leptin biosynthesis by androgens, a phenomenon that is linked to gender [94, 95]. Other regulatory parallels include the effects of glucocorticoids, which, in addition to upregulating the putative FPF in the lung [89], increase leptin production by human adipocytes [96] and enhance leptin levels in preterm

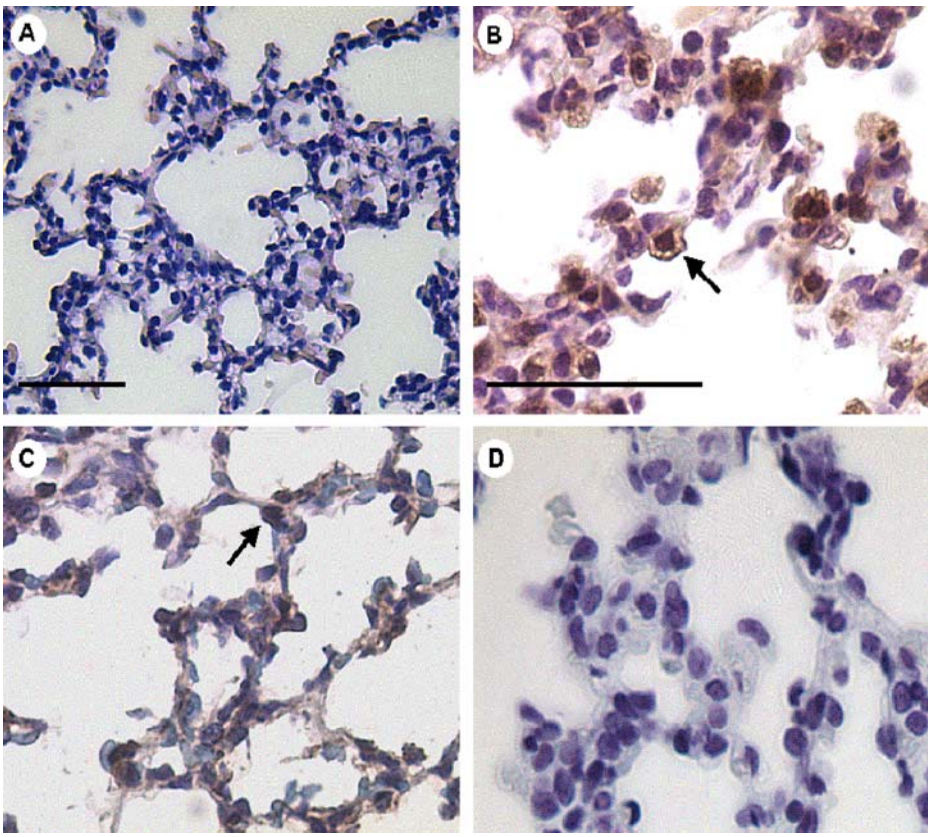

FIG. 2. Photomicrographs of lung tissue from fetal baboons in late gestation depicting the results of hematoxylin-eosin staining (**A**), and immunohistochemical localization of surfactant protein A (**B**), or LEPR (**C**) protein in pulmonary epithelial cells. A negative (**D**) (without primary antibody) immunohistochemical control for LEPR is included. Arrows denote pulmonary type II cells. Original magnification: A ×200; B–D ×400. Bars = 50 μm. Originally published in Henson et al. [100] and reproduced by permission of the Society for Reproduction and Fertility.

infants [97]. Moreover, leptin release was enhanced in human placental trophoblast cells by glucocorticoids [55] and maternal glucocorticoid treatment upregulated placental leptin receptor in rat pregnancy [98]. Therefore, with respect to commonalities with the proposed FPF [91, 99], leptin might be considered a logical FPF candidate [90]. We subsequently reported [100] that, in late baboon pregnancy, the abundance of $LEPR_L$ mRNA transcripts in fetal lung was approximately 10-fold greater and $LEPR_S$ transcript abundance was approximately 8-fold greater than in early pregnancy (Fig. 1). Leptin receptor protein, undetectable in fetal lungs at early and midgestation, was detected by Western blotting in late gestation and localized immunohistochemically in distal pulmonary epithelial cells, including type II cells (Fig. 2.). Therefore, because fetal serum leptin concentrations were significant and upregulation of leptin receptor occurred in late gestation, when the greatest progress toward fetal lung maturity is typically made, the potential exists for leptin to contribute to this vital process in primates.

Regulation of Leptin and Leptin Receptor by Steroid Hormones

Gender-based differences in the regulation of leptin synthesis are mediated by the steroid hormones [101, 102] and increases in serum leptin levels in early pregnancy may be owed to the stimulation of maternal adipose tissue by gestational steroids [103, 104]. Placental estrogens increase with advancing gestation and regulate multiple endocrine pathways [37], Thus, estradiol (E_2) administration enhanced the expression of leptin mRNA transcripts and protein secretion by adipocytes, both in vitro [102, 103] and in vivo [105]. Similarly, *Lep* expression in isolated rat adipocytes was inhibited by an estrogen receptor antagonist, while coincubation with a transcriptional inhibitor, prevented E_2-induced increases in mRNA transcripts [106]. Also in rats, ovariectomy diminished *Lep* gene expression in white adipose tissue and caused a decline in serum leptin levels [107, 108], while administration of E_2 reversed all the effects of ovariectomy. Ovariectomy was also reported to reduce serum leptin levels in humans [109]. Although leptin and E_2 demonstrate similar profiles during the human menstrual cycle [110], disparate effects of estrogen on leptin synthesis in postmenopausal women have been reported [111], possibly as a result of variations in treatment regimens or patient adiposity. Further reports [112–114] suggest that leptin levels in women were not affected by the relatively small increases in estrogen associated with normal menstrual cyclicity, but were upregulated by the large increases in estrogen that typically result from ovulation induction, effects that may cast estrogen in the role of a dose-dependent regulator. However, as commensurate administration of E_2 and progesterone to normally cycling women resulted in a dramatic increase in serum leptin concentrations, mechanisms relying on cooperation between the two steroids might also be implied [110]. Such cooperation might help explain the increased leptin concentrations common during the luteal phase of the menstrual cycle [115], although the reports that progesterone inhibited leptin secretion by rat adipocytes [116] and cultured, term human placental cells [117] further suggest species- and/or tissue-specific regulation by steroids.

Estrogens have been reported to regulate leptin expression by acting on a portion of the estrogen response element in the leptin promoter [106, 118]; with leptin production by cultured first-trimester human cytotrophoblast cells being dose-responsively potentiated by E_2 [as reviewed, 119]. The presence of estrogen receptor in primate trophoblast [120] suggests that, as in adipose tissue [121], this is an estrogen receptor-mediated phenomenon. However, this effect has not yet been reported in syncytiotrophoblast collected in early pregnancy, or in long-term cultures of either purified cyto- or syncytiotrophoblast

collected in the second trimester or at term. Certainly, significant differences with respect to mechanisms influencing hormone synthesis exist for cells collected in first vs. third trimesters [122] and Bajoria et al. [21] concluded the potential effects of gestational age must be elucidated to fully understand leptin's role in pregnancy. Estrogen administration was also reported to elicit an increase in hypothalamic expression of the long form of the leptin receptor [123] in rats. This potential was originally put forward by Lindell et al. [124], who reported that a putative estrogen response element, close to the most frequently used transcriptional start sites of the leptin receptor gene in the rat hypothalamus, might be a mechanism by which estrogen regulates the leptin receptor. Differences in peripheral leptin concentrations could, therefore, also result from enhanced concentrations of solLEPR, which could slow metabolic clearance of the polypeptide and retain it in the circulation [42]. In this regard, serum E_2 concentrations in women were correlated with circulating levels of soluble receptor, further suggesting the potential for alterations in leptin concentrations during periods of high estrogen availability, such as pregnancy [125].

We have hypothesized that elevated maternal leptin levels may be owed to enhanced transcriptional regulation in maternal adipose tissue and/or placenta, resulting from enhanced estrogen levels during pregnancy. Like the human, the baboon possesses a true maternal-fetoplacental unit, which relies on androgen precursors from the fetal adrenal gland for placental estrogen synthesis [37]. Thus, the surgical removal of the fetus, but not the placenta (fetectomy) at Day 100 of gestation inhibits estrogen production by the syncytiotrophoblast and reduces maternal serum E_2 levels to near baseline. Therefore, we collected placental villous tissue, omental adipose tissue, and subcutaneous adipose tissue from baboons in late (Day 160) pregnancy [126]. In another group of pregnant baboons, estrogen production was inhibited at Day 100 by fetectomy. Placentas were left in situ until Day 160 of gestation when, following laparotomy and hysterotomy, they were retrieved. Maternal adipose tissues were collected at both Days 100 and 160 of pregnancy. Although fetectomy did not result in a decline in maternal estradiol to a level that would approximate levels in nonpregnant baboons, it did elicit an 87% decrease in maternal serum E_2 concentrations. Leptin levels were essentially unaltered by fetectomy. However, in subcutaneous fat, the abundance of *LEP* mRNA transcripts declined about 5-fold as a consequence of fetectomy, while transcripts increased almost 3-fold in placental villous tissue. Leptin protein was quantitated by RIA in tissue homogenates collected near term. In subcutaneous fat, leptin levels in fetectomized baboons were approximately one half that of controls, while in placenta levels were 3-fold higher in fetectomized animals than in those with intact pregnancies. Therefore, although adipose leptin expression declined, increased placental expression suggested a compensatory mechanism and a tissue-specific regulatory role for estrogen (stimulatory in adipose tissue, inhibitory in placenta). In this regard, the potential for divergent transcriptional regulation in placenta and adipose tissue was previously known to exist due to the presence of a functional enhancer for the *LEP* gene in placental cells that is not present in adipocytes [127, 128]. The tissue-specific influence of estrogen in baboon pregnancy reinforces prior reports of divergent, tissue-specific effects of estrogen on leptin transcription [106, 129, 130].

As in humans, serum estrogen levels in nonpregnant baboons are dramatically lower than those during pregnancy. One might hypothesize, therefore, that, because the abundance of *LEP* mRNA transcripts in adipose tissue declined following fetectomy, increased estrogen levels in pregnancy would prompt commensurate increases in *LEP* transcripts in adipose tissue. When venous blood and adipose tissues were collected from nonpregnant baboons in the midluteal phase of the menstrual cycle and from pregnant animals throughout gestation, E_2 concentrations were lowest in cycling animals (0.06 ± 0.02 ng/ml) and increased with pregnancy and advancing gestation (4.17 ± 0.87 ng/ml on Day 160), as expected. However, although the abundance of *LEP* mRNA transcripts in adipose tissue was unchanged with regard to pregnancy or advancing gestation, tissue leptin concentrations in subcutaneous fat were significantly higher in pregnant than in nonpregnant baboons. Further, leptin increased in adipose tissue with advancing gestation. In addition, leptin receptor was assessed by immunoblotting in maternal serum, placenta, decidua, and amniochorion with advancing baboon pregnancy and with fetectomy [48]. Soluble receptor levels in serum increased approximately 60% between early and late normal pregnancy, with levels in fetectomized (estrogen-deprived) baboons being less than one half that in pregnancy-intact controls. The 3-fold increase in soluble receptor over that of nonpregnant baboons was identical to that observed by Kado et al. [42] in human pregnancy. Soluble receptor was only minimally detectable postpartum. The enhanced presence of the serum-borne receptor during pregnancy may implicate it in the regulation of maternal/fetal leptin levels and perhaps as a mediator of pregnancy-specific leptin resistance. Perhaps in this capacity, one 130-kDa isoform of the leptin receptor was identified in decidua and amniochorion. In decidua, this receptor increased 4-fold and, in amniochorion, increased 10-fold from early to late gestation. As shown in Figure 3, two isoforms (130 kDa, 150 kDa) of the leptin receptor were present in placental villous tissue. Levels of the 130-kDa isoform increased 3-fold in placental villous tissue from early to late normal gestation. Following fetectomy at midgestation, the 150-kDa isoform declined 50% ($P < 0.01$).

Glucocorticoids also enhance leptin synthesis and secretion in adipose tissues [96, 131, 132]. In ovine pregnancy, treatment with cortisol or dexamethasone increased fetal leptin concentrations, while adrenalectomy suppressed them [131], an effect reminiscent of the impaired leptin production in glucocorticoid-deficient mice [133]. Yuen et al. [134] reported that leptin infusion shortly before ovine delivery suppressed fetal cortisol concentrations by approximately 40%, providing evidence for a negative feedback loop between leptin and the fetal hypothalamic-pituitary-adrenal (HPA) axis. Leptin levels in women suffering spontaneous abortions in the first trimester were abnormally low, implying a direct role for the polypeptide in pregnancy maintenance [135]. Indeed, recombinant leptin infused into the fetal circulation inhibited activation of the HPA axis in late ovine pregnancy, suggesting that mechanisms controlling the initiation of labor might be fine tuned by a metabolic cue that is related to fetal growth and originates in the placenta or fetal adipocytes [136]. With respect to the leptin receptor, maternal treatment with dexamethasone reduced leptin receptor mRNA in both porcine adipose tissue [137] and rat placenta [138, 139], interruptions in leptin signaling that might be traced to direct inhibition of the JAK/STAT pathway [140]. Enhanced cortisol levels in female adolescents, however, were highly correlated with circulating solLEPR concentrations [141], perhaps indicative of regulation of the cleavage of membrane-bound receptor [13]. These effects suggest that glucocorticoid-induced intrauterine growth restriction (IUGR) could be mediated, at least in part, by leptin/leptin receptor regulation in fetal adipose tissue or the placenta.

Just as estrogen and corticosteroids are associated with the enhancement of leptin synthesis, androgens are linked to leptin inhibition [142]. In healthy men, testosterone concentrations were negatively correlated with leptin in serum [143, 144], while in prostate cancer patients treated with a nonsteroidal antiandrogen, leptin levels rose [145]. These effects may be mirrored to some degree by the weaker androgens, as administration of dehydroepiandrosterone (DHEA) to women exhibiting adrenal insufficiency led to a decline in serum leptin levels, as compared with placebo-treated controls [146]. Similarly, it was reported that DHEA [147], DHEA-sulfate, androstenedione, and nonaromatizable dihydrotestosterone [94] are potent inhibitors of leptin secretion by adipose tissue [147]. In contrast, Machinal-Quelin et al. [148] reported a stimulation of leptin production by DHEA and testosterone in women's adipose tissue, although such effects may be owed to subsequent aromatization to estrogens. The relative effects (stimulatory or inhibitory) of the high levels of androgens in pregnancy [37, 120] are unknown.

Leptin and Pregnancy-Associated Pathologies

Decreases in placental *LEP* mRNA have been linked with decreased leptin concentrations in umbilical vein blood in cases of IUGR [149], suggesting that leptin influences fetal growth in response to a fetal demand that is relative to placental supply [150]. Studies of a twin pregnancy noted that a growth-restricted twin had markedly lower placental and cord blood leptin than its normal-size sibling [151] and that low cord-blood leptin levels directly reflected low concentrations in placenta. Subsequent observations from monochorionic twin pregnancies revealed that fetal and cord leptin levels were at least 2-fold higher in normal-size fetuses than in their growth-restricted twins [152], indicating a pivotal role in regulating growth [153]. Decreased leptin levels in cord and placenta of growth-restricted twins may be indirectly reflected by high levels in amniotic fluid and an increased rate of premature delivery that investigators postulated was attributable to hypoxia and poor cytrophoblastic invasion [154]. Interestingly, fetuses in the normal-weight range exhibit either no correlation [155] or an inverse correlation [156] between conceptus mass and cord leptin concentrations with leptin levels in amniotic fluid, perhaps indicating a divergence in the mechanisms regulating leptin synthesis in these compartments. This specificity of mechanisms among components of the maternal-fetoplacental unit was also proposed in both normal and IUGR singleton pregnancies [157, 158]. IUGR babies maintain relatively low leptin levels as adults, suggesting permanently altered adipocyte function [159].

Perhaps related to leptin's role in implantation, preeclampsia is associated with shallow endometrial invasion, the sudden onset of maternal hypertension, and enhanced maternal and fetal leptin concentrations that are dramatically enhanced over the level of hyperleptinemia characteristic of human pregnancy [160–167]. This exacerbated increase in the maternal peripheral circulation, coupled with poor cytotrophoblastic invasion, typifies the preeclamptic state and serves as a marker for general placental insufficiency [168] and poor placental perfusion [169]. In a microarray analysis, placental susceptibility genes most likely to be associated with onset of the condition were evaluated and *LEP* was upregulated approximately 44-fold, an elevation reflected by commensurate protein levels [165]. Enhanced expression of *LEP* mRNA transcripts in placental tissue from preeclamptic women, over that of tissue from women with normal pregnancies, did not extend to a similar upregulation in maternal subcutaneous adipose tissue,

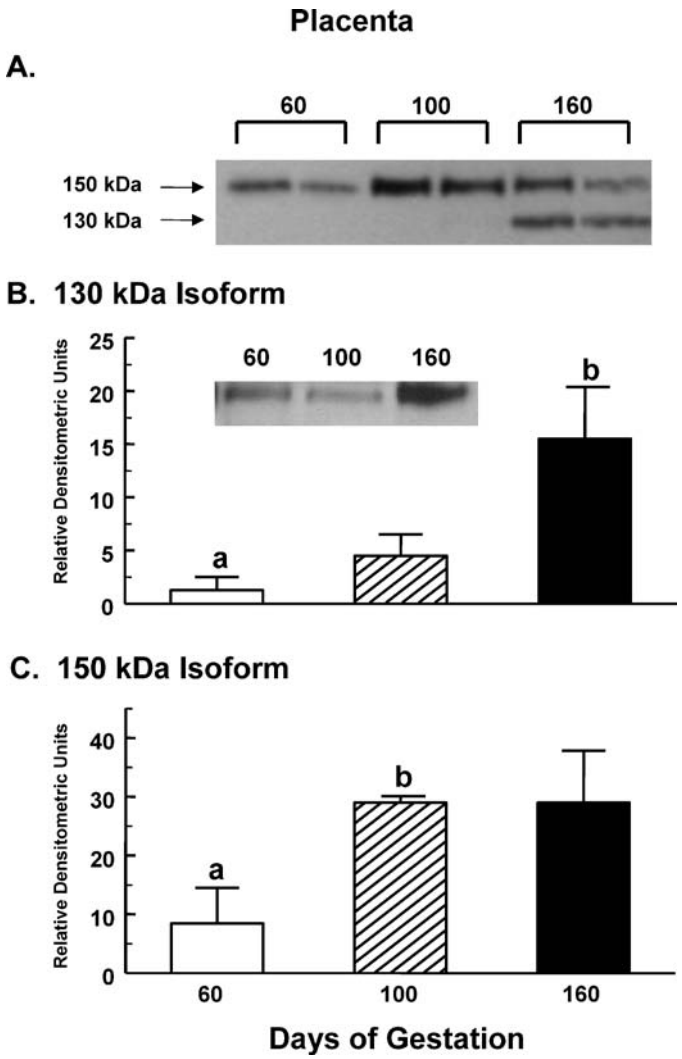

FIG. 3. Relative abundances of leptin receptor isoforms detected in placental villous tissue at approximately 60 (n = 2), 100 (n = 2), and 160 (n = 2) days of gestation (**A**). Relative densitometric units were determined for band intensities from immunoblots, and these values plotted for each isoform as the mean ± SEM. A 130-kDa isoform (**B**, n = 4) increased in abundance between days 60 and 160 of gestation (inset: representative immunoblot with conditions optimized for imaging the isoform at early and midgestation). Levels of a 150-kDa isoform (**C**, n = 4) increased between days 60 and 100 of gestation. Different lowercase letters indicate significant differences between means (ab, $P < 0.04$ and $P < 0.02$ for **B** and **C**, respectively). Originally published in Edwards et al. [48].

further suggesting a specificity of placental involvement [170]. Even in preeclamptic women that had not yet evidenced elevated peripheral leptin levels, ratios of amniotic fluid leptin to maternal serum leptin were elevated and identified the very early stages of the condition [171]. Indeed, leptin has been found to be associated with maternal hypertension that may or may not proceed to preeclampsia [172, 173]. Preliminary evidence suggests that this exaggerated hyperleptinemia is a compensatory response to increase nutrient delivery to an underperfused placenta [174] and may be linked to both maternal adiposity and changes in bioavailable estrogen concentrations [175]. Although preeclampsia-associated hyperleptinemia has also been linked to enhanced solLEPR [176], conflicting reports [177, 178] call for further investigation.

As previously reviewed [11], pregnancy-associated diabetes is another pathology characterized by increased placental leptin contributions to enhanced maternal leptin levels [179, 180].

Cord leptin levels in diabetic pregnancies were strongly correlated with both conceptus growth and the degree of glycemic control [181, 182], and among the offspring of gestational diabetics, serum leptin levels were enhanced over population norms until at least 9 yr of age [183]. Yuen et al. [184] reported that leptin administered in ovine pregnancy regulated fetal fat storage, leptin synthesis, and thermogenesis, suggesting a lipostatic function in utero. This role may be important when the fetus is exposed to an increased transplacental energy supply, as in pregnancies complicated by maternal glucose intolerance and fetal hyperglycemia. Although there is no evidence of leptin production in the ovine placenta [185], the potential of the placenta to contribute to the maternal leptin pool exists in primates as an enhanced hyperleptinemia in early pregnancy that is predictive of gestational diabetes is independent of maternal adiposity [186]. Interestingly, a recent report contends that leptin release from placental explants was less for tissues derived from women with gestational diabetes than for tissue derived from women with normal pregnancies [187]. Maternal adipose and skeletal muscle tissues from gestational diabetics, however, released significantly more leptin than did the same tissues from unaffected women.

Both preeclampsia [188] and pregnancy-associated diabetes [189] are associated with fetal hypoxia. To this end, Grosfeld et al. [190, 191] investigated the potential for decreased oxygen tension to upregulate leptin gene expression in human trophoblast-derived BeWo choriocarcinoma cells. The *LEP* gene was upregulated in this cell line by hypoxia, as previously demonstrated in preadipocytes [192], an effect mediated through activation of distinct *cis*-acting sequences of the leptin promoter [193]. This result may confirm the specificity of the placental gene promoter, although the effects of hypoxia have yet to be studied in normal trophoblast cells.

Leptin and the Fetal Origins of Adult Health and Disease

Since Barker et al. [194, 195] originally postulated the relationship between low birthweight and the later manifestation of diseases, such as diabetes mellitus, hypertension, and coronary heart disease in adulthood, much interest has been generated in the fetal-programming paradigm. Into this arena, leptin has emerged as an important player, with Bouret and colleagues [196, 197] suggesting that alterations in leptin levels in utero prompt substantive hypothalamic changes in fetuses that eventually result in altered nutritional intake, energy metabolism, and adiposity in children and adults. In the rat, dexamethasone-induced IUGR, which culminates in high rates of adverse outcomes in adult offspring, is now known to directly result in a decline in fetal leptin concentrations due to a reduction in the transplacental passage of the polypeptide [77]. Intriguingly, the likely effects of reduced fetal leptin in IUGR-induced fetal programming (obesity, hyperinsulinemia, hyperphagia, reduced locomotor activity, etc.) may be effectively counteracted by neonatal leptin treatment [198]. In addition to studies in rodents, observations in sheep mimic those in women subjected to famine, which suggest that cardiovascular physiology and phenotypic predisposition to obesity are programmed as a natural component of fetal development [199]. With respect to fetal undernutrition, neonatal mice subjected to poor nutrition in utero responded to a high-fat diet with a premature onset of the leptin surge typical of young mice subjected to normal nutrition in utero [200]. This earlier-than-expected advent of the routine neonatal leptin surge strongly suggests that alterations to the fetal hypothalamic circuitry can be responsible for alterations in adiposity and energy homeostasis in later life. Recently, this interaction of leptin with mechanisms potentially responsible for a fetal origin for many adult diseases was addressed quite clearly by Lecklin and colleagues [201]. Female rats that were injected with a recombinant adeno-associated virus vector that encoded the leptin gene, evidenced decreased food intake and commensurate loss of body weight, traits that were maintained throughout their subsequent breeding, pregnancies, and deliveries. Although these primary results served to illustrate the investigators' main goal of demonstrating the long-term efficacy of *LEP* gene therapy to elicit weight loss, further observations confirmed that the first generation offspring of leptin-transgene-expressing females also weighed significantly less than peer controls and maintained this difference into adulthood. While elucidation of the mechanisms by which leptin-induced reductions in maternal weight elicited weight losses in offspring must await further investigation, results of this and prior studies further confirm leptin's role in potentiating normal conceptus development and programming metabolic processes important to adult health.

SUMMARY

In only a little more than a decade since leptin's discovery and its initial association with satiety and energy balance, it is now evident that the "fat hormone" also plays important roles in reproductive biology. Thus, a thorough review of this field is no longer complete without its inclusion. With this in mind, we have summarized those findings relating leptin and the physiology of pregnancy reported since our last review [9] and observed that leptin is now known to play a wide range of important roles, which extend from maternal physiology to implantation and from paracrine effects in the placenta to regulation of conceptus development and fetal growth. Perinatologists and neonatologists are faced with much fertile ground for the planning of future leptin-centered investigations. However, with respect to both the current knowledge in the field and the principal concerns of the medical community, we propose that they might be well advised to focus first on better understanding 1) the tissue-specific roles and mechanisms regulating leptin in individual components of the primate maternal-fetoplacental unit, 2) the interaction(s) of the polypeptide with common pathologies, such as IUGR, preeclampsia, and pregnancy-associated diabetes, and 3) the role played by leptin in utero with respect to those metabolic anomalies associated with childhood and adult obesity and the developmental origins of adult health and diseases.

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