Physiological and pathological regulation of feto/placento/maternal leptin expression

K. Linnemann*, A. Malek†, H. Schneider† and C. Fusch*

*Neonatology, Department of Pediatrics, Ernst-Moritz-Arndt University, D-17489 Greifswald, Germany, and †Department of Obstetrics and Gynecology, Inselspital, University of Bern, CH-3012 Bern, Switzerland

Abstract
There is clear evidence of placental leptin production, as shown recently in trophoblast cultures and by dual In vitro placenta perfusion (median production of 225 pg/min per g of tissue; 98.4 % released into the maternal and 1.6 % into the fetal circulation). However, the physiological impact for the mother and the fetus is unclear. The classical role of leptin is to provide information about energy stores to the central nervous system, and to reduce appetite if the energy stores are full. In pregnancy, maternal plasma leptin concentrations are elevated, and lack the well established correlation with body fat energy stores that is observed in non-pregnant women, indicating an alternative function for leptin during pregnancy and fetal development. Maternal and fetal plasma leptin levels are dysregulated in pathological conditions such as gestational diabetes, pre-eclampsia and intra-uterine growth retardation, representing an effect or a cause of disturbances in the feto/placento/maternal unit.

Findings suggesting placental leptin production
Leptin plays a key role in weight-control mechanisms by signalling information on total body energy stores to the central nervous system (CNS) [1]. This information is mediated by the long form of the leptin receptor, which is expressed in many tissues, including the CNS and the placenta [2,3]. In addition, leptin originating from adipose tissue has a number of roles in reproduction: leptin seems to trigger the onset of puberty, and is necessary for ovulation, as it signals nutritional status to the reproductive axis [4,5].

During pregnancy, leptin levels show marked changes, suggesting the placenta as a putative source of production of leptin in addition to adipose tissue. Maternal plasma leptin levels rise sharply during the first trimester [6-10] and decline back to normal values after delivery [11-13]. Maternal leptin levels increase by a factor of 2-4 in early pregnancy [14,15] and are about 2-5-fold higher than fetal levels at term (Table 1) [16-19]. In the fetus, leptin concentrations are higher in venous than in arterial cord blood. After birth, neonatal serum leptin decreases markedly, again suggesting the placenta as an additional source of leptin during pregnancy [20,21]. However, the classical role of increased leptin levels of diminishing appetite in adults as a feedback signal from increased body energy stores to the CNS seems unlikely in pregnancy, so a new approach is required for a better understanding of the impact of elevated leptin levels in the feto/placento/maternal unit.

Evidence for placental leptin production
The suspected placental production of leptin was confirmed in cell culture experiments using trophoblasts and BeWo cells: the syncytiotrophoblast could be identified as the leptin-producing cell in the placental tissue. Green et al. [22] and Masuzaki and co-workers [23] described leptin production in the placenta, BeWo cells, a choriocarcinoma cell line and trophoblasts maturing to syncytiotrophoblasts. The expression of placental leptin was demonstrated by detection of leptin mRNA in early-gestation, mid-gestation and term placentas [24]. The transcripts of leptin and its receptor were localized in the syncytiotrophoblasts, and the expression of leptin mRNA declined during gestation [24], which is in contrast with increasing maternal plasma leptin levels in pregnancy.

Cell culture experiments, however, do not allow the precise quantification of placental leptin production or assessment of the extent to which leptin is released into the fetal and maternal circulations. Recently we demonstrated substantial leptin release in the dual-closed-loop in vitro perfusion model of the term placenta [25-27]. Briefly, in this study ten placentas from normal pregnancies were perfused for 240-840 min (me-
Cytokines and Cytokine Receptors in Fetal Growth and Development

Table I

Fetal and maternal plasma leptin levels at term

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Maternal plasma</th>
<th>Fetal cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helland et al. [16]</td>
<td>166</td>
<td>17.7 (35th week)</td>
<td>Girls 10.8; boys 7.6</td>
</tr>
<tr>
<td>Schubring et al. [14]</td>
<td>27</td>
<td>20.0</td>
<td>Vein 8.9; artery 9.7</td>
</tr>
<tr>
<td>Yura et al. [21]</td>
<td>38</td>
<td>29.5</td>
<td>Vein 12.9; artery 9.8</td>
</tr>
<tr>
<td>Geary et al. [17]</td>
<td>39</td>
<td>11.8</td>
<td>4.2*</td>
</tr>
<tr>
<td>McCarthy et al. [19]</td>
<td>24</td>
<td>27.0</td>
<td>5.4*</td>
</tr>
<tr>
<td>Lin et al. [20]</td>
<td>42</td>
<td>22.36</td>
<td>Vein 5.7; artery 0.6</td>
</tr>
</tbody>
</table>

*Origin not specified.

dian 480 min) with NCTC 135 and Earl's buffer (1:2, v/v), and leptin release into the fetal and maternal circuits was measured separately by RIA (Mediagnost, Tubingen, Germany). The total placental production rate was 225 pg of leptin/min per g of placental tissue, with 98.4% of total release into the maternal circulation and 1.6% into the fetal circulation. When compared with the release of other placental proteohormones such as human chorionic gonadotropin (hCG) and human placental lactogen (hPL), measured simultaneously in the same perfusion experiments, the relative release of leptin into the fetal circulation was considerably greater than expected for the molecular mass (leptin, 16 kDa, 1.6%; hCG, 39 kDa, 0.05%; hPL, 22 kDa, 0.05%) (Figure 1). Assuming that specific placental transport of leptin does not occur, this finding may be explained by leptin production by placental villous tree en-

![Figure 1](maternal_and_fetal_release_of_leptin_hpl_and_hcg.png)

Maternal (□) and fetal (■) release of leptin, hPL and hCG


Physiological regulation of leptin production in the feto/placento/maternal unit

Maternal

The observed increase in maternal leptin levels during pregnancy is presumably caused by placental leptin production, as well as increased leptin production by the adipose tissue. The contribution of placental leptin to plasma levels is only about 15% (estimated from our in vitro perfusion data [25]), and cannot explain the up to 2-4-fold increase in leptin levels of pregnant women at term. The residual leptin supply must come from maternal adipose tissue, possibly due to stimulation by placental hormones. Hardie et al. [12] showed a significant correlation between circulating oestradiol, hCG and leptin levels during pregnancy. Stimulatory effects on leptin production were also described for 17β-oestradiol and hCG in cell culture experiments [10,29]. hCG and leptin appear to stimulate each other's production in a mutual manner, as hCG production was also increased by leptin, as demonstrated in cytotrophoblastic cell culture in the presence or absence of Cetrorelix, an antagonist of luteinizing-hormone-releasing hormone which inhibits leptin-induced hCG secretion [29].

Insulin is another hormone involved in the regulation of placental leptin. Placental leptin mRNA and protein levels are elevated in insulin-treated diabetic pregnancies: fetal concentrations of leptin and insulin are increased in venous cord blood without modification of maternal circulating leptin levels [30]. In fact, cord blood leptin levels are elevated in infants of diabetic mothers and in
large-for-gestational-age newborns; from the current data it cannot be deduced whether this rise in leptin is caused by increased leptin production due to increased fetal fat mass or if a primary increase in leptin production stimulated by insulin may act as a fetal growth factor, therefore giving rise to large-for-gestational-age infants [31,32]. In adipocyte cell culture experiments, insulin administration provoked a dose-dependent increase in leptin protein production, and cortisol was found to potentiate this effect of insulin [33]. The physiological role of hyperleptinaemia with regard to maternal feeding behaviour during pregnancy is not fully understood, but animal data suggest that pregnancy is a maternal leptin-resistant state [34,35].

Fetal plasma leptin is derived from the placenta (leptin mRNA is detected from early gestation, i.e. weeks 7–14, up to term [24]) and from fetal adipose tissue, which appears and develops progressively from 14 weeks of gestation to term [36]. Fetal plasma leptin increases during development in utero [37], and studies have shown a significant correlation with birth weight [31,38–40]. Gender differences (lower leptin levels in males when compared with females with identical amounts of body fat) are already present at birth, and persist during later life [11,40,41]. These gender-specific differences may be due to the fact that testosterone seems to suppress leptin production. In fact, a negative correlation between leptin and testosterone levels has been demonstrated [11].

Very few investigations have been carried out into leptin regulation in the fetus. It is generally accepted that fetal leptin reflects fetal fat mass, as it does in the adult [39,42].

Insulin levels are correlated with leptin levels in large-for-gestational-age infants, and leptin is overexpressed in placentas of diabetic pregnancies [30,43]. In pre-term infants a 3-fold elevation of cord blood leptin levels was seen when mothers had received steroids antenatally compared with untreated pregnancies of the same gestational age [31]. This finding confirms the stimulatory effects of steroids on leptin production. It is likely that placental leptin release is more important for fetal than for maternal leptin levels: almost all hCG is released into the maternal circulation, thus stimulating leptin production by maternal adipose tissue. Only a very small amount of the hCG produced is released into fetal blood [25], and therefore stimulation of leptin production by hCG in fetal adipose tissue does not occur.

Fetal leptin levels are also correlated with fetal growth; leptin levels in growth-retarded fetuses are lower than in controls [43–45]. The high level of expression of leptin (and its receptor [3]) in fetal bone suggests a role for leptin in bone or cartilage development, as well as in the development of ossification and haematopoiesis during intra-uterine development [3]. The presence of mature leptin protein in several tissues of the fetus contrasts with the absence of leptin from the corresponding adult tissues [3,46]; this suggests that leptin is a growth factor in fetal development, rather than acting as a signal of fetal energy stores to the fetal CNS, as it does in adults.

In addition to factors known to be directly involved in fetal growth, recently other factors, such as retinoids, have been identified to have an impact on leptin production, at least in cell cultures. The physiological significance of these findings remains unclear [47].

Pathological regulation of leptin production in the feto/placento/maternal unit

Pre-eclampsia and hypoxia

Maternal and fetal plasma leptin levels are increased in pre-eclampsia [19,48]; however, the causes of elevated leptin production are unknown. Pre-eclampsia is considered to be a hypoxia-associated placental disorder. It has been established that hypoxia is involved in the regulation of leptin expression, and may therefore contribute to elevated plasma leptin levels in pre-eclampsia [49]. On the other hand, pro-inflammatory cytokines (e.g. interleukin-1, interleukin-6) seem to be involved in the multifactorial pathogenesis of pre-eclampsia. Stimulatory effects of interleukin-1 and interleukin-6 on leptin production have been observed [29,50], suggesting that elevated pro-inflammatory activity in pre-eclampsia promotes augmented leptin production.

Intra-uterine growth retardation (IUGR)

IUGR may be caused by nutritional, genetic or placental vascular factors [51–53]. Failure of adequate leptin production and regulation may be an additional cause of IUGR; fetal leptin levels are significantly decreased in IUGR [17,37,44,45] and leptin is thought to be a growth factor in fetal development [28,32]. Recently, Lea et al. [54]...
reported a twin pregnancy where one infant was of appropriate size for gestational age and the other was growth-retarded. In situ hybridization and immunostaining of the placental tissue from these twins showed lower leptin expression in the growth-retarded infant. On the other hand, decreased fetal leptin levels could also be a consequence of reduced body fat mass resulting in reduced leptin production by fetal adipose tissue.

**Conclusion**

During pregnancy and at birth there is evidence for augmented maternal and fetal leptin levels. This increase is explained in part by leptin production by the placenta. A number of factors involved in the regulation of leptin production in the fetoplacental/maternal unit, such as hCG, β-oestradiol, insulin and cortisol. So far, the role of increased leptin production during pregnancy remains unclear. It may be hypothesized that increased leptin levels during pregnancy are part of a teleologically old and redundant system ensuring fetal growth and development, even in periods of reduced maternal energy supply.

**References**


© 2001 Biochemical Society

Received 27 November 2000