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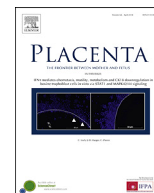
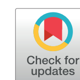


# Placental lipoprotein lipase activity is positively associated with newborn adiposity



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ABSTRACT

*Introduction:* Recent data suggest that in addition to glucose, fetal growth is related to maternal triglycerides (TG). To reach the fetus, TG must be hydrolyzed to free fatty acids (FFA) and transported across the placenta, but regulation is uncertain. Placental lipoprotein lipase (pLPL) hydrolyzes TG, both dietary chylomicron TG (CM-TG) and very-low density lipoprotein TG (VLDL-TG), to FFA. This may promote fetal fat accretion by increasing the available FFA pool for placental uptake. We tested the novel hypothesis that pLPL activity, but not maternal adipose tissue LPL activity, is associated with newborn adiposity and higher maternal TG.

*Methods:* Twenty mothers ($n = 13$ normal-weight; $n = 7$ obese) were prospectively recruited. Maternal glucose, insulin, TG (total, CM-TG, VLDL-TG), and FFA were measured at 14–16, 26–28, and 36–37 weeks, and adipose tissue LPL was measured at 26–28 weeks. At term delivery, placental villous biopsies were immediately analyzed for pLPL enzymatic activity. Newborn percent body fat (newborn %fat) was assessed by skinfolds.

*Results:* Placental LPL activity was positively correlated with birthweight ($r = 0.48; P = 0.03$) and newborn %fat ($r = 0.59; P = 0.006$), further strengthened by correcting for gestational age at delivery ($r = 0.75; P = 0.0001$), but adipose tissue LPL was not. Maternal TG and BMI were not correlated with pLPL activity. Additionally, pLPL gene expression, while modestly correlated with enzymatic activity ($r = 0.53; P < 0.05$), was not correlated with newborn adiposity.

*Discussion:* This is the first study to show a positive correlation between pLPL activity and newborn %fat. Placental lipase regulation and the role of pLPL in pregnancies characterized by nutrient excess and fetal overgrowth warrant further investigation.

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## 1. Introduction

The concept that intrauterine exposures can impact an offspring's future metabolic health is a well-established paradigm. However, the mechanism between exposure and outcome, including the critical role of the placenta, remains unclear. Developmental programming of offspring obesity and cardiometabolic disease is of high interest with rising maternal obesity and gestational diabetes (GDM) rates [1,2]. However, newborn body composition, rather than birthweight (BW), appears to be a better predictor of childhood obesity and, in a

*Abbreviations:* BW, birthweight; CM-TG, chylomicrons; EL, endothelial lipase; FA, fatty acids; FFA, free fatty acid; GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction; LPL, lipoprotein lipase; newborn %fat, newborn percent body fat; NW, normal weight; pLPL, placental LPL; TG, triglyceride; VLDL-TG, very low-density lipoprotein.

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cohort of 89 maternal/infant dyads, increased newborn adiposity rather than BW was associated with increased adiposity at 9 years [3]. While glucose and amino acids contribute to infant growth, studies also support maternal triglycerides (TG) and non-esterified free fatty acids (FFA) as important determinants of newborn percent body fat (newborn %fat), given the limited capacity of the fetus for *de novo* lipogenesis [4–8].

Humans are born with one of the highest percent body fat of all terrestrial species [9,10], and most of this fat is deposited in the 3rd trimester, coinciding with fetal adipose tissue development [7,8,11,12]. Pregnancy is normally associated with a 2–3-fold increase in maternal TG [13–17], largely due to increasing very low-density lipoprotein (VLDL-TG) synthesis stimulated by estrogen, coupled with increasing maternal insulin resistance [17,18], resulting in enhanced lipolysis in maternal adipose tissue in late pregnancy [7,8]. However, this simple supply-and-demand scheme between maternal TG and fetal fat accretion overlooks a crucial point of regulation at the level of the placenta [7,8,19–21].

To cross the placenta, TG in the form of both liver-derived VLDL-TG and dietary chylomicrons (CM-TG), must first be hydrolyzed to FFA. Two major placental lipases have been identified for FFA release: placental lipoprotein lipase (pLPL) and endothelial lipase (EL). Placental EL has phospholipase activity needed for liberating polyunsaturated fatty acids (FA) from phospholipids, and less TG hydrolase activity [22]. Maternal LPL is the major TG hydrolase in adipose tissue and likely plays a role in the placenta [15]. In maternal adipose tissue, LPL hydrolyzes VLDL-TG and CM-TG to FFA for uptake of FA into adipocytes for storage in early pregnancy, but its activity diminishes in late gestation to divert fuel to the growing fetus [7]. In the placenta, hydrolysis of TG to FFA allows them to be taken up by the syncytiotrophoblast, where they can be stored, metabolized, oxidized or transported into fetal circulation [23]. Both FA uptake from the mother and their release from placental lipid pools might provide FA for delivery to the fetus but regulation of this process is unclear, as is the role of pLPL [7,8]. Data suggest that pLPL can act as a gatekeeper molecule [15], facilitating the liberation of FFA from maternal TG, and contributing to the pool of FFA available for placental lipid uptake and transport into fetal circulation [11].

To date, studies in humans have demonstrated disparate results regarding the impact of maternal obesity and GDM on pLPL [24–28], but most measure pLPL gene expression rather than enzymatic activity, an important distinction given that LPL is post-transcriptionally regulated [29]. When pLPL activity was measured, it was increased in a small cohort of obese mothers [24] and decreased with intrauterine growth restriction (IUGR) [28], suggesting that pLPL may be a point of regulation in fetal growth. In an earlier study by Kaminsky et al., two separate placental lipase activities were measured, and findings supported increased placental lipolytic activity in pregnancies complicated by diabetes, and a positive association with birthweight [30]. However, the optimal pH activity of the lipase associated with birthweight was 4 rather than 8, which is the optimal activity for LPL, therefore it was unlikely to be LPL. Additionally, while implied, no studies have directly measured pLPL activity in conjunction with newborn fat adiposity estimates. Here, we test the hypothesis that human pLPL activity, but not adipose tissue LPL activity, is positively associated with newborn adiposity and that pLPL activity is influenced by maternal metabolism and TG availability.

## 2. Methods

### 2.1. Patient recruitment

Written informed consent was obtained according to the protocol approved by the Colorado Multiple Institutional Review Board (COMIRB). Healthy normal-weight (NW; $n = 13$) and obese ($n = 7$) pregnant women were recruited at 12–14 weeks gestation as part of a larger prospective, NIH-funded cohort study. Exclusion criteria included: age <18 or >35 years, multiple gestation, delivery <37 weeks, and pre-existing diabetes or GDM by ACOG criteria [31]. To exclude most risk factors for growth restriction, patients with chronic medical problems or a history of IUGR, stillbirth, or placental abruption were excluded.

### 2.2. Maternal serum measurements

Fasting maternal blood samples were collected at 14–16, 26–28, and 36–37 weeks gestation. Fasting blood glucose, insulin, FFA, and TG were measured and HOMA-IR values calculated as previously described [32,33]. Postprandial TG were measured at 14–16 and 26–28 weeks following a liquid breakfast containing 30% of total estimated daily caloric needs (50% carbohydrate; 35% fat; 15% protein), with TG subsequently assessed at 10 time points over 4 h. Postprandial CM-TG and VLDL-TG lipoprotein sub-fractions were isolated from fresh plasma using a sequential flotation, ultracentrifugation method, as previously described [34,35]. Serum and plasma were spun promptly and frozen at −80 °C until batch-processed.

### 2.3. Maternal adipose tissue and placental tissue collection

Subcutaneous adipose tissue was biopsied from the upper gluteal/flank region of fasting mothers at 26–28 weeks gestation, using our established protocol [36]. All placentas analyzed were delivered at term (≥37 weeks gestation) and were labored deliveries, with $n = 16$ vaginal and $n = 4$ cesarean deliveries following labor for obstetric or fetal indications. Immediately after delivery, placentas were weighed and placed on ice. Villous biopsies were obtained from central regions of the placenta after dissecting away the basal plate including decidua [15,37]. For gene expression analyses, villous samples were rinsed in ice-cold sterile 1X PBS to remove all visible blood before flash-frozen. For lipase activity, adipose tissue and villous biopsies were rinsed separately in ice-cold Krebs Ringer phosphate (KRP) buffer (pH 7.4), all visible vessels and connective tissue were dissected away, and tissues were minced to 1–2 $mm^3$ pieces. Tissues were quickly dried on filter paper prior to weighing. LPL activity was then run in triplicate from three separate samples from this minced pool.

### 2.4. Placental and adipose tissue LPL activity

LPL activity was determined using the methods described previously [38]. Since LPL, unlike other lipases, is displaced from proteoglycans by heparin, tissue-bound LPL was released by incubating 50 mg of minced adipose tissue or 100 mg of minced placental villous tissue in 0.1 or 0.5 mL, respectively, of KRP buffer containing 15 μg/mL heparin sulfate for 45 min at 37 °C with agitation. A 100 μL aliquot of supernatant containing the heparin-released enzyme was then incubated with 100 μL of a $^{14}$C-triolein phosphatidylcholine-stabilized substrate containing ApoC2 for an additional 45 min at 37 °C with agitation. The reaction was optimized for LPL activity by using neutral pH of 7.4 and inclusion of human serum ApoC2, a requisite cofactor for LPL activity. The reaction was then stopped by addition of 3.4 mL of Belfrage solution containing chloroform, methanol, and heptane, and the aqueous phase extracted by addition of 0.96 mL of bicarbonate buffer and agitation. The $^{14}$C-labeled FA were partitioned by centrifugation at 4 °C. An aliquot of the resulting aqueous supernatant containing lipase-released $^{14}$C-labeled FFA was counted by β-scintillation

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