REPLY TO CARBILLON:
Fetal/placental weight ratio and placental function

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In his Letter to the Editor, Carbillon (1) maintains that our mouse model of maternal obesity leading to fetal overgrowth (2) may not be relevant for the clinical condition because the fetal/placental weight ratio was not decreased, as is sometimes found in obese pregnant women. We disagree with Carbillon's (1) assessment.

First, we would like to point out an inaccuracy that invalidates one of Carbillon's arguments: It is stated that we previously have reported a decreased fetal/placental weight ratio in the same model (3). However, the model used by Lager et al. (3) is not the same as the model of maternal obesity used by Aye et al. (2). For example, in the previous model, fetal growth is typically restricted rather than increased, proven breeders were not used, and animals had ad libitum access to sweetened condensed milk rather than to sucrose.

Second, although fetal/placental weight is used as a read out of placental efficiency, we argue it is a crude proxy for placental function, at best. For example, in a recent study of 41,441 births in which the placental/fetal weight ratio distribution was stratified by birth weights, there was a higher proportion of small-for-gestational infants in both low and high placental/fetal weight ratio groups (4). In other words, both high and low fetal/placental weight ratio (the inverse of placental/fetal weight ratio) predicted small size at birth, a finding that is inconsistent with the idea that fetal/placental weight ratio is a sensitive marker for placental function or efficiency.

Third, and more importantly, in the present study (2) we determined placental function directly by measuring placental signaling, placental nutrient transport in vivo, and trophoblast plasma membrane nutrient transporter isoform expression in vitro. We report (per unit tissue weight or per unit protein) increased placental nutrient transport in vivo, activation of placental insulin and mammalian target of rapamycin (mTOR) signaling, and increased trophoblast plasma membrane protein expression of nutrient transporters, including SNAT2. Our study therefore represents yet another example of the poor correlation between fetal/placental weight ratio and placental function. Moreover, these findings are strikingly similar to the activation of placental insulin and mTOR signaling, increased microvillous plasma membrane SNAT2 expression, and increased microvillous plasma membrane amino acid transporter activity previously reported in large babies born to obese women (5). These data strongly support the conclusion that our mouse model is valid for obese women delivering large babies.

1 Carbillon L (2016) Fetal/placental weight ratio in a mouse model of maternal diet-induced obesity. *Proc Natl Acad Sci USA* 113:E260.
2 Aye ILMH, Rosario FJ, Powell TL, Jansson T (2015) Adiponectin supplementation in pregnant mice prevents the adverse effects of maternal obesity on placental function and fetal growth. *Proc Natl Acad Sci USA* 112(41):12858–12863.
3 Lager S, et al. (2014) Diet-induced obesity in mice reduces placental efficiency and inhibits placental mTOR signaling. *Physiol Rep* 2(2): e00242.
4 MacDonald EM, Koval JJ, Natale R, Regnault T, Campbell MK (2014) Population-based placental weight ratio distributions. *Int J Pediatr* 2014:291846.
5 Jansson N, et al. (2013) Activation of placental mTOR signaling and amino acid transporters in obese women giving birth to large babies. *J Clin Endocrinol Metab* 98(1):105–113.

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The authors declare no conflict of interest.

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