Window of Opportunity: Targeting ANGPTL4 Improves Triglyceride Levels in Maternal Obesity During Pregnancy

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During pregnancy, maternal dyslipidemia is a physiological response that provides fuel and nutrients for both the placenta and the developing fetus (1). Although less appreciated than glucose and amino acids, maternal lipids promote fetal growth and are essential for normal development (2). During the first and second trimester of pregnancy, fat accumulates in maternal tissues, and by the third trimester of pregnancy, maternal hyperlipidemia, defined here as increased serum triglycerides (TG) and total cholesterol (TC), is significantly elevated due to moderately increased maternal insulin resistance and lipolysis of lipids in adipose tissues as well as attenuated lipid uptake by peripheral tissues (Fig. 1A). Both TG and TC are taken up by the placenta, and placental lipases can hydrolyze TG to free fatty acids for fetal-placental availability (3). It is important to note that while both TG and TC levels rise throughout pregnancy, the TG increase is disproportionately higher in comparison with other lipid fractions and subsequently falls precipitously to prepregnancy levels following delivery (4).

In this issue of *Diabetes*, Qiao et al. (5) focus on identifying the mechanisms by which maternal blood TG trajectory is impaired in obese dams during pregnancy (Fig. 1A and B). To understand the regulation of TG metabolism in maternal obesity during pregnancy, Qiao et al. used various genetic mouse models with a primary focus on angiopoietin-like proteins (ANGPTL). Tissue lipoprotein lipase (LPL) is negatively regulated by members of the ANGPTL family (ANGPTL3, ANGPTL4, and ANGPTL8). Among the ANGPTL proteins, ANGPTL4 is the most potent LPL inhibitor and is mainly expressed in the adipose tissue and the liver (6). In their analysis, Qiao et al. characterized maternal TG in C57BL/6J female mice fed with a high-fat diet (HFD) (60% kcal from fat) for 12 weeks prior to pregnancy followed by a normal chow diet throughout gestation to identify the molecular mechanisms of obesity-impaired rise of maternal blood TG

during pregnancy. As expected, before pregnancy, obese HFD-fed dams exhibited insulin resistance and normal blood TG compared with control dams. Qiao et al. determined the TG profile in control chow-fed dams and identified that TG concentrations steadily increased and peaked at embryonic day (e)14.5 of 19 days' gestation. However, HFD-fed dams' TG levels increased and peaked earlier at e7.5, then declined rapidly and remained lower than those of control dams for the rest of period tested. Qiao et al. further identified that HFD-fed dams demonstrated normal gene expression of LPL but an increase in LPL activity that correlated with reduced gene expression of the LPL inhibitor ANGPTL4 (Fig. 1B). Next, the group directly tested whether ANGPTL4 is required for the pregnancy-induced hypertriglyceridemia by using $Angptl4^{-/-}$ mice and an adenovirus-mediated overexpression of ANGPTL4 (Fig. 1C and D). The authors also demonstrated that changes in obesity-linked TG clearance were unrelated to $Ucp1$ expression. Their analysis revealed that the increase in maternal TG was abolished in the $Angptl4^{-/-}$ dams and, more importantly, overexpression of $Angptl4$ in HFD-fed dams reestablished elevated TG levels. These data lead the authors to conclude that ANGPTL4 expression underlies the obesity-induced changes of maternal TG in circulation during pregnancy.

Qiao et al. bring a logical and compelling finding that ANGPTL4 plays an important role in increasing maternal blood TG concentrations during pregnancy. However, there are limitations of the study as pointed out by the authors. First, caution should be taken when interpreting mechanistic data from animal work and extending this to human biology. Indeed, it is difficult to accurately model human obesity in mice when taking into consideration the duration of obesity status, diet composition, and other confounding factors such as hyperglycemia and insulin resistance. Second, it is important to point out that in
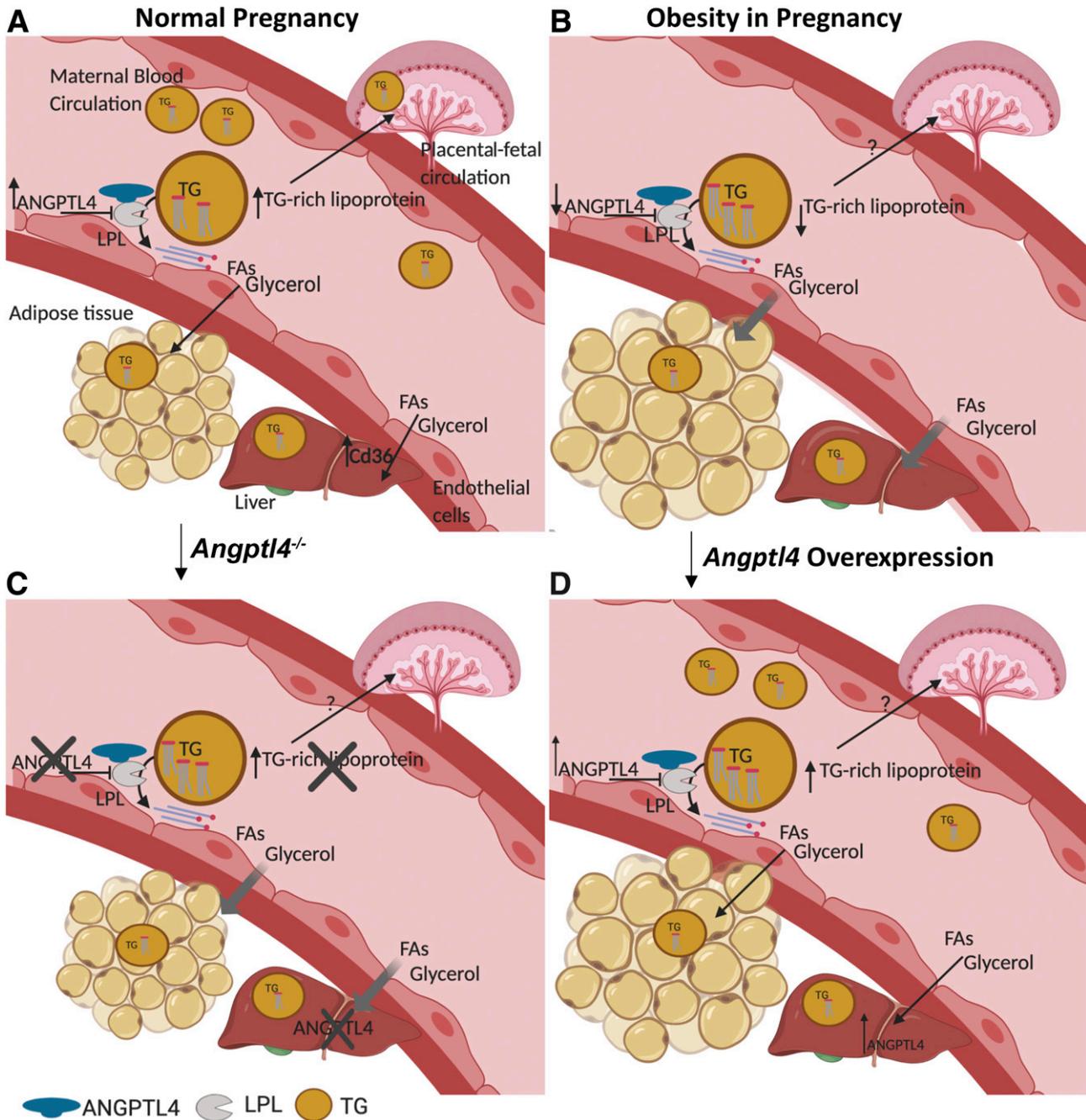
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COMMENTARY

Figure 1—Physiological elevation in maternal blood TG in pregnancy is regulated by increased ANGPTL4 expression in mice. *A*: During normal pregnancy, maternal blood TG concentrations are increased in part by insulin resistance in peripheral tissues to ensure TG supply for the placenta and fetus. These alterations result in increased adipose tissue lipolysis, increasing the release of free fatty acids (FAs) and glycerol from adipose tissue and their transfer to the liver and the placenta. During pregnancy, increased expression of ANGPTL4 inhibits LPL, regulating TG clearance from the blood serum. ANGPTL4 expression is increased during pregnancy in inguinal brown adipose tissue (iBAT) and gonadal white adipose tissue (gWAT). Moreover, during pregnancy, the fatty acid transporter CD36 is upregulated in the liver. *B*: In C57BL/6J dams fed HFD (60% kcal) for 12 weeks before pregnancy and normal chow diet during pregnancy, reduced ANGPTL4 expression in gWAT, iBAT, and the liver associated with reduced TG levels in maternal blood circulation. *C*: The increase in TG in maternal blood during pregnancy is abolished in *Angptl4*$^{-/-}$ mice. *D*: The reduction of maternal blood TG concentrations in obese dams is attenuated by hepatic *Angptl4* overexpression.

maternal obesity, there are other lipid substrates such as cholesterol that should be examined given that cholesterol levels are also linked to fetal growth and pregnancy outcomes (7).

Despite the understanding the Qiao et al. study brings to maternal-fetal TG metabolism, there remain several key unanswered questions. For example, to what degree do reduced maternal TG levels impact TG availability in the

placental and fetal circulation? Does the obesity-driven reduction in ANGPTL4 fuel LPL activity at the adipose tissue bed sufficiently to draw circulating lipid stores toward adipose depots and away from placental-fetal utilization? Fetal TG level is regulated in part by TG levels in maternal circulation but also to the extent that these lipids cross the placenta. Are the decreased TG levels seen in obese dams fed HFD for 12 weeks prior to pregnancy (5) also seen in the placenta and fetus? In nonobese pregnant dams fed HFD during the course of pregnancy, TG levels in maternal circulation are reduced while placental TG is increased (8). Does the increase in LPL activity and gene expression of free fatty acid transporters in placentas of HFD-fed dams increase the efficiency of placental TG hydrolysis and FA uptake? Finally, a characterization of the metabolic health of the offspring in $Angptl4^{-/-}$ HFD-fed dams or HFD-fed dams with overexpression of $Angptl4$ will be important to ascertain the translational implication of these studies.

In summary, the work of Qiao et al. is important and provides a timely insight on the maternal TG levels during pregnancy. From the public health perspective, approximately two-thirds of women in the U.S. and around the world are overweight or obese at the time of conception (9,10) (11) and they have significantly higher atherogenic lipid profiles than normal-weight women during the period of early pregnancy (12). Both maternal obesity during pregnancy and gestational diabetes mellitus alter the physiological profile of maternal lipids, and these maternal metabolic diseases are associated with pregnancy complications and poor fetal outcome such as preterm birth, preeclampsia, and macrosomia (13–16). Moreover, maternal obesity and gestational diabetes mellitus increase the risk of childhood and adult obesity and other metabolic diseases such as cardiovascular disease and diabetes in the offspring (17,18). It is an opportune time to pursue research directions that can open avenues to effectively control weight gain during pregnancy and to prevent and reduce the population trapped with metabolic diseases.

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