During pregnancy, there are several coordinated and dynamic maternal adaptations that take place to meet the demands of the growing and developing fetus. This includes significant physiological, endocrine, and metabolic adaptations that produce a diabetogenic state of progressive insulin resistance.1,2 It is thought that these metabolic adaptations occur so that nutrients, such as glucose, are conserved and directed toward the fetus to sustain its constant nutritional and oxygen requirements. Pregnancy is also associated with significant physiological remodeling of the cardiovascular system, which includes increases in ventricular wall mass, ventricular hypertrophy, myocardial contractility, and cardiac compliance.1,2 These cardiac adaptations combined with an increase in heart rate and cardiac output further ensure the optimization of nutrient and oxygen delivery to the growing fetus. Although the maternal cardiovascular and metabolic adaptations that allow for optimal nutrient delivery to the fetus during pregnancy are well understood, one particular area where knowledge is lacking in pregnancy relates to maternal cardiac energy metabolism profiles. Because pregnancy results in an increased maternal cardiac hypertrophy, and both physiological and pathophysiological cardiac hypertrophy are associated with several alterations in myocardial energy metabolism,3,4 it is likely that pregnancy-associated cardiac hypertrophy is also accompanied by altered myocardial metabolism. In support of this, in this issue of Circulation Research, Liu et al5 provide evidence that the cardiac hypertrophy associated with late pregnancy is accompanied with reductions in myocardial glucose oxidation rates and increases in fatty acid oxidation rates (Figure).

The study by Liu et al5 used several complementary in vitro and in vivo techniques to understand the metabolic adaptations that take place in the myocardium during late pregnancy (day 18 of gestation in C57BL/6J mice). Using a luciferin-conjugated long-chain fatty acid analog that liberates luciferin within the cardiac myocyte, the authors measured fatty acid uptake during late pregnancy. Of interest, the authors observed that myocardial free fatty acid uptake was increased by ≈20% in late pregnant dams versus their nonpregnant control females. To supplement these findings, the authors carried out 13C metabolic tracer experiments in Langendorff-perfused mouse hearts with [U-13C]glucose, [U-13C]lactate, or [U-13C]palmitate and used mass spectrometry to measure the incorporation of 13C-labeled isotopomers into glycolytic and tricarboxylic acid cycle metabolites. Supporting their in vivo bioluminescence findings, they observed an equivalent 20% increase in 13C-labeled citrate, α-ketoglutarate, glutamate, and succinate during their perfusions with [U-13C]palmitate, demonstrating increases in fatty acid oxidation. Conversely, the authors observed a significant reduction (30%–50%) of these 13C-labeled tricarboxylic acid cycle intermediates during their perfusions with [U-13C]glucose and [U-13C]lactate, demonstrating reductions in myocardial glucose oxidation rates. These metabolic findings are consistent with the glucose–fatty acid cycle advanced by Randle et al6 >50 years ago, where carbohydrates and fatty acids compete for oxidative energy (ATP) production and show an inverse relationship in the heart.

To understand these perturbations in myocardial energy metabolism, the authors assessed insulin signaling because the endocrine and metabolic adaptations of pregnancy produce a state of progressive insulin resistance.1,2 However, insulin treatment of overnight-fasted nonpregnant control females and late pregnant dams produced no discernible differences in phosphatidylinositol-3-kinase and Akt phosphorylation. Furthermore, glucose transporter 4 mRNA and protein expression levels were also similar in hearts from late pregnant dams. Hence, changes in insulin signaling and insulin-stimulated glucose uptake could not account for the reduced carbohydrate oxidation and increased fatty acid oxidation observed during late pregnancy. Of interest, what appears responsible for these myocardial metabolic adaptations during pregnancy is an increased expression of pyruvate dehydrogenase (PDH) kinase 4 (PDHK4), which phosphorylates and inhibits PDH activity—the rate-limiting enzyme of glucose oxidation (Figure).7 Indeed, PDH phosphorylation at all 3 inhibitory sites was markedly increased in hearts from late pregnant dams. The authors demonstrated that the increased PDHK4 expression was likely because of increased progesterone levels during late pregnancy because progesterone treatment of neonatal rat ventricular cardiac myocytes increased PDHK4 expression. These actions were dependent on the progesterone receptor since co-treatment with mifepristone (progesterone receptor partial agonist/antagonist) abolished the progesterone-mediated increase in PDHK4 expression. Finally, the authors demonstrated that concurrent treatment of Langendorff-perfused hearts with dichloroacetate—a PDHK inhibitor—reversed
the late pregnancy-mediated decrease in myocardial glucose oxidation.

These observations in a rat model of pregnancy have several important implications. First and foremost, both cardiac hypertrophy and insulin resistance/diabetes mellitus are accompanied by robust changes in myocardial energy metabolism, so it would be expected that pregnancy, which induces maternal adaptations promoting cardiac hypertrophy and insulin resistance, should also produce changes in myocardial energy metabolism. The question is whether the observed energy metabolism changes in the study by Liu et al could also potentially compromise cardiac function in the maternal heart during pregnancy. In pathological hypertrophy because of pressure overload, although glycolysis rates increase, a decrease in glucose oxidation rates is seen. These decreases in glucose oxidation contribute to the severity of heart failure that develops in these animals. In addition, the ability of insulin to stimulate glucose oxidation is impaired during pathological hypertrophy, resulting in a state of myocardial insulin resistance. In contrast, the hypertrophy associated with exercise is associated with increases in myocardial glucose oxidation. As a result, in late pregnancy, the maternal myocardial glucose metabolism profile more closely resembles that seen in pathological hypertrophy, which is not compatible with the notion that pregnancy-induced cardiac hypertrophy is a form of physiological hypertrophy. Perhaps it is worth revisiting how we define this specific type of cardiac hypertrophy, as the hypertrophy itself may be pathological to the mother, but a required physiological adaptation for the developing fetus.

During pregnancy, the fetal heart relies heavily on glycolysis as an energy source, and fatty acid oxidation does not mature until post-birth. A similar phenomena may also occur in the skeletal muscle of the fetus. As a result, it is possible that the maternal heart (and possibly skeletal muscle) sacrifices carbohydrate metabolism to ensure a constant supply of carbohydrates for the fetus. Although this has the possibility of potentially compromising cardiac function in the maternal heart, it may ensure that the fetal heart is not energy starved. Because endocrine and metabolic adaptations of pregnancy work to conserve and direct nutrient and oxygen delivery toward the fetus, the observations of Liu et al are consistent with energy metabolism in the developing and neonatal heart.

The observations of Liu et al also suggest that myocardial fatty acid metabolism in the maternal heart during pregnancy more closely reflects the metabolic alterations observed in diabetes mellitus than that seen in cardiac hypertrophy/heart failure. In diabetes mellitus and insulin resistance, myocardial fatty acid oxidation increases, whereas in hypertrophy, a decrease in fatty acid oxidation is seen. Conversely, other studies have demonstrated that augmenting myocardial fatty acid oxidation can prevent further deterioration in cardiac function in response to pathophysiological cardiac hypertrophy. Taking this into consideration, the increased reliance on fatty acid oxidation by the heart during pregnancy may be an adaptive mechanism to limit pregnancy-induced declines in cardiac function.

The specific study by Liu et al would have greatly benefited from measurements of myocardial glucose uptake. Unfortunately, the 13C-tracer techniques used by the authors simply provide us an index of the relative contribution of the various substrates to overall energy production in the heart and do not provide us with any specific information on glucose uptake. Thus, it is not clear whether the decrease in glucose oxidation observed in the maternal heart during pregnancy is also related to a decreased pyruvate supply from glycolysis, or due entirely to a decrease in PDH activity (because of both an increase in PDH expression and increased inhibition of PDH secondary to the elevation of fatty acid oxidation).

With regards to the mechanisms of PDH inhibition, the authors attributed these actions to progesterone-mediated increases in PDHK4 expression, whereas both estrogen and prolactin were devoid of any such stimulatory effect. It is unknown how progesterone regulates PDHK4 expression in the heart during pregnancy, although previous studies have demonstrated that the progesterone receptor induces FoxO1 (forkhead box O1) activity. It is possible this mechanism may be at play here, in light of recent findings indicating that FoxO1 is a major regulator of PDHK4 transcription and subsequent glucose oxidation rates in the heart. Conversely, insulin is a potent inhibitor of FoxO1 activity, and the endocrine/metabolic adaptations producing insulin resistance during pregnancy could thereby prevent insulin from inhibiting FoxO1-induced PDHK4 expression in the heart. Because Liu et al did not observe deficiencies in myocardial insulin signaling during pregnancy, it is possible that progesterone-induced activation of FoxO1, rather than diminished insulin-mediated FoxO1 inhibition, is responsible for pregnancy-mediated reductions in glucose oxidation. PPARα (peroxisome proliferator-activated receptor α) is another transcription factor linked to PDHK4 expression in the heart, although information on whether the progesterone receptor controls PPARα activity is lacking. The possibility also remains that as a nuclear receptor, the progesterone receptor itself may directly control PDHK4 transcription and expression, although this remains to be explored. Nevertheless, it will be important for future studies to delineate how progesterone controls PDHK4 expression and subsequent glucose oxidation in the heart during pregnancy, especially...
when considering that the authors observed an attenuation of the cardiac hypertrophy associated with pregnancy in response to treatment with the PDHK inhibitor dichloroacetate.

Although Liu et al. performed extensive experimentation to delineate how pregnancy decreases myocardial glucose oxidation rates at a molecular level, the increase in myocardial fatty acid oxidation rates does not involve molecular changes. Instead, increased fatty acid supply arising from the increase in circulating free fatty acid and triacylglycerol levels in late pregnant dams likely increased myocardial fatty acid oxidation rates. Of interest, early pregnancy in rats is associated with increased adipose tissue insulin responsiveness and enhanced lipolysis. Of interest, early pregnancy in rats is associated with increased adipose tissue insulin responsiveness and enhanced lipolysis. Such findings are consistent with the circulating lipid profile observed by Liu et al in late pregnancy, which would increase myocardial fatty acid oxidation rates and inhibit glucose oxidation, thereby conserving glucose for the developing fetus.

Taken together, the observations of Liu et al. add provocative new information surrounding the physiological, endocrine, and metabolic adaptations of the myocardium during pregnancy. The observed increase and decrease in myocardial fatty acid oxidation and glucose oxidation rates, respectively, are consistent with pregnancy inducing several adaptations in the mother that act in unison to conserve and direct glucose toward the fetus to sustain its constant requirement for nutrients and oxygen. This is especially important considering that fatty acid oxidation is immature in the developing and neonatal heart. As such, the adaptations in the mother during pregnancy that conserve glucose/carbohydrates are likely physiologically essential for the health of the fetus. Because pregnancy produces a state of insulin resistance, it will be important to determine whether these myocardial metabolic alterations are exacerbated in pregnant women with gestational diabetes mellitus because diabetes mellitus itself decreases myocardial glucose oxidation rates. Furthermore, increasing myocardial glucose oxidation rates has salutary actions on cardiac efficiency and function in obesity and diabetes mellitus. Accordingly, such a strategy may be useful to improve cardiac function in pregnant women with gestational diabetes mellitus but may have adverse effects on the developing fetus if glucose metabolism is redirected toward the mother. Thus, future studies are needed to address these clinically relevant questions and to investigate how pregnancy-mediated alterations in myocardial energy metabolism contribute to other pregnancy-related diseases (e.g., preeclampsia and peripartum cardiomyopathy).

Sources of Funding
This study was supported by grants from the Canadian Institutes of Health Research, the Canadian Diabetes Association (CDA), and the Heart and Stroke Foundation of Canada. J.R. Ussher is a Scholar of the CDA and a New Investigator of the Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut.

Disclosures
None.

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Key Words: Editorials ■ energy metabolism ■ glucose oxidation ■ heart ■ pregnancy ■ progesterone ■ pyruvate dehydrogenase kinase
Decreased Maternal Cardiac Glucose Oxidation: Taking One for the Fetus

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Circ Res. 2017;121:1299-1301
doi: 10.1161/CIRCRESAHA.117.312098

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