# Adiponectin and β-Cell Adaptation in Pregnancy

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Pregnancy poses a unique physiological challenge to the pancreatic β-cells. For normal glucose tolerance to be maintained in the setting of the insulin resistance of late gestation, the β-cells must markedly increase their secretion of insulin. It is believed that this enhanced secretion is achieved through the expansion of β-cell mass in response to circulating factors, including prolactin and placental lactogens (1,2). Conversely, failure of this compensatory response will result in maternal hyperglycemia or gestational diabetes mellitus (GDM) (3). However, our understanding of the mechanisms underlying normal islet adaptation in pregnancy and its failure in GDM remains limited at this time. In this context, the importance of elucidating the biology of this adaptive response is underscored by the novel insight that it could provide into the pathophysiology of β-cell dysfunction, with implications for not only GDM but also subsequent type 2 diabetes (1,2).

Adiponectin is an adipocyte-derived hormone with pleiotropic effects on a broad array of physiological processes including energy homeostasis, vascular function, systemic inflammation, and cell growth (4,5). Most notably, it has emerged as an antidiabetic adipokine, with low serum adiponectin shown to predict incident type 2 diabetes in several populations (6). Similarly, hypoadiponectinemia in early pregnancy, or even prior to gestation, can predict the subsequent development of GDM in the second or third trimester (7). These antidiabetic associations have been generally attributed to the well-established insulin-sensitizing effects of adiponectin. However, there have also been studies linking hypoadiponectinemia to β-cell dysfunction, particularly in pregnancy (8,9), thereby raising the intriguing question of whether adiponectin could be relevant to the pathophysiology of GDM (5).

In this issue of *Diabetes*, Qiao et al. (10) directly address this question through detailed characterization of pregnant mouse models with and without adiponectin deficiency. They show that adiponectin gene knockout (*Adipoq*$^{-/-}$) dams indeed develop glucose intolerance and hyperlipidemia in late pregnancy accompanied by increased fetal weight, as seen in GDM. Moreover, these defects can be abolished by adenoviral vector–mediated in vivo transduction to reconstitute adiponectin in late pregnancy. Surprisingly, insulin sensitivity did not differ between *Adipoq*$^{-/-}$ and wild-type dams. Instead, however, *Adipoq*$^{-/-}$ dams had lower serum insulin concentrations and reduced β-cell mass, both of which could be reversed with adiponectin reconstitution. Taken together, these findings suggest a previously unrecognized role for adiponectin in maternal metabolic adaptation to pregnancy and provide an array of novel insights to consider.

The first such insight is that hypoadiponectinemia potentially may play a causal role in the development of GDM. Furthermore, the observed reversal of maternal metabolic dysfunction through its reconstitution may implicate adiponectin as a potential target to consider for the treatment or prevention of GDM. Second, the metabolic effects of adiponectin deficiency and reconstitution observed in this study may not be fully attributable to the insulin-sensitizing activity of adiponectin (given the similar insulin sensitivity of *Adipoq*$^{-/-}$ and wild-type dams). In this regard, it is possible that a comparatively lesser impact of hypoadiponectinemia on insulin sensitivity may be obscured by the otherwise overwhelming insulin resistance of late pregnancy. Third, and perhaps most remarkably, this study implicates adiponectin as a factor in the expansion of β-cell mass that is believed to be necessary for the maintenance of glucose homeostasis in pregnancy.

Current understanding of the mechanism of islet adaptation in pregnancy holds that circulating factors in maternal serum, including prolactin and placental lactogens, drive the expansion of β-cell mass in concert with a series of mediators (including the transcription factor FoxM1, the serotonin synthetic enzyme Tph1, and microRNA miR-338-3p) (1,2,11–13). While adiponectin has not been previously implicated in this process, its emergence in the current study is consistent with certain earlier observations. First, both hypoadiponectinemia and deficiency of high–molecular weight adiponectin have been associated with β-cell dysfunction in women with GDM (8,9). Second, adiponectin has been reported to enhance β-cell proliferation (14). Third, while preclinical studies

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COMMENTARY

have concurred regarding adiponectin activity in the islets, they have reported conflicting findings on whether it affects insulin secretory function (15,16). In this context, it is notable that, in the current study, adiponectin affected β-cell mass and serum insulin concentrations but not glucose-stimulated insulin secretion, thereby potentially suggesting an impact on β-cell expansion but not secretory function per se.

While these data are intriguing, there are also limitations to the current findings that hold relevance for future avenues of investigation. First, autopsy samples from women who died during pregnancy have suggested that the β-cell adaptive response in human gestation may be different from that which is observed in rodents (17,18). For example, the human response appears to involve a smaller overall increase in the number of β-cells, with a greater contribution of islet neogenesis (18). Accordingly, whether adiponectin contributes to β-cell adaptation in human gestation remains to be established. Second, the methodology of the current study precludes determination of whether a particular multimeric form of adiponectin (such as high–molecular weight adiponectin) is responsible for the observed effects. Third, it remains to be seen whether a suboptimal islet adaptive response induced by hypoadiponectinemia in pregnancy could hold pathological implications for future diabetes risk of the mother. Indeed, in humans, hypoadiponectinemia in pregnancy predicts postpartum β-cell dysfunction (19). Moreover, in Hispanic women with previous GDM, declining adiponectin in the years after pregnancy has been associated with the deterioration of β-cell function that drives their risk of developing type 2 diabetes (20). Given the central role of β-cell dysfunction in the pathophysiology of both GDM and subsequent type 2 diabetes, a potential future clinical application may be the measurement of adiponectin for early identification of women at risk for these conditions.

In summary, the elegant study by Qiao et al. (10) provides intriguing data implicating an effect of adiponectin on β-cell adaptation to pregnancy in mice. In doing so, it raises a larger question of whether the antidiabetic activity of adiponectin could be due to beneficial effects on not only insulin sensitivity but also β-cell function (Fig. 1). While the applicability of such a model to human physiology in both pregnancy and the nongravid state remains to be determined, this study has opened new avenues for investigation into the potential impact of adiponectin on β-cell biology and function.

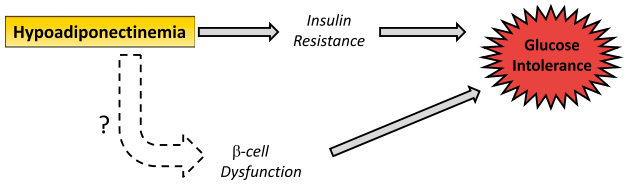


**Figure 1**—Schematic of emerging model wherein hypoadiponectinemia may have deleterious effects on glucose homeostasis through not only insulin resistance but also potentially β-cell dysfunction.

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