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RESPONSE TO COMMENT ON LAKER ET AL.

Exercise Prevents Maternal High-Fat Diet–Induced Hypermethylation of the *Pgc-1α* Gene and Age-Dependent Metabolic Dysfunction in the Offspring. Diabetes 2014;63: 1605–1611

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The letter by Cedernaes and Benedict (1) commenting on our article in this issue of *Diabetes* (2) raised some very interesting points and valuable insights that, in future studies, will further our understanding of parent-offspring transmission of disease and effective intervention strategies. We would like to address the points raised and provide additional discussion.

We agree that the timing of exercise could be extremely important. In our study, we started diet and exercise interventions prior to pregnancy for technical reasons, which limited our interpretations. We postulate that the epigenetic modification occurs during fetal development likely around midgestation when myogenesis is initiated since hypermethylation of the *Pgc-1α* promoter observed at birth was apparent in the skeletal muscle but not the liver. Other studies have reported positive impacts on offspring metabolic outcomes with maternal exercise started prior to pregnancy (3–5). Carefully designed timing studies will be of great value to human situations where pregnancy may not be noticed or diagnosed for some weeks or months after conception.

Cedernaes and Benedict discussed a very interesting study showing paternal obesity causing an early onset of β-cell dysfunction in the offspring (6). Ascertaining whether exercise is effective in preventing this or other types of negative impacts of paternal obesity to the offspring is clearly very important. The findings will be pertinent to the timing question as well.

Finally, based on findings by Barrès et al. (7), the authors raised the possibility of intergenerational impact of a single bout of exercise during pregnancy. Considering the following, we speculate that this is unlikely. First, we showed that under normal chow conditions, in the absence of maternal obesity, maternal exercise did not cause *Pgc-1α* hypomethylation or impact later metabolic function in the offspring. Second, our findings were in the offspring muscle, and it was the mothers that performed the exercise. Third, we measured basal level *Pgc-1α* methylation while Barrès et al. (7) detected transiently induced methylation possibly through the action of a different epigenetic machinery. In sum, we suspect that the epigenetic effect of maternal exercise we observed is not a direct response to muscle contraction, but likely to an improved uterine milieu in the mother.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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