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PERSPECTIVE

Maternal obesity: influencing the heart right from the start

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Children of women with obesity have a higher risk of cardiovascular and metabolic disease. Understanding how maternal obesity affects the heart of offspring during development might provide an evidence base for lifestyle and other interventions during pregnancy or in early childhood to reduce future cardiovascular risk. Several clinical and experimental studies have investigated how obesity during pregnancy predisposes offspring to hypertension, insulin resistance, obesity, cardiovascular disease and premature mortality (Shrestha et al., 2021). However, few studies have considered whether the sex of the offspring influences cardiovascular and metabolic outcomes.

In this issue of *The Journal of Physiology*, Vaughan and colleagues use their established mouse model of maternal obesity to investigate the metabolic disturbances underpinning adverse cardiac remodelling and dysfunction in offspring of obese dams (Vaughan et al., 2022). A strength of the study is that the authors assessed cardiac function of both male and female offspring up to 2 years of age (the approximate lifespan of a mouse). This longitudinal assessment extends their previous findings, which revealed the emergence of diastolic dysfunction by 3 months of age in male offspring of obese dams and at 6 months of age in female mice (Vaughan et al., 2020). Although group sizes at some time points might have been too small to reveal subtle changes in function, the present study points to a persistent impairment in diastolic function in male offspring of obese dams throughout lifespan, and a progressive worsening of diastolic function in females. The authors speculate that this sexual dimorphism might be attributable to the cardioprotective effects of oestrogen, because the marked decline in diastolic dysfunction observed in female mice at 9 months of age coincides approximately with a decline in circulating oestradiol in the mouse strain used. Additional studies are needed to draw further conclusions regarding the cardioprotective effects of oestrogen and the role of androgens and progestogens in this setting.

Both male and female fetuses of obese dams were heavier and had significantly heavier hearts (even when normalized to body weight) than fetuses from control dams. Interestingly, cardiac hypertrophy was no longer evident in offspring of obese dams at 6 months of age, and body weight had also normalized. Histopathological changes (e.g. interstitial fibrosis and capillary density) were not examined at either time point. To investigate transcriptional changes associated with fetal cardiac hypertrophy, the authors conducted RNA sequencing and downstream pathway analyses on fetal heart samples 18.5 days postcoitum. The overall transcriptomic response to maternal obesity was strongly influenced by sex, with only 66 commonly altered genes between males and females. Ingenuity analysis identified contrasting macromolecular pathways upregulated by maternal obesity: lipid synthesis and metabolism in males, and carbohydrate uptake in females. These data suggest that metabolic perturbances in response to maternal obesity are influenced by sex, despite exposure to the same metabolic milieu *in utero*.

A key finding of this study was the identification of *Pparg*, the gene encoding peroxisome proliferator activated receptor gamma (PPARγ), as a critical node of the fetal myocardial transcriptomic response to maternal overnutrition. PPARγ is a ligand-activated transcription factor responsible for modulating the expression of genes involved in fatty acid uptake, oxidation and storage in the heart. The PPARγ agonist pioglitazone is used in the treatment of type 2 diabetes and reduces the risk of major adverse cardiovascular outcomes in diabetic patients (Liao et al., 2017; Sinha & Ghosal, 2020). However, pioglitazone also increases the risk of heart failure (Liao et al., 2017; Sinha & Ghosal, 2020), and transgenic overexpression of *Pparg* in mice leads to cardiac hypertrophy and systolic dysfunction (Son et al., 2007), indicating a potential structural and functional role for this key metabolic protein. In this study, Vaughan et al. (2022) report that *Pparg* expression was increased in both male and female hearts at embryonic day 18.5 and at 6 months of age and was strongly correlated with diastolic dysfunction (E/E′ ratio) in male animals and with left ventricular end-diastolic volume in female animals. Follow-up experiments in adult offspring revealed differential expression of *Pparg* target genes (e.g. *Acox1*) in male and female hearts despite a comparable increase in *Pparg* expression, suggesting sexual dimorphism in the post-transcriptional regulation of PPARγ function, for example by co-regulators or other interacting proteins. A recent investigation identified PPARα as a key modulator of the fetal cardiac lipidome in response to maternal obesity (Pantaleao et al., 2022), and dual activation of PPARα and PPARγ induces cardiac dysfunction in mice (Kalliora et al., 2019). Thus, further investigation into this important family of metabolic regulators will be important for improving our understanding of the cardiometabolic response to overnutrition *in utero*.

Finally, the authors measured cardiac lipid and glucose uptake, in addition to respiration in left ventricular tissue, to examine energy metabolism between male

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and female adult offspring. Perturbations in fatty acid oxidation were observed in male offspring of obese dams, and females had impaired myocardial glucose uptake. Lipid uptake was not altered by maternal obesity in either sex. Interestingly, impaired glucose uptake in the female mice was not accompanied by differences in expression of the major cardiac glucose transporters, GLUT1 or GLUT4, although Western blot analysis revealed a reduction in insulin receptor phosphorylation suggestive of insulin resistance. Collectively, these data suggest that metabolic programming *in utero* sets the stage for myocardial metabolism throughout life, with an increased reliance on fatty acids (via different mechanisms) in adult male and female offspring.

In summary, this paper adds to the growing body of evidence that maternal obesity reprograms cardiac metabolism of offspring, with lasting effects on cardiac function. Importantly, it reveals differences in cardiac metabolic and functional responses of male and female offspring to maternal obesity. Improved understanding of the mechanisms underpinning these responses will take us a step closer to developing sex-specific strategies to mitigate the detrimental cardiometabolic consequences of an obesogenic *in utero* environment.

References

Kalliora, C., Kyriazis, I. D., Oka, S. I., Lieu, M. J., Yue, Y., Area-Gomez, E., Pol, C. J., Tian, Y., Mizushima, W., Chin, A., Scerbo, D., Schulze, P. C., Civelek, M., Sadoshima, J., Madesh, M., Goldberg, I. J., & Drosatos, K. (2019). Dual peroxisome-proliferator-activated-receptor-alpha/gamma activation inhibits SIRT1-PGC1alpha axis and causes cardiac dysfunction. *JCI Insight*, **4**(17), e129556.

Liao, H. W., Saver, J. L., Wu, Y. L., Chen, T. H., Lee, M., & Ovbiagele, B. (2017). Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: A systematic review and meta-analysis. *BMJ Open*, **7**(1), e013927.

Pantaleao, L. C., Inzani, I., Furse, S., Loche, E., Hufnagel, A., Ashmore, T., Blackmore, H. L., Jenkins, B., Carpenter, A. A. M., Wilczynska, A., Bushell, M., Koulman, A., Fernandez-Twinn, D. S., & Ozanne, S. E. (2022). Maternal diet-induced obesity during pregnancy alters lipid supply to mouse E18.5 fetuses and changes the cardiac tissue lipidome in a sex-dependent manner. *Elife*, **11**, e69078.

Shrestha, A., Prowak, M., Berlandi-Short, V. M., Garay, J., & Ramalingam, L. (2021). Maternal obesity: A focus on maternal interventions to improve health of offspring. *Frontiers in Cardiovascular Medicine*, **8**, 696812.

Sinha, B., & Ghosal, S. (2020). Assessing the need for pioglitazone in the treatment of patients with type 2 diabetes: A meta-analysis of its risks and benefits from prospective trials. *Science Reports*, **10**(1), 15781.

Son, N. H., Park, T. S., Yamashita, H., Yokoyama, M., Huggins, L. A., Okajima, K., Homma, S., Szabolcs, M. J., Huang, L. S., & Goldberg, I. J. (2007). Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. *Journal of Clinical Investigation*, **117**(10), 2791–2801.

Vaughan, O. R., Rosario, F. J., Chan, J., Cox, L. A., Ferchaud-Roucher, V., Zemski-Berry, K. A., Reusch, J. E. B., Keller, A. C., Powell, T. L., & Jansson, T. (2022). Maternal obesity causes fetal cardiac hypertrophy and alters adult offspring myocardial metabolism in mice. *Journal of Physiology*, **600**(13), 3169–3191.

Vaughan, O. R., Rosario, F. J., Powell, T. L., & Jansson, T. (2020). Normalisation of circulating adiponectin levels in obese pregnant mice prevents cardiac dysfunction in adult offspring. *International Journal of Obesity (London)*, **44**(2), 488–499.

Additional information

Competing interests

None declared.

Author contributions

N.M.S., J.R.B. and K.L.W.: conception or design of the work; and drafting the work or revising it critically for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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