

**Maternal Adiposity and Offspring Blood Pressure: A Call for Primordial Prevention Strategies.**

Scott Chiesa<sup>1</sup>, George Georgiopoulos <sup>2</sup>, Marietta Charakida<sup>2</sup>

<sup>1</sup> Vascular Physiology Unit, UCL Institute of Cardiovascular Science, London, UK

<sup>2</sup> School of Imaging Sciences and Biomedical Engineering, King's College London, UK

Correspondence to Marietta Charakida

Senior Lecturer & Consultant in Fetal and Paediatric Cardiology

School of Biomedical Engineering and Imaging Sciences

3<sup>rd</sup> Floor Lambeth Wing, St Thomas' Hospital

Email:charakidadoc@gmail.com

Obesity is reaching epidemic proportions worldwide and is predicted to affect ~ 20% of the global population by 2025<sup>1</sup>. Rates of maternal obesity have also increased significantly in the last decades in line with this global obesity epidemic. Currently, almost 50% of women of reproductive age and 20% of pregnant women at first antenatal visit are reported as being overweight or obese in UK. While population data for low- to middle-income countries is less reliable, obesity prevalence rates in pregnant women in the region of 20-30% are not uncommon<sup>2</sup>. Although efforts to address this global health crisis have met with some success in high-income countries, the increasing urbanisation and rapid westernisation of low and middle-income countries suggests that the overall global situation is expected to worsen further in years to come<sup>1</sup>.

Maternal obesity increases the risk of pregnancy complications and adverse neonatal outcomes and may also induce long-lasting adverse effects in the offspring with an associated burden on health care costs. For instance, a number of mother-child cohorts have demonstrated an independent relationship between maternal body mass index (BMI), and increasing levels of adiposity in the offspring<sup>3</sup>. In addition, maternal BMI has been associated with cardiometabolic abnormalities in the offspring that may persist into adulthood<sup>4</sup>. With the majority of research focused on maternal adiposity, the impact of father's health status prior to pregnancy is also poorly understood, with some studies demonstrating a small but detectable effect, while others show no impact at all<sup>5</sup>.

In the paper published in *European Journal of Preventive Cardiology*, Jansen et al report the relationship between parental BMI and offspring blood pressure in an Indonesian cohort of 587 parents and infants, a subgroup of the Breastfeeding Attitude and Volume Optimization (BRAVO) trial<sup>6</sup>. The authors recorded blood pressure on up to seven occasions over the first year of life, and reported that higher maternal, but not paternal, BMI was associated with persistently higher levels of blood pressure across this timespan. This increased risk followed

a linear relationship between maternal BMI and offspring blood pressure, which appeared evident even from the first week of life. Importantly, while elevations in diastolic blood pressure appeared to be mediated largely through offspring adiposity levels, systolic blood pressure remained significantly elevated even after accounting for birth-size of the child, height and weight over time, and various other potential confounding factors such as gestational diabetes, hypertension, and socioeconomic status – suggesting potential intra-uterine mechanisms underlying these changes independent of postnatal exposures. In contrast, lack of association with paternal BMI suggested limited influence from father's health pre-conception, although it should be noted that previous studies in larger cohorts have reported contrasting findings<sup>7</sup>.

The mechanisms which underlie these associations remain unclear, as most clinical studies are observational and causal relationships cannot be established. Experimental interventional studies have provided some insights into the potential programming effect of maternal obesity, which may be secondary to pathogenic effects of maternal obesity on the placenta, or may result from direct effects on the developing foetus. For instance, maternal obesity has been associated with macrophage accumulation and increased expression of pro-inflammatory cytokines in the placenta and this is thought to contribute to the programmed alterations in offspring metabolism with the development of insulin resistance<sup>8</sup>. Maternal obesity has also been shown to result in excess exposure of the fetal liver to lipids and adipokines, as well as being associated with alterations in the expression of genes which upregulate lipogenesis and inflammation<sup>9</sup>. These metabolic changes have been linked in animal studies with increased blood pressure and evidence of subclinical atherosclerotic disease.

The current study by Jansen et al has a number of strengths. It is the first such study of this scale to assess relationships between parental BMI and offspring health in a low- to middle-income country, a setting in which medical recommendations are often made based on findings

translated from higher-income nations. In addition, the use of multiple measures of blood pressure across the very earliest months of life reduces the potential of confounding from postnatal environmental exposures and suggests the presence of potential *in utero* mechanisms/pathways regulating blood pressure control which are independent of future offspring adiposity status. As is common in population cohort studies, however, there are also certain limitations and potential confounding influences. Firstly, while the changes in blood pressure reported in the current study are statistically significant, they remain – in absolute terms – relatively modest, and the clinical importance of such small changes at this young age remains unknown. However, as pointed out by the authors in the manuscript, blood pressure levels in childhood are known to track into adulthood, and early identification and intervention in higher-risk individuals from a young age may therefore offer the potential for a significant reduction in total cumulative exposure across the lifespan. Secondly, whether the increased blood pressure levels in this study result from permanent change arising from unfavourable conditions *in utero*, or are due to other undetermined factors, cannot be established. Finally, no information on gestational weight gain was available during pregnancy, a factor which may also be important in the development of adverse offspring risk factors.

Overall, these findings further strengthen calls for the continued development of public health strategies and prevention programmes aimed at reducing the rising tide of obesity in young women of child-bearing age. Although lifestyle interventions in pregnancy are difficult to perform, studies suggest that a modest decrease in weight gain may be achievable. However, there is currently no strong evidence to suggest that these interventions reduce the risk of maternal and offspring outcomes<sup>10</sup>.

Finally, while the issue of maternal obesity may be important at a population level, care must be taken to place this research into context at an individual level, where scrutiny or blame is frequently apportioned to expectant mothers for a whole range of lifestyle factors (e.g. being

overweight, foregoing breastfeeding, returning to work, etc). It is therefore important to emphasise that findings such as those reported are intended to serve as a means of empowering women to make informed choices about the health of themselves and their offspring, rather than a means of demonising a global health issue and adding further stress to expectant mothers.

## References

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, Adams RJ, Aekplakorn W, Afsana K, Aguilar-Salinas CA. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128· 9 million children, adolescents, and adults. *The Lancet* 2017;**390**(10113):2627-2642.
2. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, Gillman MW. Preconceptional and maternal obesity: epidemiology and health consequences. *The lancet Diabetes & endocrinology* 2016;**4**(12):1025-1036.
3. Golab BP, Santos S, Voerman E, Lawlor DA, Jaddoe VW, Gaillard R, Barros H, Bergström A, Charles M-A, Chatzi L. Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: an individual participant data meta-analysis. *The Lancet Child & Adolescent Health* 2018;**2**(11):812-821.
4. Hochner H, Friedlander Y, Calderon-Margalit R, Meiner V, Sagy Y, Avgil-Tsadok M, Burger A, Savitsky B, Siscovick DS, Manor O. Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation* 2012;**125**(11):1381-1389.
5. Labayen I, Ruiz JR, Ortega FB, Loit H-M, Harro J, Veidebaum T, Sjöström M. Intergenerational cardiovascular disease risk factors involve both maternal and paternal BMI. *Diabetes Care* 2010;**33**(4):894-900.

6. Jansen MA, Pluymen LP, Dalmeijer GW, et al Hypertensive disorders of pregnancy and cardiometabolic outcomes in childhood: A systematic review. *Eur J Prev Cardiol*. 2019
7. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Smith GD. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation* 2004;**110**(16):2417-2423.
8. Challier J, Basu S, Bintein T, Minium J, Hotmire K, Catalano P, Hauguel-de Mouzon S. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta* 2008;**29**(3):274-281.
9. Samuelsson A-M, Morris A, Igosheva N, Kirk SL, Pombo JM, Coen CW, Poston L, Taylor PD. Evidence for sympathetic origins of hypertension in juvenile offspring of obese rats. *Hypertension* 2010;**55**(1):76-82.
10. Rogozinska E, Marlin N, Betran AP, Astrup A, Bogaerts A, Cecatti JG, Devlieger R, Dodd JM, El Beltagy N, Facchinetti F. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials The International Weight Management in Pregnancy (i-WIP) Collaborative Group. *BMJ-British Medical Journal* 2017;**358**:j3119