

**Holistic MRI Acquisition in Preeclamptic Pregnancies: A New Avenue for Clinical Investigations?**

Adam James Lewandowski<sup>1\*</sup>, Prenali Dwisthi Sattwika<sup>1,2,3</sup>

<sup>1</sup>Cardiovascular Clinical Research Facility, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, United Kingdom

<sup>2</sup>Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia

<sup>3</sup>Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia

\*Corresponding author:

Adam James Lewandowski

Oxford Cardiovascular Clinical Research Facility, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford

Level 1 Oxford Heart Centre, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom

[adam.lewandowski@cardiov.ox.ac.uk](mailto:adam.lewandowski@cardiov.ox.ac.uk)

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In this issue of Hypertension, Hall *et al.*<sup>1</sup> developed and implemented multi-organ imaging to investigate maternal cardiac, placental, and fetal brain changes in preeclamptic pregnancies. They reported on a prospective cohort study applying a comprehensive magnetic resonance imaging (MRI) protocol that is safe and acceptable to pregnant women. This study revealed that placental T2\* was lower in the preeclamptic placenta, reflecting reduced placental oxygenation. Preeclampsia was also associated with lower fetal brain T2\* and reduced fetal brain volume. Women with preeclampsia demonstrated cardiac remodelling affecting the left ventricular outflow tract with an eccentricity pattern.

#### **Insights Into the Pathophysiology of Preeclampsia**

Placental functional MRI in this study by Hall *et al.* showed altered oxygenation, represented by significantly reduced placental T2\*, and altered microstructure in the preeclamptic placenta. Early onset preeclampsia was associated with low placental T2\* that remained low during the last trimester.<sup>2</sup> The study by Hall *et al.* included both early- and late-onset preeclampsia, contributing to the variation in placental T2\* values. They also showed that in preeclamptic pregnancies without any reduction in placental T2\*, placental histopathology was normal and deliveries were at later gestations, suggesting that placental T2\* may aid to differentiate the severity of preeclampsia. Placental malperfusion in preeclampsia is a primary placental disorder resulting from placental syncytiotrophoblast stress.<sup>3</sup> However, in the third trimester of pregnancy, cardiovascular maladaptation has been shown to precede the diagnosis of preeclampsia.<sup>4</sup> Comprehensive maternal and fetal MRI throughout pregnancy may provide insight into whether the onset of uteroplacental hypoperfusion in the preeclamptic placenta is purely mediated by placental dysfunction<sup>3</sup> or associated with

48 suboptimal maternal cardiovascular performance.<sup>5</sup> Unfortunately, this observation could  
49 not be assessed from the current study since preeclamptic participants were not recruited  
50 until a confirmed diagnosis of preeclampsia, but could be an area of further investigation for  
51 future studies.

52 The reduced fetal brain volume and T2\* imaging in preeclamptic pregnancies observed by  
53 the authors is of particular interest. This finding may provide insight into the later life  
54 cognitive impairments and increased risk for neurological diseases seen in offspring of  
55 preeclamptic pregnancies.<sup>6</sup> It has been proposed that neurological deficits in offspring of  
56 preeclamptic pregnancies result from complex genetic and environmental factors.<sup>6</sup>  
57 Interestingly, the authors showed a direct correlation between mean placental and fetal  
58 brain T2\* z-scores in preeclamptic pregnancies, supporting previous evidence that placental  
59 dysfunction in preeclampsia may directly affect fetal brain development.<sup>7</sup> During the fetal  
60 period, the brain undergoes significant constitutional changes and growth. Any  
61 uteroplacental circulation deprivation may lead to a shift in blood flow priority, resulting in  
62 brain-sparing effects. This study has confirmed the need to consider the impact placental  
63 dysfunction has on fetal brain development.

64 In recent years, it has become increasingly recognised that preeclamptic women undergo  
65 significant cardiac remodelling, mainly assessed using echocardiography.<sup>8</sup> Hall *et al.*  
66 demonstrated preeclamptic women had higher left ventricular mass and a unique three-  
67 dimensional cardiac shape, including eccentric remodelling and outflow tract changes.  
68 Higher left ventricular mass has also been observed in women 5-10 years after preeclamptic  
69 pregnancies using MRI and creation of a three-dimensional computational atlas.<sup>9</sup> However,  
70 in the study by Boardman *et al.*,<sup>9</sup> the left ventricular remodelling manifested as global  
71 concentric remodelling. Differences in the remodelling pattern may indicate a time-

dependent change relative to the index pregnancy but would require repeat pre- and postnatal measurements in the same women to confirm this. Since only three out of 65 pregnant women in the study of Hall *et al.* attended follow-up scans, the data were not sufficient to look at the longitudinal trajectories of cardiac remodelling in preeclamptic women for this cohort. Nevertheless, it is plausible that antenatal maternal cardiac MRI may serve to risk stratify women who are most likely to show postnatal cardiac remodelling and would benefit from personalised approaches to optimise hypertension management.<sup>10</sup>

## **Implications for Future Research in Preeclampsia**

The article by Hall *et al.* underscores the complex interactions between the maternal, placental, and fetal environments in preeclampsia. The inclusion of a chronic hypertension group demonstrated the unique impact of preeclampsia, which may be expected given the higher rate of hypoxic vascular anomalies seen in the preeclamptic placenta. The MRI feasibility measures in preeclamptic women after gestational week 24 could be the basis for designing a longitudinal study during pregnancy to enrich the evidence of pathological changes in the maternal heart, placenta, and fetal brain. Future work should integrate antenatal and postnatal data in the same individuals to determine how these alterations progress over time. In addition, fetal-maternal investigations using MRI could be extended to other organ systems. For instance, work by Siepmann *et al.* showed unique brain changes using MRI in women with a history of preeclampsia five to 15 years after the indexed pregnancy, including temporal lobe white matter changes and reduced cortical volumes.<sup>11</sup> Whether these changes first emerge during pregnancy is currently unknown and would provide additional insight into the heart-brain axis in women with a history of preeclampsia.

In addition, there is an opportunity for future studies using these methods to incorporate fetal cardiac MRI. The addition of state-of-the-art cardiac MRI methods<sup>12</sup> would help build on studies that used echocardiography to show placental dysfunction may be a driving factor for fetal cardiac remodelling in preeclamptic pregnancies.<sup>13</sup>

## **Implications for the Management of Preeclampsia**

Current diagnosis of preeclampsia considers uteroplacental dysfunction, including abnormal umbilical artery Doppler waveform analysis, fetal growth restriction, and stillbirth. It is recommended that assessment of fetal biometry, amniotic fluid, and umbilical artery Doppler ultrasound be carried out at first diagnosis of preeclampsia, with follow-up intervals no greater than two weeks.<sup>14</sup> Fetal ultrasound evaluation is the cornerstone for fetal assessment in preeclamptic pregnancies, given that fetal deterioration is an indication for pregnancy termination. A reduction in middle cerebral artery pulsatility index <10<sup>th</sup> percentile represents sub-optimal brain vasodilatation and has been associated with emergency caesarean delivery.<sup>15</sup> However, ultrasound-based assessment of placental volume and vascularisation indices as predictors of preeclampsia onset and severity are still approached with caution for screening,<sup>15</sup> suggesting a need for novel methods to improve risk stratification. Due to the limited availability of MRI facilities worldwide, it is unlikely that comprehensive MRI assessments will be incorporated into clinical pathways for preeclampsia in the same way other more accessible tools have been, such as biomarker measurements and obstetric ultrasound. Nevertheless, application of these multi-system, fetal-maternal *in utero* MRI methods as presented by Hall *et al.* could play a unique role in

117 the earlier diagnosis of preeclampsia and investigation of high-risk pregnancies, adding  
118 additional clinical value.

119 Fetal brain MRI measures may provide unique clinical value in the future. For instance, fetal  
120 counselling and formulation of tailored management plans for preeclamptic pregnancies  
121 with severely reduced fetal brain T2\* measurements (reduced oxygenation) may be  
122 considered. As the field advances to a more precise and personalized approach to  
123 management strategies, antenatal MRI scans may also offer an opportunity for more  
124 extensive collaboration and joint patient management for obstetric and neonatal teams.

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#### 132 **References**

133 Hall M, de Marvao A, Schweitzer R, et al. Pre-eclampsia associated differences in the  
134 placenta, fetal brain and maternal heart can be demonstrated antenatally: An observational  
135 cohort study using MRI. *Hypertension*. 2024 (In press).

136 Ho AEP, Hutter J, Jackson LH, et al. T2\* placental magnetic resonance imaging in preterm  
137 preeclampsia: an observational cohort study. *Hypertension*. 2020;75(6):1523-1531.

138 Staff AC. The two-stage placental model of preeclampsia: An update. *J Reprod Immunol*.  
139 2019;134-135:1-10.

440 Garcia-Gonzalez C, Georgiopoulos G, Azim SA, et al. Maternal cardiac assessment at 35 to 37  
 141 weeks improves prediction of development of preeclampsia. *Hypertension*. 2020;76(2):514-  
 142 522.

543 Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or  
 144 victim? *Am J Obstet Gynecol*. 2022;226(2):S954-S962.

645 Gumusoglu SB, Chilukuri ASS, Santillan DA, Santillan MK, Stevens HE. Neurodevelopmental  
 146 outcomes of prenatal preeclampsia exposure. *Trends Neurosci*. 2020;43(4):253-268.

747 Liu D, Gao Q, Wang Y, Xiong T. Placental dysfunction: The core mechanism for poor  
 148 neurodevelopmental outcomes in the offspring of preeclampsia pregnancies. *Placenta*.  
 149 2022;126:224-232.

850 Cutler HR, Barr L, Sattwika PD, et al. Temporal patterns of pre- and post-natal target organ  
 151 damage associated with hypertensive pregnancy: a systematic review. *Eur J Prev Cardiol*.  
 152 Published online August 22, 2023:1-23.

953 Boardman H, Lamata P, Lazdam M, et al. Variations in cardiovascular structure, function,  
 154 and geometry in midlife associated with a history of hypertensive pregnancy. *Hypertension*.  
 155 2020;75:1542-1550.

106 Kitt J, Krasner S, Barr L, et al. Cardiac remodeling after hypertensive pregnancy following  
 157 physician-optimized blood pressure self-management: The POP-HT randomized clinical trial  
 158 imaging sub-study. *Circulation*. Published online November 11, 2023.

119 Siepmann T, Boardman H, Bilderbeck A, et al. Long-term cerebral white and gray matter  
 160 changes after preeclampsia. *Neurology*. 2017;88(13):1256-1264.

121 Lloyd DFA, Pushparajah K, Simpson JM, et al. Three-dimensional visualisation of the fetal  
 162 heart using prenatal MRI with motion-corrected slice-volume registration: a prospective,  
 163 single-centre cohort study. *The Lancet*. 2019;393(10181):1619-1627.

164 Youssef L, Miranda J, Paules C, et al. Fetal cardiac remodeling and dysfunction is associated  
165 with both preeclampsia and fetal growth restriction. *Am J Obstet Gynecol*.  
166 2020;222(1):79.e1-79.e9.

167 Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP  
168 classification, diagnosis, and management recommendations for international practice.  
169 *Hypertension*. 2018;72(1):24-43.

170 Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, et al. ISUOG Practice Guidelines: role of  
171 ultrasound in screening for and follow-up of pre-eclampsia. *Ultrasound in Obstetrics and*  
172 *Gynecology*. 2019;53(1):7-22.

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