The Journal of Physiology



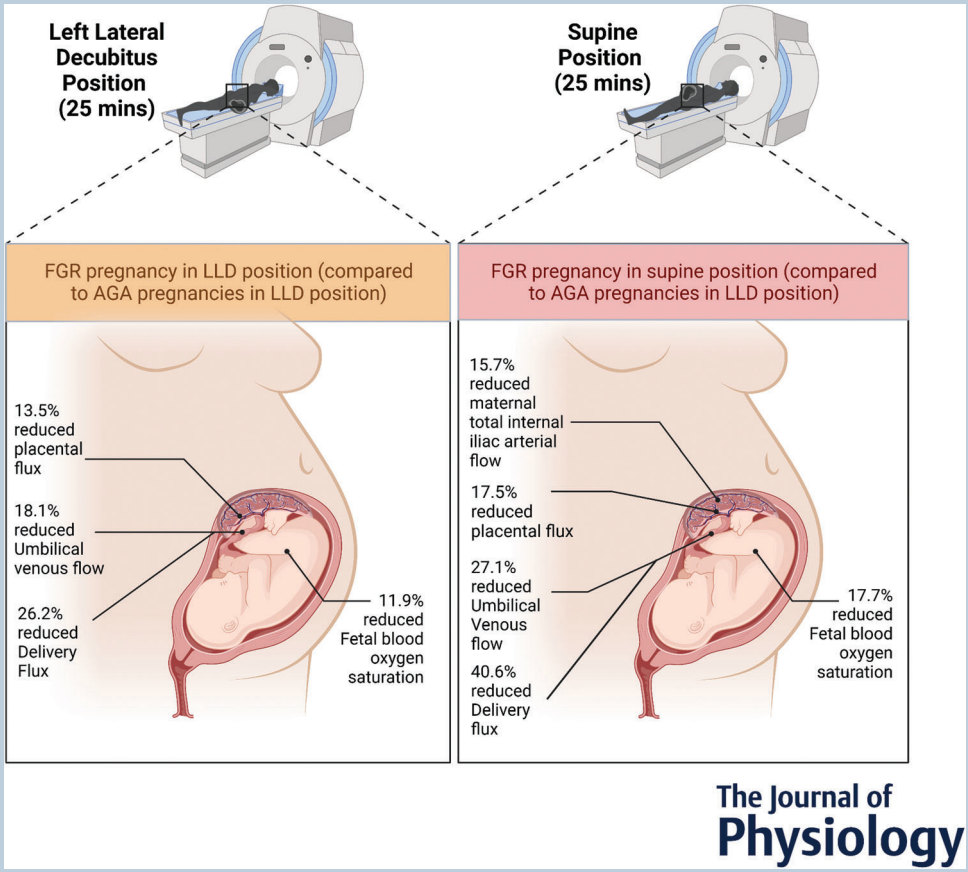
# The effect of maternal position on placental blood flow and fetoplacental oxygenation in late gestation fetal growth restriction: a magnetic resonance imaging study

Devanshi Jani[1], Alys Clark[2], Sophie Couper[1], John M. D. Thompson[1,3], Anna L. David[4], Andrew Melbourne[5], Ali Mirjalili[6], Anna-Maria Lydon[7] and Peter R. Stone[1]

[1]*Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand*
[2]*Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand*
[3]*Department of Paediatrics and Child Health, University of Auckland, Auckland, New Zealand*
[4]*Elizabeth Garrett Anderson Institute for Women's Health, University College Huntley Street, London, UK*
[5]*School of Biomedical Engineering and Imaging, Kings College London, London, UK*
[6]*Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand*
[7]*Centre for Advanced MRI, University of Auckland, Auckland, New Zealand*

Handling Editors: Harold Schultz & Rebecca Simmons

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP284269#support-information-section).




**Abstract** Fetal growth restriction (FGR) and maternal supine going-to-sleep position are both risk factors for late stillbirth. This study aimed to use magnetic resonance imaging (MRI) to quantify the effect of maternal supine position on maternal-placental and fetoplacental blood flow, placental



DOI: 10.1113/JP284269

oxygen transfer and fetal oxygenation in FGR and healthy pregnancies. Twelve women with FGR and 27 women with healthy pregnancies at 34–38 weeks' gestation underwent MRI in both left lateral and supine positions. Phase-contrast MRI and a functional MRI technique (DECIDE) were used to measure blood flow in the maternal internal iliac arteries (IIAs) and umbilical vein (UV), placental oxygen transfer (placental flux), fetal oxygen saturation ($FO_2$), and fetal oxygen delivery (delivery flux). The presence of FGR, compared to healthy pregnancies, was associated with a 7.8% lower $FO_2$ ($P = 0.02$), reduced placental flux, and reduced delivery flux. Maternal supine positioning caused a 3.8% reduction in $FO_2$ ($P = 0.001$), and significant reductions in total IIA flow, placental flux, UV flow and delivery flux compared to maternal left lateral position. The effect of maternal supine position on fetal oxygen delivery was independent of FGR pregnancy, meaning that supine positioning has an additive effect of reducing fetal oxygenation further in women with FGR, compared to women with appropriately grown for age pregnancies. Meanwhile, the effect of maternal supine positioning on placental oxygen transfer was not independent of the effect of FGR. Therefore, growth-restricted fetuses, which are chronically hypoxaemic, experience a relatively greater decline in oxygen transfer when mothers lie supine in late gestation compared to appropriately growing fetuses.

(Received 1 January 2023; accepted after revision 3 July 2023; first published online 19 July 2023)
**Corresponding author** P. R. Stone: Department of Obstetrics and Gynaecology, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. Email: p.stone@auckland.ac.nz

**Abstract figure legend** Women with appropriately grown for age (AGA) pregnancies and pregnancies with fetal growth restriction (FGR) were studied using a novel functional MRI technique for 25 min in both maternal supine and left lateral decubitus positions. Compared to AGA pregnancies, FGR pregnancies have significantly lower amounts of placental oxygen transfer, umbilical venous flow, fetoplacental blood oxygen saturation and oxygen delivery to the fetus. When mothers with FGR pregnancies lie in supine position, an acute reduction in maternal-placental blood flow occurs, leading to further decline in placental oxygen transfer, fetoplacental oxygen saturation and fetal oxygen delivery.

**Key points**

- Fetal growth restriction (FGR) is the most common risk factor associated with stillbirth, and early recognition and timely delivery is vital to reduce this risk.
- Maternal supine going-to-sleep position is found to increase the risk of late stillbirth but when combined with having a FGR pregnancy, maternal supine position leads to 15 times greater odds of stillbirth compared to supine sleeping with appropriately grown for age (AGA) pregnancies.
- Using MRI, this study quantifies the chronic hypoxaemia experienced by growth-restricted fetuses due to 13.5% lower placental oxygen transfer and 26% lower fetal oxygen delivery compared to AGA fetuses.
- With maternal supine positioning, there is a 23% reduction in maternal-placental blood flow and a further 14% reduction in fetal oxygen delivery for both FGR and AGA pregnancies, but this effect is proportionally greater for growth-restricted fetuses.
- This knowledge emphasises the importance of avoiding supine positioning in late pregnancy, particularly for vulnerable FGR pregnancies.

## Introduction

Late stillbirth, the death of a fetus after 28 weeks of gestation, continues to be a global burden. In high income countries, 1.3–8.8 in 1000 total births are affected (Flenady et al., 2016), while a stillbirth rate of up to 30 per 1000 total births is estimated in low income regions, albeit limited by under-reporting (Lawn et al., 2011). To reduce this wide variation in stillbirth rates between nations, further research and action is required to address preventable risk factors and early recognition of at-risk pregnancies. Fetal growth restriction (FGR) is the most common condition associated with stillbirth (43%) (Gardosi et al., 2005). FGR can be multifactorial, but a major contributing factor is placental dysfunction. A Delphi survey of experts on FGR created consensus-based definitions for early- and

late-onset FGR based on gestation at diagnosis, fetal size and evidence of placental dysfunction (Gordijn et al., 2016). These aim to provide more uniformity in clinical research that compares FGR with normally grown fetuses. Undetected FGR is the strongest risk factor for stillbirth in normally formed singleton pregnancies, with 5 times greater risk of stillbirth compared to when FGR is detected (Gardosi et al., 2013). As there is no proven strategy to prevent death or disability in FGR other than surveillance and appropriately timed delivery, clinicians must balance the risks of worsening hypoxia with the consequences of iatrogenic premature delivery.

Population-based studies have observed associations between maternal supine sleeping and late stillbirth (Cronin et al., 2019). Going to sleep in the supine position in late pregnancy has been found to independently increase the risk of late stillbirth 3.7-fold (McCowan et al., 2017). Since this discovery, the 'Sleep on Side: Stillbirth Prevention Campaign' has been promoted internationally to improve education and awareness of this modifiable risk factor (Cure Kids, 2018). This advice is of high importance for women with small-for-gestational age (SGA) and FGR pregnancies, as the combined effect of having a SGA baby and supine going-to-sleep position is 15 times greater odds of stillbirth compared to supine positioning in pregnancies with appropriately grown for age (AGA) fetuses, or compared to non-supine positioning in SGA pregnancies (Cronin et al., 2019). A likely explanation is that the growth-restricted fetus experiences a state of chronic hypoxia and adapts to this environment through mechanisms including preferentially increasing blood flow to high oxygen-consuming vital organs such as the brain, adrenal glands, liver and heart, at the expense of reduced growth velocity (Baschat, 2004; Figueras & Gratacós, 2014). Maternal supine position is believed to cause acute hypoxic stress, for which AGA fetuses can compensate through vasodilatation of the middle cerebral and umbilical arteries to increase blood flow to the brain and placenta, and assuming a low energy-consuming behavioural state (Khatib et al., 2014; Stone et al., 2017b). In comparison, chronically hypoxic fetuses have a limited ability to compensate for further oxygen deficiency due to their exhausted oxygen reserves and progressive acidosis, making them more vulnerable to this acute stressor (Edelstone, 1984; Rurak et al., 1990).

Magnetic resonance imaging (MRI) enables non-invasive, direct evaluation of the placenta, addressing the current lack of antenatal methods for directly assessing placental oxygenation, diffusion and perfusion in pregnancies with faltering fetal growth. The non-invasive and ionising radiation-free nature of MRI means it is an acceptable method of *in vivo* placental imaging. Identifying and quantifying placental oxygenation may be a useful marker of placental dysfunction in FGR pregnancies. T2 relaxometry is the most sensitive available technique for quantifying placental oxygen saturation in FGR and healthy pregnancies (Anderson et al., 2021; Derwig et al., 2013; Gowland et al., 1998; Lackman et al., 2001; Portnoy, Osmond et al., 2017; Portnoy, Seed et al., 2017; Saini et al., 2020; Saini et al., 2021). However, most methodologies consider the entire placenta and do not account for the separate maternal-placental and fetoplacental circulations within the placenta. Separating maternal and fetal circulations within the placenta is important as they may independently contribute to, or be affected by, the pathophysiology of FGR (Ghidini, 1996; Kingdom et al., 2000). MRI techniques that enable the measurement of blood flow and oxygen saturation within each compartment (maternal blood, fetal blood and villous tissue) may aid our understanding of the functional differences between placentae of healthy and complicated pregnancies (Clark et al., 2022; James et al., 2017; Melbourne, 2021; Slator et al., 2019). Diffusion-relaxation Combined Imaging for Detailed Placental Evaluation (DECIDE) is a placenta-specific three-compartment model combining T2 relaxation and the Intravoxel Incoherent Motion model of diffusion weighted imaging (DWI-IVIM) to separate the maternal blood, fetal blood and cellular tissue components of the placental MR signal. DECIDE is advantageous for concurrently measuring diffusion, perfusion and oxygen saturation using a simple protocol that is feasible on most clinically available MRI machines and takes less than 25 min (Melbourne et al., 2019).

Previous studies have combined phase contrast MRI (PC-MRI) with DECIDE to estimate maternal-placental blood flow and oxygenation in AGA pregnancies to investigate the physiological consequences of maternal supine positioning (Couper et al., 2021). However, the effect of maternal supine position on maternal-placental

**Dr Devanshi Jani** is a Bachelor of Medicine and Surgery, and Bachelor of Medical Sciences (Hons) graduate from the University of Auckland, and currently working as a junior doctor in Auckland, New Zealand. She was drawn to this project as it combined her interests in clinical obstetrics and maternal–fetal physiology. She aspires to continue working clinically and academically towards expanding our understanding of perinatal physiology and improving the healthcare we provide to vulnerable pregnancies.

and fetoplacental blood flow and oxygenation in FGR pregnancies has not yet been investigated. Understanding the degree of acute fetal hypoxaemia occurring in the maternal supine position, and the fetal tolerance and adaptation to this change will contribute to the explanation for why FGR pregnancies have a higher stillbirth risk. This study uses DECIDE and PC-MRI to explore the paradigm that growth-restricted fetuses exist in a chronically hypoxic state and therefore are more vulnerable to the hypoxic stress from maternal supine positioning. The two aims of this study were, firstly, to determine the differences in maternal-placental and fetoplacental blood flow, placental oxygen transfer, fetal oxygen saturation and fetal oxygen delivery between AGA and FGR pregnancies; and secondly, to determine the effect of the maternal supine position, compared to left lateral decubitus (LLD) position, on each of these outcomes in both AGA and FGR pregnancies.

## Methods

### Ethical approval

Ethical approval was received from the Health and Disabilities Ethics Committee of New Zealand, reference number 15/NTB/144/AM02 AM04 AM09. Informed consent in writing and an MRI safety questionnaire were completed by each participant prior to entry into this study. This study conformed to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database.

### Participant recruitment

Women were recruited through the National Women's Health, Auckland City Hospital Women's Day Assessment Unit, ultrasound clinics and fetal medicine clinics. Participants also volunteered through information disseminated using brochures, posters and social media communications. The criteria for inclusion were: maternal pre-pregnancy body mass index (BMI) $\geq$18 to $\leq$30 kg/m$^2$; gestational age 34 to 38 completed weeks by first trimester ultrasound; normal fetal anatomy at first trimester ultrasound scan. In the AGA group, inclusion required a symphyseal-fundal height $>$10th to $\leq$95th percentile on customised Gestation Related Optimal Weight (GROW) charts from $\geq$28 weeks' gestation (Gardosi et al., 2018), or, if available, estimated fetal weight (EFW) on ultrasound $>$10th to $\leq$95th centile by customised antenatal GROW chart from $\geq$28 weeks' gestation. In the FGR group, inclusion required an EFW on ultrasound $\leq$3rd percentile by customised GROW charts, or EFW $\leq$10th percentile with abnormal Doppler examination (any of the following Doppler parameters: uterine artery pulsatility index (PI) $>$95th centile, umbilical artery PI $>$95th centile, middle cerebral artery PI $<$5th centile, cerebroplacental ratio $<$5th centile). Women with multiple pregnancies, maternal medical conditions (including pre-existing, or pregnancy-related conditions, gestational diabetes or any form of hypertension), fetal anomalies, or structural placental anomalies (such as a bilobed placenta) or location in the lower uterine segment were ineligible for the study.

The following data were collected about each participant before the MRI: National Health Index; age at MRI scan; self-identified level 1 ethnicity code (Ministry of Health NZ, 2010); pre-pregnancy weight (self-reported) and height and weight at the date of MRI (using stadiometer and electronic scales); gestational age at date of MRI; gestational age at which FGR was detected; and any abnormal investigations during pregnancy. Data from participants' fetal growth assessment ultrasound and Doppler scans, when clinically indicated, closest to the time of the MRI were recorded. Birth outcome data were collected about the mother and neonate, including gestational age and sex at birth; mode of delivery; birthweight in grams and customised percentile on GROW charts (calculator version 6.7.8.3 (NZ) 2016; Gestation Network, 2020); APGAR scores; and admission to the neonatal intensive care unit.

### Pre-MRI assessment

Participants were advised to refrain from strenuous exercise or caffeine consumption in the 2 h prior to the MRI appointment. Immediately prior to the MRI, a cardiotocograph (CTG) was performed with the participant in a supine position for 20 min. Baseline fetal heart rate, fetal heart rate variability and presence of decelerations were reviewed by a co-investigator who was a senior obstetrician. This was performed to ensure that there was no evidence of acute fetal compromise detectable by standard CTG monitoring when the woman lay supine.

### MRI protocol

All MRI scans were performed on the 1.5-tesla Siemens Healthcare GmbH, Erlangen, Germany Magnetom Avanto-fit scanner at Auckland City Hospital by an experienced MRI technologist from the Centre for Advanced MRI (CAMRI). Each participant was scanned in both left lateral decubitus (LLD) (the referent position), and supine position (the intervention). The starting position was randomised using a Microsoft Excel random number generator. The total scan duration in each position was approximately 25 min, with a minimum of 5 min in between positions for the participant to sit or stand up and adjust into the second position. To ensure participant comfort during the scan, pillows were placed

underneath the knees when supine, and behind the back and between the knees in LLD. MRI imaging was as reported by Couper et al. (2021) in AGA pregnancy participants, and all participants were imaged in the same scanner with the same machine settings as in this prior study.

In each position, images were acquired in the following order: (1) DECIDE imaging of the placenta; (2) PC-MRI of the internal iliac arteries; and (3) PC-MRI of the umbilical vein.

## Diffusion-relaxation combined imaging for detailed placental evaluation (DECIDE)

The DECIDE combined acquisition method, first published by Aughwane et al. (2018), uses variable diffusion weighting with low *b*-values overlapped with T2 relaxometry at multiple echo times (TE). These subsets of possible combinations of *b*-values and echo times were used to allow manageable imaging times (under 25 min) while simultaneously providing measures of diffusivity and relaxivity. Seven *b*-values were used: 0, 50, 100, 150, 200, 400 and 600 s/mm$^2$. All *b*-values were acquired at TE = 96 ms, and all TE were acquired at *b*-value = 0 s/mm$^2$ for T2 fitting. Also, data were obtained for 10 TEs (81, 90, 120, 150, 180, 210 and 240 ms) at *b*-values 50 and 200 s/mm$^2$. This sequence used repetition times of 3900–9200 ms, signal to noise ratio of 1.00 and voxel resolution of 1.9 mm × 1.9 mm × 6.0 mm.

In the placenta, each voxel of the image can be divided into three compartments: tissue (myometrial/trophoblast), maternal blood and fetal blood (Melbourne, 2021; Melbourne et al., 2019). The fraction of moving blood within the total tissue volume (per voxel) can be divided into maternal perfusion fraction ($v$) and fetal perfusion fraction ($f$). Five parameters are estimated within each placenta: (1) diffusivity ($D$, mm$^2$/s), the rate of random movement (diffusion) of water molecules within intervillous spaces (maternal blood) and cellular tissue within the placenta; (2) pseudo-diffusivity ($D^*$, mm$^2$/s), quantifying pseudo-random blood movement within the fetal capillaries in chorionic villi; (3) maternal perfusion fraction ($v$, no units); (4) fetal perfusion fraction ($f$, no units); and (5) fetal blood T2 (ms), the transverse relaxation time in the fetal blood compartment. From this, fetal blood T2 time can be used to directly approximate fetal blood oxygen saturation within the placenta ($FO_2$) (Portnoy, Osmond et al., 2017).

## Phase contrast imaging of the internal iliac arteries

Phase contrast (PC-MRI) images were acquired in the axial plane just below the bifurcation of the common iliac arteries into the internal and external iliac arteries, at 90 degrees to the left and right internal iliac arteries (IIAs). A finger pulse oximeter, Philips Medical Systems, Eindhoven, The Netherlands was used to acquire maternal heart rate for flow-gating. Images were acquired during a 12 s breath-hold to ensure minimal artefact interference from maternal respiration. The imaging parameters for this sequence included: repetition time = 56.9 ms, TE = 3.1 ms, field of view = 450 mm, field of view phase = 69.4%, matrix base resolution = 288 pixels, velocity encoding level (VENC) = 200 cm/s, flip angle = 20 degrees, voxel size = 1.6 mm × 1.6 mm × 4.5 mm, and number of phases = 20. Right and Left IIA blood flow (ml/min) and total IIA blood flow (ml/min) were calculated from PC-MRI. IIAs were imaged with PC-MRI in all participants except one in the FGR group, due to operator error in acquiring images at an incorrect axial plane.

## Phase contrast imaging of the umbilical vein

The umbilical vein (UV) was imaged using PC-MRI, with synthetic gating to the upper end of typical fetal heart rate of 150 bpm (Von Steinburg et al., 2013). Images were oversampled to allow for the effect of variable fetal HR which could be considered in post-processing. Localiser (T2-weighted) images were used to manually identify a suitable section of the umbilical cord to acquire a short axis view of the UV. Images were acquired during a maternal 10 s breath hold to reduce artefact; however, if there was excessive fetal movement then repeated images were required. The parameters of the conventional gradient echo phase contrast sequence used were: repetition time = 57.2 ms, TE = 3.2 ms, field of view = 450 mm, field of view phase = 69.4%, matrix base resolution = 288 pixels, VENC = 50 cm/s, flip angle = 20 degrees, voxel size = 1.6 mm × 1.6 mm × 5 mm, and number of phases = 20. Umbilical venous blood flow (ml/min) was the primary metric derived from this imaging.

## Image analysis

**DECIDE images.** ITK-SNAP (version 3.8.0, 2019, www.itksnap.org) software was used to manually segment the placenta within the axial-plane DECIDE images in both LLD and supine positions. Segmentation involved manually drawing a mask around the placental borders, distinguishing the placenta from the myometrium and amniotic fluid or fetus. This was performed for as many of the 26 image slices of the placenta where the placental tissue and myometrium could be distinguished. These placental masks and the images acquired through the DECIDE MRI protocol (150 voxels × 150 voxels × 26 slices) were used for DECIDE model fitting in MATLAB (The MathWorks, Natick, MA, USA).

**PC-MRI.** Syngo.via software (Siemens Healthcare GmbH, Erlangen, Germany) was used to calculate blood flow in the maternal IIAs and the UV in combination with the maternal heart rate (bpm) measured at the time of acquisition or the synthetic fetal heart rate of 150 bpm. This method was previously published by our group in Couper et al. (2021). Blood flow in the right and left IIAs was added together as a surrogate for the total blood flow to the maternal uterus, assuming that changes in total IIA flow were proportional to changes in uteroplacental blood flow.

### Additional outcomes

Using the parameters derived from DECIDE and PC-MRI methods, two more parameters of interest were calculated to create a clearer correlation between the MRI-derived measurements and physiological oxygen movement.

(1) Placental flux – a measure of the rate of oxygen movement and transfer across the villous membrane into fetal capillaries within the placenta.
Placental flux ($mm^2/s$) = Diffusivity ($mm^2/s$) × [Fetal blood oxygen saturation (%)/100]
(2) Delivery flux – the rate of oxygen delivery, through the movement of oxygenated blood in the umbilical vein, from the fetal compartment of the placenta to the fetus.
Delivery flux (ml/min) = Umbilical vein blood flow (ml/min) × [Fetal blood oxygen saturation (%)/100]

Each of these flux calculations excludes the impact of haemoglobin, which was not measured in this study, and so assumes that haemoglobin levels are constant within the duration of a scan, and between the two cohorts assessed in this study.

### Statistical analysis

Previous work using DECIDE-MRI has shown statistically significant differences in maternal-placental blood flow and fetal oxygenation parameters between the supine and LLD positions in AGA pregnancies with a sample size of 20 (Couper et al., 2021), and with a sample size of 12 participants was able to detect statistically significant differences in fetal oxygen saturation between FGR and AGA pregnancies (Aughwane et al., 2021). Therefore, the current study aimed to collect data for 12–20 participants in each study group to be sufficiently powered.

Participant characteristics were compared using Student's independent samples *t* test for continuous variables, and Fisher's exact test was conducted for categorical variables using R v4.1.1 (R Core Team, Vienna, Austria). For all primary outcomes, a multivariable repeated measures linear model with two factors (pregnancy group and maternal position) was used to analyse the effects of FGR pregnancy compared to AGA pregnancy, and the effects of supine position compared to LLD. '*n*' refers to each participating woman or fetus that was imaged. Analyses were conducted using the PROC GENMOD procedure in SAS v9.4 (SAS Institute, Cary, NC, USA) to estimate the mean differences in outcomes (95% confidence intervals) between pregnancy groups and maternal positions. The measurements of the AGA pregnancy participants in LLD position were chosen as the referent to assess group and position effects. Statistical significance was defined as $P < 0.05$.

To assess intra-observer reliability of DECIDE outcomes, manual placental segmentation was performed twice by one observer for 8 data sets, and a second observer for 5 datasets, with each set consisting of supine and LLD images from each participant. Additionally, interobserver reliability was evaluated for 25 data sets from segmentation performed by observer 1 and 2, and 8 data sets from segmentations by all 3 observers. Intra- and interobserver reliability of placental segmentation methodology for DECIDE MRI were assessed using paired *t* tests, and intraclass correlations calculated for the datasets scored by all scorers. Differences in outcome measurements from each segmentation were presented as mean percentage difference (with standard deviations) and a *P*-value $< 0.05$ was considered a statistically significant difference.

## Results

### Participant demographics

This study reports results on 39 women between 34 and 38 weeks' gestational age, 27 uncomplicated AGA pregnancies ($n = 27$) and 12 with FGR ($n = 12$). Participants were recruited between 2019 and 2021, and 20 of the healthy participants were reported in a previous study by our research group (Couper et al., 2021). For all tables and figures of results, '*n*' refers to the number of participating women or fetuses imaged. As shown in Table 1, both AGA and FGR groups had comparable maternal age at MRI ($P = 0.116$) and gestational age at MRI ($P = 0.818$). However, women in the FGR group had a lower pre-pregnancy BMI than women with AGA pregnancies by 1.8 $kg/m^2$ ($P = 0.0357$). Most women identified as European ethnicity in both AGA (81%) and FGR (75%) groups, based on the New Zealand Ministry of Health level 1 ethnicity codes (Ministry of Health NZ, 2010). In both AGA and FGR groups, most women were nulliparous (81% and 67%, respectively). Three women in the FGR group had a history of one or two previous unexplained early miscarriages. Details of the antenatal ultrasound markers of FGR that led to their inclusion in this study are presented in Table 2. Four women had

**Table 1. Participant demographics and pregnancy information**

| | AGA ($n$ = 27) | FGR ($n$ = 12) | $P$ |
|---|---|---|---|
| Maternal age at MRI (mean ± SD, years) | 32 ± 4.1 | 34 ± 3.03 | 0.116 |
| Gestational age at MRI (mean ± SD, weeks) | 35.7 ± 1.2 | 35.8 ± 1.03 | 0.818 |
| Pre-pregnancy body mass index (mean ± SD, kg/m$^2$) | 22.9 ± 1.95 | 21.1 ± 3.12 | 0.0357* |
| Ethnicity ($n$ (%)) | | | |
| European | 22 (81) | 9 (75) | 0.830 |
| Māori | 0 | 0 | |
| Pacific peoples | 1 (4) | 1 (8) | |
| Asian | 4 (15) | 2 (17) | |
| Parity ($n$ (%)) | | | |
| 0 | 22 (81) | 8 (67) | 0.521 |
| ≥1 | 5 (19) | 4 (33) | |
| Gravidity ($n$ (%)) | | | |
| 1 | 18 (67) | 5 (42) | 0.004* |
| 2+ | 9 (33) | 7 (58) | |
| Fetal position at MRI ($n$ (%)) | | | |
| Right or left occipital lateral | 24 (89) | 9 (75) | 0.163 |
| Occipital posterior or anterior | 2 (7) | 0 | |
| Breech | 1 (4) | 3 (25) | |
| Placental location at MRI ($n$ (%)) | | | |
| Anterior | 6 (22) | 5 (42) | 0.536 |
| Posterior | 17 (63) | 6 (50) | |
| Lateral | 4 (15) | 1 (8) | |
| Position randomised first ($n$ (%)) | | | |
| Supine | 15 (55.6) | 5 (41.7) | 0.501 |
| LLD | 12 (44.4) | 7 (58.3) | |

$n$ is number of pregnant women or fetuses imaged in each study group.
*Statistically significant independent samples $t$ test or Fisher's exact test ($P < 0.05$). CPR, cerebro-placental ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

early-onset FGR (diagnosis of FGR at <32 weeks of gestation) and 8 women had late onset FGR (diagnosis of FGR at ≥32 weeks of gestation).

## Birth outcomes

All participants in the AGA pregnancy (control) and FGR groups gave birth at 37–42 completed weeks of gestation to live neonates, between 4 days and 7 weeks after the MRI. In the control group, most women (19, or 70.4%) had spontaneous or induced vaginal deliveries, three (11.1%) had elective caesarean section, while five (18.5%) required emergency caesarean section for indications including a pathological CTG during labour, placental abruption and failure of labour progress. All neonates in this group were born between 2675 and 4350 g (6–94th percentile). Twenty-five neonates had a birth weight appropriate for gestational age (AGA) at >10th customised centile, and two were on the 6th and 10th customised percentile, and therefore were considered small for gestational age (SGA) but not FGR (Gordijn et al., 2016; New Zealand Maternal Fetal Medicine Network, 2014). Both pregnancies had AGA EFW during antenatal ultrasound scans and went into spontaneous labour with vaginal deliveries after 38 weeks' gestation. One neonate experienced mild meconium aspiration syndrome and bilateral pneumothoraces requiring brief admission to the special care baby unit.

Of the 12 women in the FGR group, six (50%) had planned caesarean sections, two had induced vaginal deliveries, one had a spontaneous vaginal delivery, and three had emergency caesarean sections following finding of a pathological CTG during induction of labour. The range of birth weights in this group was 1890–2890 g (<1–15th percentile). All neonates had APGAR scores between 7 and 10 at 1 and 5 min, except one neonate in the FGR group who scored 6 at 1 min then 9 at 5 min. This neonate was one of two in the FGR group that experienced hypoglycaemia and required paediatric care on the postnatal ward. Only one neonate from our FGR group required neonatal intensive care unit care due to transient tachypnoea of the newborn. All participants remained in the study group they were assigned to at the time of MRI.

**Table 2. Antenatal information for participants who met the inclusion criteria for fetal growth restriction**

| FGR pregnancy characteristic | FGR ($n$ = 12) |
|---|---|
| EFW and Doppler ultrasound velocimetry at time of MRI ($n$) | |
| EFW ≤ 3rd percentile | |
| Normal Doppler ultrasound | 3 |
| Only UA-PI > 95th percentile | 1 |
| Only MCA-PI < 5th percentile | 1 |
| EFW ≥ 4–10th percentile | |
| Only UtA-PI > 95th percentile | 1 |
| Only UA-PI > 95th percentile | 3 |
| Only MCA-PI < 5th percentile | 1 |
| Both MCA-PI < 5th percentile and CPR < 5th percentile | 1 |
| All of UA-PI > 95th percentile, MCA-PI < 5th percentile and CPR < 5th percentile | 1 |
| Gestation at detection of FGR ($n$) | |
| <32 weeks | 4 |
| ≥32 weeks | 8 |
| History of previous FGR pregnancy ($n$) | |
| 0 | 4 |

$n$ is number of fetuses imaged. CPR, cerebro-placental ratio; EFW, estimated fetal weight; FGR, fetal growth restriction; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

## MRI imaging

The mean and standard deviation for all primary outcomes are presented in Table 3, showing the absolute magnitude of these parameters in each group, but not statistical differences between groups, which is assessed via a multivariable model in Table 4. The multivariable model estimates of the effect of having a FGR pregnancy compared to AGA pregnancy, and the effect of supine position compared to LLD. Table 4 outlines the effects of FGR and supine position in this multivariable model. Table 4 also shows the effect of maternal body mass index (BMI) for all maternal parameters, there are no significant effects of this metric.

With regard to the DECIDE parameters, compared to AGA pregnancy, FGR had no effect on $D$ ($P = 0.717$), $D^*$ ($P = 0.226$), or $v$ ($P = 0.130$). In contrast, $f$, the fractional blood volume within a voxel of the placenta comprising fetal blood, was significantly increased in FGR pregnancies by 0.078 or 7.8% of a voxel (95% CI: 0.03, 0.125). FGR pregnancies exhibited significantly reduced T2 relaxation time of fetal blood within the placenta by 17.9 ms (95% CI: −33.4, −2.4), compared to AGA pregnancies. As $FO_2$ is directly related to T2 time, the presence of FGR was also seen to cause a significant reduction in absolute $FO_2$ by 7.8% (95% CI: −14.2, −1.5), compared to AGA pregnancies.

Supine positioning, compared to LLD, had no significant effect on $D$ ($P = 0.775$), $D^*$ ($P = 0.066$), $v$ ($P = 0.953$) or $f$ ($P = 0.214$). The effect of supine position resulted in a significant reduction in fetal blood T2 by 7.4 ms (95% CI: −13.5, −1.2), and a significant reduction in absolute $FO_2$ by 3.8% (95% CI: −6.2, −1.5), independent of pregnancy group. Therefore, supine positioning results in a total 11.6% reduction in $FO_2$ for FGR pregnancies, a relative decline of 17.7% compared to AGA pregnancies in the LLD position.

With regard to PC-MRI, the presence of FGR pregnancy had no effect on total IIA flow ($P = 0.403$). FGR pregnancies demonstrated a significantly lower UV flow by 56 ml/min compared to the AGA pregnancies (95% CI: −97, −15).

Supine position significantly reduced IIA flow by 189 ml/min (95% CI: −283, −95). The effect of supine position on UV flow was also significant, causing a 28 ml/min reduction in UV flow (95% CI: −49, −7), independent of the 56 ml/min decrease in UV flow associated with being FGR. Therefore, FGR pregnancies experienced a combined effect of 127.3 ml/min (15.7%) reduction in total IIA flow and 85 ml/min (27%) reduction in UV flow when mothers are positioned supine, compared with AGA pregnancies in the LLD position.

With regard to placental and delivery flux, FGR was associated with a significant reduction in placental flux by $0.148 \times 10^{-3}$ mm$^2$/s (95% CI: $-0.283 \times 10^{-3}$, $-0.013 \times 10^{-3}$), and a significant reduction in delivery flux by 53.1 ml/min (95% CI: −82.7, −23.5), compared to AGA pregnancies.

Supine maternal position caused a significant reduction in placental flux by $0.073 \times 10^{-3}$ mm$^2$/s (95% CI: $-0.131 \times 10^{-3}$, $-0.014 \times 10^{-3}$) and delivery flux by 29.1 ml/min (95% CI: −46.0, −12.3), compared to LLD. Thus, the combined effect of supine position and FGR on delivery flux was a reduction by 82.2 ml/min (40.6%) compared to AGA pregnancies in the LLD position. The presence of FGR pregnancy and supine positioning together results in a combined reduction of 0.191 mm$^2$/s (17.5%) in placental flux, compared to AGA pregnancies in the LLD position.

A summary of the independent effect of fetal growth restriction, compared to AGA pregnancy, on maternal, placental and fetal outcomes found through this multivariable modelling is presented in Fig. 1. Similarly, Fig. 2 exhibits a summary of the independent effect of supine position, compared to left lateral decubitus, on these primary outcomes. Figure 3 shows the combined effect of FGR pregnancy and supine positioning. For clarity, only results that were statistically significant are presented in these figures.

**Table 3. Mean measurements for the primary outcomes from DECIDE placental imaging and PC-MRI during supine and left lateral decubitus positions, in AGA and FGR pregnancies**

| | AGA ($n$ = 27) | | FGR ($n$ = 12) | |
|---|---|---|---|---|
| | LLD | Supine | LLD | Supine |
| DECIDE Outcomes | | | | |
| Diffusivity ($D$) ($\times 10^{-3}$ mm$^2$/s) | 1.67 ± 0.25 | 1.59 ± 0.22 | 1.53 ± 0.21 | 1.67 ± 0.41 |
| Pseudo-diffusivity ($D^*$) (mm$^2$/s) | 0.063 ± 0.019 | 0.072 ± 0.034 | 0.067 ± 0.019 | 0.086 ± 0.036 |
| Fetal perfusion fraction ($f$)† | 0.341 ± 0.062 | 0.372 ± 0.066 | 0.447 ± 0.072 | 0.421 ± 0.105 |
| Maternal perfusion fraction ($v$)† | 0.275 ± 0.09 | 0.288 ± 0.085 | 0.345 ± 0.125 | 0.314 ± 0.097 |
| Fetal blood T2 (ms) | 132 ± 22.58 | 122.36 ± 22.89 | 110.44 ± 22.04 | 108.13 ± 30.5 |
| Fetal oxygen saturation ($FO_2$) (%) | 65.6 ± 8.3 | 61.1 ± 8.7 | 56.7 ± 8.8 | 54.3 ± 13.1 |
| PC-MRI outcomes | | | | |
| Right IIA flow (ml/min) | 375 ± 115 | 297 ± 108 | 372 ± 115 | 313 ± 97 |
| Left IIA flow (ml/min) | 434 ± 108 | 317 ± 114 | 488 ± 171 | 379 ± 134 |
| Total IIA flow (ml/min) | 810 ± 189 | 614 ± 187 | 859 ± 271 | 687 ± 221 |
| UV flow (ml/min) | 310 ± 77 | 275 ± 65 | 242 ± 80 | 230 ± 63 |
| Combined outcomes | | | | |
| Placental flux ($\times 10^{-3}$ mm$^2$/s) | 1.093 ± 0.201 | 0.973 ± 0.196 | 0.868 ± 0.018 | 0.902 ± 0.286 |
| Delivery flux (ml/min) | 202.7 ± 56.6 | 167.3 ± 44.218 | 139.3 ± 56.6 | 124.5 ± 44.8 |

Values are means ± SD. $n$ is the number of pregnant women or fetuses imaged in each study group.
† Perfusion fractions can be interpreted as a percentage of a voxel when multiplied by 100. AGA, appropriately grown for age; FGR, fetal growth restriction; LLD, left lateral decubitus.

The absolute differences in measurements for DECIDE analysis derived from placental segmentations conducted twice by each of two observers (one observer for 8 data sets and a second observer for 5 data sets) are presented in Table 5. The differences in measurements derived from segmentations by three observers were compared for 25 data sets between observer 1 and 2, and eight data sets between all three observers (Table 6). Paired $t$ test analysis and intraclass correlations showed that the absolute differences between measurements for all comparisons were not statistically significantly different from null ($P > 0.05$) for all outcomes other than $D^*$.

## Discussion

This study used non-invasive MRI techniques to compare the effect of maternal supine positioning on fetal oxygenation in FGR and AGA pregnancies. The presence of FGR was associated with a significant reduction in $FO_2$, UV flow, placental oxygen transfer and fetal oxygen delivery compared to AGA pregnancies. Maternal supine position caused a significant reduction in maternal IIA blood flow, and a further decline in $FO_2$, UV flow, placental oxygen transfer and fetal oxygen delivery. The effects of supine position on total IIA flow, UV flow, fetal blood T2, $FO_2$ and delivery flux were independent of whether the woman had a normal or FGR pregnancy. Due to the lower baseline $FO_2$, placental flux and delivery flux in FGR pregnancies, a further decline in these outcomes with the maternal supine position meant that the growth-restricted fetus experienced a proportionally greater reduction in placental oxygen transfer and oxygen delivery when the mother was supine.

### The effects of FGR

Through an established T2–oxygen saturation relationship validated for fetal blood (Portnoy, Seed et al., 2017; Saini et al., 2020, 2021), this study found that growth-restricted fetuses had a 7.8% lower absolute $FO_2$ than AGA pregnancies ($P = 0.02$). This demonstrates a chronic hypoxia in FGR compared to healthy fetuses, independent of maternal position. This is consistent with invasive cordocentesis studies showing FGR fetuses are hypoxaemic and acidaemic compared to AGA fetuses (Hecher et al., 1995; Nicolaides et al., 1989). These findings are also consistent with Aughwane et al. (2021), the only prior DECIDE study in FGR pregnancies, which measured a significant reduction in fetal blood T2 and $FO_2$ in FGR compared to healthy pregnancies. Although the $FO_2$ measured in our group of FGR pregnancies (56.7 ± 8.8%) is similar, our mean $FO_2$ in AGA pregnancies (65.6 ± 8.3%) is less than reported by Aughwane et al. (2021) using DECIDE. Our study includes late gestation pregnancies while Aughwane et al. (2021) imaged women at 24–34 weeks' gestational age, and $FO_2$ is known to reduce with gestational age (Siggaard-Andersen & Huch, 1995).

**Table 4. Multivariable modelling estimates of the effect of FGR pregnancy (compared to AGA pregnancy) and the effect of supine position (compared to left lateral decubitus) on primary outcomes**

| | | Effect of FGR pregnancy compared to AGA | | Effect of supine position compared to LLD | | Effect of maternal BMI (for maternal parameters) | |
|---|---|---|---|---|---|---|---|
| | Referent: AGA LLD (mean ± SD) | Absolute difference (95% CI) | *P* | Absolute difference (95% CI) | *P* | Absolute difference (95% CI) | *P* |
| DECIDE outcomes | | | | | | | |
| Diffusivity (*D*) ($\times 10^{-3}$ mm$^2$/s) | 1.67 ± 0.25 | −0.032 (−0.203, 0.139) | 0.717 | −0.012 (−0.094, 0.070) | 0.775 | | |
| Pseudo-diffusivity (*D**) (mm$^2$/s) | 0.063 ± 0.019 | 0.0091 (−0.0056, 0.0238) | 0.226 | 0.0123 (−0.0008, 0.0253) | 0.066 | | |
| Fetal perfusion fraction (*f*)† | 0.341 ± 0.062 | **0.078 (0.03, 0.125)*** | **0.001** | 0.013 (−0.008, 0.034) | 0.214 | | |
| Maternal perfusion fraction (*v*)† | 0.275 ± 0.09 | 0.048 (−0.014, 0.11) | 0.130 | −0.001 (−0.022, 0.021) | 0.953 | 0.0071 (−0.0045, 0.0188) | 0.230 |
| Fetal blood T2 (ms) | 132 ± 22.6 | **−17.9 (−33.4, −2.4)*** | **0.024** | **−7.4 (−13.5, −1.2)*** | **0.019** | | |
| Fetal oxygen saturation ($FO_2$) (%) | 65.6 ± 8.3 | **−7.8 (−14.2, −1.5)*** | **0.016** | **−3.8 (−6.2, −1.5)*** | **0.001** | | |
| PC-MRI outcomes | | | | | | | |
| Right internal iliac arterial flow (ml/min) | 375 ± 115 | 8 (−56, 72) | 0.807 | **−73 (−101, −47)*** | **<0.0001** | 2.3 (−8.0, 23.7) | 0.659 |
| Left internal iliac arterial flow (ml/min) | 434 ± 108 | 57 (−32, 146) | 0.206 | **−115 (−147, −84)*** | **<0.0001** | 5.3 (−7.2, 17.8) | 0.408 |
| Total internal iliac arterial flow (ml/min) | 810 ± 189 | 62 (−64, 187) | 0.403 | **−189 (−283, −95)*** | **<0.0001** | 7.7 (−11.2, 26.7) | 0.424 |
| UV flow (ml/min) | 310 ± 77 | **−56 (−97, −15)*** | **0.008** | **−28 (−49, −7)*** | **0.010** | | |
| Combined outcomes | | | | | | | |
| Placental flux ($\times 10^{-3}$ mm$^2$/s) | 1.093 ± 0.201 | **−0.148 (−0.283, −0.013)*** | **0.032** | **−0.073 (−0.131, −0.014)*** | **0.015** | | |
| Delivery flux (ml/min) | 202.7 ± 56.6 | **−53.1 (−82.7, −23.5)*** | **0.0004** | **−29.1 (−46.0, −12.3)*** | **0.0007** | | |

† Perfusion fraction can be interpreted as a percentage of a voxel when multiplied by 100.
* Statistically significant *t* test ($P < 0.05$). AGA, appropriately grown for age; FGR, fetal growth restriction; LLD, left lateral decubitus.
Measures shown in bold showed statistical significance.

**Table 5. Intraobserver reliability analysis**

| | Intraobserver 1 comparison | | Intraobserver 2 comparison | |
|---|---|---|---|---|
| | Absolute difference (mean ± SD) | *P* | Absolute difference (mean ± SD) | *P* |
| Maternal perfusion fraction (*v*) | 0.0027 ± 0.01 | 0.278 | −0.0119 ± 0.020 | 0.078 |
| Fetal perfusion fraction (*f*) | 0.0064 ± 0.02 | 0.234 | 0.002 ± 0.01 | 0.576 |
| Diffusivity (*D*) ($\times 10^{-3}$ mm$^2$/s) | 0.008 ± 0.02 | 0.179 | 0.006 ± 0.07 | 0.793 |
| Pseudo-diffusivity (*D**) (mm$^2$/s) | 0.00054 ± 0.004 | 0.628 | −0.00113 ± 0.003 | 0.175 |
| Fetal blood T2 (ms) | −0.56 ± 4.4 | 0.680 | 0.75 ± 2.6 | 0.375 |
| Fetal oxygen saturation ($FO_2$) (%) | −0.29 ± 2.2 | 0.599 | 0.22 ± 1.2 | 0.553 |

Prior studies have estimated placental oxygenation using T2-MRI of the placenta and have also reported that placental T2 is significantly reduced in FGR compared to AGA pregnancies (Anderson et al., 2021; Derwig et al., 2013; Gowland et al., 1998). The combined T2-DWI DECIDE technique used in this study differs from previous placental studies as it enables specific measurement of the T2 relaxation time of fetal blood within the placenta, separately from the maternal blood and cellular tissue which have a T2 rate fixed at literature values (Melbourne et al., 2019). Alternatively, to measure the oxygenation of fetal blood flowing from the placenta to the fetus, Zhu et al. (2016) measured T2 of the UV in FGR pregnancies. One limitation of T2 imaging of the UV rather than the placenta is that the umbilical cord is highly susceptible to fetal motion, and 20% of measurements had to be repeated. In contrast, none of the DECIDE placental imaging in our study needed to be repeated. T2 of UV blood was estimated 145 ± 31 ms in FGR pregnancies (Zhu et al., 2016), comparable to our result of 110.44 ± 22.04 ms in FGR pregnancies during LLD positioning.

The FGR group in this study contained both early- and late-onset FGR, and a combination of pregnancies with and without Doppler velocimetry changes. Although we did not analyse differences between sub-groups due to small sample size, Aughwane et al. (2021) have exhibited a downward gradient in $FO_2$ with increasing FGR severity. Therefore, measuring $FO_2$ with DECIDE

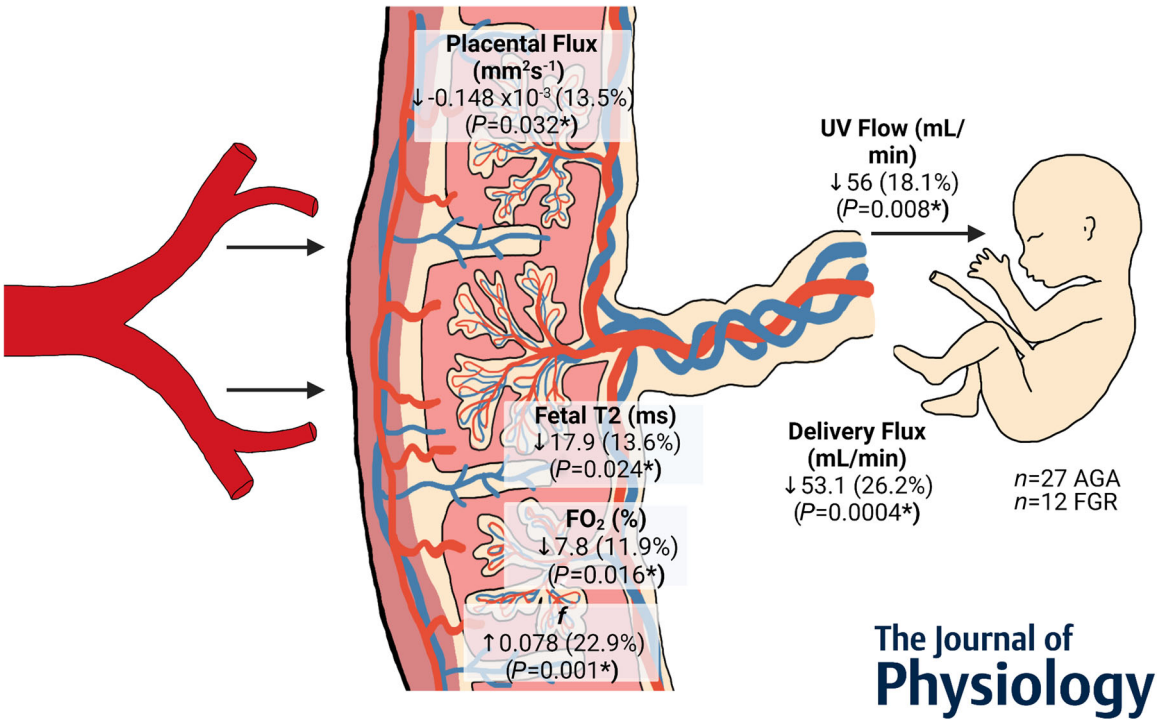



**Figure 1. Maternal, placental and fetal changes in the presence of fetal growth restriction**
Absolute and relative effect sizes are presented, where relative effect (%) is calculated from the absolute differences compared to the mean values for AGA pregnancies in LLD position. *Statistically significant effect ($P < 0.05$). *n* is number of pregnant women or fetuses imaged in each study group. (Created with BioRender.com.)

**Table 6. Interobserver reliability analysis**

| | Interobserver comparison | | | | | | |
|---|---|---|---|---|---|---|---|
| | Observer 1 *vs.* observer 2 | | Observer 1 *vs.* observer 3 | | Observer 2 *vs.* observer 3 | | |
| | Mean ± SD | *P* | Mean ± SD | *P* | Mean ± SD | *P* | ICC |
| Maternal perfusion fraction (*v*) | −0.005 ± 0.03 | 0.547 | −0.014 ± 0.04 | 0.220 | −0.009 ± 0.03 | 0.192 | 0.96 |
| Fetal perfusion fraction (*f*) | 0.0021 ± 0.05 | 0.863 | 0.0004 ± 0.05 | 0.975 | −0.0017 ± 0.02 | 0.757 | 0.92 |
| Diffusivity (*D*) ($\times 10^{-3}$ mm$^2$/s) | 0.007 ± 0.01 | 0.688 | 0.024 ± 0.03 | 0.154 | 0.017 ± 0.02 | 0.302 | 0.95 |
| Pseudo-diffusivity (*D**) (mm$^2$/s) | −0.005 ± 0.007 | 0.013 | −0.005 ± 0.01 | 0.037 | 0.0004 ± 0.007 | 0.819 | 0.97 |
| Fetal blood T2 (ms) | 0.90 ± 5.5 | 0.548 | 0.05 ± 10.3 | 0.986 | −0.85 ± 6.8 | 0.646 | 0.97 |
| Fetal oxygen saturation ($FO_2$) (%) | 0.79 ± 2.2 | 0.185 | 0.65 ± 4.4 | 0.589 | −0.145 ± 2.9 | 0.855 | 0.97 |

ICC, intraclass correlation.

MRI may provide an earlier and more direct indication of the degree of placental dysfunction and fetal hypoxaemia than that which becomes apparent using Doppler ultrasound, which is also highly user-dependent (Browne et al., 2015). A prior study in sheep and humans conducted an assessment of the relationship between DECIDE parameters and fetal weight, and showed that fractional parameters *v* and *f* did not relate to fetal weight (Flouri et al., 2022). Diffusivity values represent the micro-environment of the placenta, with lower values reflecting reduced diffusion of water/blood, and in FGR pregnancies changes in these values may be driven by a reduced fetal blood volume, or as observed anatomically, be due to lower calibre fetoplacental blood vessels (Kingdom et al., 2000). Blood gas sampling in sheep indicates that DECIDE $FO_2$ is a good predictor of measured blood gases, and so this parameter is likely to be useful for distinguishing fetal hypoxia in the growth-restricted fetus from constitutionally small but normoxic fetuses (Flouri et al., 2022).

Placental flux quantifies the diffusive movement of oxygen within the placenta, and its transfer across the

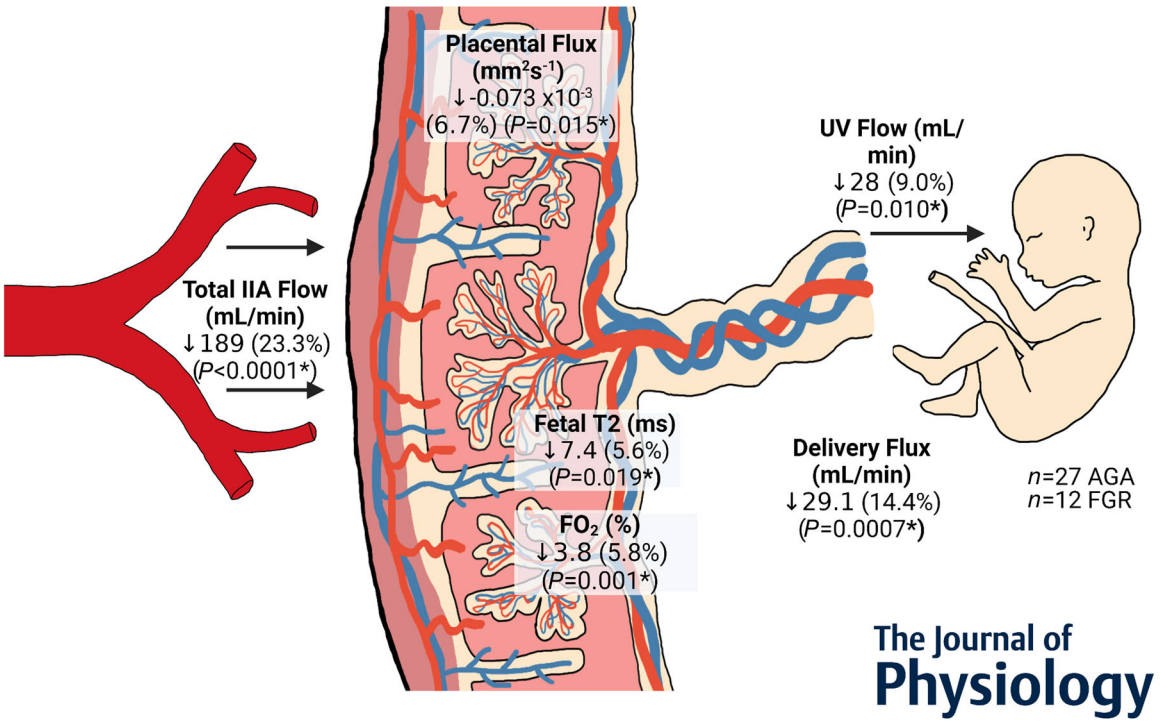



**Figure 2. The effect of supine maternal position on maternal, placental and fetal outcomes**
Absolute and relative effect sizes are presented, where relative effect (%) is calculated from the absolute differences compared to the mean values for AGA pregnancies in LLD position. *Statistically significant effect ($P < 0.05$). *n* is number of pregnant women or fetuses imaged in each study group. (Created with BioRender.com.)

villous membrane into fetal blood. Placental flux was found to be 0.148 $mm^2/s$ (13.5%) lower in the presence of FGR, compared to the AGA pregnancies during the LLD position ($P = 0.03$). The finding that placental oxygen transfer is reduced in FGR compared to AGA pregnancies is consistent with the morphological differences found in FGR placentae, for example, fibrosis, infarction, villitis, a 47% reduced villous exchange surface area and reduced villous membrane permeability (Jackson et al., 1995; Keeling & Khong, 2007; Mayhew et al., 2007; Moore et al., 2000). These pathologies can be expected to increase diffusion distance and reduce exchange surface area, therefore reducing the efficiency of oxygen transfer from maternal to fetal blood. Our MRI results are also supported by direct measurements of oxygen partial pressure ($P_{O_2}$) in human FGR pregnancies. Pardi et al. (1992) found that although maternal UtA $P_{O_2}$ is similar in FGR and AGA pregnancies; FGR pregnancies had reduced UV and umbilical arterial $P_{O_2}$, indicating an impaired oxygen gradient from uterine to umbilical circulation. Further studies with larger sample sizes are required to correlate placental flux, a non-invasive functional parameter, with structural and physiological changes in the placenta. If validated, this parameter has the potential to non-invasively detect placental dysfunction in FGR.

Fetal oxygen delivery is the rate of oxygen movement from the placenta to the fetal body, which is determined by the rate of UV blood flow and oxygen content in UV blood, and is an important physiological measure of adequate fetal oxygenation (Edelstone, 1984; Saini et al., 2021). Using PC-MRI, this study revealed a significantly lower UV blood flow in FGR compared to healthy pregnancies in the LLD position (−56 ml/min (18%), $P = 0.008$). In this study, UV flow was not adjusted for estimated fetal weight because the field of view used in our protocol could not capture both placenta and fetus entirely and thus could not calculate fetal volume at the time of imaging. Reduced UV flow in FGR pregnancies was also reported by Zhu et al. (2016), the only other PC-MRI study to compare UV flow in FGR and AGA pregnancies (respectively 105 ± 26 *versus* 134 ± 29 ml/min/kg, $P = 0.004$). Evidence from ultrasound studies suggests that UV flow is significantly reduced in FGR pregnancies even after normalising for the abdominal or head circumferences and EFW (Di Naro et al., 2002; Ferrazzi et al., 2000; Rigano et al., 2001). In fact, it was found that in FGR with assumed placental dysfunction, there was a reduced fraction of cardiac output distributed to the placental circulation while total cardiac output was maintained (Kiserud et al., 2006). Thus, our finding of reduced UV flow in FGR is physiologically plausible and

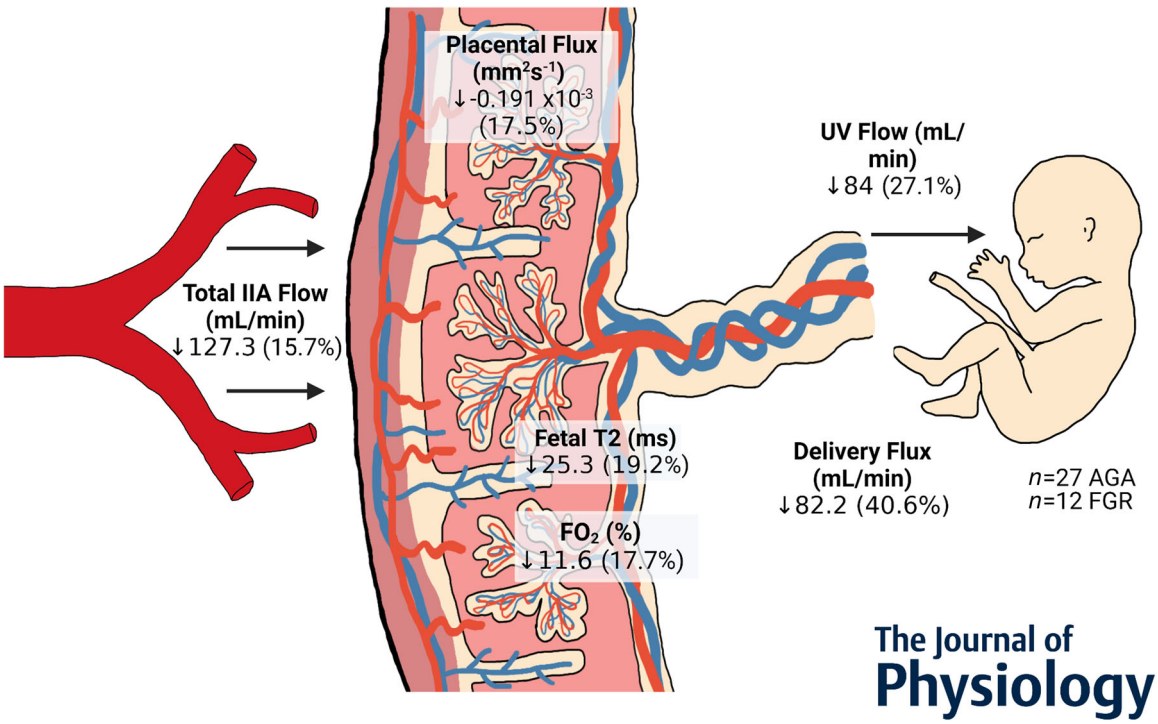



**Figure 3. The combined effect of supine maternal position and fetal growth restriction pregnancy on maternal, placental and fetal outcomes**
Absolute and relative effect sizes are presented, where relative effect (%) is calculated from the absolute differences compared to the mean values for AGA pregnancies in LLD position. *n* is number of pregnant women or fetuses imaged in each study group. (Created with BioRender.com.)

supported by current literature, although the mechanism for this adaptation is unclear, and the current study cannot distinguish between a reduction in UV flow due to decreased fetal size, and other mechanisms.

Delivery flux approximates the amount of oxygenated blood delivered from the villous capillaries within the placenta to the fetus. A 53.1 ml/min (26%) reduction in delivery flux was attributed to the presence of FGR, when compared to AGA pregnancies in LLD position ($P = 0.0004$), independent of the effect of maternal position. Therefore, this study indicates that growth-restricted fetuses receive a substantially lower rate of oxygen delivery from the placenta than healthy AGA fetuses. This finding is supported by the results from Zhu et al. (2016), who also found that fetal oxygen delivery was significantly decreased in FGR compared to AGA pregnancies. Zhu et al. calculated fetal oxygen delivery as the product of UV flow and oxygen content (1.36 × haemoglobin concentration × $FO_2$), using UV blood T2 for $FO_2$ estimation and gestational age-related empirical measures of fetal haemoglobin concentration (Nicolaides et al., 1988). We followed Couper et al. (2021), which assumes a constant haemoglobin/oxygen content to avoid the unknown variation between estimated and true haematocrit and potential error; we did not calculate absolute oxygen content. However, we here conduct an analysis of implications of this assumption. Fetal blood haemoglobin has been suggested to be elevated during chronic hypoxaemia (Bonds et al., 1987). Data in FGR pregnancies suggest that the effect of this condition on blood haemoglobin is variable, but that there may be small differences in this parameter at term, from with an increase of approximately 2 g/dl in FGR (Pardi et al., 1993). Portnoy, Seed et al. (2017) analysed the relationship between T2 and oxygen saturation in fetal cord blood over a range of haematocrit and proposed a model for the relationship between these parameters. Fitting the following model to the data from Portnoy et al.

$$\mathrm{T2\ (s)} = \frac{1}{b_1\mathrm{Hct} + b_2 + (b_3\mathrm{Hct} + b_4)\left(1 - \frac{s}{100}\right) + (b_5\mathrm{Hct} + b_6)\left(1 - \frac{s}{100}\right)^2}$$

where $s$ is oxygen saturation ($FO_2$), Hct is haematocrit, and $b_1$–$b_6$ are fitted constants, we explored the effect of elevated haematocrit by up to 6% in FGR compared to normal fetuses, assuming the relationship between haematocrit and haemoglobin to be linear (Kokholm, 1990). The effect of increased haematocrit on T2–$FO_2$ relationships is to flatten the sigmoidal curve that defines this relationship (i.e. at high haematocrit T2 is less influenced by $FO_2$ than at low haematocrit). Variability in T2–$FO_2$ relationships with haematocrit is most pronounced at high saturation ($FO_2 > \sim 70\%$). Increasing assumed haemoglobin in all FGR participants by 2 g/dl resulted in <1% change in modelled $FO_2$ for every participant, and did not impact the significance of intergroup comparisons.

Of course, the true delivery of oxygen to the fetus requires knowledge of patient-specific haemoglobin levels. In future studies, where cord gas analysis is not possible, T1 relaxometry may be used to estimate haemoglobin (Xu et al., 2020). However, due to the combined phase contrast and DECIDE imaging in this study, additional scan time was not feasible. We can estimate the possible impact of elevated haemoglobin in FGR fetuses on oxygen delivery by considering the extent of change in haemoglobin that would be required in the FGR cohort to explain the observed differences in placental and delivery flux. In a normal pregnancy population, Nicolaides et al. (1988) provided a reference range for haemoglobin with mean of 14.3 g/dl at 34 weeks and a reported standard deviation of 1.0 g/dl. For placental flux there is a 13.5% difference between cohorts; to account for this difference, the haemoglobin in the FGR cohort would need to increase to 16.2 g/dl (1.9 standard deviations above the population mean). For delivery flux there is a 26.1% difference between cohorts, which would require a shift to 18.0 g/dl (>3 standard deviations) in the FGR group. Given the overlap in haemoglobin in normal and FGR pregnancies (Pardi et al., 1993) it is possible that an elevated haemoglobin in FGR would bring placental and delivery flux nearer to the normal values but would not account for all of the observed changes.

## The effects of maternal supine position

Supine position led to an average 189 ml/min (23%) reduction in total internal iliac arterial (IIA) flow compared to the total IIA flow in AGA pregnancies during LLD ($P < 0.0001$). This effect was independent of the type of pregnancy, meaning that women with late gestation FGR or normal pregnancies experience the same absolute change in total IIA flow. This result aligns with the evidence that supine position causes a 16.4% reduction in maternal cardiac output and 32.3% reduction in abdominal aortic flow compared to LLD (Humphries et al., 2019). Assuming that the reduction in total IIA observed signifies reduced maternal-placental blood supply, supine positioning in late pregnancy is a physiological stressor for the maternal circulation which has a similar impact between AGA and FGR pregnancies.

Supine maternal position had a significant negative effect on the T2 relaxation rate of fetal blood (−7.4 ms, $P = 0.02$), and consequentially on $FO_2$ (−3.8%, $P = 0.001$). This equates to a 5.8% reduction relative to the mean $FO_2$ for AGA pregnancies in LLD position. While this is a small change, the effect of maternal supine position was independent to the 7.8% lower $FO_2$ found in FGR compared to AGA pregnancies. Therefore, while the

absolute effect of supine position was the same in both groups, FGR pregnancies experienced a proportionally greater hypoxic effect than AGA pregnancies. This has the potential for clinically significant effects. One possible explanation for the reduction in $FO_2$ with supine position is reduced maternal blood flow rate and reduced $P_{O_2}$ gradient between maternal and fetal blood. Due to the left-shift of the fetal oxyhaemoglobin dissociation curve, the fetal blood $P_{O_2}$ will reduce by a larger amount than in adult blood before a significant change in $FO_2$ occurs, giving the fetus a margin of safety for reductions in maternal-placental oxygen supply (Rothstein & Longo, 1998). The fact that a significant reduction in $FO_2$, albeit small, was observed suggests that a considerable decline in fetal $P_{O_2}$ may have occurred. The mean $FO_2$ in LLD position was 65.6 ± 8.3% and 56.7 ± 8.8% in AGA and FGR pregnancies, respectively. Given the sigmoid shape of the fetal oxyhaemoglobin dissociation curve, these $FO_2$ estimates lie on the steep aspect of the curve. Therefore, it is reasonable to suggest that FGR and healthy pregnancies experienced the same acute reduction in $FO_2$ with presumably the same amount of $P_{O_2}$ decline in supine position.

Maternal supine positioning has a significant negative effect on placental flux in both AGA and FGR placentae. This absolute difference equates to a 6.7% reduction relative to the mean placental flux in AGA pregnancies during LLD position, congruent with the effect published earlier in a subset of normal pregnancies from this study (Couper et al., 2021). The reduction in placental flux is contributed to by the significant fall in $FO_2$ and a downward trend in $D$ which was not statistically significant ($-0.012 \times 10^{-3}$ mm$^2$/s, $P = 0.77$). Therefore, it appears that the maternal supine position impairs oxygen transfer across the villous membrane from maternal to fetal blood, and this may be a contributing factor to the acute hypoxia observed in both FGR and AGA pregnancies. Unlike most parameters in this study, the effect of the supine position on placental flux was not independent of pregnancy group, and a slightly larger decline in placental flux was observed in FGR compared to AGA pregnancies. Our finding is consistent with current knowledge about placental physiology in response to acute stressors. For example, when uterine blood flow rate reduces during contractions in labour, there is a significant transient reduction in oxygen transfer to the fetus (Longo et al., 1986). While in healthy placentae, a hypoxic fetoplacental vasoconstriction response is seen to redirect fetal blood to areas with greater oxygen availability to maintain fetal oxygenation, this response may be diminished in FGR due to fewer and smaller tertiary villous capillaries and reduced membrane conductance (Giles et al., 1985; Hampl et al., 2002; Jackson et al., 1995; Mayhew et al., 2007; Ramasubramanian et al., 2006).

The present study has shown that supine position leads to a 28 ml/min (9%) reduction in UV flow compared to that measured in AGA pregnancies during the LLD position ($P = 0.01$). The effect of supine positioning was independent of the effect of FGR pregnancy, indicating that the absolute reduction in UV flow was not dependent on fetal size or the presence of placental dysfunction. This is the first study to assess the effect of supine position on UV flow in FGR pregnancies. The mechanism underlying this reduction in UV flow with supine position is not fully understood. It is possible that UV flow reduction is an active fetal response to an acute decrease in maternal-placental blood supply, and thus, decreased oxygen transfer. In fetal lambs, inducing hypoxaemia led to more than doubling of resistance in the UV, while resistance in the umbilical arteries and placental vessels was not affected (Paulick et al., 1990). It is unclear what the duration of the hypoxaemia was, but this evidence suggests that the reduction in UV flow in response to hypoxaemia is an active response to improve oxygen uptake before blood returns to the fetus.

As a result of reduced UV flow and $FO_2$ with supine positioning, delivery flux is significantly reduced by 29.1 ml/min (14.4%) compared to AGA pregnancies in the LLD position. Therefore, it is evident that supine positioning during late gestation impairs the rate of oxygen delivery from the placenta to the fetus. As participants acted as their own control in LLD, the difference in delivery flux observed in the supine position is proportional to the change in fetal oxygen delivery (UV flow × UV oxygen content) since fetal haematocrit is constant. The effects of supine positioning on UV flow and delivery flux were independent of the presence of FGR compared to AGA pregnancies. This is supported by the hypothesis that the reduction in UV flow with supine positioning occurs in response to reduced maternal oxygenated blood supply, which is affected to the same extent in both groups. However, as FGR pregnancies are already experiencing a 53.1 ml/min lower delivery flux than AGA pregnancies, this additional reduction could have a greater effect on the growth-restricted fetus.

The FGR pregnancies in this study represented a milder severity of hypoxia on the spectrum of FGR, compared to those that participated in the GRIT and TRUFFLE studies (Frusca et al., 2018; GRIT Study Group, 2003), reflected in the fact they all survived to term. Therefore, the response to supine positioning seen in these participants may not reflect those pregnancies where the fetus has already maximised its adaptations to chronic hypoxaemia, such as 'brain sparing' circulatory redistribution and increased haemoglobin synthesis (Bonds et al., 1987). In these fetuses, any further reduction in $FO_2$ with supine positioning would likely be of a smaller degree than healthy fetuses until at some unknown terminal point

when asphyxia occurs. This study's results suggest that even in less severe FGR, MRI can detect differences between growth-restricted fetuses that may or may not be able to tolerate such stressors, and therefore, in the future, may identify pregnancies that require imminent delivery.

Whether a fetus can survive acute reductions in oxygen delivery and $FO_2$ is believed to be dependent on their oxygen reserve or 'oxygen margin of safety' (Edelstone, 1984). This margin is provided by the 3.7-fold surplus of fetal oxygen delivery which exceeds the rate of fetal oxygen consumption required to maintain aerobic metabolism in appropriately grown human fetuses (Saini et al., 2021). When acute fetal hypoxaemia was simulated in normal sheep pregnancies through UtA occlusion over 30 min, oxygen consumption and base excess remained unchanged until fetal oxygen delivery declined by more than 50% of the control value (Wilkening & Meschia, 1983), after which oxygen consumption reduced and lactic acidosis developed. Although we cannot repeat similar experiments in humans, observational evidence from human fetuses during delivery shows that $FO_2$ must decline to $\leq$30% for $\geq$10 min before fetal pH declines (Seelbach-Göbel et al., 1999). Therefore, whether supine positioning leads to a fetus exhausting its oxygen margin of safety depends upon their oxygenation status at baseline, the severity of acute hypoxaemia and the duration of supine positioning. In this study, supine positioning caused delivery flux to reduce by less than 50%, so the margin of safety was not likely breached in healthy fetuses, but it is possible in growth-restricted fetus since they are closer to exhausting their reserves due to chronic hypoxia. Furthermore, the $FO_2$ recorded during supine position for all FGR and AGA pregnancy participants in this study remained above the 30% 'critical boundary for fetal compromise' (Seelbach-Göbel et al., 1999). However, it is very plausible that $FO_2$ may reduce beyond this oxygen margin of safety in FGR pregnancies that have severe chronic hypoxia and/or in mothers who sleep in supine position for longer periods.

## Strengths

This study imaged pregnancies at 34–38 gestational weeks for all participants with the aim to restrict the effect of gestational age as a confounding factor and investigate pregnancies less likely to have later diagnosed maternal or fetal comorbidities. This gestational range was important because it is known that placental volume growth is stable after 34 weeks' gestation, reducing the variability between participants (Geirsson et al., 1985). Maternal age, ethnicity and parity of women were statistically similar in both study groups. Maternal BMI was statistically significantly different, with the FGR group having a lower BMI by 1 kg/m$^2$, but all women were still within a healthy BMI range and the estimated fetal weight was based on charts customised for pre-pregnancy weight and height, maternal age, ethnicity and parity (Gardosi et al., 2018). The inclusion criteria for FGR were narrow and specific, based on a Delphi consensus of international experts and on New Zealand clinical guidelines (Gordijn et al., 2016; New Zealand Maternal Fetal Medicine Network, 2014), which improved the external validity of our results. The delivery and birth outcomes for our FGR participants showed that all except one neonate were born below the 10th customised percentile for gestational age, and the majority were below the third percentile. The data collected from the neonate that had a birth weight on the 15th percentile did not show any outliers from the remainder of the FGR group. Therefore, we consider that the fetuses in our study were likely truly growth-restricted rather than constitutionally small. Each participant underwent MRI scans in both supine and LLD positions so that they acted as their own controls, with the starting position randomised. These paired measurements limited the effect of confounding factors and enabled us to determine that the effects of group and position were independent of each other for most parameters. Our statistical model includes by design an assessment of the between-group differences in imaged parameters, and includes a comparison between AGA and FGR groups, which are defined by fetal weight. Therefore, the data suggest that the smaller size of FGR babies does not impact maternal parameters in this cohort (IIA flows, or $v$), but does impact fetal parameters (UV flow, $f$, T2, $FO_2$, and both delivery and placental flux). As the UV flow and delivery flux measurements could not be standardised by fetal weight (in ml/min/kg) due to limited time during the MRI, this study is not able to characterise whether AGA and FGR differences are attributable primarily to fetal weight. However, importantly the effect of maternal supine position is of the same magnitude whether the fetus is AGA or FGR, and therefore we conclude that the impact of positioning on already reduced oxygen-related parameters would have an important effect on these pregnancies.

Intraobserver (Table 5) and interobserver (Table 6) comparisons of the DECIDE measurements obtained from placental segmentations by a total of three different observers show low variability, with differences between measurements being insignificantly different from null ($P > 0.05$) other than $D^*$ ($D^*$ is typically reported as variable in the placenta (Moore et al., 2000) and changes in this parameter between groups were not observed). The intraobserver correlations statistic was high for all measurements giving confidence to the differences seen by position. Fetal T2 and $FO_2$ showed the most reliability (least variability), likely due to being least susceptible to fetal movements during the MRI.

## Limitations

This sample size of 12 FGR pregnancies is smaller than some comparable placental MRI studies cited. Recruitment was challenging because women with FGR pregnancies were already required to attend multiple hospital visits per week and so were reluctant to give further time to hospital-based investigations. Also, lying in an MRI scanner for 25–30 min with a gravid uterus was a barrier for many potential participants, especially those with claustrophobia and breathlessness, gastric reflux, or hypotensive symptoms when supine. Despite a limited sample size of 12 and 27 participants in each group, this met our target sample size based on previous studies and our study was adequately sized to detect statistically significant differences in most primary outcomes between groups. Further data collection from a larger sample of FGR pregnancies is needed to allow analysis of the differences between early-onset and late-onset FGR, and between FGR with and without Doppler abnormalities to gain a better understanding of the differences in placental function leading to these clinical manifestations.

This study is a simulation of the positional effects we expect to occur when women go to sleep in the supine position. Participants were studied in each position for 25–30 min. In reality, the going-to-sleep position is maintained for approximately 62 min after sleep onset for women in late pregnancy (Stone et al., 2017a) It is possible that the observed effects of supine positioning are different during sleep, compared to when the mother is awake, due to the reduction in maternal blood pressure observed while asleep (Seligman, 1971). However, simulating this is not logistically feasible or comfortable for participants.

The current study imaged the maternal IIAs, rather than uterine arteries (UtA) which supply 80% of the total maternal blood supply to the placenta (Osol & Moore, 2014). Due to the varying origin and route of UtAs, their small diameter, and the voxel resolution required for whole-placental imaging, UtAs are not consistently identified with MRI (Chantalat et al., 2014; Hwuang et al., 2019; Liapis et al., 2020; Pates et al., 2010). To balance the aims of obtaining reliable images of maternal anatomy and accurately estimating maternal-placental blood flow, we imaged the IIAs directly upstream of UtAs with PC-MRI which has been reported previously by our research group to have high interobserver and intraobserver reliability at 34–38 weeks of gestation (Couper et al., 2021; Humphries et al., 2019).

## Conclusion

This study found that MRI detected significant reductions in $FO_2$, placental oxygen transfer, UV blood flow and fetal oxygen delivery in late-gestation FGR pregnancies compared to healthy pregnancies. Furthermore, this study provides strong evidence that the maternal supine position, compared to LLD position, is an acute stressor which causes significant deterioration in maternal-placental blood flow, placental flux, $FO_2$, UV flow and delivery flux in late gestation FGR and healthy pregnancies. From this experimental model, it is concluded that while the maternal supine position has the same absolute effect on $FO_2$ and delivery flux in FGR and AGA pregnancies, the growth-restricted fetus experiences a proportionally greater hypoxic effect. The study has provided further support for educating all pregnant women, especially those with FGR pregnancies, to avoid resting and going to sleep in the supine position to reduce their risk of late stillbirth. It is evident that these functional MRI techniques provide a direct, non-invasive method for identifying fetal hypoxia and fetoplacental responses to acute stress that may be useful for guiding management of FGR pregnancies in the future.

## References


Anderson, K. B., Andersen, A. S., Hansen, D. N., Sinding, M., Peters, D. A., Frokjaer, J. B., & Sorensen, A. (2021). Placental transverse relaxation time (T2) estimated by MRI: Normal values and the correlation with birthweight. *Acta Obstetricia et Gynecologica Scandinavica*, **100**(5), 934–940.

Aughwane, R., Magdalena, B. A., Atkinson, D., Kendall, G., Deprest, J., Vercauteren, T., David, A. L., Ourselin, S., & Melbourne, A. (2018). MRI Measurement of Placental Perfusion and Fetal Blood Oxygen Saturation in Normal Pregnancy and Placental Insufficiency. In *Medical Image Computing and Computer Assisted Intervention – MICCAI 2018*, pp. 913–920. Springer International Publishing.

Aughwane, R., Mufti, N., Flouri, D., Maksym, K., Spencer, R., Sokolska, M., Kendall, G., Atkinson, D., Bainbridge, A., Deprest, J., Vercauteren, T., Ourselin, S., David, A. L., & Melbourne, A. (2021). Magnetic resonance imaging measurement of placental perfusion and oxygen saturation in early-onset fetal growth restriction. *BJOG*, **128**(2), 337–345.

Baschat, D. A. A. (2004). Fetal responses to placental insufficiency: An update. *BJOG*, **111**(10), 1031–1041.

Bonds, D., Cheek, T., Crosby, L., & Gutsche, B. (1987). Term human fetal umbilical vein oxygen content, placental weight, and maternal blood pressure. *Journal of Perinatology*, **7**(2), 114–117.

Browne, V. A., Julian, C. G., Toledo-Jaldin, L., Cioffi-Ragan, D., Vargas, E., & Moore, L. G. (2015). Uterine artery blood flow, fetal hypoxia and fetal growth. *Philosophical Transactions of the Royal Society B: Biological Sciences*, **370**(1663), 20140068.

Chantalat, E., Merigot, O., Chaynes, P., Lauwers, F., Delchier, M. C., & Rimailho, J. (2014). Radiological anatomical study of the origin of the uterine artery. *Surgical and Radiologic Anatomy*, **36**(10), 1093–1099.

Clark, A., Flouri, D., Mufti, N., James, J., Clements, E., Aughwane, R., Aertsen, M., David, A., & Melbourne, A. (2022). Developments in functional imaging of the placenta. *The British Journal of Radiology*, **96**(1147), 20211010.

Couper, S., Clark, A., Thompson, J. M. D., Flouri, D., Aughwane, R., David, A. L., Melbourne, A., Mirjalili, A., & Stone, P. R. (2021). The effects of maternal position, in late gestation pregnancy, on placental blood flow and oxygenation: An MRI study. *The Journal of Physiology*, **599**(6), 1901–1915.

Cronin, R. S., Li, M., Thompson, J. M. D., Gordon, A., Raynes-Greenow, C. H., Heazell, A. E. P., Stacey, T., Culling, V. M., Bowring, V., Anderson, N. H., O'Brien, L. M., Mitchell, E. A., Askie, L. M., & Mccowan, L. M. E. (2019). An Individual participant data meta-analysis of maternal going-to-sleep position, interactions with fetal vulnerability, and the risk of late stillbirth. *EClinicalMedicine*, **10**, 49–57.

Cure Kids. (2018). Sleep On Side, https://www.sleeponside.org.nz/.

Derwig, I. E., Barker, G. J., Poon, L., Zelaya, F., Gowland, P., Lythgoe, D. J., & Nicolaides, K. (2013). Association of placental T2 relaxation times and uterine artery Doppler ultrasound measures of placental blood flow. *Placenta*, **34**(6), 474–479.

Di Naro, E., Raio, L., Ghezzi, F., Franchi, M., Romano, F., & Addario, V. D. (2002). Longitudinal umbilical vein blood flow changes in normal and growth-retarded fetuses. *Acta Obstetricia et Gynecologica Scandinavica*, **81**(6), 527–533.

Edelstone, D. I. (1984). Fetal compensatory responses to reduced oxygen delivery. *Seminars in Perinatology*, **8**(3), 184–191.

Ferrazzi, E., Rigano, S., Bozzo, M., Bellotti, M., Giovannini, N., Galan, H., & Battaglia, F. C. (2000). Umbilical vein blood flow in growth-restricted fetuses. *Ultrasound in Obstetrics and Gynecology*, **16**(5), 432–438.

Figueras, F., & Gratacós, E. (2014). Update on the diagnosis and classification of fetal growth restriction and proposal of a Stage-based management protocol. *Fetal Diagnosis and Therapy*, **36**(2), 86–98.

Flenady, V., Wojcieszek, A. M., Middleton, P., Ellwood, D., Erwich, J. J., Coory, M., Khong, T. Y., Silver, R. M., Smith, G. C. S., Boyle, F. M., Lawn, J. E., Blencowe, H., Leisher, S. H., Gross, M. M., Horey, D., Farrales, L., Bloomfield, F., Mccowan, L., Brown S. J., …, Goldenberg R. L. (2016). Stillbirths: Recall to action in high-income countries. *The Lancet*, **387**(10019), 691–702.

Flouri, D., Darby, J. R., Holman, S. L., Cho, S. K., Dimasi, C. G., Perumal, S. R., Ourselin, S., Aughwane, R., Mufti, N., & Macgowan, C. K. (2022). Placental MRI predicts fetal oxygenation and growth rates in sheep and human pregnancy. *Advanced Science*, **9**(30), 2203738.

Frusca, T., Todros, T., Lees, C., Bilardo, C. M., Hecher, K., Visser, G. H., Papageorghiou, A. T., Marlow, N., Thilaganathan, B., & van Wassenaer-Leemhuis, A. (2018). Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: Insights from the Trial of Umbilical and Fetal Flow in Europe. *American Journal of Obstetrics and Gynecology*, **218**(2), S783–S789.

Gardosi, J., Francis, A., Turner, S., & Williams, M. (2018). Customized growth charts: Rationale, validation and clinical benefits. *American Journal of Obstetrics and Gynecology*, **218**(2), S609–S618.

Gardosi, J., Kady, S. M., Mcgeown, P., Francis, A., & Tonks, A. (2005). Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ*, **331**(7525), 1113–1117.

Gardosi, J., Madurasinghe, V., Williams, M., Malik, A., & Francis, A. (2013). Maternal and fetal risk factors for stillbirth: Population based study. *BMJ*, **346**, f108–f108.

Geirsson, R., Ogston, S., Patel, N., & Christie, A. (1985). Growth of total intrauterine, intra-amniotic and placental volume in normal singleton pregnancy measured by ultrasound. *BJOG*, **92**(1), 46–53.

Gestation Network. (2020). Centile Calculator. https://www.gestation.net/cc/about.htm

Ghidini, A. (1996). Idiopathic fetal growth restriction: A pathophysiologic approach. *Obstetrical & Gynecological Survey*, **51**(6), 376–382.

Giles, W. B., Trudinger, B. J., & Baird, P. J. (1985). Fetal umbilical artery flow velocity waveforms and placental resistance: Pathological correlation. *BJOG*, **92**(1), 31–38.

Gordijn, S. J., Beune, I. M., Thilaganathan, B., Papageorghiou, A., Baschat, A. A., Baker, P. N., Silver, R. M., Wynia, K., & Ganzevoort, W. (2016). Consensus definition of fetal growth restriction: A Delphi procedure. *Ultrasound in Obstetrics & Gynecology*, **48**(3), 333–339.

Gowland, P. A., Freeman, A., Issa, B., Boulby, P., Duncan, K. R., Moore, R. J., Baker, P. N., Bowtell, R. W., Johnson, I. R., & Worthington, B. S. (1998). In vivo relaxation time measurements in the human placenta using echo planar imaging at 0.5 T. *Magnetic Resonance Imaging*, **16**(3), 241–247.

GRIT Study Group. (2003). A randomised trial of timed delivery for the compromised preterm fetus: Short term outcomes and Bayesian interpretation. *BJOG*, **110**(1), 27–32.

Hampl, V., Bíbová, J., Stranˇák, Z., Wu, X., Michelakis, E. D., Hashimoto, K., & Archer, S. L. (2002). Hypoxic fetoplacental vasoconstriction in humans is mediated by potassium channel inhibition. *American Journal of Physiology-Heart and Circulatory Physiology*, **283**(6), H2440–H2449.

Hecher, K., Snijders, R., Campbell, S., & Nicolaides, K. (1995). Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: Relationship with fetal blood gases. *American Journal of Obstetrics and Gynecology*, **173**(1), 10–15.

Humphries, A., Mirjalili, S. A., Tarr, G. P., Thompson, J. M. D., & Stone, P. (2019). The effect of supine positioning on maternal hemodynamics during late pregnancy. *The Journal of Maternal-Fetal & Neonatal Medicine*, **32**(23), 3923–3930.

Hwuang, E., Vidorreta, M., Schwartz, N., Moon, B. F., Kochar, K., Tisdall, M. D., Detre, J. A., & Witschey, W. R. T. (2019). Assessment of uterine artery geometry and hemodynamics in human pregnancy with 4d flow mri and its correlation with doppler ultrasound. *Journal of Magnetic Resonance Imaging*, **49**(1), 59–68.

Jackson, M. R., Walsh, A. J., Morrow, R. J., Mullen, J., Lye, S. J., & Ritchie, J. (1995). Reduced placental villous tree elaboration in small-for-gestational-age pregnancies: Relationship with umbilical artery Doppler waveforms. *American Journal of Obstetrics and Gynecology*, **172**(2), 518–525.

James, J. L., Chamley, L. W., & Clark, A. R. (2017). Feeding your baby in utero: How the uteroplacental circulation impacts pregnancy. *Physiology*, **32**(3), 234–245.

Keeling, J. W., & Khong, T. Y. (2007). *Fetal and neonatal pathology*. Cham: Springer. 2015.

Khatib, N., Weiner, Z., Beloosesky, R., Vitner, D., & Thaler, I. (2014). The effect of maternal supine position on umbilical and cerebral blood flow indices. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **175**, 112–114.

Kingdom, J., Huppertz, B., Seaward, G., & Kaufmann, P. (2000). Development of the placental villous tree and its consequences for fetal growth. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **92**(1), 35–43.

Kiserud, T., Ebbing, C., Kessler, J., & Rasmussen, S. (2006). Fetal cardiac output, distribution to the placenta and impact of placental compromise. *Ultrasound in Obstetrics and Gynecology*, **28**(2), 126–136.

Kokholm, G. (1990). Simultaneous measurements of blood pH, p CO2, p O2 and concentrations of hemoglobin and its derivates-A multicenter study. *Scandinavian Journal of Clinical and Laboratory Investigation*, **50**(sup203), 75–86.

Lackman, F., Capewell, V., Gagnon, R., & Richardson, B. (2001). Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. *American Journal of Obstetrics and Gynecology*, **185**(3), 674–682.

Lawn, J. E., Blencowe, H., Pattinson, R., Cousens, S., Kumar, R., Ibiebele, I., Gardosi, J., Day, L. T., Stanton, C., & Committee LsSSS. (2011). Stillbirths: Where? When? Why? How to make the data count? *The Lancet*, **377**(9775), 1448–1463.

Liapis, K., Tasis, N., Tsouknidas, I., Tsakotos, G., Skandalakis, P., Vlasis, K., & Filippou, D. (2020). Anatomic variations of the Uterine Artery. Review of the literature and their clinical significance. *Turkish Journal of Obstetrics and Gynecology*, **17**(1), 58.

Longo, L. D., Dale, P. S., & Gilbert, R. D. (1986). Uteroplacental O2 uptake: Continuous measurements during uterine quiescence and contractions. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **250**(6), R1099–R1107.

Mayhew, T., Manwani, R., Ohadike, C., Wijesekara, J., & Baker, P. (2007). The placenta in pre-eclampsia and intra-uterine growth restriction: Studies on exchange surface areas, diffusion distances and villous membrane diffusive conductances. *Placenta*, **28**(2–3), 233–238.

McCowan, L. M. E., Thompson, J. M. D., Cronin, R. S., Li, M., Stacey, T., Stone, P. R., Lawton, B. A., Ekeroma, A. J., & Mitchell, E. A. (2017). Going to sleep in the supine position is a modifiable risk factor for late pregnancy stillbirth; Findings from the New Zealand multicentre stillbirth case-control study. *PLoS ONE*, **12**(6), e0179396.

Melbourne, A. (2021). On the use of multicompartment models of diffusion and relaxation for placental imaging. *Placenta*, **112**, 197–203.

Melbourne, A., Aughwane, R., Sokolska, M., Owen, D., Kendall, G., Flouri, D., Bainbridge, A., Atkinson, D., Deprest, J., Vercauteren, T., David, A., & Ourselin, S. (2019). Separating fetal and maternal placenta circulations using multiparametric MRI. *Magnetic Resonance in Medicine*, **81**(1), 350–361.

Ministry of Health NZ (2010). Ethnicity code tables. https://www.health.govt.nz/nz-health-statistics/data-references/code-tables/common-code-tables/ethnicity-code-tables.

Moore, R. J., Strachan, B. K., Tyler, D. J., Duncan, K. R., Baker, P. N., Worthington, B. S., Johnson, I. R., & Gowland, P. A. (2000). In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM echo-planar MRI. *Placenta*, **21**(7), 726–732.

New Zealand Maternal Fetal Medicine Network. (2014). Guideline for the management of suspected small for gestational age singleton pregnancies and infants after 34 weeks gestation.

Nicolaides, K., Clewell, W., Mibashan, R., Soothill, P., Rodeck, C., & Campbell, S. (1988). Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. *The Lancet*, **331**(8594), 1073–1075.

Nicolaides, K. H., Economides, D. L., & Soothill, P. W. (1989). Blood gases, pH, and lactate in appropriate- and small-for-gestational-age fetuses. *American Journal of Obstetrics and Gynecology*, **161**(4), 996–1001.

Osol, G., & Moore, L. G. (2014). Maternal uterine vascular remodeling during pregnancy. *Microcirculation*, **21**(1), 38–47.

Pardi, G., Cetin, I., Marconi, A. M., Bozzetti, P., Buscaglia, M., Makowski, E. L., & Battaglia, F. C. (1992). Venous drainage of the human uterus: Respiratory gas studiesin normal and fetal growth-retarded pregnancies. *American Journal of Obstetrics and Gynecology*, **166**(2), 699–706.

Pardi, G., Cetin, I., Marconi, A. M., Lanfranchi, A., Bozzetti, P., Farrazzi, E., Buscaglia, M., & Battaglia, F. C. (1993). Diagnostic value of blood sampling in fetuses with growth retardation. *New England Journal of Medicine*, **328**(10), 692–696.

Pates, J. A., Hatab, M. R., McIntire, D. D., Cunningham, F. G., & Twickler, D. M. (2010). Determining uterine blood flow in pregnancy with magnetic resonance imaging. *Magnetic Resonance Imaging*, **28**(4), 507–510.

Paulick, R., Meyers, R., Rudolph, C., & Rudolph, A. (1990). Venous responses to hypoxemia in the fetal lamb. *Journal of Developmental Physiology*, **14**(2), 81–88.

Portnoy, S., Osmond, M., Zhu, M. Y., Seed, M., Sled, J. G., & Macgowan, C. K. (2017). Relaxation properties of human umbilical cord blood at 1.5 Tesla. *Magnetic Resonance in Medicine*, **77**(4), 1678–1690.

Portnoy, S., Seed, M., Sled, J. G., & Macgowan, C. K. (2017). Non-invasive evaluation of blood oxygen saturation and hematocrit from T1 and T2 relaxation times: In-Vitro validation in fetal blood. *Magnetic Resonance in Medicine*, **78**(6), 2352–2359.

Ramasubramanian, R., Johnson, R. F., Downing, J. W., Minzter, B. H., & Paschall, R. L. (2006). Hypoxemic fetoplacental vasoconstriction: A graduated response to reduced oxygen conditions in the human placenta. *Anesthesia & Analgesia*, **103**(2), 439–442.

Rigano, S., Bozzo, M., Ferrazzi, E., Bellotti, M., Battaglia, F. C., & Galan, H. L. (2001). Early and persistent reduction in umbilical vein blood flow in the growth-restricted fetus: A longitudinal study. *American Journal of Obstetrics and Gynecology*, **185**(4), 834–838.

Rothstein, R. W., & Longo, L. D. (1998). Respiration in the Fetal-Placental Unit. In *Principles of Perinatal—Neonatal Metabolism*, pp. 451–485. Springer New York.

Rurak, D., Richardson, B. S., Patrick, J. E., Carmichael, L., & Homan, J. (1990). Oxygen consumption in the fetal lamb during sustained hypoxemia with progressive acidemia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **258**(5), R1108–R1115.

Saini, B. S., Darby, J. R. T., Marini, D., Portnoy, S., Lock, M. C., Yin Soo, J., Holman, S. L., Perumal, S. R., Wald, R. M., Windrim, R., Macgowan, C. K., Kingdom, J. C., Morrison, J. L., & Seed, M. (2021). An MRI approach to assess placental function in healthy humans and sheep. *The Journal of Physiology*, **599**(10), 2573–2602.

Saini, B. S., Darby, J. R. T., Portnoy, S., Sun, L., van Amerom, J., Lock, M. C., Soo, J. Y., Holman, S. L., Perumal, S. R., Kingdom, J. C., Sled, J. G., Macgowan, C. K., Morrison, J. L., & Seed, M. (2020). Normal human and sheep fetal vessel oxygen saturations by T2 magnetic resonance imaging. *The Journal of Physiology*, **598**(15), 3259–3281.

Seelbach-Göbel, B., Heupel, M., Kühnert, M., & Butterwegge, M. (1999). The prediction of fetal acidosis by means of intrapartum fetal pulse oximetry. *American Journal of Obstetrics and Gynecology*, **180**(1), 73–81.

Seligman, S. (1971). Diurnal blood-pressure variation in pregnancy. *BJOG*, **78**(5), 417–422.

Siggaard-Andersen, O., & Huch, R. (1995). The oxygen status of fetal blood. *Acta Anaesthesiologica Scandinavica*, **39**(s107), 129–135.

Slator, P. J., Hutter, J., Palombo, M., Jackson, L. H., Ho, A., Panagiotaki, E., Chappell, L. C., Rutherford, M. A., Hajnal, J. V., & Alexander, D. C. (2019). Combined diffusion-relaxometry MRI to identify dysfunction in the human placenta. *Magnetic Resonance in Medicine*, **82**(1), 95–106.

Stone, P. R., Burgess, W., McIntyre, J., Gunn, A. J., Lear, C. A., Bennet, L., Mitchell, E. A., Thompson, J. M., & Auckland MSIPRGTUo. (2017a). An investigation of fetal behavioural states during maternal sleep in healthy late gestation pregnancy: An observational study. *The Journal of Physiology*, **595**(24), 7441–7450.

Stone, P. R., Burgess, W., McIntyre, J. P., Gunn, A. J., Lear, C. A., Bennet, L., Mitchell, E. A., Thompson, J. M., & Maternal Sleep In Pregnancy Research Group TUoA. (2017b). Effect of maternal position on fetal behavioural state and heart rate variability in healthy late gestation pregnancy. *The Journal of Physiology*, **595**(4), 1213–1221.

Von Steinburg, S. P., Boulesteix, A.-L., Lederer, C., Grunow, S., Schiermeier, S., Hatzmann, W., Schneider, K.-T. M., & Daumer, M. (2013). What is the "normal" fetal heart rate? *PeerJ*, **1**, e82.

Wilkening, R. B., & Meschia, G. (1983). Fetal oxygen uptake, oxygenation, and acid-base balance as a function of uterine blood flow. *American Journal of Physiology. Heart and Circulatory Physiology*, **244**(6), H749–H755.

Xu, J., Duan, A. Q., Marini, D., Lim, J. M., Keunen, J., Portnoy, S., Sled, J. G., McCrindle, B. W., Kingdom, J., Macgowan, C. K., & Seed, M. (2020). The utility of MRI for measuring hematocrit in fetal anemia. *American Journal of Obstetrics and Gynecology*, **222**(1), 81.e1–81.e13.

Zhu, M. Y., Milligan, N., Keating, S., Windrim, R., Keunen, J., Thakur, V., Ohman, A., Portnoy, S., Sled, J. G., Kelly, E., Yoo, S. J., Gross-Wortmann, L., Jaeggi, E., Macgowan, C. K., Kingdom, J. C., & Seed, M. (2016). The hemodynamics of late-onset intrauterine growth restriction by MRI. *American Journal of Obstetrics and Gynecology*, **214**(3), 367.e1–367.e17.

## Additional information

### Data availability statement

Data supporting the results in this manuscript are presented within the tables and figures. All raw data that support the findings of this study are securely stored in non-identifying format at the Faculty of Medical and Health Sciences, The University of Auckland. Raw data will be made available by the corresponding author upon reasonable request.

### Competing interests

All authors of this study declare that they have no competing interests to disclose.

### Author contributions

A.C., J.T., A.D., A. Melbourne, A. Mirjalili, A.L. and P.S. – conceptualisation and design of the methodology. A.C., J.T., A. Melbourne, A. Mirjalili and P.S. – funding acquisition. D.J. and S.C. – recruitment and data acquisition. D.J., A.C., S.C., J.T. and P.S. – analysis and interpretation of the data. D.J., A.C., S.C., J.T., A.D., A. Melbourne, A. Mirjalili, A.L. and P.S. – drafting of the work and revising it critically for publication. All authors have approved the final version of the 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.

### Funding

This study was funded by Cure Kids New Zealand, grant number 3 720 229. A.L.D. is supported by the National Institute

for Health Research University College London Hospital Biomedical Research Centre.

## Acknowledgements

The authors acknowledge the MRI technologists at the University of Auckland Centre for Advanced MRI (CAMRI) and Dr Rebecca Gandhi for their help in acquiring the MRI data required for this study.

Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

## Keywords

fetal size, magnetic resonance imaging, placenta, pregnancy

## Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

**Statistical Summary Document**
**Peer Review History**

## Translational perspective

Using novel functional MRI techniques and a multivariable model, we have shown that in late-gestation pregnancies with fetal growth restriction (FGR), there is a significant reduction in placental oxygen transfer and fetal oxygenation in comparison to healthy pregnancies.

The *in vivo* model of physiological stress created by the maternal supine position shows that the growth-restricted fetus is more vulnerable to the development of acute hypoxia with a relatively higher reduction in oxygen delivery compared with healthy pregnancies. This acute stressor may exceed the fetus's ability to adapt to hypoxia and lead to intrauterine death. This could explain the higher risk of stillbirth associated with the maternal supine position in FGR compared to healthy pregnancies.

Using these non-invasive techniques, it may be possible to identify fetuses that are hypoxaemic and require earlier delivery as opposed to those that are small but can tolerate a longer time *in utero*. Furthermore, this study supports the education of all pregnant women, particularly FGR, to avoid going to sleep in the supine position to reduce their risk of stillbirth. Future studies using functional MRI to image pregnant women or fetuses *in utero* should be consistent in positioning women on their side, rather than supine, to reduce bias and improve accuracy of results.