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The effects of maternal position, in late gestation pregnancy, on placental blood flow and oxygenation: an MRI study

Running Title MRI study of effect of maternal position on placental function

Keywords: Placental oxygenation; magnetic resonance imaging; maternal position, pregnancy

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Table of contents category: Placenta, Pregnancy and Perinatal Physiology

Key Point summary:

- Maternal supine sleep position in late pregnancy is associated with an increased risk of stillbirth.
- Maternal supine position in late pregnancy reduces maternal cardiac output and uterine blood flow.
- Using MRI, this study shows that compared to the left lateral position, maternal supine position in late pregnancy is associated with reduced uteroplacental blood flow, oxygen transfer across the placenta with an average 6.2% reduction in oxygen delivery to the fetus and an average 11% reduction in fetal umbilical venous blood flow.

Abstract:

Maternal sleep position in late gestation is associated with an increased risk of stillbirth though the pathophysiological reasons for this are unclear. Studies using MRI have shown that compared with lateral positions, lying supine causes a reduction in cardiac output, reduced abdominal aortic blood flow and reduced vena caval flow which is only partially compensated for by increased flow in the azygos venous system. Using functional MRI techniques, including an acquisition termed Diffusion-Relaxation Combined Imaging of the Placenta (DECIDE), which combines diffusion weighted imaging and T2 relaxometry, blood flow and oxygen transfer were estimated in the maternal, fetal and placental compartments when subjects were scanned both supine and in left lateral positions. In late gestation pregnancy, lying supine caused a 23.7% ($p < 0.0001$) reduction in total internal iliac arterial blood flow to the uterus. In addition, lying in the supine position caused a 6.2% ($p = 0.038$) reduction in oxygen movement across the placenta. The reductions in oxygen transfer to the fetus, termed delivery flux, of 11.2% ($p = 0.0597$) and in fetal oxygen saturation of 4.4% ($p = 0.0793$) did not reach statistical significance. It is concluded that even in healthy late gestation pregnancy, maternal position significantly affects oxygen transfer across the placenta and may in part provide an explanation for late stillbirth in vulnerable fetuses.

Introduction

Stillbirth is a devastating outcome for a pregnancy. This is a worldwide problem with an estimated rate of 18.4/1000 births after 28 week's gestation (Lawn *et al.* 2016). Even in high income countries, the rate of stillbirth after 28 weeks varies from 1.7/1000 to 8.7/1000 births (Flenady *et al.*, 2016). Excluding congenital anomalies and preterm labour, unexplained stillbirth is the most common reason for the death of a fetus in New Zealand and other high income nations (Perinatal and Maternal Morality Review Committee (PMMRC), 2018; Reinebrant, 2018). In New Zealand, as in other high income countries, the rate of unexplained stillbirth occurring after 28 week's gestation has not changed significantly since 2012, unlike other causes of stillbirth such as maternal hypertension, fetal growth restriction, or hypoxic peripartum events, where reductions in the rate of stillbirth have been noted (Flenady *et al.*, 2016).

Considerable research efforts have been focused on seeking causes and modifiable risk factors to reduce the burden of these perinatal losses (Wojcieszek *et al.*, 2018; Cronin *et al.*, 2019). Epidemiological studies have found that women who went to sleep in a supine position in late

gestation had a 2 to 3-fold increased risk of stillbirth, compared to women who went to sleep on their left side (Stacey *et al.*, 2011; Gordon *et al.*, 2015; Heazell *et al.*, 2018; Cronin *et al.*, 2019). A triple risk model developed by Warland and Mitchell suggests that fetal risk, combined with a maternal factor, such as preeclampsia and an acute event or stressor, such as maternal supine sleep position, causing reduced uteroplacental, and fetoplacental blood flow, creates a scenario of increased risk of stillbirth. The vulnerable fetus and mother do not compensate for the stressor and this has been proposed to lead to an increased risk of intrauterine death (Warland & Mitchell, 2014). A recent meta-analysis conducted on sleep position stillbirth studies identified going to sleep position as an independent risk factor for stillbirth, thus, sleep position itself may be sufficient to explain these stillbirths (Cronin *et al.*, 2019). Studies showing increased risk of stillbirth with supine sleep collectively suggest that there is an underlying pathophysiological process associated with intrauterine death. As sleep position is a modifiable risk factor for stillbirth, an understanding of the mechanisms associated with this risk is important.

Two primary mechanisms for the elevated risk of stillbirth with supine sleep have been proposed (Cronin *et al.*, 2020): increased maternal sleep disordered breathing when supine leading to maternal hypoxia, and a compression of the inferior vena cava that has been shown to decrease maternal cardiac output when supine in late pregnancy (Humphries *et al.*, 2019) which could lead to fetal hypoxia. No study has assessed the impact of maternal position on the delivery of blood and oxygen to the placenta. Invasive studies of utero-placental blood flow in human pregnancy are not possible. Ultrasound has become the predominant form of imaging used in pregnancy since the technique was first introduced in 1958. Comparatively, MRI is a newer form of imaging, beginning clinical use in the 1980s and whilst theoretical fetal risks are still being considered when used in pregnancy, no long-term effects have been observed (Lum & Tsiouris 2020). Functional MRI techniques, though not routinely used in pregnancy, can measure parameters apart from structure, such as blood flow, and more recently oxygen diffusion across the placenta (Aughwane *et al.*, 2020). Whilst ultrasound has been used extensively to estimate utero-placental and fetal blood flow indices using Doppler ultrasound, MRI techniques can interrogate the movement of molecules and oxygenation, as well as measure blood flow in tissues and circulatory compartments beyond the capabilities of ultrasound.

Most MRI techniques for imaging the placenta were developed initially from cerebral MRI (Bihan *et al.*, 1988; Siauve *et al.*, 2015), however, the placenta differs from the brain in that the placenta has two circulations, maternal and fetal (Moore *et al.*, 2000). Multiple MRI techniques have been attempted in human and animal studies to find an efficient method that can be utilised in clinical practice and in research to image the placenta. Four main MRI techniques have been developed to

measure placental blood flow and oxygenation, these being arterial spin labelling (ASL) and velocity selective labelling (Derwig *et al.*, 2013; Shao *et al.*, 2018; Zun & Limperopoulos, 2018; Ludwig *et al.*, 2019), blood oxygen level dependent imaging (BOLD) (Huen *et al.*, 2013; Sørensen *et al.*, 2013; Avni *et al.*, 2016; Schabel *et al.*, 2016; Luo *et al.*, 2017; Ginosar *et al.*, 2018; Sinding *et al.*, 2018), diffusion weighted imaging (DWI, including Intravoxel Incoherent Motion (IVIM) for measuring perfusion) (Moore *et al.*, 2000; Manganaro *et al.*, 2010; Capuani *et al.*, 2017; You *et al.*, 2017; Jakob *et al.*, 2018; Melbourne *et al.*, 2019; Siauve *et al.*, 2019), and dynamic-contrast enhanced imaging (DCE-MRI) (Frias *et al.*, 2015; Yadav *et al.*, 2016; Ludwig *et al.*, 2019). DCE-MRI is the gold-standard but cannot be used in ongoing human pregnancies due to concerns regarding the injection of contrast agents into the circulation.

It is well established that maternal and fetal haemoglobin have different properties that protect oxygen transport in pregnancy, and potentially safeguard the fetus from reductions in oxygen supply (Carter, 2009; Avni *et al.*, 2016; Melbourne *et al.*, 2019). The differing haemoglobin composition in the fetus enables higher affinity for binding oxygen (Avni *et al.*, 2016; Melbourne *et al.*, 2019). In addition, the haematocrit differs between maternal and fetal blood (Soothill *et al.*, 1986; Soothill *et al.*, 1987). Thus whilst fetal vascular PO_2 is low in comparison to that of the adult, the higher haemoglobin concentration and higher affinity for oxygen means that the fetus has a high oxygen content and saturation; a situation which provides an “oxygen margin of safety” if required (Richardson, 1989). Fetal haemoglobin also has a lower P50 value than adult blood, which ensures that in the low pressure fetal environment, oxygen can reach tissues with low partial pressure. In 2016, it was revealed that the oxygen-saturation curve, previously calculated by physiologists in the laboratory, can be derived through MRI (Avni *et al.*, 2016). This paved the way for the different oxygen content of maternal and fetal haemoglobin to be utilized to separate out the maternal and fetal circulation with MRI. Using a combination of DWI-IVIM and T2 relaxometry, a novel acquisition has been developed which has the ability to differentiate between maternal and fetal contributions to uteroplacental blood flow and oxygen delivery across the human placenta (Melbourne *et al.*, 2019). This process has been termed Diffusion-Relaxation Combined Imaging of the Placenta (DECIDE).

The aim of this study was to compare the effects of the maternal supine with left lateral decubitus (LLD) positions on the blood flow and oxygen delivery to the placenta, across the placenta and from the placenta to the fetus, in healthy late gestation pregnancy. Phase contrast MRI was used to measure flow in the large vessels and DECIDE to estimate intra-placental perfusion and oxygenation to determine whether previously reported changes in maternal cardiac output when moving from LLD to supine positions in late gestation (Humphries *et al.*, 2019), are sufficient to impact upon placental oxygenation.

Methods

Ethical Approval

Ethical approval was provided by the Health and Disabilities Ethics Committee of New Zealand, reference number 15/NTB/144/AM08. Informed consent and a separate MRI safety questionnaire were completed in writing prior to entry into this study. The procedures, approved by the Health and Disability Ethics Committees of the New Zealand Government, conformed to the standards set by the Declaration of Helsinki. The study was not registered as a clinical trial.

Participant Recruitment

Twenty two pregnant women were recruited in Auckland, New Zealand from December 2018 until September 2019 using social media, midwife clinics, posters and brochures. Criteria for inclusion in the study were; a healthy singleton uncomplicated pregnancy, between 34-38 weeks of gestation by early (1st trimester) ultrasound, with a pre-pregnancy Body Mass Index (BMI) between 18 and 30. Women with multiple pregnancies, gestational hypertension (defined as new onset hypertension after 20 weeks gestation with no features of preeclampsia) or preeclampsia (defined as new onset hypertension after 20 weeks gestation and one or more of renal, haematological, hepatic neurological or fetal growth anomalies, (Lowe *et al.*, 2015)), gestational diabetes (defined absence of pre-existing diabetes as a fasting glucose ≥ 5.5 mmol/L or a 2 hour value \geq on a 75gram oral glucose tolerance ≥ 9.0 mmol/L (Ministry of Health, 2014) , fetal growth restriction (FGR) defined as ultrasound estimated fetal weight $< 10^{\text{th}}$ percentile using customised centile charts (Gardosi *et al.*, 2018) , placenta praevia and pre-existing maternal conditions including cardiovascular, renal, diabetic and autoimmune conditions were excluded from the study.

Birth outcome data including, customised percentile birthweight (Gardosi *et al.*, 2018) gestation, sex, condition at birth, need for resuscitation and/or admission to neonatal intensive care and presence of congenital anomalies were recorded to confirm normal pregnancy outcome. Mode of delivery and indications for abnormal delivery (instrumental vaginal or caesarean section) were also recorded as additional indicators of fetal condition.

Participants were asked to refrain from consuming caffeine or taking part in strenuous exercise in the two hours prior to the study. All studies were performed in the morning. An ultrasound assessment of fetal welfare was conducted prior to the MRI, by a qualified obstetrician with obstetric ultrasound

expertise which included ultrasound estimation of amniotic fluid depth, presence of fetal movements and an umbilical arterial Doppler ultrasound pulsatility index <95th percentile (Acharya *et al.*, 2005).

MRI Protocol

All MRI scans were performed on a 1.5 Tesla scanner, housed at the Centre for Advanced MRI (CAMRI), University of Auckland, New Zealand, by a qualified MRI technician. Two maternal positions were studied, left lateral decubitus (LLD) and supine to ensure that there were no systematic effects of order or time that could not be assessed. The starting position, either LLD or supine was randomly allocated using an Excel^R random number generator. The DECIDE analysis was performed blinded to maternal position. The MRI scans as described below were completed in both positions for each participant. Total scan time was approximately 1 hour, excluding time taken to change position. The time to acquire sequences was usually between 20 and 25 minutes.

Time in each position was similar as both the initial scout scans and the running of the MRI sequences used the same technical procedures. Participants were able to alert the technicians should they feel discomfort and were provided with headphones to listen to music of their choice during the scan procedures.

Participants were positioned head first in the MRI. In the supine position it was usually beneficial to place a pillow under the knees and in LLD a pillow was placed behind the back. The uterus was not manipulated away from the midline when the women lay supine. After the completion of the first position, the subjects rolled to the second position without mobilising. A 20-channel body matrix coil was placed over the centre to middle of the abdomen for acquiring images. The participants' heart rate (HR), and blood pressure (BP) were monitored and recorded throughout the duration of the MRI via a pulse oximeter and an automated BP cuff, which could be operated remotely from the control room. The pulse oximeter was also used for flow gating. In each position, first, localiser (scout) images, were completed in coronal and axial planes (voxel size 0.74mm x 0.74mm x 5mm). These enabled visualisation of the placenta, and the required blood vessels. Scanning was then undertaken to acquire the following images: 1. Phase contrast imaging (PC MRI) of internal iliac arteries, 2. PC MRI of fetal umbilical vein, 3. The DECIDE imaging procedure (Melbourne *et al.*, 2019).

Phase Contrast Imaging of the Internal Iliac Arteries

Axial slices were selected just below the bifurcation of the maternal common iliac arteries into the internal and external iliac arteries. PC MRI was acquired during a breath hold of 10 to 15 seconds. All images were obtained in the axial plane to the artery of interest at 90 degrees to the flow in the vessel (repetition time (TR) = 50-60 ms, echo time (TE) = 3.1 ms, field of view (FOV) = 450 mm², FOV phase = 69.4%, matrix = 256 pixels, velocity encoding (VENC) = 200 cm/s, number of phases = 20, time for each image = 12 s, number of images = 20, flip angle = 20 degrees, voxel size = 1.6 mm x 1.6 mm x 4.5 mm). All parameters are heart rate dependent so may not be identical for all participants.

Phase Contrast Imaging of the Umbilical Vein

PC MRI was also acquired in the umbilical vein during a maternal breath hold with synthetic gating to a typical fetal heart rate (HR) of 150bpm. Images were oversampled to allow for the effect of a variable fetal HR to be accounted for in post-processing. Scout images were used to manually identify a section of the umbilical cord from which to obtain a short axis with vessels visible. Repeat scanning in a subset of axial slices was sometimes needed to relocate the cord due to fetal movement since the initial scouts. Images were acquired under a maternal breath hold as before. PC MRI acquisition was in a single slice, with no parallel imaging at 90 degrees to the UV. A conventional gradient echo phase contrast sequence was used (TR = 57.20 ms, Field of FOV = 450mm, FOV Phase = 69.4%, TE = 3.2 ms, Matrix = 192-256 pixels, VENC= 50 cm/s, Flip angle = 20 degrees, 1 average and 4 views per segment, Voxel size = 1.6 mm x 1.6 mm x 5 mm).

Diffusion-Relaxation Combined Imaging of the Placenta (DECIDE)

The DECIDE protocol combines diffusion weighted imaging (acquired at 7 b-values), and T2 imaging (10 echo times), and fits a three-compartment model to the change in per-voxel image signal at each acquired combination of b-value and echo time. The method is summarised in Figure 1. The DECIDE method assumes that within the placenta a voxel is made up of three compartments: fetal blood, maternal blood and tissue (trophoblastic and myometrium) with each of these compartments having their own perfusion volume fraction, diffusivity (D) and T2 relaxation rate. The model fitted to MR signal has nine parameters, four of which are known and fixed, thus five fitted parameters describe individual placental function: 1) the fraction of moving maternal blood (v), 2) the fraction of moving fetal blood (f), 3) diffusivity (D) of blood movement in maternal spaces and tissue, 4) the pseudo-diffusivity (D^*) of faster blood movement (relative to D), seen in the fetal blood, 5) feto-placental T2 relaxation time, from which the feto-placental blood oxygen saturation is estimated for the fetal compartment (Portnoy *et al.*, 2017).

Model parameters are fitted using non-linear least squares as previously described (Melbourne *et al.*, 2019).

The DECIDE procedure, and parameters derived from it are outlined in Figure 1.

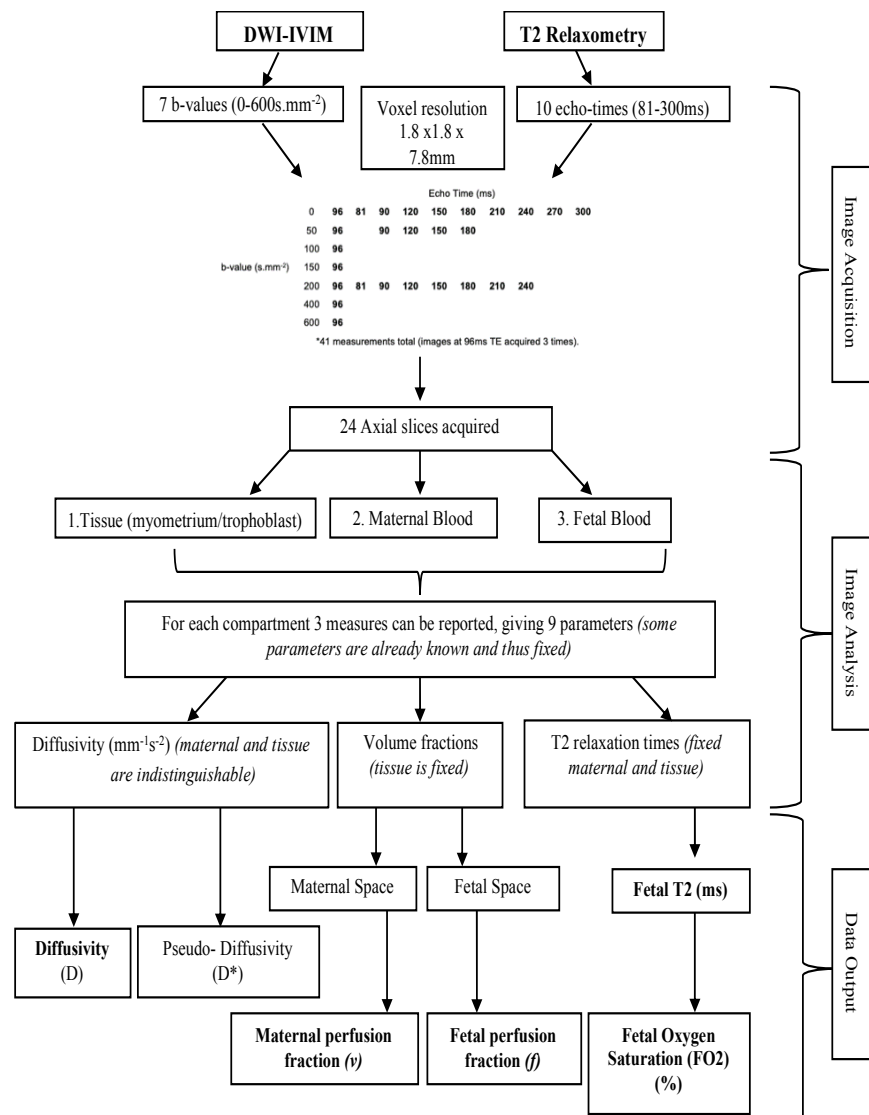


Figure 1: A flow chart summarising the steps involved in the DECIDE protocol, and the maternal and fetal parameters derived from imaging.

MRI Analysis

PC-MRI analysis

Blood flow was quantified, using the PC-MRI images acquired from the right and left internal iliac arteries in supine and LLD positions and the fetal umbilical vein. Using Syngo Via^R (Siemens)

software, vessels of interest were identified. A circular region of interest (ROI) was manually created around the lumen of each vessel. This ROI was then superimposed on all 20 slices that were taken from the same level over 16 cardiac cycles. Each slice was manually checked to ensure that the ROI accurately encompassed the vessel of interest, as the software attempted to accommodate the pulsatility of the vessel over the cardiac cycles. From this, Syngo Via^R was used to calculate the vessel net forward volume (L). By multiplying participant HR (bpm) by net forward volume, volume flow in mL/minute was calculated (Humphries *et al.*, 2019). Intra-observer measurements were compared between the initial analysis and a subsequent repeat at least 2 weeks later, using a t-test to determine if the difference between measurements was equivalent to zero. The first measurement was used for the analysis of left lateral versus supine outcomes

DECIDE Analysis

The placental volume was manually segmented by one author (A.C.) and verified by a second author (S. C.) using the images acquired with b-value = 0 s/mm², and lowest echo time = 96 ms. Analysis of the DECIDE parameters within these masked regions was conducted as described previously by Melbourne *et al* (2019) (Melbourne *et al.*, 2019). Briefly, the segmentations were of the entire placenta and as the ROIs were consistent between left lateral and supine, there was no need to match the regions. Figure 2 shows an example of a placental segmentation and DECIDE parameters determined as a parametric map in a single slice of that placental volume in a single participant.

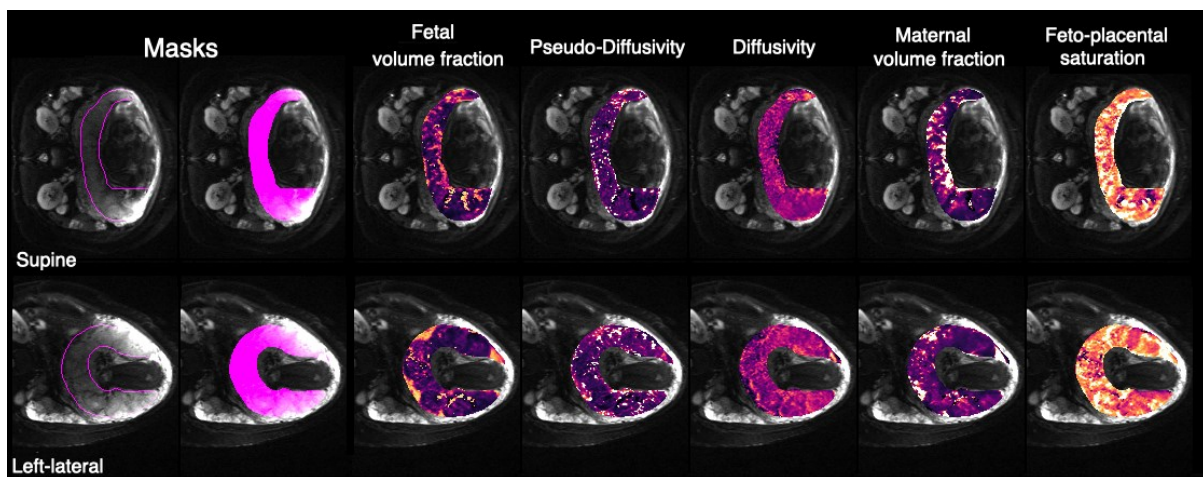


Figure 2: An example of placental segmentation (left panels) and DECIDE parameters derived from imaging in supine (top) and left lateral (bottom) positions. All images are oriented in the same way (with image oriented to show the participant on the left side) to allow visualisation of the change placental presentation between imaged positions.

Additional Parameters derived from DECIDE and PC-MRI imaging

We also defined two additional physiological markers of placental function to indicate fetal oxygen flux, which may be more indicative of oxygen delivery from the placenta to the fetus than the original DECIDE parameters. Flux is a measurement of the transfer of substance through a surface and is related to the diffusivity of the substance and the net concentration gradient across the surface. These are represented by the extra-cellular diffusivity, measured by diffusion imaging where we assume that free oxygen has a proportional diffusivity to that of free water and the oxygen saturation difference between maternal and fetal blood compartments. Two flux indices we defined were calculated from parameters in the PC-MRI and DECIDE methods;

Placental Flux – representing oxygen movement within the placenta:

$$\text{Placental Flux} = \text{Diffusivity (mm}^2 \text{ s}^{-1}) \times \text{Fetal Oxygen saturation(\%)}$$

This flux definition assumes that water diffusivity is proportional to free oxygen diffusivity.

Delivery Flux –representing the rate of movement of oxygenated blood in the umbilical vein:

$$\text{Delivery Flux} = \text{Fetal oxygen saturation (\%)} \times \text{umbilical vein flow (mL/min)}$$

This flux definition assumes that blood flow is proportional to erythrocyte flow.

Statistical Analysis

Demographic data were expressed as the mean and standard deviation. Paired t-tests were used to compare blood flow (PC MRI) and placental (DECIDE) results between the two positions.

Results

Participant demographics and birth outcomes

Twenty-two women were recruited over 8 months for this study. Of these, 20 completed scans in both supine and LLD positions. Only results from the 20 completed protocols are reported. None of the 20 women smoked cigarettes. The remaining 2 women were excluded as they were unable to lie supine for the entire sequence and thus did not have adequate data for comparison between positions. The pregnancy outcomes are presented Table 1.

All neonates were normally formed and of a healthy birth weight >10th customised percentile. All neonates were born in good condition with the range of Apgar scores being 7 to 10 at 1 and 5 minutes.

Table 1: Participant demographics and birth outcomes.

		Participants (n = 20)
Maternal age at MRI (mean (SD) age in years)		32 (\pm 4.1)
Gestational age at MRI (range in weeks + days)		34+0 - 37+5
Pre-pregnancy BMI mean kg/m² (SD)		23 (\pm 1.9)
Gravidity	1	14
	>1	6
Parity	0	17
	1	3
Birth weight mean (SD) (grams)		3415 (\pm 497)
Gestational age at delivery (range weeks + days)		37+1 - 41+6
Sex of fetus	Male	11
	Female	9
APGAR SCORE at 5 minutes (Range)		7-10

MRI Analysis

A summary of the impact of maternal position on MRI-derived maternal and fetal haemodynamics, as well as placental function via DECIDE, is given in Table 2.

Table 2: The effect of maternal position on blood flow measures derived from PC-MRI and placental function determined by a DECIDE analysis.

	LLD	Supine	Absolute difference in supine compared to LLD (95% CI)	p-value	Percentage difference in supine compared to LLD (95%CI)	p-value
PC-MRI ANALYSIS						
Right internal iliac artery (ml/min)	353± 123	281± 102	-72 (-109, -34)	0.0007	-19.0 (-29.3, -8.7)	0.0011
Left internal iliac artery (ml/min)	400± 86	290 ± 102	-110 (-153, -66)	<0.0001	-27.0 (-37.1, -16.8)	<0.0001
Total internal iliac artery (ml/min)	754 ± 180	572 ± 177	-182 (-251, -113)	<0.0001	-23.7 (-32.3, -15.1)	<0.0001
Umbilical vein (ml/min)	296 ± 80	263 ± 68	-33 (-68, 3)	0.0680	-8.4 (-18.1, 1.3)	0.0867
DECIDE ANALYSIS						
Maternal perfusion fraction (<i>v</i>)*	0.238 ± 0.068	0.254 ± 0.064	0.016 (-0.001, 0.034)	0.0629	9.0 (0.4, 17.7)	0.0418
Fetal perfusion fraction (<i>f</i>)*	0.314± 0.042	0.344 ± 0.051	0.028 (0.004, 0.051)	0.0249	9.6 (1.5, 17.8)	0.0234
Diffusivity (x10 ⁻³) (mm ² s ⁻¹)	1.59± 0.13 x10 ⁻³	1.55 ± 0.20 x10 ⁻³	-0.03 (-0.09, 0.20) x10 ⁻³	0.2010	-2.4 (5.9, -1.1)	0.1717
Pseudo-Diffusivity (mm ² s ⁻¹)	0.058 ± 0.017	0.076 ± 0.051	0.018 (-0.008, 0.043)	0.1603	40.3 (-6.6, 87.2)	0.0879
Fetal Blood T2 (ms)	135.48 ± 21.54	130.19 ± 21.66	-5.29 (-14.6, 4.03)	0.2496	-2.9 (-9.5, 3.7)	0.3679
Fetal oxygen saturation (FO ₂) (%)	67.20± 7.95	63.90 ± 8.32	-3.29 (-6.77, 0.18)	0.0615	-4.4 (-9.4, 0.6)	0.0793

Results reported as mean (\pm SD). *Perfusion fractions can be interpreted as percentages when multiplied by 100. LLD - left lateral decubitus

Maternal internal iliac and fetal umbilical vein flow and the effect of position

Highly significant reductions of 19.0% ($p=0.0011$) and 27.0% ($p<0.0001$) were found in the right and left internal iliac arterial flows respectively when the women were supine compared with being in LLD position. When right and left blood flows were combined (total internal iliac flow) a 23.7% decrease ($p<0.0001$) was seen when women lay supine compared to LLD. No significant differences in left and right internal iliac flows were found, indicating no dominant side. Umbilical venous (UV) flow was not significantly reduced (8.4%, $p=0.0867$) when women lay supine compared to LLD (296 ± 80 mL/min LLD to 263 ± 68 mL/min supine). The results of changes in both maternal and fetal blood flow with maternal position are summarised in Table 2.

Effect of maternal position on placental perfusion and oxygen delivery (DECIDE Analysis)

Diffusivity measures: Diffusivity (D), reduced 2.4% ($p=0.17$) when supine compared to LLD (0.00155 ± 0.0002 vs 0.00159 ± 0.00013 mm^2s^{-1}). Pseudo-diffusivity (D^*) was not significantly increased (40.3%, $p=0.0879$) when women moved supine (0.0580 ± 0.017 LLD vs 0.0760 ± 0.051 mm^2s^{-1} supine).

Perfusion fractions: Maternal perfusion fraction (v) showed a significant difference when women were in the supine position; with an average increase of 9.0% ($p = 0.0418$) for v (0.238 ± 0.068 LLD vs 0.254 ± 0.064 supine). The fetal perfusion fraction (f) showed a significant increase of 9.6% ($p=0.0234$) for f (0.314 ± 0.042 LLD vs 0.344 ± 0.051 supine). Regardless of maternal position, significant relationships were found between perfusion fraction and PC-MRI blood flow in maternal arteries for v and the fetal umbilical vein for f . On the maternal side there was a significant correlation between v and PC-MRI derived total maternal iliac blood flow ($r=0.51$, $p=0.001$), no significant correlation existed with v and fetal umbilical PC-MRI ($r=0.24$, $p=0.14$). There was also a significant correlation between f and PC-MRI derived umbilical venous flow ($r=-0.36$, $p=0.035$), and no significant relationship between f and internal iliac flow ($r=0.29$, $p=0.063$).

Fetal T2 and fetal oxygen saturation: Parameters relating to fetal blood oxygen saturation in the fetal region of the placenta, were found to show no statistically significant changes between supine and

LLD positions. The T2 relaxation rate of the fetal blood was 2.9% lower (135.48 ± 21.54 ms LLD to 130.19 ± 21.66 ms ($p=0.23679$) when in the supine position. Fetal oxygen saturation (FO_2), calculated from these T2 measures, was 4.4% lower [$67.20 \pm 7.95\%$ LLD to $63.90 \pm 8.32\%$ ($p=0.0793$)] when women lay supine.

Placental flux and Delivery flux: Placental flux showed a statistically significant difference between supine and left lateral positions. The placental flux index, the product of D (mm^2s^{-1}) and FO_2 , as a measure of oxygen movement across the placenta reduced by 6.2% ($p=0.0380$) when women were supine compared to LLD (0.000976 ± 0.00021 supine vs 0.001064 ± 0.00020 LLD). The delivery flux, the product of UV flow and FO_2 described oxygen delivery from the fetal compartment of the placenta to the fetus. This reduction did not reach statistical significance (11.2%, $p=0.0597$) when women lay supine compared to LLD (from 199.38 ± 60.70 LLD to 168.62 ± 48.22 supine).

A summary of DECIDE findings, and their relationship with placental function is displayed graphically in Figure 3.

Summary of maternal-fetal interaction and the effect of position

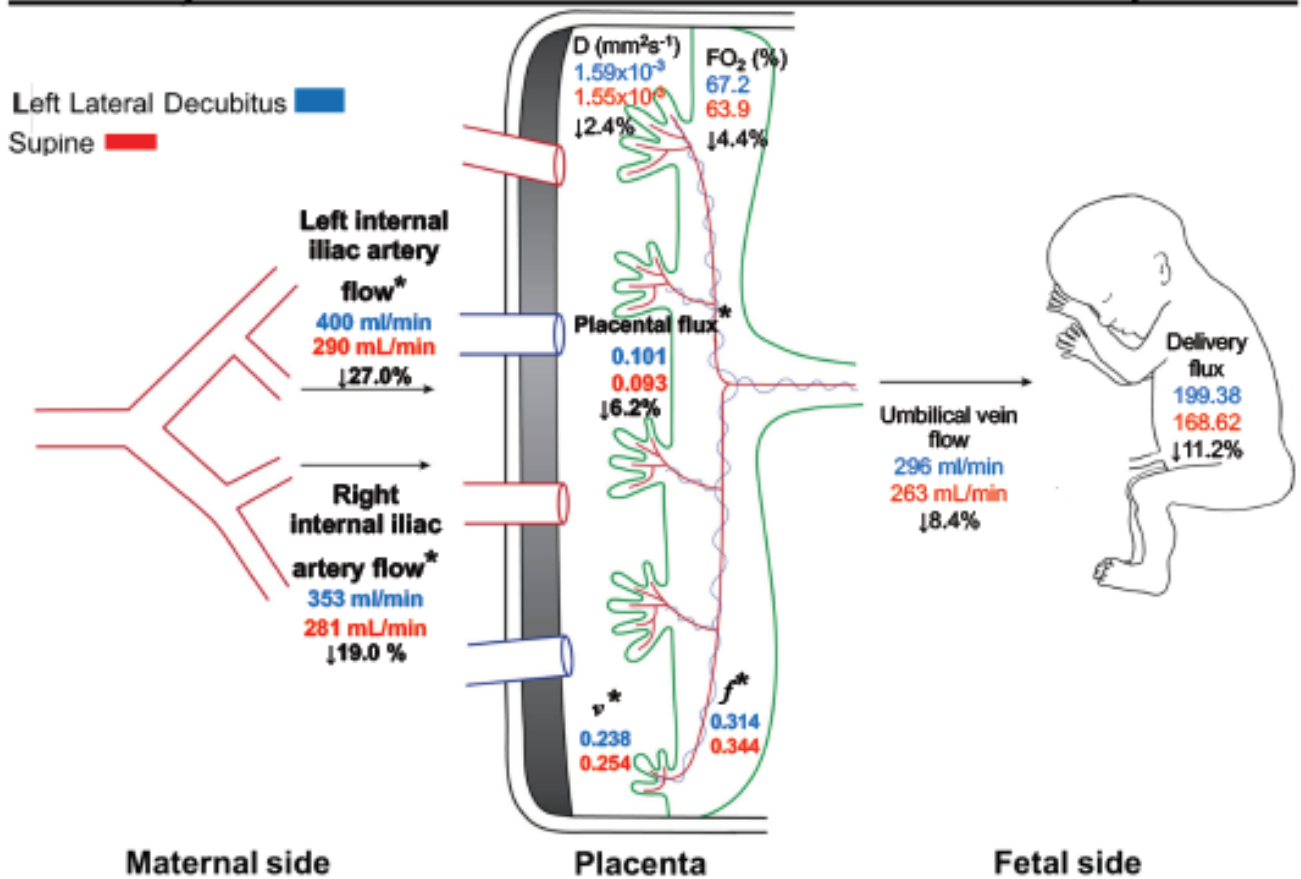


Figure 3 The Summary Effect of Maternal Position on uteroplacental blood flow and oxygen delivery. results which reached statistical significance are shown with an asterisk

Discussion

This study has shown the effect of maternal position on utero-placental and fetoplacental blood flow and oxygenation, in healthy late gestation pregnancy. When lying supine compared to left lateral decubitus (LLD) there were significant reductions in utero-placental blood flow (as reflected in the internal iliac arteries) and oxygen transfer or flux in the placenta and to the fetus. The fetal and fetoplacental response to an acute reduction in oxygen in healthy late gestation pregnancy has not been demonstrated previously where subjects served as their own controls. This protocol is as standardised an investigative paradigm as possible given the constraints of MRI.

This study was performed in late gestation (34-38 weeks), a period when most unexplained stillbirths occur. Maternal position was found to be associated with large changes in the internal iliac blood

flow. It was not possible to directly image and resolve the uterine arteries, due to voxel resolution and variable anatomy. The internal iliac arteries branch into the uterine arteries which are the principal vessels supplying oxygen and nutrients to the placenta. The consequence of the positional effects was a reduction of oxygen transfer across the placenta to the fetus. This is reflected in reduced fetal oxygen saturation (FO₂) in the placenta and blood flow to the fetus (summary figure, Figure 3).

The current study has provided a physiological explanation for the previously discussed epidemiological studies which found a correlation between supine sleep position in late gestation pregnancy and an increased risk of stillbirth. The current study supports and expands the findings of Humphries *et al.* (2019) (Humphries *et al.*, 2019), where a significant reduction in maternal abdominal aortic blood flow (32.3%) was identified when mothers lay supine compared to left lateral decubitus (LLD) in late gestation healthy pregnancy. Significant findings in the present study show that when a healthy pregnant woman is put under the physiological stress of lying supine, compared to LLD, the effect is a clear reduction in blood flow in the utero-placental and feto-placental units.

Humphries *et al.* (2019) also reported a 16.4% reduction in maternal cardiac output using PC-MRI, in addition to a 32.3% reduction in maternal abdominal aortic flow (Humphries *et al.*, 2019). Assessments in the present study have shown that this leads to a significant 24.1% reduction in the total maternal internal iliac arterial flow. A smaller study investigating the effects of exercise on uterine blood flow using Doppler ultrasound reported a 34% reduction in right ascending uterine artery volume flow when women in late gestation were in the supine compared with left lateral position (Jeffreys *et al.*, 2006). In a study using transvaginal ultrasound, volume flow in the left ascending uterine artery was found to be a mean of 342ml/min in late pregnancy (Thaler *et al.*, 1990), and similar results were found by Palmer in a study of 18 women where at 36 week's gestation, unilateral uterine artery blood flow was a mean of 312±22mL/min (Palmer *et al.*, 1992). Our upstream MRI estimates of blood flow in the internal iliac arteries are consistent with these results.

In the current study, using PC MRI, it was observed that the umbilical vein (UV) blood flow reduced from a mean 296 mL/min when LLD to 264 mL/min when lying supine (8.4% decrease). Whilst this result was not statistically significant it was consistent with previous reports of UV blood flow using PC MRI of 232 mL/min, (position not stated) (Krishnamurthy *et al.*, 2018) and 356 mL/min in LLD (Sussman *et al.*, 2019). Both of these studies found strong interobserver correlation coefficients demonstrating the reliability of PC MRI for measuring UV blood flow. It has been observed in sheep, that an occlusion above 90% in the uterine arteries was required to induce any effect on the UV blood flow (Gu *et al.*, 1985). Although in this study we reported a much smaller reduction in internal iliac blood flow when changing from LLD to supine positions, the 24% significant reduction in total iliac flow was accompanied by an 11% drop in umbilical venous flow. In healthy pregnancy, UV blood

flow may only drop once a threshold reduction in maternal flow has been met. This is also supported by a lack of a significant relationship between internal iliac and UV blood flows measured in this study ($r=0.017$, $p=0.92$). These findings together are suggestive of a non-linear relationship between maternal and UV blood flow. If a pregnancy had complications such as FGR, one might expect the UV flow to drop earlier with a lower maternal blood flow threshold, due to an already stressed system (Jensen *et al.*, 1991).

The reduction in blood flow to the placenta related to maternal position was expected to be associated with hypoxia in the fetoplacental unit and this has been confirmed using these MRI techniques. The DECIDE MRI technique used in this study had only previously been applied in a feasibility study of six pregnant women in mid-gestation (26-30 weeks) (Melbourne *et al.*, 2019) and in early onset FGR (Aughwane *et al.*, 2020) and this is the first demonstration of its use in late gestation. Studies in fetal sheep have shown that a reduction in uterine blood flow leads to reduced fetal oxygen delivery and redistribution of oxygenated fetal blood (Jensen *et al.*, 1991). Inducing acute hypoxia in the fetal sheep has also been shown to increase resistance to blood flow in the UVs with no change in the resistance in the umbilical arteries or placenta (Paulick *et al.*, 1990). It was speculated that this may enhance oxygen uptake by the umbilical venous circulation. A review of human ultrasound studies reported measures of umbilical venous blood flow consistent with those described by the DECIDE analysis (Najafzadeh & Dickinson, 2012) and changes seen in umbilical venous flow or ductus venosus shunting in hypoxia reflect our findings (Tchirikov *et al.*, 2006).

In aiming to provide an estimate of the effect of maternal position on the magnitude of placental oxygen transfer reduction when supine, we developed the concept of placental flux. We defined this as the product of Diffusivity (D) and FO_2 to provide an indication of oxygen transfer across the placenta. This was seen to significantly reduce by 6.2% when women took up the supine position compared to LLD. Placental flux, and its distinct reduction when supine, supports the hypothesis that in this physiologically stressed position, less oxygen can diffuse from the maternal to the fetal compartment within the placenta.

The DECIDE analysis as described also permitted an estimate of oxygen delivery to the fetus which we termed delivery flux. Delivery flux was derived from the product of UV flow and FO_2 . The reduction in this index seen when the women were supine compared with being LLD (11.2%) was not found to be statistically significant. Further studies will be needed to determine if this was an issue of power of the current study. The index was derived from DECIDE and PC MRI parameters and as such there are no direct comparators in the literature. The aim of this index was to provide an indication of the oxygen delivery rate to the fetus from the placenta, and how it was affected by maternal position changes.

The results of this study provide further evidence that even short periods in the supine position (20-30minutes) act as a stressor to the fetus. These results are consistent with the previously reported change to fetal behavioural state 1F when women assumed a supine position in late pregnancy (Stone *et al.*, 2017). Studies utilising Doppler ultrasound have shown that the supine lying position is a sufficient physiological stress to induce the so-called brain sparing compensatory mechanism by the fetus.(Khatib *et al.*,2014)) Significant reductions in placental flux (6.2%), and delivery flux (11.2%), as well as a non statistically significant but physiologically relevant reduction in FO2 (4.4%) in our results would suggest that even in healthy late gestation pregnancy, the reduction in umbilical venous flow that is thought to facilitate increased fetal oxygen uptake by matching flow to intervillous oxygen delivery (Talbert & Sebire, 2004) is insufficient to completely compensate for the effects of the supine position.

The response of the fetus to the effect of maternal change from LLD to a supine position is likely to be rapid. In *in vitro* studies with perfused human placental lobules, it was shown that the onset of hypoxic vasoconstriction was observed within 5 minutes of reduced oxygen delivery and by 10 minutes of reduced oxygen delivery, a stable response was reached (Jakoubek *et al.*, 2006). Similar time periods were involved in *in vivo* human Doppler studies (Khatib *et al.*, 2014). This would suggest that in the current MRI study, at the time of data acquisition, a compensated fetus was imaged. There was an average of 15 minutes between initiation of a supine or LLD position and collection of images used for analysis, due to movement of the participant to and from the MR bore, and preliminary scout imaging. This time period is estimated to be sufficient to induce a hypoxic fetal compensatory response.

Strengths

Each woman who took part in this study completed scans in supine and LLD positions, and therefore acted as her own control. In addition the order of maternal positioning was randomly determined and all scans were completed under standardised conditions. There are correlations and consistency between PC-MRI blood flow and DECIDE results in maternal and fetal metrics, separately, which support the validity of the DECIDE method to separate the placenta into maternal and fetal compartments. PC MRI has been shown to be reliable for Syngo Via^R (Siemens) analysis and vessel selection. Previous studies have reported strong interobserver reproducibility for PC MRI in other maternal vessels (Humphries *et al.*, 2019). Strong interobserver reliability has also been reported for PC MRI analysis of UV flow (Krishnamurthy *et al.*, 2018; Sussman *et al.*, 2019).

The results presented in this study show a strong association between the effect of position and measures of oxygenation despite a moderate cohort size. In addition, this study is unique in its

approach to investigating normal human pregnancy in late gestation MRI studies, as we assess the impact of position on placental parameters, allowing a direct comparison of maternal and fetal parameters in the same pregnancies.

Limitations

Motion artefacts and distortion of images are a commonly reported issue and complication of an MRI scan (Derwig *et al.*, 2013; Siauve *et al.*, 2015). This is only made more challenging during pregnancy. The present study was not immune to these challenges. Acquisition of the UV PC MRI was the most at risk of distortion, and often required repeated imaging of the vessel, adding to total scan time. The internal iliac arteries were only at risk of maternal movement, which was controlled for by breath holding during acquisition of all PC MRI. When acquiring the placenta images, maternal motion was more of a problem than fetal activity. Nevertheless, any motion that could have potentially affected the images used for DECIDE analysis was corrected retrospectively (Flouri *et al.*, 2019). Where obvious large motion occurred during the DECIDE protocol, these images were repeated. In the event, for both PC MRI and DECIDE imaging in the 20 cases reported, no images were rejected due to motion artefact.

The current lack of MRI compatible fetal heart rate monitors prevented the ability to gain beat to beat fetal HR information during the MRI, as was done for the assessment of the maternal HR and blood pressure. Fetal HR was manually gated at 150bpm for both supine and the LLD positions. Controversy surrounds the discussion of how much fetal HR changes in different maternal positions. Tamás *et al.* (Tamás *et al.*, 2007) reported a significant increase in fetal HR when supine compared to LLD, assessed using non-stress test (NST), of 139.3 ± 8.1 bpm supine and 134.4 ± 15.8 bpm LLD. NST is an assessment of fetal welfare used in late gestation, focusing on fetal HR activity using electronic monitoring. In contrast, Jeffreys *et al.* (2006) found, using Doppler ultrasound, no change between LLD and supine position fetal HR (Jeffreys *et al.*, 2006).

The arcuate and radial arteries which in turn supply the spiral arterioles are too small to be seen by current MRI techniques. Due to requiring the capture of the entire placenta, in our MRI the field of view, voxel thickness, and resolution meant the uterine arteries could not be identified, and thus the internal iliac arteries were measured. However, it has been shown in this study and illustrated in the functional model, that by combining with the DECIDE method, we were able to assess the intervillous space in the placenta and specifically the activity of oxygen. The added scan time, cost, lack of reliability of the uterine arteries, would not provide new information, in comparison to what would be gained from the assessment of the oxygen itself within the placenta.

The sample size for this study was pragmatic in nature due to fact that this work is novel and thus pre-existing data to make power calculations was unavailable, nor is it known what a clinically relevant change in these parameters is. Previous MRI work by members of the authorship group on other outcomes has used samples in the order of 10-12 subjects, thus a sample size of 20 subjects was considered to be in the expected order of magnitude to be relevant. This study now provides baseline data that can be used to estimate sample size for studies measuring similar parameters

Conclusion

In this novel study, it has been found that the effect of maternal supine position in late gestation healthy pregnancy is a reduction in not only maternal internal iliac arterial blood flow (the principal blood flow to the uterus), but also oxygen diffusion across the placenta which we termed placental flux. The delivery flux, relating umbilical blood flow to the fetal oxygen saturation was not significantly reduced in this study although UV flow reduction was observed in the supine position. This observation is likely due to vasoconstriction within the placenta and a fetal chemoreflex response, suggesting that the healthy fetus adapted to the positional hypoxia. The effect of the supine position in vulnerable growth restricted pregnancies may be less well tolerated.

It is speculated that our observed 11.2% reduction in delivery flux across the placenta, whilst tolerated in healthy fetuses, is potentially a major stressor in the vulnerable fetus such as one with growth restriction (Warland & Mitchell, 2014). The data presented in this study show that in healthy late gestation pregnancy, simply by encouraging women to lie on their left side in pregnancy would prevent a 6.2% reduction in oxygen delivery across the placenta.

Additional Information

All data in a non identifying format are securely stored at the Faculty of Medical and Health Sciences, The University of Auckland. The data are available upon request. The basic data has been collated in Excel^R.

The authors declare no competing interests.

Author contributions

Conceptualisation of the study PS, AC, AMi, AMe, AD

Data curation was performed by JT and SC

Formal analysis was undertaken by JT, SC with advice from AC, AMe,

Funding acquisition was by PS and AC.

The investigation both clinical and of the MRI data was by SC, AC, AMe.

The methodology included both clinical and MRI analytical components and was contributed to by SC, AC, PS, JT, AMe, DF, RA.

The project was administered by PS, Ami.

The resources were provided by the University of Auckland.

Software was proprietary and its use supervised by JT.

Supervision overall was by PS, Ami and AC.

Writing of the original draft was by SC, PS JT and AC, with subsequent contributions from all other authors, DF, RA, AD, AMe.

Writing for the response to reviewers was from all authors.

The final version of the manuscript was approved by all authors, who agree to be accountable for all aspects of the work.

It is confirmed that all authors do qualify for authorship.

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Translational perspective

Late stillbirth is independently associated with the maternal supine sleep position. Previous studies from our group had shown reductions in cardiac output and abdominal aortic blood flow when women assumed a supine position in late pregnancy. We had also shown that compared with being in state 2F in the left lateral position, there was a 30% increased chance of the fetus being in 1F and over a 60% reduction in 4F during supine sleep. A switch to state 1F or fetal quiescence when the mother was supine suggested the fetus was adopting a low oxygen-consuming state. In the current study, using novel MRI analytical technology, we sought to determine oxygen transfer across the placenta in healthy late gestation pregnancy, hypothesising that in the supine compared with the left lateral

maternal position there would be a reduction in oxygen transfer to the fetus. The results confirmed a significant 23.7% reduction in total internal iliac arterial blood flow to the uterus in the supine position compared to left lateral and was associated with a significant reduction in an index we termed placental flux of 6.2% which described oxygen movement across the placenta to the fetus. In this study, the reductions in umbilical venous blood flow and fetal oxygen saturation in the supine position were not statistically significant. This study has shown that the maternal supine position in healthy late pregnancy does reduce oxygen transfer across the placenta and has provided a baseline for future studies assessing the impact of a physiological stressor such as maternal position on placental oxygenation. We speculate that vulnerable fetuses, such as those that are growth restricted and which may already be hypoxic, are unable to adapt to the stressor of maternal supine position change.

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Finding passion for research so early on in one's career is a rare privilege that is not lost on me, nor is the endless support from my supervisors. As a medical student, this project has been pivotal in my limited career with further research and completing a PhD now high priorities. Perinatal health and women's health are areas of medicine that I hope to contribute to as a clinician and academic. Through my exposure to, and experience of, research in these areas, I now see how important both are for any chance to change practice, and improve health outcomes.

