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Near to One's Heart: The Intimate Relationship Between the Placenta and Fetal Heart

Emily J. Camm, Kimberley J. Botting and Amanda N. Sferruzzi-Perri*

Department of Physiology, Development and Neuroscience and Centre for Trophoblast Research, University of Cambridge, Cambridge, United Kingdom

The development of the fetal heart is exquisitely controlled by a multitude of factors, ranging from humoral to mechanical forces. The gatekeeper regulating many of these factors is the placenta, an external fetal organ. As such, resistance within the placental vascular bed has a direct influence on the fetal circulation and therefore, the developing heart. In addition, the placenta serves as the interface between the mother and fetus, controlling substrate exchange and release of hormones into both circulations. The intricate relationship between the placenta and fetal heart is appreciated in instances of clinical placental pathology. Abnormal umbilical cord insertion is associated with congenital heart defects. Likewise, twin-to-twin transfusion syndrome, where monochorionic twins have unequal sharing of their placenta due to inter-twin vascular anastomoses, can result in cardiac remodeling and dysfunction in both fetuses. Moreover, epidemiological studies have suggested a link between placental phenotypic traits and increased risk of cardiovascular disease in adult life. To date, the mechanistic basis of the relationships between the placenta, fetal heart development and later risk of cardiac dysfunction have not been fully elucidated. However, studies using environmental exposures and gene manipulations in experimental animals are providing insights into the pathways involved. Likewise, surgical instrumentation of the maternal and fetal circulations in large animal species has enabled the manipulation of specific humoral and mechanical factors to investigate their roles in fetal cardiac development. This review will focus on such studies and what is known to date about the link between the placenta and heart development.

Keywords: placenta, heart, hypoxia, altered nutrition, genetic mouse models

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****Correspondence:***
Emily J. Camm
ejc68@cam.ac.uk

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INTRODUCTION

Since David Barker first documented the relationship between infant birth weight and adult onset disease (Barker and Osmond, 1986; Barker et al., 1989), there has been a revolutionary shift in thinking about how the early environment can impact life-long health and susceptibility to disease. The contribution of the placenta to this association and as an independent risk factor for future cardiovascular risk has more recently been identified. One of the first studies to link the placenta to cardiovascular disease was by Martyn and colleagues who identified that both the highest and lowest quintiles for placental efficiency (placenta weight as a proportion of birth weight) were associated with a greater number of deaths due to coronary heart disease in men

born in the UK (Martyn et al., 1996). More recent studies of men born in Helsinki identified that a combination of maternal height, body mass index (BMI) and the shape of the placenta predict coronary heart disease in men (Eriksson et al., 2011). Specifically, short women who had a greater difference between the length and breadth of their placental surface were more likely to have a son with an increased risk of coronary heart disease. Likewise, tall women that either had a greater BMI and a placenta with a small surface area, or a lower BMI and reduced placental efficiency, conferred an elevated risk of coronary heart disease to their sons (Eriksson et al., 2011). Furthermore, having a thin placenta, or a large placenta area relative to birth weight, is associated with a greater incidence of sudden cardiac death in men and women, respectively (Barker et al., 2012). Altered placenta size and shape may be a reflection of a poor maternal environment, but may also contribute to a poor fetal environment. The placenta is the main interface between the mother and fetus, and regulates intrauterine development by supplying oxygen and nutrients required for fetal growth. There is now clear evidence that the placenta can adapt morphologically and functionally to supply signals arising from the mother, and demand signals from the fetus (Sferruzzi-Perri and Camm, 2016). The intricate relationship between the placenta and fetal heart is appreciated in instances of clinical placental pathology. Abnormal umbilical cord insertion (when the umbilical cord inserts abnormally into the fetal membranes instead of the center of the placenta), is associated with congenital heart defects (Albalawi et al., 2017). Likewise, twin-to-twin transfusion syndrome, where monochorionic twins have unequal sharing of their placenta due to inter-twin vascular anastomoses, results in one twin being under-perfused with blood and the other being over-perfused, can result in cardiac remodeling and dysfunction in both fetuses (Delabaere et al., 2016; Albalawi et al., 2017). Normally the placental circulation is considered one of low vascular resistance (Trudinger et al., 1985; Thompson and Trudinger, 1990), but in instances of poor placental development associated with fetal growth restriction, deficient remodeling of uterine spiral arteries can lead to malperfusion of the placenta and an increase in placental vascular resistance, which impair the placenta's endocrine and nutrient transport functions (For review, Chaddha et al., 2004; Burton and Jauniaux, 2018). As ∼45% of the combined ventricular output from the fetal heart is directed toward the placenta, an increase in placental vascular resistance may also increase cardiac afterload, thus increasing the mechanical force that the heart beats against. To date, the mechanistic basis of the relationships between the placenta, fetal heart development and later risk of cardiac dysfunction have not been fully elucidated. However, studies using environmental exposures and gene manipulations in experimental animals are providing insights into the pathways involved.

Abbreviations: BMI, body mass index; CaMKII, calcium/calmodulin-dependent protein kinase II; E, embryonic day; ERK, extracellular signal-regulated kinase; GLUT4, glucose transport protein 4; HIF, hypoxia-inducible factor; IGF-1, insulin-like growth factor-1; IGF-1R, type 1 IGF receptor; IGF-2R type 2 IGF receptor/mannose-6-phosphate receptor; IR, insulin receptor; IUGR, intrauterine growth restriction; Jz, junctional zone; LV, left ventricle; LVDP, left ventricular developed pressure; LVEDP, left ventricular end diastolic pressure; Lz, labyrinthine zone; MAP, mean arterial pressure; NO, nitric oxide; NOS, nitric oxide synthase; PI, pulsitility index; PI3K, phosphoinositol-3 kinase; RV, right ventricle; SUAL, single umbilical artery ligation; T3, thyroid hormone (triiodothyronine); T4, thyroid hormone (thyroxine); TGF-β, transforming growth factor-beta; UPE, umbilico-placental embolization; VEGF, vascular endothelial growth factor.

ANIMAL MODELS OF ALTERED PLACENTATION, HYPOXAEMIA AND NUTRIENT RESTRICTION

Animal studies allow for manipulation of the placenta and the maternal and fetal environments to understand the mechanisms that underlie the placenta's influence on heart health. Of the animal models that describe both placental and heart phenotypes, there are broadly three groups that best categorize them: 1. Those that reduce oxygen and nutrient delivery to the fetus (carunclectomy, umbilico-placental embolization (UPE), single umbilical artery ligation (SUAL), maternal hyperthermia in sheep, unilateral uterine artery ligation in guinea pigs and bilateral uterine artery and vein ligation in rats; 2. Those that reduce oxygen availability for transfer to the fetus (maternal inhalation hypoxia in sheep, guinea pigs and rats); and 3. Those that alter nutrient availability for the fetus (global calorie restriction, low protein diet and high-fat/high-sugar diet). However, maternal hypoxia may result in reduced maternal food intake or alterations in the placenta's ability to deliver nutrients to the fetus. Likewise, altering the maternal diet may affect placenta development and thus decrease oxygen transfer capacity. For simplicity sake, the animal models have been divided into those that report fetal hypoxaemia (**Table 1**) and those that do not (**Table 2**). A key point highlighted by both tables is that changes to placental weight do not predict cardiac outcome as reduced, increased and unaltered placenta weight may all be associated with an altered cardiac phenotype in the offspring. It is clear that work is still required to characterize the morphometry and resource supply capacity of the placenta in animal models with cardiac phenotypes, and likewise cardiac phenotype in models with altered placentation.

Due to the different benefits and limitations that come with each animal model of human development, it is the use of a range of animal models that allows for a better understanding of the influence the placenta has on both the fetal and postnatal heart. For instance, mice, rats and guinea pigs are small animals with short gestations (weeks to months) and lifespans, which allows for a high throughput of pregnancy, postnatal and intergenerational studies. The rodent and guinea pig placentae are discoid in nature, trophoblast invade and remodel the uterine vasculature to promote blood flow and the trophoblast is directly bathed in maternal blood, which is similar to the human (Adamson et al., 2002; Mess, 2007; Mess et al., 2007; Rennie et al., 2014). The caveat to using small animal models, however, is that instrumentation to repeatedly assess fetal haemodynamics and concentrations of humoral factors across gestation is not possible. As such, determining whether alterations in postnatal cardiac structure and function were present prenatally or arose in adulthood as a result of a secondary factor such as postnatal hypertension, for instance, is difficult to determine. Furthermore,

TABLE 1 | Animal models with fetal hypoxemia and altered placenta and heart.

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Sheep	**(Gestation ~150 d)**					
Caruncle ctomy surgical removal of the majority of endometrial caruncles prior to conception; causes IUGR	↓ number of placentomes ↓ total weight of placenta ↑ placental efficiency ↑ volume density of trophoblast in each placentome ↑ volume density of maternal capillaries in each placentome ↓ volume density of fetal and maternal connective tissue in the placenta ↑ surface area for exchange in each placentome ↑ VEGF, VEGFR2, TIE2 and ANGPT2 mRNA (angiogenesis) ↑ IGF2 mRNA (growth) ↑ LC3B mRNA (autophagy)	↓ PaO_2 ↓ $\%SaO_2$ ↓ CaO_2 ↑ %Hct ↑ $PaCO_2$ ↓ or = pH ↓ glucose = lactate ↓ plasma insulin ↓ plasma IGF-1 ↑ plasma IGF-2 ↑ plasma cortisol ↓ plasma T3 and T4 ↓ plasma prolactin ↑ plasma noradrenaline and adrenaline	↓ uterine artery blood flow ↓ umbilical artery blood flow = fetal SBP = fetal DBP = fetal MAP = fetal HR ↓ fetal femoral/peripheral blood flow ↑ fetal femoral/peripheral vascular resistance	↓ absolute heart weight = heart weight relative to body weight ↓ cardiomyocyte number = Ki67+ (proliferation) = TUNEL+ (apoptosis) ↑ % mononucleated cardiomyocytes ↓ % binucleated cardiomyocytes ↓ cardiomyocyte size ↑ cardiomyocyte size relative to heart weight ↑ capillary density = blood flow to whole heart, LV, RV, and septum ↓ oxygen delivery to whole heart, LV, RV, and septum ↓ glucose delivery to whole heart, LV, RV, and septum ↑ IGF2 mRNA ↑ IGF1R mRNA and protein ↑ IGF2R mRNA	= (3 weeks) or ↓ (1 year) heart weight relative to body weight ↑ LV weight relative to body weight (LV hypertrophy) (3 weeks) = LV wall thickness (1 year) • cardiomyocyte number positively associated with birth weight (1 year) ↓ total length of capillaries (3 weeks) ↓ AT_1R protein (3 weeks) ↑ IGF2 and IGF2R mRNA (3 weeks) ↑ Akt1 and p-Akt protein (3 weeks) ↑ p-IR and p-AS160 protein (21 days) ↑ GLUT1 protein (3 weeks) = LV TGFβ, Collagen II, Collagen III, MMP2, TIMP1-3 mRNA (3 weeks)	Robinson et al., 1979; Harding et al., 1985; Owens et al., 1987, 1989; Jones et al., 1988; Phillips et al., 1996, 2001; Simonetta et al., 1997; Edwards et al., 1999; Morrison et al., 2007; Wang et al., 2011, 2013, 2015a,b; Botting et al., 2014; Poudel et al., 2015; Zhang et al., 2016; Vranas et al., 2017
Umbilicoplacental embolization from ~110 to 130 d gestation; or ~120 d gestation to birth; causes IUGR	↓ placenta weight ↓ cross-sectional area of interdigitation between fetal and maternal tissue ↑ calcium deposition	↓ PaO_2 ↓ $\%SaO_2$ ↓ CaO_2 = Hb = pH = or ↑ $PaCO_2$ ↓ plasma glucose = plasma lactate = or ↑ plasma cortisol ↑ plasma noradrenaline	= (Louey et al., 2000; Thompson et al., 2011, 2013) or↓HR Murotsuki et al., 1997 = (Louey et al., 2000; Thompson et al., 2011, 2013) or ↑ MAP (Murotsuki et al., 1997) ↑ placental vascular resistance ↑ umbilical artery resistance index ↓ umbilical blood flow	↓ heart weight (Duncan et al., 2000) = (Duncan et al., 2000; Thompson et al., 2013) or ↑ (Murotsuki et al., 1997) heart weight relative to body weight ↑ LV and RV wall thickness relative to body weight (Murotsuki et al., 1997) ↑ fibrosis and procollagen I and III mRNA in RV (Thompson et al., 2013) ↑ procollagen I mRNA in LV (Thompson et al., 2013) ↑ TGFβ mRNA and protein in LV and RV (Thompson et al., 2013) = p-/Smad2and3, Smad, p-/ERK and p-/p38 protein in LV and RV (Thompson et al., 2013) ↑ protein content and protein:DNA ratio in RV (Murotsuki et al., 1997) ↑ (LV) or = (RV) % mononucleated cardiomyocytes ↓ (LV) or = (RV) % binucleated cardiomyocytes ↑ coronary artery sensitivity to vasoconstrictors (*ex vivo*)	↓ heart weight = heart weight relative to body weight (2 months)	Trudinger et al., 1987; Murotsuki et al., 1997; Duncan et al., 2000; Louey et al., 2000; Bubb et al., 2007; Thompson et al., 2011

(Continued)

TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Single umbilical artery ligation ~110 d gestation; causes IUGR	↓ placenta weight	↓ PaO_2 ↓ $\%SaO_2$ = (Supramaniam et al., 2006; Miller et al., 2009a; Tare et al., 2014) or ↓ pH (Oyama et al., 1992) = (Oyama et al., 1992) or ↑ (Supramaniam et al., 2006) $PaCO_2$ ↑ Hb and %Hct ↓ fetal glucose uptake = glucose per weight of fetus ↑ plasma cortisol (at labor)	= fetal MAP = fetal HR ↓ umbilical blood flow	↓ heart weight	= heart weight and heart weight relative to body weight (1 day) ↑ LVDP, LV +dP/dt and LV -dP/dt (1 day) = RVDP, RV +dP/dt and RV -dP/dt (1 day) ↑ I/R infarct area (1 day) ↑ coronary eNOS, COX2, collagen II mRNA (1 day) = coronary COX1, collagen I and II and tropoelastin mRNA (1 day)	Oh et al., 1975; Oyama et al., 1992; Supramaniam et al., 2006; Miller et al., 2009a,b; Tare et al., 2014
Maternal hyperthermia Pregnant ewes housed at 35–40 ^{O}C from ~80 to 120 d gestation; causes IUGR	↓ total weight of placenta ↓ GLUT8 mRNA and protein ↑ IGF-1 protein ↑ p-mTOR, p-ERK, and p-Akt ↓ p70S6K and p-XIAP ↑cleaved caspase ↓ telomerase activity ↓ eNOS mRNA (fetal) ↑ eNOS mRNA (maternal) ↓ Tie2 mRNA ↓ Angiopoietin 2 protein (fetal) ↑ PIGF mRNA and protein (maternal) ↓ VEGF and VEGFR1 mRNA and VEGF protein (fetal)	↓ PaO_2 ↓ $\%SaO_2$ = pH = PaCO2 ↑ Hb ↑ %Hct ↓ plasma glucose ↓ plasma insulin = plasma lactate = or ↑ plasma amino acids ↑ plasma cortisol in males ↑ plasma noradrenaline ↓ umbilical uptake of O_2, glucose, lactate and 11 amino acids per kg of fetus	↓ uterine and umbilical blood flow ↑ uterine blood flow per kg of fetus ↓ umbilical blood flow per kg of fetus ↑ umbilical artery PI and resistance = (Barry et al., 2016) or ↑ fetal MAP (Galan et al., 2005; Regnault et al., 2007) = fetal HR (Galan et al., 2005; Barry et al., 2016)	↓ absolute heart weight = heart weight relative to body weight = basal LV myocardial blood flow per gram of LV tissue = basal LV myocardial oxygen delivery, oxygen uptake, and oxygen extraction efficiency = basal LV myocardial glucose delivery and uptake ↑ insulin-stimulated LV myocardial blood flow per gram of LV tissue ↑ Insulin-stimulated LV myocardial glucose delivery and uptake ↑ GLUT4 and IRβ protein ↑ glycogen		Bell et al., 1987; Walker et al., 1990; Thureen et al., 1992; Regnault et al., 2003, 2007, 2013; Limesand et al., 2004, 2006; Galan et al., 2005; Hagen et al., 2005; Barry et al., 2006, 2016; Ziebell et al., 2007; Arroyo et al., 2009; Monson et al., 2017
Maternal hypoxia 10–11% O_2 from 105 to 138 d gestation; causes IUGR	= placenta weight	NB values only available for 10 days of maternal hypoxia ↓ PaO_2 ↓ $\%SaO_2$ = pH = $PaCO_2$ ↑ %Hct = glucose = lactate = plasma ascorbic acid ↑ plasma urate	NB values only available for 10 days of maternal hypoxia ↑ carotid and femoral artery blood flow ↓ delivery of O_2 through the carotid and femoral artery ↑ carotid: femoral O_2 delivery ratio = delivery of glucose through the carotid and femoral artery = carotid:femoral glucose delivery ratio	= LVDP ↑ LVEDP ↓ +dP/dt and -dP/dt		Brain et al., 2015; Allison et al., 2016

(Continued)

TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Guinea pig **Unilateral uterine artery ligation** Performed at ~30 d gestation; causes IUGR	**(Gestation ~ 68 d)** = (Briscoe et al., 2004) or ↓ (Lafeber et al., 1984) placenta weight	↓ CaO_2 ↓ pH ↓ plasma glucose = plasma lactate ↓ plasma insulin		↓ heart weight (Detmer et al., 1991)	= heart weight (2 months) ↑ heart weight relative to body weight (2 months) ↑ LV collagen (2 months) ↑ myofiber width (2 months) ↓ LV lumen area (2 months) = LV wall thickness (2 months) ↑ LV wall thickness/lumen area ratio (2 months)	Jones et al., 1984; Lafeber et al., 1984; Detmer et al., 1991; Briscoe et al., 2004
Chronic maternal hypoxia 10.5–12% O_2 commencing in the second half of pregnancy; causes IUGR	↑ placenta weight ↑ placental efficiency ↑ fetal capillary growth ↑ fetal capillary branching and coiling ↓ fetal capillary diameter ↓ diffusion distance + hypoxyprobe-1 in cytotrophoblasts and labyrinth ↑ VEGF mRNA ↑ PGF mRNA ↓ PAPPA, PTGS2, COMT mRNA (Preeclampsia markers)	↑ %Hct	↑ maternal MAP	↑ HIF-1a and HIF-2a mRNA and HIF-1α protein ↑ eNOS mRNA and protein in coronary arteries ↓ eNOS mRNA and protein in cardiac tissue ↑ iNOS mRNA and protein in cardiac tissue ↑ nitrite/nitrates and 3-nitrotyrosine ↑ proinflammatory cytokines ↓ apoptosis ↑ collagen ↓ cytochrome C oxidase activity	= heart weight and heart weight relative to body weight (4 months; males and females) = LV weight and LV weight relative to heart weight (4 months; males and females) ↓ (female) or = (male) cardiomyocyte number (4 months) ↓ cytochrome C oxidase activity (3 months) ↓ COX1 and COX4 protein (3 months) ↑ PPARα, FATP1, FABPpm, FATP6 and GLUT4 mRNA (4 months; males and females) ↓ (males) or = (females) FACS and AMPKα2 mRNA (4 months) = PPARβ/δ, PGC-1α, CD36, ACC, MCD, CPT-Iβ, ACADM, ACADL, ACADVL, IGF1, IGF2, IGF1R, IGF2R and ANP mRNA (4 months; males and females) ↑ (female) or = (male) p-AMPKα (4 months) = ACC, p-ACC, AS160, p-AS160, GLUT1, GLUT4, AMPKα2, p-AMPKα1, Akt1, Akt2, p-Akt (thr308), p-Akt (ser473), CaMKII, p-CamKII (thr286) and P-CaMKII (thr305) protein (4 months; males and females)	Bacon et al., 1984; Scheffen et al., 1990; Dong and Thompson, 2006; Thompson et al., 2009, 2016; Evans et al., 2012a,b; Al-Hasan et al., 2013, 2014; Botting et al., 2018

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TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Rat	**(gestation ~ 21 d)**					
Bilateral uterine artery and vein ligation Performed at 18 d gestation; causes IUGR*	= placental weight ↑ placental efficiency ↑ placental diameter = total placental area = labyrinth area, % of total ↑ PTHrP, PTH/PTHrP receptor and AT_{1a} mRNA ↓ PTHrP protein	= ionic and total calcium = PTHrP		= heart weight ↓ (male) or = (female) JAK2, STAT3 and GLUT1 mRNA = STAT5, PGC1α and NRF-2 mRNA ↑ (females) or = (male) SOCS3 mRNA ↓ (females) or = (male) PI3K mRNA ↑ IGF1, IGF2, Bcl2 and Cmyc mRNA (males)	↓ heart weight (1 month; males and females), but = heart weight relative to body weight ↓ heart weight (2 months; males), but = heart weight relative to body weight = heart weight and heart weight relative to body weight (6 months; females) = heart weight, but ↑ heart weight relative to body weight (6 months; males) = heart weight (13 months; postpartum females) ↓ cardiomyocyte number, but not if fostered onto a control dam (1 week; males) ↓ total cardiac protein (6 months; males) = total cardiac mRNA (6 months; males) = total and p-Akt (ser473; 6 months; males) ↑ Spp1 and Rhoa mRNA (6 months; male) ↓ Ckm mRNA (6 months; male) ↓ (male) or = (female) JAK2 mRNA (1 day, week and month) ↓ STAT3 mRNA (1 day, week and month; males) ↑ STAT3 and STAT5 mRNA (1 day; females) ↓ STAT3 mRNA (1 week; females) = STAT5 mRNA (1 day, week and month; males) ↓ (female) or ↑ (male) PGC-1α mRNA (1 week) = PGC-1α mRNA (1 week and 1 month; males and females) = NRF-2, COX III and GLUT4 mRNA (1 day, 1 week and 1 month; males and females) ↓ mtTFA mRNA (1 day males and 1 month females) ↓ MnSOD mRNA (1 month; males and females)	Wigglesworth, 1974; Wlodek et al., 2005; Wadley et al., 2010, 2013, 2016; Black et al., 2012; Cheong et al., 2016

(Continued)

TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
					↑ (female) or = (male) SOD activity (1 week and 1 month) ↑ (female) or = (male) GLUT1 mRNA (1 day) = GLUT4 mRNA (1 day, 1 week and 1 month; males and females) = IGF1, IGF2, Bcl2, Cmyc mRNA (1 day; males) = IGF1, IGF2, Gata4, Nppa, Myl2 and Myh7 mRNA (1 week; males) ↑ Bcl2, Cmyc, Agtr1a and Agtr1b mRNA (1 week; males) = Nppa, Myh7, Vegfa, Col1α1, Col3, TGFβ1, Mmp2 and Timp2 (6 months; males) ↑ (females) or = (males) p-/AMPKa, p-/p38 MAPK and p-/Akt (6 months) ↑ (male) or = (female) oxidative stress (GSSG/TGSH; 6 months)	
Maternal Hypoxia 10.5–12% O_2 from 15 to 21 d gestation or 6 to 21 d gestation (Zhou et al., 2013) gestation; causes IUGR	= (Phillips et al., 2017) or ↓ (Rueda-Clausen et al., 2011) placenta weight ↑ oxidative stress (DCF) ↓ trophoblast invasion (Zhou et al., 2013) • spiral artery remodeling (Zhou et al., 2013) ↑ prepro ET-1 mRNA (Zhou et al., 2013) ↑ ET_A and AT_1R protein (Zhou et al., 2013) = ET_B and AT_2R protein (Zhou et al., 2013)		↑ maternal SBP, DBP and MBP (Zhou et al., 2013)	= heart weight ↓ LV and septal wall thickness ↑ heart weight relative to body weight = collagen content and collagen III protein ↓ collagen I protein ↓ MMP-1 protein = MMP-2, MMP-9, TIMP1 and TIMP-2 protein ↑ MMP-13, MMP-14, TIMP-3 and TIMP-4 protein ↓ GR mRNA and protein ↑ GR promoter methylation ↓ transcription factor binding to GR exon 1 promoter ↓ CpG methylation at the CREs and Sp1 binding sites ↑ % binucleated cardiomyocytes ↓ Ki67+ ↑ apoptotic cardiomyocytes ↑ caspase 3 and 8 activity ↓ Bcl-2 protein = Bax protein ↓ Hsp70 protein ↑ βAR_1 protein = βAR_2 protein	↓ heart weight, LV and septal wall thickness (1 week) = heart weight relative to body weight (1 week and 2 months) = (female) or ↑ (male) heart weight relative to body weight (12 months) = (female) or ↑ (male) LV weight relative to heart weight (12 months) ↑ LV cardiomyocyte size (2 months) • dilated RV and LV hypertrophy in males not females (*in vivo*; 12 months) • diastolic dysfunction (*in vivo* and *ex vivo*; 12 months) = LVDP and LVEDP (*ex vivo*; 6 months)	Bae et al., 2003; Li et al., 2003, 2004; Xu et al., 2006; Rueda-Clausen et al., 2009, 2011, 2012; Xue and Zhang, 2009; Tong et al., 2011; Zhou et al., 2013; Paradis et al., 2014; Xiong et al., 2016

(Continued)

TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
					= LV contractility (*ex vivo*; 6 months) ↑ infarct size (*ex vivo*; 6 months) = (female) or ↑ (male) susceptibility to I/R injury (*ex vivo*) and MI (*in vivo*) (3 months) ↑ susceptibility to I/R injury in both males and females (12 months) = (female) or ↓ (male) PKCε and p-PKCε (3 months) = (female) or ↑ (male) lipid peroxidation (MDA; 12 months) = (female) or ↑ (male) ratio of oxidized to reduced glutathione (12 months) ↑ β/α MHC ratio (4 and 7 months) ↓ Hsp70 protein ↓ eNOS protein = cleaved caspase 3 and DNA fragmentation = βAR_1 ↓ βAR_2 protein ↑ collagen content and collagen I protein (1 week, 4 and 7 months) = collagen III protein (1 week) ↑ collagen III protein (4 and 7 months) ↑ MMP-1, MMP-13, TIMP-3 and TIMP-4 protein (1 week) = MMP-2, MMP-9, MMP-14, TIMP-1 and TIMP-2 protein (1 week) ↓ MMP-2 protein (4 and 7 months)	

(Continued)

TABLE 1 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
					= plasma levels of iron homeostasis markers and myocardial iron (4 and 12 months) ↓ Ki67+ (1 week)	
13% O_2 from 6 to 20 d gestation; does not result in IUGR	↑ placenta weight ↓ placental efficiency = placental volume, compartmental volumes and compartment to whole volume ratios ↑ Hsp70 and HNE	↑ %Hct		= heart weight, heart weight relative to body weight, LV and RV area	= heart weight and heart weight relative to body weight (4 months) = LV developed pressure and end diastolic pressure (4 months) ↑ LV contractility (4 months) ↑ responsiveness to β_1-adrenoreceptor agonists (4 months) ↓ reactivity to muscarinic agonists (4 months) ↑ Hsp70 protein	Giussani et al., 2012; Richter et al., 2012; Kane et al., 2013

*ACADL, long chain acyl-CoA dehydrogenase; ACADM, medium chain acyl-CoA dehydrogenase; ACADVL, very long chain acyl-CoA dehydrogenase; ACC, acetyl-CoA carboxylase; Agtr1a, angiotensin II receptor type 1a; Agtr1b, angiotensin II receptor type 1b; Akt, protein kinase B; AMPKα, 5′ adenosine monophosphate-activated protein kinase, α subunit; ANGPT2, angiopoietin 2; AS160, Akt substrate of 160 kilodaltons; AT_1R, angiotensin II type 1 receptor; AT_2R, angiotensin II type 2 receptor; β-AR, beta-adrenergic receptor; Bak, Bcl-2 homologous antagonist/killer; Bax, Bcl-2-associated X protein; Bcl2/Bcl-2, B-cell lymphoma 2 (gene/protein); CaO_2, arterial oxygen content; CD36, fatty acid translocase; Ckm, creatine kinase muscle; Col1α1, collagen type I alpha 1; Col3, collagen type III; COMT, catechol-o-methyl-transferase; COX, cytochrome oxidase; CPT-Iβ, carnitine palmitonyl transferase I beta; CRE, cyclic adenosine monophosphate response element; d, day; DBP, diastolic blood pressure; DCF, 2′-7′-dichlorofuorescein; +dP/dt, the rate of left ventricular pressure rise in early systole, measure of contractility; −dP/dt, the rate of left ventricular pressure fall in diastole, measure of relaxation; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET-1, endothelin−1; $ET_{A/B}$, endothelin receptor A or B; FACS, long chain fatty acyl-CoA synthetase; FABPpm, plasma membrane fatty acid binding protein; FATP, fatty acid transport protein; GLUT, glucose transporter; GR, glucocorticoid receptor; GSSG, glutathione disulphide/oxidized glutathione; Hb, hemoglobin; Hct, haematocrit; HIF, hypoxia-inducible factor; HNE, 4-Hydroxynonenal; Hsp70, 70 kilodalton heat shock protein; HR, heart rate; IGF1/IGF-1, insulin-like growth factor 1 (gene/protein); IGF1R/IGF-1R, IGF-1 receptor (gene/protein); IGF2/IGF-2, insulin-like growth factor 2 (gene/protein); IGF2R/IGF-2R, IGF 2 receptor (gene/protein); iNOS, inducible nitric oxide synthase; I/R, ischaemia/reperfusion; IR, insulin receptor; JAK2, janus activated kinase 2; LV, left ventricle; LVDP, left ventricular developed pressure; LVEDP, left ventricular end diastolic pressure; MAP, mean arterial pressure; MBP, mean blood pressure; MCD, malonyl-CoA decarboxylase; MDA, malondialdehyde; MHC, myosin heavy chain; MI, myocardial infarct; MMP, matrix metalloproteinase; MnSOD, manganese form of superoxide dismutase; mTOR, mammalian target of rapamycin; mtTFA, mitochondrial transcription factor-A; Myh7, myosin heavy chain 7; Myl2, myosin light chain 2; Nppa, natriuretic peptide type A; NRF-2, nuclear respiratory factor−2; p-, phosphorylated form of protein; p38 MAPK, p38 mitogen-activated protein kinase; p70S6K, 70 kilodalton ribosomal protein S6 kinase 1; $PaCO_2$, partial pressure of arterial carbon dioxide PaO_2, partial pressure of arterial oxygen; PAPPA, pregnancy-associate plasma protein A; PI, pulsatility index; PlGF, placental growth factor; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PPAR, peroxisome proliferator-activated receptor; PTGS2, prostaglandin synthase−2; PTHrP, parathyroid hormone-related protein; Rhoa, Ras homolog gene family member A; RV, right ventricle; RVDP, right ventricular developed pressure; SaO_2, saturation of hemoglobin with oxygen; SBP, systolic blood pressure; SOD, superoxide dismutase; Spp1, secreted phosphoprotein 1; Sp1, specificity protein 1; STAT, signal transducer and activator of transcription protein; T3, thyroid hormone (Triiodothyronine); T4, Tie-2, angiopoietin receptor−2; Thyroid hormone (thyroxine); TGFβ, transforming growth factor beta 1; TGSH, total glutathione; TIE2, angiopoietin receptor; TIMP, tissue inhibitor of metalloproteinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; XIAP, X-linked inhibitor of apoptosis protein. *Direct evidence of fetal hypoxaemia has not been published in the bilateral uterine artery and vein ligation model in rats. However, as less severe models of uterine artery ligation in other species have reported evidence of fetal hypoxaemia, it is assumed bilateral uterine vessel ligation results in fetal hypoxaemia; =, unchanged.*

TABLE 2 | Animal models of altered nutrition with altered placenta and heart.

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Rat 30% UN^ from 1 d of gestation to birth; causes IUGR, ↓ birth weight	↓ placental weight ↑ AgRP mRNA ↓ NPY mRNA ↓ POMC mRNA ↓ CART mRNA ↑ apelin mRNA ↓ APJ mRNA ↑ mtDNA content ↑ Nrf1 mRNA ↑ Tfam mRNA ↑ PGC-1α mRNA ↓ mt-co1 mRNA ↓ ATP6 mRNA ↑ mt-co2 mRNA ↑ efficiency of the mitochondrial respiratory chain ↓ UCP2 mRNA ↑ Ant1 mRNA ↓ Ant2 mRNA ↓ ATP content and ATP/ADP ratio	↓ fetal plasma apelin concentrations ↓ plasma IGF-1 ↓ plasma insulin ↓ plasma IGFBP-1 and−2			↑ systolic blood pressure (between 1 and ∼11–12 months) ↑ HR (∼12 months) ↓ or = in heart weight (up to ∼14 months) (males and/or females)	Woodall et al., 1996a,b, 1999; Vickers et al., 2000, 2002; Riviere et al., 2005; Caminos et al., 2008; Mayeur et al., 2013, 2016
Rat 50% UN^ from 10 d of gestation to birth; causes IUGR	↓ placental weight ↓ Lz and Jz weights ↓ Bcl2 and Bcl-XL protein ↑ Bax and Bak protein ↑ activated caspase-3 protein, mediated in part via Fas signaling pathway ↓ PPARγ protein ↑ 11β-HSD-I protein ↓ 11β-HSD-2 protein = NR3C1 protein ↓ SLC2A3, SLC38A1, and SLC38A2 protein (GLUT3, SNAT1, SNAT2) ↑ SLC38A4 (SNAT4) protein ↑ leptin protein ↓ AQP1 protein ↑ AQP8 and AQP9 protein	↑ fetal plasma osmolality and Na+ concentrations			↑ elastin and GAG in aorta (1 day of age) ↓ collagen in aorta (1 day of age) ↑ MMP-9 mRNA in aorta (1 day of age) ↓ VEGF protein expression in aorta (1 day of age) ↑ smooth muscle in aorta due to hypertrophy (1 day of age) ↑ smooth muscle α-actin in aorta (1 day of age) ↑ lumen diameter and media thickness in aorta (1 day of age) ↑ eNOS in aortas (1 day of age) ↑ 189 miRNA in aorta (1 day of age) ↓ 29c, 183, 422b miRNA in aorta (1 day of age) ↑ systolic blood pressure (2 months) ↑ elastin in aorta (2 months) ↑ collagen in aorta (2 months) ↓ GAG in aorta (2 months) ↑ MMP-9 and MMP-2 mRNA in aorta (4 months)	Desai et al., 2005; Khorram et al., 2007a,b,c, 2010; Belkacemi et al., 2009, 2011a,b,c; Jelks et al., 2009

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TABLE 2 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
					↑ VEGF protein expression in aorta (4 months) ↓ 200a, 129, 215 and 200b miRNA in aorta (12 months) ↑ 337 miRNA in aorta (12 months) ↓ relative heart weight (9 months) ↑ smooth muscle in aorta due to hypertrophy (2 months) (females and/or males)	
Rat **50% UN** from 14 d gestation to weaning; causes IUGR	= placental weight ↓ fetus/placental weight ↓ BDNF mRNA and protein ↑ TrkB-FL mRNA = TrkB-FL and TrkB-T1 protein ↓ GLUT3 protein = GLUT1, GLUT4 protein ↓ 11β-HSD-2 mRNA	= plasma glucose ↑ plasma corticosterone	↓ utero-placental blood flow ↓ maternal cardiac output		↑ plasma B (newborns) then ↓ 2 h later ↑ plasma ACtH (newborns) ↑ MAP (6 months) ↑ pulse rate (6 months) • cross-fostering prevents ↑ MAP (6 months) (males)	Ahokas et al., 1981, 1983; Lesage et al., 2001, 2002; Mayeur et al., 2010; Wattez et al., 2014
Guinea Pig **10–30% UN** (30% from −28 to 34 d gestation then 10% from 35 d gestation to term); causes IUGR	↓ placental diameter, weight and volume ↑ placental/body weight ↓ Lz weight and % Lz ↓ trophoblast volume ↓ maternal and fetal blood space volume ↓ total surface area (Lz) ↑ barrier thickness ↑ EPO protein in female fetuses = EPOR protein ↑ VEGF protein in male fetuses	↑ hemoglobin ↓ plasma glucose		↑ relative heart weight	↓ absolute and relative heart weight (~1 month) = absolute heart weight (~3–4 months) ↓ relative heart weight (~3–4 months) (males and females)	Sohlstrom et al., 1998; Roberts et al., 2001a,b, 2002; Elias et al., 2016, 2017; Nevin et al., 2018

(Continued)

TABLE 2 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Rat **8% protein** from 1 d gestation to weaning; causes IUGR	↑ placental volume =, ↑ or ↓ placental weight ↓ placental/body weight ↓ Lz % ↑ surface area density and total surface area of materno-fetal interface = fetal capillary surface area, diameter or length ↓ VEGF protein = VEGF receptors and expression-regulating miRNA	= plasma corticosterone			↓ absolute heart weight (1 month) ↓ β-adrenergic responsiveness and attenuated adrenergic and signaling (3 months, males) ↑ basal heart rate (3 months, males) = MAP, HR (1 month, males) =, ↓ or ↑ MAP (3–4.5 months, males) = HR (3 months, males) ↑ low frequency oscillations of systolic pressure (3 months, males) ↑ cardiovascular sympathetic tone (3 months, males) ↓ cardiac mitochondrial oxidative phosphorylation (~3 months, males) ↓ cardiac enzymatic antioxidant capacity (~3 months, males)	Snoeck et al., 1990; Doherty et al., 2003; Fernandez-Twinn et al., 2003, 2006; Hoppe et al., 2007; de Brito Alves et al., 2014, 2015, 2016; Liu et al., 2014; Nascimento et al., 2014; Barros et al., 2015; Paulino-Silva and Costa-Silva, 2016
Mouse **9% protein** from 1 d gestation to birth; causes IUGR	↓ placental weight ↓ maternal and fetal blood vessel length in Lz • perturbation of vascular endothelial cadherin and β-catenin protein				↑ systolic blood pressure (~3 to 12 months) ↓ relative heart weight (~6 months, females) = relative heart weight (~6 months, males)	Rutland et al., 2007; Watkins et al., 2008, 2011, 2015
Rat **9% protein** from 1 d gestation to birth; = fetal weight	↑ placental volume =, ↑ or ↓ placental weight ↓ 11β-HSD-2 and ↑ GSase activity ↓ 11β-HSD-2 mRNA = 11β-HSD-1 mRNA ↑ Aff3, Asns, SNAT2 mRNA ↑ ATF4, p-eIF2α protein		↓ maximal and overall relaxation to VEGF in uterine arteries		= absolute heart weight (~1 month) • alteration in cardiac fatty acids composition (~1 month) ↑ systolic blood pressure (~1–6 months) ↑ relative heart weight (~5 months, females only) • altered cardiac triacylglycerol concentration contingent on post-weaning fat intake and sex (24 h and ~3 months) ↑ cardiac PPARα mRNA (24 h and ~3 months) ↓ cardiac PPARα promoter methylation (neonate and ~3 months)	Langley and Jackson, 1994; Langley-Evans et al., 1994, 1996; Langley-Evans and Jackson, 1995; Gardner et al., 1997; Langley-Evans, 1997a,b; Langley-Evans and Nwagwu, 1998; Sherman and Langley-Evans, 2000; Aihie Sayer et al., 2001; Bertram et al., 2001; Itoh et al., 2002; Jackson et al., 2002; Koumentaki et al., 2002; Brawley et al., 2003; Burdge et al., 2003

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TABLE 2 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
					↓ eNOS mRNA levels in thoracic aorta (~3 months) = vasoconstriction of thoracic aorta (~ 4 months) • longer maximum heart rate response following isoproterenol infusion (6 months) • prenatal diet had no effect on maximal left ventricular response (6 months) = LVDP, but longer LVDP isoproterenol response in males ↑ cardiac β2-adrenergic receptors mRNA (2 weeks, females only) • impaired recovery of LVDP after ischaemia (6 months, males only) ↓ LVDP upon early reperfusion (6 months) ↑ systolic blood pressure in F2 generation, = in F3 generation (1–2 months) (males and/or females)	Torrens et al., 2003, 2006, 2008; Musha et al., 2006; Elmes et al., 2007, 2008, 2009; Harrison and Langley-Evans, 2009; Strakovsky et al., 2010; Slater-Jefferies et al., 2011; Bai et al., 2012
Rat **6% protein** from 1 d gestation to birth; = or ↓ fetal weight	= placental weight = Lz weight ↓ Jz weight ↓ placental efficiency ↓ number of giant and glycogen cells in Jz, thickness of Lz • altered placental mitochondrial function ↓ IGF2 (11–17KD) protein in Lz ↓ IGFBP2 protein in Lz (males only) • altered expression of marker genes for trophoblast lineages ↑ 17β-HSD-2 mRNA in Jz ↓ 11β-HSD-2 mRNA in Lz ↓ ACE2 mRNA in Lz ↓ ACE2 protein in Lz				↑ MAP (2 and 6 months) ↑ hypotensive response to ACh (12 months) ↑ hypertensive response to PE (12 months) = absolute or relative heart weight ↑ cardiac collagen fiber content, Cx43 mRNA, cardiomyocyte size (2 months) ↓ cardiomyocyte density (2 months)	Sathishkumar et al., 2009, 2012, 2015; Gao et al., 2012a,b,c, 2013; Rebelato et al., 2013, 2016; Rossini et al., 2017

(Continued)

TABLE 2 | Continued

Animal model and experimental protocol	Placenta outcomes (late gestation)	Fetal blood gas, metabolite and hormone profile	Materno-fetal haemodynamic outcomes	Fetal cardiac outcomes (late gestation)	Postnatal cardiac outcome	References
Mouse **High fat** (12x fat) from −28 d to weaning (fetal weight not reported)	↓ placental weight ↓ number of trophoblast cells ↑ oxidative stress-mediated endothelial cell damage				↑ systolic and diastolic blood pressure (6 and 12 months, females)	Liang et al., 2009a,b, 2010
Mouse **High fat/high sugar** (∼5x fat, ∼5x sugar) from −84 d to lactation = fetal or birth weight	placental weight ↑ lipid accumulation in Db/Jz ↑ HIF1-α protein				• accelerated cardiac growth and cardiomyocyte cell hypertrophy at 3 weeks and 2 months of age, = by 3 months ↑ absolute and relative heart weight (2 months) ↑ left ventricular free wall width (2 months) ↑ cardiac NPPB, ACTA1, MHY7:MYH6 mRNA (3 weeks), = by 3 months ↑ cardiac miR-133 mRNA (2 months) ↓ cardiac GATA-4 mRNA (2 months) • activation of AKT-ERK-mTOR pathway in cardiac tissue ↓ LVDP and dP/dtmax (3 months) ↑ LVEDP (3 months) ↑ cardiac sympathetic dominance (3 months)	Fernandez-Twinn et al., 2012, 2017; Blackmore et al., 2014
Rat **High fat** (4.5x) from −21d to lactation; = in fetal weight or causes IUGR	↓ placental weight Lz weight ↓ Jz weight (females only) ↑ LPL, SNAT2, GLUT1, and GLUT4 mRNA (males only) ↑IL-1β, TNFα, and CD68 mRNA (males only)				↑ systolic blood pressure (∼3-∼5 months)	Reynolds et al., 2014, 2015; Gray et al., 2015; Albert et al., 2017

ACE, angiotensin converting enzyme; ACh, acetylcholine; ACTH, adrenocorticotropic hormone; ACTA; actin alpha; Aft, activating transcription factor; AgRP, agouti related peptide; Ant, adenine nucleotide translocator; AKT, protein kinase B; ANT, adenosine nucleotide translocase; APJ, apelin receptor; Asns, asparagine synthetase; ATF4, activating transcription factor-4; ATP6, mitchondrially encoded ATP Synthase 6; AQP, aquaporin; Bak, Bcl-2 homologous antagonist/killer, Bax, bcl2-like protein 4; Bcl2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma-extra large; BDNF, brain-derived neurotrophic factor; CART, cocaine and amphetamine regulated transcript; CD68, cluster of differentiation 68; CPT-1, carnitine palmitoyltransferase I; Cx43, connexin 43; d, day; Db, decidua basalis; eNOS, endothelial nitric oxide synthase; EPO, erythropoietin; EPOR, erythropoietin receptor; ERK, extracellular signal-regulated kinase; GAG, glycosaminoglycans; GLUT, glucose transporter; GSase, corticosterone-inducible glutamine synthase; HIF1-α, hypoxia-inducible factor 1 alpha subunit; HR, heart rate; 11β-HSD, 11-hydroxysteroid dehydrogenase β; 17β-HSD, 17β-hydroxysteroid dehydrogenase; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor binding protein; IL-1β, interleukin 1 beta; Jz, junctional zone; LPL, lipoprotein lipase; LVDP, left ventricular developed pressure; LVEDP, left ventricular end diastolic pressure; Lz, labyrinthine zone; MAP, mean atrial pressure; miRNA, microRNA; MHY, myosin heavy chain; MMP, matrix metalloproteinase; mt, mitochondrial; mt-co, mitochondrially encoded cytochrome C oxidase; mTOR, mammalian target of rapamycin; NEAA, nonessential amino acids NEAA; Nrf, Nuclear respiratory factor; NPPB, natriuretic peptide precursor B; NPY, neuropeptide Y; NR3C1, nuclear receptor subfamily 3 group C member 1; p-eIF2α, phosphorylated eukaryotic translation initiation factor 2α; PE, phenylephrine; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; POMC, pro-opiomelanocortin; PPAR, peroxisome proliferator-activated receptor; SNAT, sodium-dependent neutral amino acid transporter; Tfam, transcription factor A, mitochondrial; TNFα, tumor necrosis factor alpha; TrkB-FL, tyrosine kinase receptor B full-length; TrkB-T1, tyrosine kinase receptor truncated; UCP: uncoupling protein; VEGF, vascular endothelial growth factor; UN, undernutrition. ^cross-fostered to ad libitum control dam, =, unchanged.

mouse and rat cardiomyocytes are immature at birth and undergo their final maturation and terminal differentiation in the weeks after birth (Li et al., 1996; Soonpaa et al., 1996). This is in contrast to humans, whose pool of cardiomyocytes begin to terminally differentiate in late gestation (Kim et al., 1992), and as such, *in utero* insults may have a more profound impact on the postnatal heart. Sheep also have benefits and limitations as an experimental animal model. Due to their size, this allows for the chronic instrumentation of the fetal circulation to assess fetal haemodynamics, concentrations of humoral factors and cardiac function. However, the caveat to this is that they have a long gestation (almost 5 months) and also take a year to reach adulthood. Further, there are a limited number of facilities in the world that allow for postnatal longitudinal studies. The sheep placenta is cotyledonary in nature, composed of many individual placentomes, which form at sites in the uterus called caruncles. There is no trophoblast invasion of maternal vessels, and an epithelial layer separates maternal blood from the trophoblast (Wooding and Burton, 2008). The temporal maturation of sheep cardiomyocytes (Burrell et al., 2003; Jonker et al., 2007b), cardiac sympathetic innervation (Lebowitz et al., 1972; Lipp and Rudolph, 1972; Tucker, 1985), and maturation of the parasympathetic nervous system (Llanos et al., 1980; Yiallourou et al., 2013), however, are better matched to humans than rodents.

ANIMAL MODELS WITH REPORTED FETAL HYPOXAEMIA

The most common consequence of complicated pregnancy is fetal hypoxaemia, which has been reported in human intrauterine growth restriction (IUGR) (Economides et al., 1991; Mori et al., 1993; Baschat et al., 2000). One of the more comprehensive sets of paired placenta and cardiac data in a model of altered placentation comes from the carunclectomy model in sheep. The removal of the majority of endometrial caruncles from the non-pregnant uterus results in the formation of less placentomes, and reduced total placental weight and uterine blood flow in subsequent pregnancies (Robinson et al., 1979; Jones et al., 1988). This model is one of placental insufficiency from conception, and results in fetal hypoxaemia, hypoglycaemia, hypoinsulinaemia, hypercortisolaemia, hypothyroidism [reduced thyroid hormones triiodothyronine (T3) and thyroxine (T4)], elevated catecholamines (noradrenaline and adrenaline) and reduced plasma insulin-like growth factor-1 (IGF-1; for review see Morrison, 2008). T3, cortisol and IGF-1 are important modulators of cardiomyocyte growth and maturation, which are discussed below. In this model, each placentome is modified to increase its surface area for exchange between the maternal and fetal circulations, however, the fetus is still growth restricted in late gestation (Zhang et al., 2016). The fetus has reduced umbilical blood flow (although an equivalent umbilical blood flow per kg of fetus compared to controls), and is normotensive (Owens et al., 1989; Edwards et al., 1999). One of the most notable changes in fetal heart development in the carunclectomy model is a reduction in the number of cardiomyocytes in late gestation (Botting et al., 2014). Sheep, like humans, begin the transition from proliferative cardiomyocytes to terminally differentiated cardiomyocytes in late gestation (Kim et al., 1992; Burrell et al., 2003; Jonker et al., 2007b). Consequently, changes to the endowment, but also in the function of cardiomyocytes in late gestation, may have consequences throughout life. Interestingly, despite the fetus being hypoxaemic in late gestation, the fetal heart is not hypoxic, nor does it have a greater percentage of apoptotic cardiomyocyte or a diminished percentage of cardiomyocytes in the cell cycle (Botting et al., 2014). This may be due to the adaptive increase in capillary density in the fetal heart, which may increase local oxygen supply to compensate for the placental insufficiency (Botting et al., 2014). There may also be other alterations in response to placental insufficiency that decrease oxygen demand by the fetal heart, such as an increase in anaerobic metabolism, thereby protecting it from further damage. Despite there being fewer and smaller cardiomyocytes in late gestation, each cardiomyocyte is larger relative to heart weight (Morrison et al., 2007). This may suggest an alteration in the regulation of cardiomyocyte hypertrophy in late gestation due to carunclectomy. After birth, lambs born with a low birth weight develop left ventricular hypertrophy by 3 weeks of age, and have a greater signaling through the pathological hypertrophy pathway, specifically the type 2 IGF/mannose-6-phosphate receptor (IGF-2R)/Gαq/calcium calmodulin-dependent protein kinase II (CaMKII) (Wang et al., 2011, 2015b). Furthermore, the number of cardiomyocytes in the adult heart is positively correlated to birth weight (Vranas et al., 2017). Similarly, female guinea pigs exposed to maternal hypoxia have reduced cardiomyocyte number at 4 months of age, which highlights the life-long impact a reduction in cardiomyocyte endowment *in utero* may have (Botting et al., 2018). The consequence of these placenta-mediated changes on the function of the postnatal heart is yet to be determined. Further work is required to identify the contribution of low oxygen and glucose, as well as alterations in humoral factors, on the development of heart pathology in the offspring.

By comparing the carunclectomy model to UPE, which is typically induced in the last trimester in sheep, a greater understanding of the specific role of humoral and haemodynamic factors that influence the fetal heart can be determined. Infusion of insoluble microspheres into the fetal descending aorta between the renal artery and common umbilical artery results in the blockage of vessels in the fetal portion of placentomes (cotyledons), which subsequently increases placental vascular resistance and reduces gas and nutrient exchange between the fetal and maternal circulations (Trudinger et al., 1987). Similar to the carunclectomy model, UPE results in fetal hypoxaemia and elevated plasma noradrenaline concentrations, but does not lead to a persistent elevation in fetal cortisol concentrations (Louey et al., 2000; Thompson et al., 2011) or hypoglycaemia (Thompson et al., 2011). UPE results in decreased total placenta weight and IUGR. In some studies, UPE results in an increase (Murotsuki et al., 1997) or no change (Louey et al., 2000; Thompson et al., 2011, 2013) in fetal mean arterial pressure (MAP), which may be due to the timing and severity of UPE, as well as, the degree to which placental vascular resistance is increased.

Interestingly, UPE studies that report elevated fetal MAP also show an increase in relative heart weight (Murotsuki et al., 1997). This is in contrast to UPE studies that report normotensive fetuses, whose heart weights may be reduced but proportional to the reduction in fetal mass (Duncan et al., 2000; Thompson et al., 2013). The difference in fetal MAP between these UPE studies highlights that elevations in fetal MAP can promote cardiac hypertrophy (discussed below). Of note, even in the absence of an elevation in fetal MAP, UPE results in an increase in fetal cardiac fibrosis and an upregulation of collagen synthesis, likely through the transforming growth factor (TGF)-β pathway (Thompson et al., 2013). Similar to the carunclectomy model, UPE results in delayed cardiomyocyte maturation, indicated by a reduced percentage of binucleated cardiomyocytes (Bubb et al., 2007; Morrison et al., 2007). However, unlike the carunclectomy model, UPE in late gestation does not alter cardiomyocyte size but decreases cell cycle activity, indicating that UPE may instead impair the proliferation of cardiomyocytes in the fetus 20 days after embolization commences (Louey et al., 2007). The differences in the cardiac phenotype between the carunclectomy and UPE models suggest that the timing of the insult in relation to placental development and cardiomyocyte maturation may help to identify the pathogenesis of cardiac pathology. Currently, the fetal and postnatal consequences of UPE on cardiac function are unknown. However, chronic fetal hypoxaemia in late gestation in sheep due to either maternal hypoxia or SUAL results in systolic and diastolic dysfunction in the isolated fetal heart (Brain et al., 2015), and greater infarct size due to ischaemia/reperfusion in the isolated newborn heart (Tare et al., 2014), respectively. Furthermore, an increase in collagen synthesis and evidence of left ventricular (LV) hypertrophy is seen in juvenile guinea pigs exposed to unilateral umbilical artery ligation from mid-gestation (Briscoe et al., 2004). Interestingly, if the insult to the placenta and fetus is shorter, but more severe, as is the case in the rat model of bilateral uterine artery and vein ligation, the cardiac phenotype with regards to the emergence of postnatal cardiac hypertrophy is less severe (heart weight relative to body weight is equivalent to controls at 2 and 6 months of age; Wadley et al., 2016). However, caution must be taken when making direct comparisons between sheep, guinea pigs, and humans relative to rats, given rat cardiomyocytes do not mature to become binucleated until after birth (binucleation occurring from 4 to 12 days after birth; Li et al., 1996). As such, rat cardiomyocytes may have a greater capacity to repair damage caused by *in utero* insults. For example, additional evidence from the same rat model of bilateral uterine vessel ligation demonstrates that a deficit in cardiomyocyte number may be corrected if a newborn is cross fostered onto a normal (sham) mother (Black et al., 2012).

Of the various sheep models of fetal hypoxaemia, one of the most documented placental phenotypes is that resulting from maternal hyperthermia. Housing pregnant ewes at 35–40°C from ∼80 to 120 days of gestation results in reduced placental weight, decreased angiogenic signaling within the fetal portion of the placenta, and increased placental apoptosis compared to controls (Regnault et al., 2003; Monson et al., 2017). The maternal hyperthermia-induced placental restriction is likely due to the reported decrease in maternal uterine blood flow compared to controls. Interestingly, uterine blood flow is similar to controls when expressed per 100 g of placental and fetal weight (Regnault et al., 2007). Fetuses whose mothers were exposed to hyperthermia in pregnancy have reduced umbilical blood flow when expressed as absolute or relative to either placental or fetal weight and have increased umbilical artery pulsatility index (PI) and resistance (Regnault et al., 2007), likely due to increased placental vascular resistance. This results in either no change (Barry et al., 2016) or an increase (Galan et al., 2005; Regnault et al., 2007) in fetal MAP. Consequently, fetuses whose mothers were exposed to hyperthermia in pregnancy are hypoxaemic, hypoglycaemic, hypoinsulinaemic, hypercortisolaemic [males], and have elevated plasma noradrenaline levels compared to controls (Walker et al., 1990; Regnault et al., 1999, 2007); a humoral profile much like the carunclectomy fetus in late gestation. The hyperthermia model also induces IUGR. To date, not much is known about the impact of placental changes induced by maternal hyperthermia on the fetal heart. However, the LV of fetuses whose mothers were exposed to hyperthermia in pregnancy have a greater insulin stimulated blood flow per gram of LV tissue and insulin stimulated glucose delivery and uptake, which relates to an increase in insulin receptor (IR) and glucose transport protein 4 (GLUT4) abundance [right ventricle (RV) not reported] (Barry et al., 2016). These adaptations may increase the chance of survival in a hypoxaemic, hypoglycaemic, and hypoinsulinaemic environment, but the consequence to the postnatal heart is currently not known.

The majority of information known about the effect of hypoxia on postnatal cardiac structure and function has been obtained from rodent studies, for which information on placental phenotype is also available. Reducing the fraction of oxygen in maternal inspired air from 21% to 10.5% from days 6 and 20 of gestation in rats and guinea pigs, respectively, results in decreased trophoblast invasion and spiral artery remodeling, coupled with an increase in maternal MAP (Zhou et al., 2013; Thompson et al., 2016). However, there are beneficial changes in placental morphology that would be expected to optimize oxygen delivery to the fetus in hypoxic dams, such as an increase in vascular density and a reduction in the barrier to oxygen diffusion (Thompson et al., 2016). Despite these adaptations, the fetal heart appears to remain hypoxic as indicated by the upregulation of hypoxia-inducible factors (HIFs), markers of nitrosative damage, and reduced mitochondrial function (Thompson et al., 2009; Evans et al., 2012a; Al-Hasan et al., 2013). This fetal cardiac phenotype could also be related to impaired coronary artery function due to altered nitric oxide (NO) availability [disturbed expression of cardiac NO synthase (NOS)] (Thompson et al., 2004, 2009; Thompson and Dong, 2005; Dong and Thompson, 2006). Maternal hypoxia (10.5%) in rats from 15 to 21 day gestation induces IUGR, decreases fetal heart weight and cardiomyocyte cell cycle activity, increases cardiomyocyte apoptosis, and prematurely promotes cardiomyocyte quiescence (binucleation) (Bae et al., 2003; Paradis et al., 2014, 2015). Furthermore, offspring of mothers exposed to hypoxia in pregnancy are more susceptible to myocardial infarction and ischaemia/reperfusion injury (Li et al., 2003; Xu et al., 2006; Xue and Zhang, 2009; Rueda-Clausen et al., 2011; Shah et al., 2017).

Interestingly, the presence of IUGR is not required for maternal hypoxia in rats to programme altered cardiac phenotypes. Maternal hypoxia (13%) from 6 to 20 days of gestation does not alter fetal weight compared to normoxic controls, but results in differences in LV contractility and responsiveness to α_1-adrenergic and muscarinic agonists at 4 months of age (Giussani et al., 2012). Additionally, maternal hypoxia results in programmed vascular dysfunction in the offspring irrespective of birth weight (Morton et al., 2010; Giussani et al., 2012; Bourque et al., 2013; Brain et al., 2015).

From the aforementioned studies, oxygen clearly plays an important role in both placental and heart development, however, more information is needed to understand the direct effect oxygen plays in these associations. Moreover, the role of changes in both oxygen and nutrient availability on the placenta and heart may be more informative in the context of complicated human pregnancies, as both substrates are often altered.

ANIMAL MODELS WITH FETAL NUTRIENT ALTERATIONS, BUT NO REPORTED FETAL HYPOXAEMIA

An observation from the Dutch Hunger Winter Study has been the importance of timing in the programming of adult disease (Roseboom et al., 2006). Babies exposed to the famine during late gestation were born small and remained small throughout their lives, with lower rates of obesity as adults than those born before and after the famine. Conversely, babies exposed during early gestation experienced elevated rates of obesity and cardiovascular disease in later life. The Dutch Hunger Winter therefore provided valuable insight into how dietary manipulation during specific periods of development can influence subsequent health. This concept of "critical windows" during development has been tested in several different animal experimental models. Experimental studies that have manipulated maternal calorie intake or quality during pregnancy, and show alterations in both placenta and cardiovascular morphology and function, are outlined in **Table 2**. Overall, these studies show that the specific effects on the placenta or fetal heart depend on the type of challenge, as well as, the duration, severity and timing relative to the formation of these two organs.

Maternal calorie restriction (10–50%) and low-protein diets (6–9%) in mice, rats and guinea pigs, typically reduce placenta weight, as well as regional weights and/or volumes of the transport labyrinthine zone (Lz) and endocrine junctional zone (Jz) (**Table 2**). These changes are related to reduced formation of maternal blood spaces and fetal vasculature in the exchange region (Roberts et al., 2001a,b; Rutland et al., 2007), potentially mediated through vascular endothelial growth factor (VEGF) signaling (Liu et al., 2014) and/or an increase in apoptosis in the Lz (Belkacemi et al., 2009, 2011b). In addition to the effects on placental morphology, maternal undernutrition induces mitochondrial abnormalities in the placenta (Belkacemi et al., 2011b; Mayeur et al., 2013; Rebelato et al., 2013). Mitochondria are implicated in numerous critical functions for feto-placental development, including ATP production for placental growth, production of oxidative stress and hormones, and control of apoptosis (Myatt, 2006; Wakefield et al., 2011). Mitochondrial defects may modify placental activity, and could therefore contribute to the restriction of both fetal and placental growth following calorie restriction. The expression of nutrient transporters (Lesage et al., 2002; Belkacemi et al., 2011c; Reynolds et al., 2015), growth factors (Woodall et al., 1996a; Gao et al., 2012a), appetite- and metabolism-regulating peptides (Caminos et al., 2008; Mayeur et al., 2016), angiotensin-converting enzymes (Gao et al., 2012b) are also altered by calorie and protein restriction and may contribute to suboptimal fetal growth and the associated programming of adulthood hypertension in these models. The ability of the placenta to act as a barrier to circulating maternal hormones is also affected by the maternal environment. Both calorie and protein restriction in rodents alters the placental expression of 11β-hydroxysteroid dehydrogenases type 1 and 2 (Langley-Evans et al., 1996; Bertram et al., 2001; Lesage et al., 2001; Belkacemi et al., 2011c), which activate and inactivate circulating glucocorticoids, respectively. Glucocorticoids have direct effects on the heart and vasculature (Walker, 2007). Therefore, increased fetal glucocorticoid exposure due to loss of the placenta glucocorticoid barrier will adversely affect both fetal growth and cardiovascular development before birth. Maternal low protein diets or global calorie restriction, have been shown to increase systolic blood pressure or MAP in adult offspring (**Table 2**). The degree to which blood pressure is elevated varies with the specific nutritional challenge and potentially the extent of remodeling of the aorta and extracellular matrix (Khorram et al., 2007a,b,c, 2010), impairment in mitochondrial oxidative phosphorylation (Nascimento et al., 2014) and changes in the expression of genes and miRNAs involved in cardiac energy metabolism (Slater-Jefferies et al., 2011). Further, adult offspring who are hypertensive may also be more vulnerable to ischaemia/reperfusion injury, as seen in the 9% protein restriction model (Elmes et al., 2008). Alterations in the reactivity of resistance arteries to vasodilators or constrictors, may also contribute to elevated blood pressure in adult offspring (Brawley et al., 2003; Torrens et al., 2003, 2006, 2008; Sathishkumar et al., 2009, 2015). A maternal low protein diet results in a reduction in heart weight and endowment of cardiomyocytes at birth (Corstius et al., 2005). However, if protein restriction continues throughout lactation, during the period of cardiomyocyte maturation in rats, cardiomyocyte endowment is similar to controls at weaning (Lim et al., 2010).

In addition to undernutrition, excess calories during pregnancy can also affect the placenta and offspring heart. Maternal high-fat or high-fat/high-sugar diets have been associated with both unchanged (Fernandez-Twinn et al., 2006, 2012; Blackmore et al., 2014; Reynolds et al., 2015) and reduced fetal and placental weights (Reynolds et al., 2014, 2015), depending on the length of exposure to the obesogenic diet. A maternal high-fat/high-sugar diet increases placental lipid deposition (Fernandez-Twinn et al., 2017), expression of HIF1α (Fernandez-Twinn et al., 2017) and pro-inflammatory mediators (Reynolds et al., 2014) and

alters nutrient transport in a sex-specific manner (Reynolds et al., 2014). While inflammatory processes are essential for pregnancy progression and maintenance, dysregulation of immune function is a major contributor to pregnancy-related disorders (Denison et al., 2010). However, feeding an obesogenic diet during pregnancy has been shown to result in a reduced placental fetal capillary volume (Sferruzzi-Perri et al., 2013), which would impair fetal oxygen delivery (Kulandavelu et al., 2013), thereby contributing to the hypoxia-mediated response to maternal obesity. The increase in the expression of glucose and fatty acid transporters in only male fetuses by Reynolds et al. (2014), suggests an attempt to compensate for the diet-induced placental insufficiency. A maternal high fat or high-fat/high-sugar diet is associated with increases in systolic and diastolic blood pressure, left ventricular end diastolic pressure (LVEDP), and a decrease in left ventricular developed pressure (LVDP), in young adolescent and adult offspring. A decreased LVDP and increased LVEDP, indicative of decreased ventricular compliance and impaired relaxation, respectively, is most likely related to cardiac hypertrophy (Fernandez-Twinn et al., 2012; Blackmore et al., 2014), which have been determined in the high-fat/high-sugar murine model using molecular and stereological techniques. Further work is required to characterize the fetal origins of the cardiac abnormalities observed in adult offspring of high-fat/high-sugar fed dams.

GENETIC MODELS

Studies performed in genetically-modified mice have started to provide novel insights into the regulation of, and relationship between, fetal heart development and placental formation (**Table 3**). Indeed, findings of mutant mice suggest that the formation of the fetal heart requires many of the same genes that regulate the development of the placenta (e.g., *Hand1,* Firulli et al., 1998; Riley et al., 1998). The Mouse Genome Informatics database identifies 329 genes with both placental morphology *and* cardiovascular defects (search identifies 754 mutants when using broader term, extraembryonic tissue morphology in conjunction with cardiovascular; conducted on 04 February, 2018). A selection of these genes are listed in **Table 3** (e.g., *Hey1/2, Mekk3, Gab1, Hai1, Flrt2, Phd2, Cited2, Ovol1, Vcam1, Mmp14/16*). Malformations of the heart and placenta are the most commonly cited reasons for mid-gestational lethality. Heart defects also arise at around day 10 of pregnancy, when organogenesis becomes highly dependent on placental function. Previous work has largely focussed on assessing the impact of a genetic manipulation on either the formation of the placenta or the fetal heart, rather than considering an interaction between the two. In spite of several of the genes listed in **Table 3** being expressed in both the fetal heart and the placental cell lineages, the temporal expression and order of developmental defects have not always been accurately determined. However, some findings in mice comparing the fetal heart and placental expression of genes with respect to the time scale of development of defects, as well as, selective gene targeting strategies, have highlighted that fetal heart defects may arise secondary to placental abnormalities and/or insufficiency.

Loss of the homeobox gene transcription factor, *Hoxa13*, results in defective vascularization and formation of the placental labyrinthine (exchange) zone (Shaut et al., 2008), lethality from days 11 of gestation (Shaut et al., 2008; Scotti and Kmita, 2012) and thinning of the fetal ventricle walls. Interestingly, *Hoxa13* is expressed in cell lineages that will form the placenta, but is absent from the fetal heart (Shaut et al., 2008). A deficiency in the zinc finger transcription factor, *Ovol2* also causes abnormalities in both placenta and fetal heart development (Unezaki et al., 2007). Although, the *Ovol2* gene is primarily expressed by the chorion and placental trophoblast and only lowly expressed by the fetal heart when cardiac abnormalities arise (Unezaki et al., 2007). Collectively, these data suggest that malformations of the fetal heart may be a consequence of defects in placental development.

The expression of members of the activator protein-1 transcription factor family (*Fra1, Junb*), nuclear hormone receptors (*Pparg*), mitogen-activated protein kinase signaling pathway (*Erk2, p38a, Braf*) and protein modification machinery (*Senp2*) in the placenta also appear to be required for fetal heart development. Loss of any of these genes leads to reduced vascularization and development of the placental labyrinthine zone (Barak et al., 1999; Schorpp-Kistner et al., 1999; Adams et al., 2000; Schreiber et al., 2000; Hatano et al., 2003; Galabova-Kovacs et al., 2006; Chiu et al., 2008; Maruyama et al., 2016). These genetic deficiencies also result in thin ventricular walls, poor myocardial trabeculation, dilated pericardium and/or increased apoptosis in the fetal heart and lethality in mid-gestation (Barak et al., 1999; Schorpp-Kistner et al., 1999; Adams et al., 2000; Schreiber et al., 2000; Hatano et al., 2003; Galabova-Kovacs et al., 2006; Maruyama et al., 2016). During development, *p38a, Pparg, Braf, Junb,* and *Senp2* are more abundantly expressed by placental rather than fetal cell lineages (Adams et al., 2000; Mudgett et al., 2000), with no difference reported for *Erk2* or *Fra1*. However, tetraploid aggregation experiments and conditional gene manipulations to generate null embryos with wildtype placentas was shown to circumvent the fetal heart abnormalities and improve embryonic viability in response to *p38a, Erk2, Fra1, Pparg, Braf, Senp2,* and *Junb* deficiency (Barak et al., 1999; Schorpp-Kistner et al., 1999; Adams et al., 2000; Schreiber et al., 2000; Hatano et al., 2003; Galabova-Kovacs et al., 2006; Maruyama et al., 2016). These observations provide strong evidence that defects in the placenta were most likely to represent the primary cause of fetal cardiac defects and lethality in these mutant mice.

During the establishment of normal circulation, myocardial development and cardiac morphogenesis depend on the patterns of blood flow returning from the yolk sac and chorioallantoic placenta (Linask et al., 2014). Therefore, placental abnormalities may disrupt cardiac and vascular development by altering the haemodynamic forces of blood returning to the heart and result in fetal demise (Linask et al., 2014). In support of this, retaining expression of RNA binding gene, *Ott1/Rbm15* or the transcriptional regulator *Rb* gene in the placenta is sufficient to rescue the lethality of null fetuses (Wu et al., 2003; Raffel et al., 2009). Furthermore, the loss of placental, but not fetal

TABLE 3 | Genetically-modified mice which show placental and cardiac abnormalities*.

Gene	Expression in placenta and fetus/fetal heart	Impact of constitutive loss of expression in developing conceptus (unless stated otherwise)				References
		Placenta	Fetal heart development	Fetal viability	Notes	
Genes in the placenta important for fetal heart development						
Hoxa13	Allantoic mesenchyme and the Lz fetal vessels as well as umbilical arteries	d10.5–12.5: Defective Lz vessel formation and branching	d14.5: Reduced right and left ventricular wall thickness	d11–15.5: Lethal		Shaut et al., 2008
Ovol2	Highest expression by the chorion and placenta with relatively low expression in fetal heart from d8.5	d9.5: Defective chorionic and Lz vascularization	d9: Small heart, defects in the growth of myocardial and endocardial layers, resulting in the abnormal looping and chamber formation	d9.5–10.5: Lethal		Unezaki et al., 2007
P38a	Broadly expressed by embryo (including the heart, branchial arches, limb buds and somites) and placenta (Lz and chorionic plate)	d10.5: Defective development of Lz vasculature and exchange interface	d10.5: Reduction of the myocardial cell population, thin ventricle walls, poor myocardial trabeculation	d10.5–12.5: Lethal	Tetraploid aggregation experiment (WT placenta, null embryo): Rescued fetal heart and vascular anomalies and improved viability of nulls	Adams et al., 2000; Mudgett et al., 2000
Erk2	Placenta and fetal organs including heart.	d10.5: Defective Lz development and vascularization	d11.5: Thin ventricular walls	d12.5: Lethal	Tetraploid aggregation experiment (WT placenta, null embryo): Rescued fetal heart defects and lethality of nulls	Hatano et al., 2003
Fra /Fosl1	Expressed in Lz of placenta and several fetal tissues including heart	d9.5: Failed Lz vascularization	d9.5: Dilated pericardium and presence of erythroblasts in the heart	d10.5: Lethal	Tetraploid aggregation experiment (WT placenta, null embryo): Rescued heart defect and lethality of nulls	Schreiber et al., 2000
Pparg	d8.5 highly expressed by trophoblast but not embryo. From d14.5 expressed by fetal brown fat	d9.5 Defective Lz vascularization defects and disorganized structure, fewer maternal blood spaces and thickened trophoblast	d9: Premature cardiomyocyte differentiation, ventricular and septum hypoplasia, myocardial thinning and degeneration of the trabecular zone	d12.5: Lethal	Tetraploid aggregation experiment (WT placenta, null embryo): Rescued cardiac defects and delayed lethality of nulls	Barak et al., 1999

(Continued)

TABLE 3 | Continued

Gene	Expression in placenta and fetus/fetal heart	Impact of constitutive loss of expression in developing conceptus (unless stated otherwise)				References
		Placenta	Fetal heart development	Fetal viability	Notes	
Braf	d11.5: Expressed at highest levels in the placenta, relative to the fetus	d10.5: Defective Lz development and vascularization. Defective Jz development	d9.5: Increased heart apoptosis and defective vascularization	d11.5: Lethal	MeoxCre Braf null (WT placenta, null embryo): Rescued lethality and growth defects of nulls	Galabova-Kovacs et al., 2006
Junb	Ubiquitously expressed in placenta and fetus, but particularly high in placenta	d7.5: Perturbed trophoblast invasion and hormone expression d10: failure to develop and vascularise Lz	d9.5: Enlarged pericardium	d8.5–10: Lethal	Tetraploid aggregation experiment (WT placenta, null embryo): Rescued cardiac defects and improved fetal viability of nulls	Schorpp-Kistner et al., 1999
Senp2	From d7.5 widely expressed by trophoblast lineages in Lz and Jz. Expression in heart only observed from d10.5	d9–10.5: Impaired syncytium formation and fetal capillary branching in Lz. Reduced Jz and particularly giant cell formation	d9–10.5: Smaller heart chambers with pericardial effusion. Myocardial wall thinning and missing of atrioventricular cushions	d11.5: Lethal	Sox2Cre nulls (WT placenta, null embryo): Rescued cardiac abnormalities and embryonic lethality of nulls	Chiu et al., 2008; Maruyama et al., 2016
E2f7/E2f8	Most abundantly expressed by placenta relative to fetus	Placental specific loss (using cyp19cre) d10: Defective Lz formation, fewer maternal blood spaces and impaired trophoblast invasion	Placental specific loss (using cyp19cre) d10: Fetal vascular dilation and hemorrhage	Placental specific loss (using cyp19cre) d11.5: Lethal		Ouseph et al., 2012
Ott1/Rbm15	Expressed widely by embryo and placenta	d9.5: Defective Lz vascularization	d18.5: Ventricular septal defect	d10.5: Lethal	Sox2Cre nulls (WT placenta, null embryo): Rescued fetal growth defects and lethality of nulls	Raffel et al., 2009
Rb	d12.5: High expression in Lz	d12.5: Lz defective with impaired vascularization, fewer maternal blood spaces, reduced surface area and thickened trophoblast		d13.5: Lethal	Tetraploid aggregation and Meox2Cre (WT placenta, null embryo): Rescued fetal growth defects and lethality of nulls	Wu et al., 2003; Wenzel et al., 2007

(Continued)

TABLE 3 | Continued

Gene	Expression in placenta and fetus/fetal heart	Impact of constitutive loss of expression in developing conceptus (unless stated otherwise)				References
		Placenta	Fetal heart development	Fetal viability	Notes	
Examples of genes important for both placental and fetal heart development						
Mmp14/16 double KO mice (MT-MMP1/2)		d10.5: Impaired Lz vascularization and branching morphogenesis and failed formation of syncytial layers in Lz	d10.5: Dilated vasculature and enlarged pericardium	d12.5: Lethal		Szabova et al., 2010
Flrt2	Endothelial cells specifically in the placental Lz and epicardial and mesenchyme.	d12.5: Defective Lz development; aberrant alignment of the endothelium	d12.5: Reduced thickness of ventricular myocardium with systemic congestion	d13.5: Lethal		Tai-Nagara et al., 2017
Hey1/2	Both Hey genes are highly expressed in the allantois and early cardiac precursors	d10.5: Impaired Lz vascularization	d9.5: Thin myocardium trabecular defects. Impaired aortic wall formation	d14.5: Lethal		Donovan et al., 2002; Gessler et al., 2002; Fischer et al., 2004
Mekk3/Map3k3		d9.5: Impaired Lz formation and defective Lz angiogenesis	d10: Retarded development of the myocardium and less trabeculation	d11: Lethal		Yang et al., 2000
Erk5		d9.5: Defective Lz vascularization	d9.5: Abnormal cardiac looping, excessive pericardial fluid, disorganized trabeculae and myocardial lining, reduced vascularization	d10: Lethal		Regan et al., 2002
Gab1	Placenta and heart	d11.5: Reduced placental size, vascular density and trophoblast proliferation	d10–11.5: Blood in pericardial cavity. d13.5 ventricular hypoplasia and dilation and the thin ventricular wall	d12.5-d17: Lethal		Itoh et al., 2000
Hai1	Placental Lz and fetal tissues	d8.5: Thin chorionic plate and few fetal vessels d9.5: Defective Lz trophoblast differentiation and vascularization (linked to reduced Gcm1)	d10: Enlarged pericardium and thin ventricle walls	d11.5: Lethal		Tanaka et al., 2005

(Continued)

TABLE 3 | Continued

Gene	Expression in placenta and fetus/fetal heart	Impact of constitutive loss of expression in developing conceptus (unless stated otherwise)				References
		Placenta	Fetal heart development	Fetal viability	Notes	
Rxra	Ubiquitously expressed	d9.5: Reduced Lz vascularization	d13.5–16.5: Thin ventricular walls, trabeculae and septum	d12–16.5: Lethal		Kastner et al., 1994; Sapin et al., 1997; Barak et al., 1999; Wendling et al., 1999; Mascrez et al., 2009
Zfp36l1	d8.0: Expression greatest in the allantois with low and diffuse expression in embryo	d9: Failure of the allantoic mesoderm to invaginate into the chorionic trophoblast to form the Lz. Poor Lz angiogenesis due to reduced Vegfa expression	d9.5: Less developed trabeculae and sinusoids in the myocardial wall, thin myocardial wall	d10.5: Lethal		Stumpo et al., 2004; Bell et al., 2006
Phd2		d10.5: Lz defective development; thickened trophoblast, large maternal blood spaces, few fetal vessels	d11.5: Defective ventricular maturation, thin ventricles, under-developed myocardial structures and trabeculae	d13.5–14.5: Lethal		Takeda et al., 2006
Cited2	Expressed in embryo and highly by the placenta	d12.5: Smaller placenta, impaired Lz vascularization	d13.5: Severe heart malformations including ventricle outflow and septal defects	From d14.5: Lethal		Withington et al., 2006; Lopes Floro et al., 2011; Moreau et al., 2014
Vcam1	d8.5–9.5: Expressed by allantois and mycardium	d8.5: Abnormal chorioallantoic fusion and Lz vascularization	d11.5: Epicardial defects			Gurtner et al., 1995; Kwee et al., 1995

*Braf, Braf transforming gene; Cited2, Cbp/P300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2; d, day of gestation; E2f7/E2f8, E2F transcription factor 7; Erk2/5, extracellular signal-regulated kinase 2/5; Flrt2, fibronectin leucine rich transmembrane protein; Fra /Fosl1, FOS like 1, AP-1 transcription factor subunit; Gab1, growth factor receptor bound protein 2-associated protein 1; Gcm1, glial cells missing homolog 1; Hai1, PP2C protein (Clade A protein phosphatases type 2C); Hey1/2, hairy/enhancer-of-split related with YRPW motif 1/2; Hoxa13, Homeobox A13; Junb, JunB proto-oncogene, AP-1 transcription factor subunit; Jz, junctional zone; Lz labyrinthine zone; Mekk3/map3k3, mitogen-activated protein kinase kinase kinase 3; Mmp, matrix metalloproteinases; Ott1/Rbm15, RNA binding motif protein 15; Ovol2, ovo like zinc finger 2; P38a, mitogen activated protein kinase p38a; Phd2, egl-9 family hypoxia inducible factor 1; Pparg, peroxisome proliferator activated receptor gamma; Rb, RB transcriptional corepressor 1; Rxra, retinoid X receptor alpha; Senp2, SUMO/sentrin specific peptidase 2; WT, wildtype. *Note list is not comprehensive.*

expression of the transcription factor genes, *E2f7* and *E2f8*, leads to fetal vascular dilatation, multifocal hemorrhages and lethality (Ouseph et al., 2012). However, the placenta is also thought to be responsive to blood flow forces in the fetal circulation (Linask et al., 2014). Although, very little is known about the importance of the developing fetal heart for the formation of the placenta (e.g., the consequence of cardiac-specific deficiency for placentation).

HOW HAEMODYNAMIC CHANGES INFLUENCE THE HEART

Studies in fetal sheep have investigated the specific effects of altered load on the fetal heart in normoxic and euglycaemic fetuses. Specifically, increasing left ventricular afterload by partially obstructing the ascending aorta results in a thicker LV/RV wall and smaller LV chamber volume compared to control (Fishman et al., 1978). This phenomenon of left ventricular hypertrophy in response to increased afterload is seen in adults, and is a mechanism to normalize wall stress according to the law of LaPlace. In adults who have quiescent cardiomyocytes, this increase in cardiac mass is predominantly due to an increase in cardiomyocyte hypertrophy (for review, Samuel and Swynghedauw, 2008). Initially it was proposed that the increase in fetal heart mass in response to an increase in afterload was due to an increase the number of cardiomyocytes (hyperplasia) (Fishman et al., 1978). Further investigations by Jonker and colleagues determined that cardiac growth in response to increased fetal MAP and venous pressure is biphasic, initially due to cardiomyocyte hyperplasia and elongation and subsequently due to hyperplasia, premature binucleation and hypertrophy of binucleated cardiomyocytes (Jonker et al., 2007a). This phenomenon is not isolated to the LV, with an increase in pulmonary artery pressure resulting in an increase in RV weight (Segar et al., 1997). The converse is also true- obstructing blood flowing into the LV (decreasing preload) results in a smaller heart with a reduced LV/RV weight (Jonker et al., 2007a). By decreasing fetal systolic pressure with an angiotensin-converting enzyme inhibitor, O'Tierney and colleagues determined that the fetal heart is reduced in size due to a decrease in hyperplasia and not due to alteration in cardiomyocyte size (O'Tierney et al., 2010).

HOW HUMORAL FACTORS INFLUENCE CARDIOMYOCYTES EITHER *IN VIVO* OR *IN VITRO*

Treatment of fetuses *in vivo* or isolated fetal cardiomyocytes with growth factors and hormones, whose concentrations may be altered by the placenta, allows for greater understanding of how the placenta may influence the fetal heart.

IGF-1

IGF-1 is an important growth-promoting hormone that is produced by many tissues and functions throughout fetal and

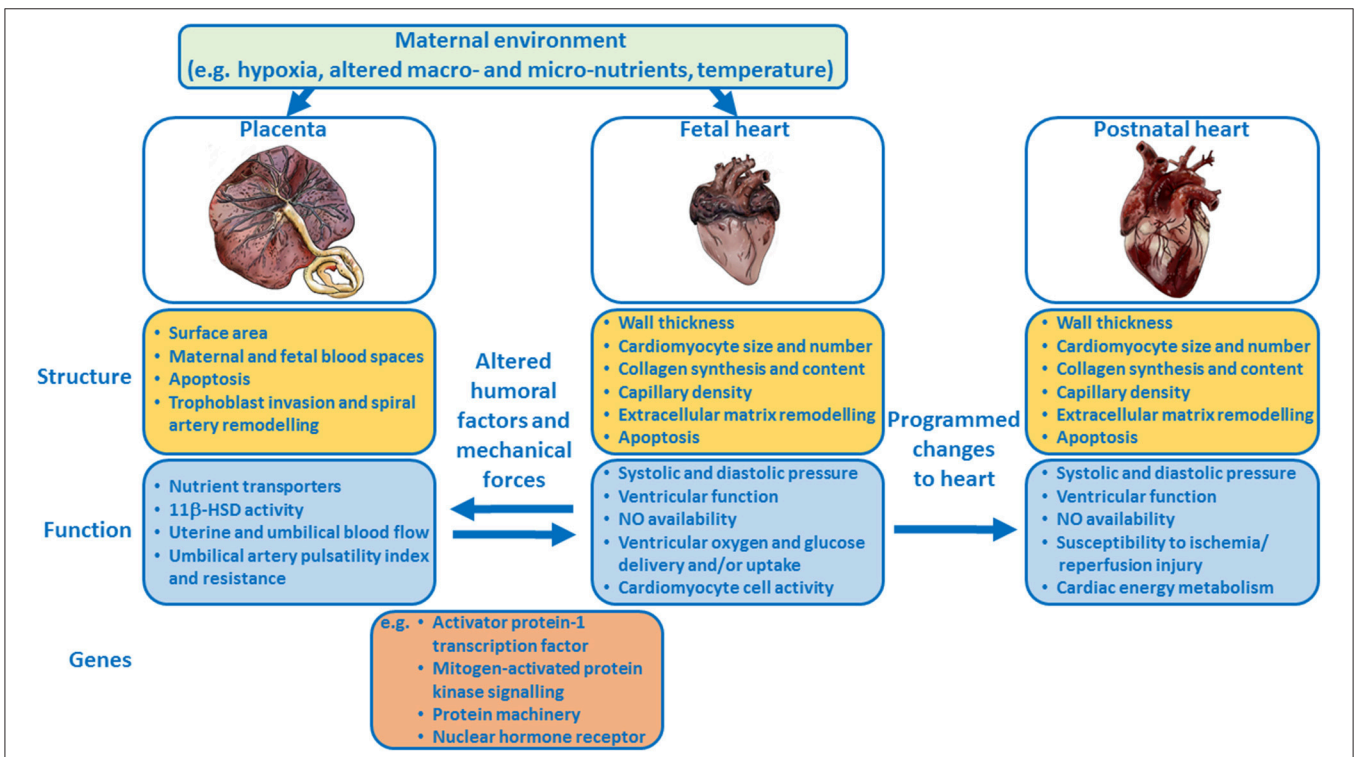

FIGURE 1 | Schematic summary showing how the placenta and fetal heart may influence each other and how the maternal environment may modulate the placenta-fetal heart axis, and the structure and function of both organs. Examples of genes that regulate the development of both the placenta and heart are listed.

postnatal development in an autocrine/paracrine fashion. IGF-1 primarily promotes growth through the type 1 IGF receptor (IGF-1R) and downstream signaling pathways, including extracellular signal-regulated kinase (ERK) and phosphoinositol-3 kinase (PI3K). The carunclectomy model in sheep (Jones et al., 1988) and undernutrition across gestation in rats (Woodall et al., 1996a), decreases fetal plasma IGF-1 concentration in late gestation. Varying results from *in vivo* experiments in fetal sheep suggest that IGF-1 can either promote cardiac growth by hypertrophy (Lumbers et al., 2009) or hyperplasia (Sundgren et al., 2003). Likewise, treating fetal sheep cardiomyocytes with a form of IGF-1 *in vitro* results in either greater (Wang et al., 2012) or equivalent (Sundgren et al., 2003) cardiomyocyte hypertrophy compared to serum-free controls. Treating neonatal rat cardiomyocytes with IGF-1 results in a similar variation of results with either cardiomyocyte hypertrophy (Bass et al., 2012) or hyperplasia (Kajstura et al., 1994) reported. Despite the inconsistency between results, IGF-1 has consistently been reported to promote fetal cardiac growth, therefore, reduced plasma concentration may in part contribute to the smaller hearts observed in fetuses from the carunclectomy and undernutrition animal models.

Cortisol

Cortisol is an important regulatory signal during fetal development, which amongst other important roles, acts to mature the cardiovascular system in preparation for birth (for review, Fowden and Forhead, 2015). Fetuses exposed to placental insufficiency due to carunclectomy (Phillips et al., 1996) or maternal hyperthermia [males only] (Walker et al., 1990), have increased plasma cortisol concentrations compared to controls in late gestation. Cortisol infusion to fetal sheep in late gestation results in a greater heart weight accompanied by either an increase in cell cycle activity (Giraud et al., 2006; Feng et al., 2013), increased cardiomyocyte hypertrophy (Lumbers et al., 2005), or decreased DNA content in the left ventricle (Rudolph et al., 1999). Due to the inconsistency in results, it is currently unclear how an increase in cortisol may affect the fetal heart in models of placental insufficiency. However, research into the effect of other humoral factors that are regulated by cortisol, such as thyroid hormone, appear clearer.

Thyroid Hormone

Thyroid hormones, especially T3, promote the maturation of a range of organs (For review, Forhead and Fowden, 2014). T4 is produced by the fetal thyroid gland and is converted to the more active T3 in late gestation. The conversion of T4 to T3 is catalyzed by deiodinases, which are upregulated by cortisol. As such, the surge in plasma T3 concentration is concurrent with the prepartum surge in plasma cortisol concentrations. T3 infusion to fetal sheep prior to the prepartum surge in T3, results in increased cardiomyocyte binucleation [a sign of increased maturation] and decreased cardiomyocyte cell cycle activity compared to controls (Chattergoon et al., 2012a). Furthermore, surgical ablation of the fetal thyroid gland results in reduced fetal cardiomyocyte binucleation and cell cycle activity (Chattergoon et al., 2012a). *In vitro*, T3 inhibits the proliferation of cardiomyocytes isolated from hearts either before or during the prepartum surge in T3 concentration (Chattergoon et al., 2007, 2012b). The carunclectomy model in sheep results in reduced fetal T3 and T4 plasma concentrations in late gestation (Harding et al., 1985). These studies provide evidence that the decreased percentage of binucleated cardiomyocytes observed in the fetal heart from the carunclectomy (Morrison et al., 2007) and UPE (Bubb et al., 2007) models may be due to reduced plasma T3 concentrations.

CONCLUSION

Epidemiological and clinical studies suggest a link between placental morphology and increased risk of cardiovascular disease in adult life. The mechanistic basis of this relationship has not been fully elucidated. However, experimental animal models and studies in genetically-modified mice, have provided novel insights into the relationship between placental formation and fetal heart development and the role humoral and mechanical forces play in the development of both of these organs (**Figure 1**). Further work characterizing placental morphology (e.g., surface area, thickness) and function (e.g., umbilical blood flow, oxygen and nutrient delivery) during complicated pregnancy, alongside echocardiographic measures of fetal cardiac structure, and function, will provide valuable insights into the placenta-heart axis. Such research may aid in the early diagnosis and monitoring of complicated pregnancies thus enabling timely interventions to modify long-term cardiovascular risk.

AUTHOR CONTRIBUTIONS

EC, KB, and AS-P contributed equally to reviewing the literature and writing and editing the manuscript.

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