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

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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

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.

**ANIMAL MODELS OF ALTERED PLACENTATION, HYPOXAEAMIA 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,
| 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 Carunclectomy surgical removal of the majority of endometrial caruncles prior to conception; causes IUGR (Gestation ∼150 d) | ↓ number of placentomes | ↓ placental weight | ↑ placental efficiency | ↓ umbilical artery blood flow | ↓ absolute heart weight = heart weight relative to body weight | 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 |
| Sheep Carunclectomy | ↓ umbilical artery blood flow | ↓ fetal femoral/peripheral blood flow | ↓ fetal femoral/peripheral vascular resistance | ↓ heart weight | = heart weight relative to body weight | |
| Umbilicoplacental embolization from ∼110 to 130 d gestation; or ∼120 d gestation to birth; causes IUGR | ↓ placental weight | ↓ cross-sectional area of interdigitation between fetal and maternal tissue | ↑ calcium deposition | ↓ umbilical blood flow | ↓ heart weight | |
| Umbilicoplacental embolization | ↓ placental weight | ↓ cross-sectional area of interdigitation between fetal and maternal tissue | ↑ calcium deposition | ↓ umbilical blood flow | ↓ heart weight | |

(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       | ↓ placenta weight                | ↓ PaO<sub>2</sub>                              | = fetal MAP                       | ↓ heart weight                         | = heart weight relative to body weight (1 day) | Oh et al., 1975; Oyama et al., 1992; Supramaniam et al., 2006; Miller et al., 2009a,b; Tare et al., 2014 |
|                                        |                                 | ↓ %SaO<sub>2</sub>                             | = fetal HR                        |                                        | ↑ LVDP, LV +dP/dt and LV -dP/dt (1 day) |           |
|                                        |                                 | ↓ PaCO<sub>2</sub>                             | ↓ umbilical blood flow            |                                        | ↓ RVDP, RV +dP/dt and RV -dP/dt (1 day) |           |
|                                        |                                 | ↑ Hb and %Hct                                  |                                |                                        | ↑ I/R infarct area (1 day) |           |
|                                        |                                 | ↓ fetal glucose uptake                         |                                |                                        | ↓ coronary eNOS, COX2, collagen II mRNA (1 day) |           |
|                                        |                                 | = glucose per weight of fetus                  |                                |                                        | = coronary COX1, collagen I and II and tropoelastin mRNA (1 day) |           |
|                                        |                                 | ↑ plasma cortisol (at labor)                   |                                |                                        |                         |           |
| Maternal hyperthermia                  | ↓ total weight of placenta       | ↓ PaO<sub>2</sub>                              | = absolute heart weight           | ↓ heart weight                         | = heart weight relative to body weight (1 day) | Bell et al., 1987; Walker et al., 1990; Thureen et al., 1992; Regnault et al., 2003, 2007, 2013; Limesand et al., 2001, 2006; Galan et al., 2005; Hagen et al., 2005; Barry et al., 2006, 2016; Ziegel et al., 2007; Anzey et al., 2009; Monson et al., 2017 |
|                                        | ↓ GLUT8 mRNA and protein         | ↓ %SaO<sub>2</sub>                             | = basal LV myocardial blood flow per gram of LV tissue |                                        |                                |           |
|                                        | ↑ IGF-1 protein                  | = PaCO<sub>2</sub>                             | = basal LV myocardial oxygen delivery, oxygen uptake, and oxygen extraction efficiency |                                        |                                |           |
|                                        | ↑ p-mTOR, p-ERK, and p-Akt       | ↑ Hb                                           | = basal LV myocardial glucose delivery and uptake |                                        |                                |           |
|                                        | ↑ p70S6K and p-XAP               | ↑ %Hct                                         | ↑ insulin-stimulated LV myocardial blood flow per gram of LV tissue |                                        |                                |           |
|                                        | ↓ cleaved caspase                | ↓ plasma glucose                               | ↑ insulin-stimulated LV myocardial glucose delivery and uptake |                                        |                                |           |
|                                        | ↓ telomerase activity            | ↓ plasma insulin                               | ↑ GLUT4 and IRβ protein           |                                        |                                |           |
|                                        | ↓ eNOS mRNA (fetal)              | ↓ plasma lactate                               | ↑ glycogen                        |                                        |                                |           |
|                                        | ↑ eNOS mRNA (maternal)           | ↓ plasma cortisol (fet/                      |                                |                                        |                                |           |
|                                        | ↑ Tie2 mRNA                      | males                                          |                                |                                        |                                |           |
|                                        | ↑ Angiopoietin 2 protein (fetal)  | ↑ plasma noradrenaline                         |                                |                                        |                                |           |
|                                        | ↑ PROF mRNA and protein (maternal) | ↑ umbilical uptake of O<sub>2</sub>, glucose, lactate and 11 amino acids per kg of fetus |                                |                                        |                                |           |
|                                        | ↑ VEGF and VEGFR1 mRNA and VEGF protein (fetal) | ↑ uterine blood flow per kg of fetus |                                |                                        |                                |           |
|                                        |                                   | ↑ uterine and umbilical blood flow             |                                |                                        |                                |           |
| Maternal hypoxia                       | ↓ placenta weight                | NB values only available for 10 days of maternal hypoxia | = LVDP                           | Brain et al., 2015; Allison et al., 2016 |
|                                        |                                 | ↓ PaO<sub>2</sub>                              | ↓ delivery of O<sub>2</sub> through the carotid and femoral artery |           |
|                                        |                                 | ↓ %SaO<sub>2</sub>                             | ↑ carotid and femoral artery blood flow |           |
|                                        |                                 | = pH                                          | ↑ delivery of O<sub>2</sub> through the carotid and femoral artery |           |
|                                        |                                 | ↑ %Hct                                         | ↑ carotid/femoral O<sub>2</sub> delivery ratio |           |
|                                        |                                 | = glucose                                      | = delivery of glucose through the carotid and femoral artery |           |
|                                        |                                 | = lactate                                      | = carotid/femoral glucose delivery ratio |           |
|                                        |                                 | = plasma acetoic acid                          |                                |           |
|                                        |                                 | ↑ plasma urate                                 |                                |           |
|                                        | NB values only available for 10 days of maternal hypoxia | = delivery of glucose through the carotid and femoral artery |                                |           |
### 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** (Gestation ∼ 68 d) | Unilateral uterine artery ligation | Performed at ∼30 d gestation; causes IUGR | ↓ CaO₂ | ↓ heart weight (Detmer et al., 1991) | = heart weight (2 months) | (Briscoe et al., 2004) or ↓ (Lafeber et al., 1984) placenta weight ↓ pH ↓ plasma glucose = plasma lactate ↓ plasma insulin ↓ 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) |
| **Chronic maternal hypoxia** 10.5–12% O₂ 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 ↑ PPARα, PTGS2, COMT mRNA (Preeclampsia markers) | ↑ %Hct ↑ maternal MAP ↑ HIF-1α and HIF-2α 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 ↑ nNOS/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, FABP4, FABPpm, FABP6 and GLUT4 mRNA (4 months; males and females) ↑ (female) or = (male) FACS and AMPKα2 mRNA (4 months) = PPARβ/δ, PGC-1α, CD36, ACC, MCD, OXPHOS, ACO, ACD, ACDIV, IGF1R, IGF2, IGF1R, IGF2R and AMPmRNA (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) |

Jones et al., 1984; Lafeber et al., 1984; Detmer et al., 1991; Briscoe et al., 2004; 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
| 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 | = heart weight | ↓ (male) or ↑ (female) JAK2, STAT3 and GLUT1 mRNA | Wigglesworth, 1974; Wlodek et al., 2005; Wadley et al., 2010, 2013, 2016; Black et al., 2012; Cheong et al., 2016 |
| | | | ↑ placental efficiency | ↓ heart weight weight relative to body weight | ↓ heart weight (1 month; males and females), but = heart weight relative to body weight | |
| | | | ↑ placental diameter | ↓ heart weight (2 months; males), but = heart weight relative to body weight | = heart weight and heart weight relative to body weight (6 months; females) | |
| | | | = total placental area | = heart weight, but ↓ heart weight relative to body weight (6 months; males) | = heart weight, but ↓ heart weight relative to body weight (6 months; females) | |
| | | | = labyrinth area, % of total | ↓ heart weight (1 month; males and females), but = heart weight relative to body weight | = heart weight, but ↓ heart weight relative to body weight (6 months; males) | |
| | | | ↑ PTHrP, PTH/PTHrP receptor and AT1a mRNA | = heart weight, but ↓ heart weight relative to body weight (6 months; females) | Wadley et al., 2010, 2013, 2016; Black et al., 2012; Cheong et al., 2016 |
| | | | ↓ PTHrP protein | = total cardiac protein (6 months; males) | = heart weight and heart weight relative to body weight (6 months; females) | |
| | | | = ionic and total calcium | = total cardiac mRNA (6 months; males) | = heart weight and heart weight relative to body weight (6 months; males) | |
| | | | = PTHrP | = total and p-Akt (ser473; 6 months; males) | = heart weight, but ↓ heart weight relative to body weight (6 months; females) | |
| | | | = heart weight | ↑ Spp1 and Rhoa mRNA (6 months; male) | ↓ total cardiac protein (6 months; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ Ckm mRNA (6 months; male) | = total cardiac mRNA (6 months; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ JAK2 mRNA (1 day, week and month) | = total and p-Akt (ser473; 6 months; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ STAT3 mRNA (1 day, week and month; males) | ↑ Spp1 and Rhoa mRNA (6 months; male) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↑ STAT3 and STAT5 mRNA (1 day; females) | ↓ Ckm mRNA (6 months; male) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ STAT3 mRNA (1 week; females) | ↓ Ckm mRNA (6 months; male) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | = STAT5 mRNA (1 day, week and month; males) | ↓ STAT3 mRNA (1 day, week and month; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ (female) or ↑ (male) PGC-1a mRNA (1 week) | = STAT3 mRNA (1 day, week and month; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | = PGC-1a mRNA (1 week and 1 month; males and females) | = STAT5 mRNA (1 day, week and month; males) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | = NRF-2, CXX III and GLUT4 mRNA (1 day, 1 week and 1 month; males and females) | = NRF-2, CXX III and GLUT4 mRNA (1 day, 1 week and 1 month; males and females) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | = mTFA mRNA (1 day males and 1 month females) | = mTFA mRNA (1 day males and 1 month females) | |
| | | | = heart weight (1 month; males and females), but = heart weight relative to body weight | ↓ MnSOD mRNA (1 month; males and females) | ↓ MnSOD mRNA (1 month; males and females) | |
| 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 |
|----------------------------------------|-----------------------------------|-----------------------------------------------|----------------------------------|----------------------------------------|--------------------------|------------|
| Maternal Hypoxia                        | 10.5–12% O₂ from 15 to 21 d gestation or 6 to 21 d gestation (Zhou et al., 2013) | pregnancy or hypoxic ischemia (Zhou et al., 2013) | maternal hypoxia (Rueda-Clausen et al., 2011) | fetal hemodynamic (Zhou et al., 2013) | heart weight, LV and septal wall thickness (1 week) | heart weight, LV and septal wall thickness (1 week) |
|                                        | = (Phillips et al., 2017) or ↓(Rueda-Clausen et al., 2011) placenta weight | ↓ oxidative stress (DCF) | ↓ trophoblast invasion (Zhou et al., 2013) | ↑ ETα and AT1-R protein (Zhou et al., 2013) | ↓ heart weight | ↓ heart weight relative to body weight (1 week) |
|                                        | = ETβ and AT2-R protein (Zhou et al., 2013) | ↓ heart weight relative to body weight | ↓ collagen content and collagen III protein | ↓ heart weight relative to body weight (12 months) | ↓ heart weight relative to body weight (12 months) | ↓ heart weight relative to body weight (12 months) |
|                                        | ↑ maternal SBP, DBP and MBP (Zhou et al., 2013) | ↓ LV and septal wall thickness | ↓ collagen α1 protein | ↓ collagen α1 protein | ↓ LV and septal wall thickness (1 week) | ↓ LV and septal wall thickness (1 week) |
|                                        | ↓ LV and septal wall thickness | ↓ heart weight relative to body weight | ↓ Mmp-1 protein | ↓ Mmp-1 protein | ↓ heart weight | ↓ heart weight relative to body weight (1 week) |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ Mmp-2, Mmp-9, Timp-1 and Timp-2 protein | ↓ Mmp-2, Mmp-9, Timp-1 and Timp-2 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ Mmp-13, Mmp-14, Timp-3 and Timp-4 protein | ↓ Mmp-13, Mmp-14, Timp-3 and Timp-4 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ GR mRNA and protein | ↓ GR mRNA and protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ GR protein and mRNA | ↓ GR protein and mRNA | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ GR promoter methylation | ↓ GR promoter methylation | ↓ LV and septal wall thickness (1 week) | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ transcription factor binding to GR exon 1 promoter | ↓ transcription factor binding to GR exon 1 promoter | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ GR methylation at the CREs and Spt1 binding sites | ↓ GR methylation at the CREs and Spt1 binding sites | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ % binucleated cardiomyocytes | ↓ % binucleated cardiomyocytes | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ apoptotic cardiomyocytes | ↓ apoptotic cardiomyocytes | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ caspase 3 and 8 activity | ↓ caspase 3 and 8 activity | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ Bcl-2 protein | ↓ Bcl-2 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ Bax protein | ↓ Bax protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ Hep70 protein | ↓ Hep70 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ PAR1 protein | ↓ PAR1 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |
|                                        | ↓ heart weight relative to body weight | ↓ heart weight relative to body weight | ↓ PAR2 protein | ↓ PAR2 protein | ↓ LV and septal wall thickness | ↓ LV and septal wall thickness |

(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
= βAR1
↓ αAR 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)
| 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 |
|----------------------------------------|-----------------------------------|-----------------------------------------------|--------------------------------|---------------------------------|--------------------------|----------|
| 13% O₂ from 6 to 20 d gestation; does not result in IUGR | ↑ placental weight | ↑ %Hct | heart weight, heart weight relative to body weight, LV and RV area | LV contractility (4 months) | heart weight and heart weight relative to body weight (4 months) | Giussani et al., 2012; Richter et al., 2012; Kane et al., 2013 |

### TABLE 1

**Placenta outcomes (late gestation)**

- ↑ placental weight
- ↑ %Hct
- ↓ Ki67 (1 week)
- ↑ LV developed pressure and end diastolic pressure (4 months)
- ↑ responsiveness to β₁-adrenoreceptor agonists (4 months)
- ↓ reactivity to muscarinic agonists (4 months)
- ↑ Hsp70 protein

**Fetal blood gas, metabolite and hormone profile**

- ↑ placental volume
- ↓ heart weight, heart weight relative to body weight, LV and RV area
- ↑ %Hct
- ↓ Ki67 (1 week)
- ↑ LV contractility (4 months)
- ↑ responsiveness to β₁-adrenoreceptor agonists (4 months)
- ↓ reactivity to muscarinic agonists (4 months)
- ↑ Hsp70 protein

**Materno-fetal haemodynamic outcomes**

- ↑ placental blood flow
- ↓ heart weight, heart weight relative to body weight, LV and RV area
- ↑ %Hct
- ↓ Ki67 (1 week)
- ↑ LV contractility (4 months)
- ↑ responsiveness to β₁-adrenoreceptor agonists (4 months)
- ↓ reactivity to muscarinic agonists (4 months)
- ↑ Hsp70 protein

**Fetal cardiac outcomes (late gestation)**

- ↑ LV developed pressure
- ↓ heart weight, heart weight relative to body weight
- ↓ %Hct
- ↓ Ki67 (1 week)
- ↑ LV contractility (4 months)
- ↑ responsiveness to β₁-adrenoreceptor agonists (4 months)
- ↓ reactivity to muscarinic agonists (4 months)
- ↑ Hsp70 protein
| 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 | ↓ placental weight | ↓ fetal plasma apelin concentrations | ↓ plasma IGF-1 | ↓ plasma insulin | ↓ plasma IGFBP-1 and –2 | ↑ systolic blood pressure (between 1 and ∼11–12 months) | Woodall et al., 1996a,b, 1999; Vickers et al., 2000, 2002; Riviere et al., 2005; Cannons et al., 2008; Mayeur et al., 2013, 2016 |
| Rat 50% UN* from 10 d of gestation to birth; causes IUGR | ↓ placental weight | ↓ fetal plasma osmolality and Na+ concentrations | ↓ 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) | ↑ elastin and GAG in aorta (1 day of age) | Desai et al., 2005; Kharram et al., 2007a,b,c, 2010; Belkasemi et al., 2009, 2011a,b,c; Jelks et al., 2009 |

(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 50% UN from 14 d gestation to weaning; causes IUGR | = placental weight | ↓ fetal/placental weight | ↑ BDNF mRNA and protein | ↑ TrkB-FL mRNA = TrkB-FL and TrkB-T1 protein | ↓ utero-placental blood flow | ↓ maternal cardiac output | ↑ plasma B (newborns) then ↓ 2 h later | ↑ plasma ACH (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/baby weight | ↓ Lz weight and % Lz | ↓ trophoblast volume | ↓ maternal and fetal blood space volume | ↓ total surface area (Lz) | ↑ barrier thickness | ↑ EPOR protein in female fetuses | ↑ VEGF protein in male fetuses | ↓ relative heart weight (~1 month) = absolute heart weight (~3–4 months) | ↓ relative heart weight (~3–4 months) (males and females) | Sahlihrom et al., 1998; Roberts et al., 2001a,b, 2002; Elias et al., 2016, 2017; Nevin et al., 2018 |
### TABLE 2 | Continued

| Animal model and experimental protocol | Placental 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 | ↓ Lz % = or ↑ placental body weight | ↓ 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 mRNA | ↓ absolute heart weight (1 month) | 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; Nasimento 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 | ↓ VEGF protein = VEGF receptors and expression-regulating mRNA | ↑ systolic blood pressure (~3 to 12 months) | Rutland et al., 2007; Watkins et al., 2008, 2011, 2015 |
| **Rat** 9% protein from 1 d gestation to birth; causes IUGR | ↑ placental volume = or ↓ placental weight | ↓ 11β-HSD-2 and ↑ GSase activity | ↓ 11β-HSD-1 mRNA = 11β-HSD-1 mRNA | ↓ maximal and overall relaxation to VEGF in uterine arteries | = absolute heart weight (~1 month) | 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; Ahire Sayet 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 |
| 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 6% protein from 1 d gestation to birth; = or ↓ fetal weight | = placental 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 | 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-Jeffries et al., 2011; Bai et al., 2012 |

(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 | ↓ placental weight | | | | ↑ systolic and diastolic blood pressure (6 and 12 months, females) | Liang et al., 2009a,b, 2010 |
| (12x fat) from −28 d to weaning (fetal weight not reported) | ↓ number of trophoblast cells | ↑ oxidative stress-mediated endothelial cell damage | | | | |
| **Mouse** | | | | | | |
| High fat/high sugar (−5x fat, ~6x sugar) from −84 d to lactation | ↑ lipid accumulation in Db/Jz | ↑ HIF1-α protein | | | | |
| = fetal or birth weight | | | | | | |
| | | | | | | |
| **Rat** | | | | | | |
| High fat (4.5x) from −21 d to lactation; = in fetal weight or causes IUGR | ↓ placental weight | ↓ Jz weight | ↑ 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; ANP, atrial natriuretic peptide; APJ, apelin receptor; Atras, asparagine synthetase; ATR, activating transcription factor-4; ATP6, mitochondrially 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; 17β-HSD, 17β-hydroxysteroid dehydrogenase; IGF-1, insulin-like growth factor 1; IGFIR, insulin-like growth factor binding protein; IL-1β, interleukin 1 beta; Jz, junctional zone; LPL, lipoprotein lipase; LVEDP, left ventricular end diastolic pressure; LVDP, left ventricular developed pressure; MAP, mean arterial pressure; mRNA, microRNA; MHC, myosin heavy chain; MMP, matrix metalloproteinase; mt, mitochondrial; mt-co, mitochondrially encoded cytochrome C oxidase; mTOR, mammalian target of rapamycin; NEAA, nonessential amino acids; NPY, neuropeptide Y; NR3C1, nuclear receptor subfamily 3 group C member 1; p-eIF2α, phosphorylated eukaryotic translation initiation factor 2α; PE, phenylephrine; POC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; POMC, pro-opiomelanocortin; PPAR, peroxisome proliferator-activated receptor; SNAT, sodium-dependent neutral amino acid transporter; Tgfα, 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 HYPOXAEAMIA**

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 placentaion 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)/Gaq/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 ureterine 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 ureterine 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 \(\alpha_1\)-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 (Sfruzzu-Peri 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, Hiat1, 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 Knita, 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 (Frai1, 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 Frai1. 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, Frai1, 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 choioallantoic placenta (Lindsay 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 (Lindsay 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) | Notes | References |
|------|---------------------------------------------|------------------------------------------------------------------------------------|-------|------------|
|      | Placenta                                   | Fetal heart development                                                            | Fetal viability |                          |
|      |                                             |                                                                                   |                  |                          |
|      |                                             |                                                                                   |                  |                          |
| 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 |
| Ovo2  | 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        | Ueszaki et al., 2007 |
| P38ka | 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       | 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             | Hatano et al., 2003 |
| Fra /Fosl1 | Expressed in Lz of placenta and several fetal tissues including heart               | d9.5: Failed Lz vascularization                                                     | d9: Premature cardiomyocyte differentiation, ventricular and septum hypoplasia, myocardial thinning and degeneration of the trabecular zone | d10.5: Lethal             | 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             | Barak et al., 1999 |

(Continued)
| Gene   | Expression in placenta and fetus/fetal heart | Impact of constitutive loss of expression in developing conceptus (unless stated otherwise) | References |
|--------|---------------------------------------------|----------------------------------------------------------------------------------------|------------|
| **Braf** | d1 1.5: 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 | MecoxCre 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 |
| **Serp2** | 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 MecoxCre (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 |
|------|---------------------------------------------|--------------------------------------------------------------------------------------|------------|
|      | **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 syncytiotrophoblast layers in Lz | d10.5: Dilated vasculature and enlarged pericardium | d12.5: Lethal | Szabova et al., 2010 |
| Flt2 | Endothelial cells specifically in the placentalisland 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 distal 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 Gcn1) | d10: Enlarged pericardium and thin ventricle walls | d11.5: Lethal | Tanaka et al., 2005 |
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                        | References                                      |
|        |                                             | Fetal viability                                                                      | Notes        |                                |                                                  |
|        |                                             |                                         |               |                                |                                                  |
| Rxra   | Ubiquitously expressed                       | d9.5: Reduced Lz vascularization                                                      | d12–16.5: Lethal | Kastner et al., 1994; Sapin et al., 1997; Barak et al., 1999; Wendling et al., 1999; Mascrez et al., 2009 |
|        |                                             | d13.5–16.5: Thin ventricular walls, trabeculae and septum                              |               |                                |                                                  |
|        |                                             | d9: Failure of the allantoic mesoderm to invaginate into the chorionic trophoblast to form the Lz. Poor Lz angiogenesis due to reduced Vegfa expression | d10.5: Lethal | Stumpo et al., 2004; Bell et al., 2006 |
|        |                                             | d9: Less developed trabeculae and sinusoids in the myocardial wall, thin myocardial wall |               |                                |                                                  |
|        |                                             | d10.5: Lethal                                                                          |               |                                |                                                  |
| Zfp361 | 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 | d10.5: Lethal | Stumpo et al., 2004; Bell et al., 2006 |
|        |                                             | d9.5: Less developed trabeculae and sinusoids in the myocardial wall, thin myocardial wall |               |                                |                                                  |
|        |                                             | d10.5: Lethal                                                                          |               |                                |                                                  |
| 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 | 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 myocardium                                         | d8.5: Abnormal chorioallantoic fusion and Lz vascularization                          | d11.5: Epicardial defects | Gurthner et al., 1995; Kwee et al., 1995 |

Braf, Braf transforming gene; Cited2, Cbp/P300 interacting transactivator with Glu/Asp carboxy-terminal domain 2; d, day of gestation; E2f7/E2f8, E2F transcription factor 7; Erk2/5, extracellular signal-regulated kinase 2/5; Phd2, fibronectin leucine rich transmembrane protein; Fis/FosF1, FOS like 1, AP-1 transcription factor subunit; Gab1, growth factor receptor bound protein 2-associated protein 1; Gcm1, glial cells missing homolog 1; Ha1, PSPC 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; Ovo2, ovo like zinc finger 2; P38a, mitogen activated protein kinase p38a; Phd2, egl-9 family hypoxia inducible factor 1; Ppar, peroxisome proliferator activated receptor gamma; Rb, RB transcriptional corepressor 1; Rera, 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...
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.

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

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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