Postnatal cardiovascular adaptation

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ABSTRACT

The heart undergoes rapid transformations in function during the transition to extrauterine life. Our understanding of the adaptive physiology underlying this process is able to inform the clinical management of infants who are struggling to complete this complex transition. Much of our knowledge of the cardiac transition is derived from the preterm infant in whom the preparative adaptations are incomplete and clinical sequelae all too common. This review will re-examine the cardiac transition highlighting the physiology that drives it and suggest appropriate clinical intervention to support the process.

THE FETAL HEART AND CIRCULATION

The fetus is reliant on the placental circulation for essential gas exchange, nutrient supply and waste elimination.[1] In humans, the fetal placental perfusion is via two umbilical arteries arising as branches of the internal iliac arteries.[1] The seminal work on the fetal circulation was performed by Rudolph and Heymann in the early 1960s using a combination of the Fick principle and microsphere distribution.[2] This work has since been validated using gated MRI techniques.[3] The placenta receives 40% of the combined fetal cardiac output (CO) mainly arising from the right ventricle (RV) via the ductus arteriosus (DA). Nutrient and oxygen-rich blood returns from the placenta via a single umbilical vein and distributes blood to the fetal liver and directly through the ductus venosus (DV) to the inferior vena cava and right atrium. The proportion of blood passing through the DV is responsive to variations in the physiological status of the fetus.[4] In utero, the right heart provides around 60% of the CO and is the dominant ventricle. The RV receives blood from both vena cavae, including the hepatic portion of placental return. RV ejection is into the pulmonary artery and then via the ductal arch feeding the descending aorta perfusing the lower torso and the placenta. In utero, a small but variable proportion of CO travels through the pulmonary circulation, blood flow increasing at the end of the second trimester at the time of maximal pulmonary development and then decreasing again towards term.[5] By contrast, the left ventricle (LV) receives nutrient and oxygen-rich blood from the DV through the foramen ovale (FO) with a minor contribution from the pulmonary veins. Outflow is via the aortic valve to coronary vessels, the head and upper torso, with less than 25% of the LV outflow perfusing the lower torso. The in utero fetal circulation ensures appropriate distribution of nutrients to those organs with greatest metabolic demand: the heart and the brain. The heart in utero has a near constant workload with a relatively high- volume and low-resistance circulation, the myocardium can be considered metabolically stable but mechanically less efficient than the adult heart.

THE POSTNATAL HEART

In the few minutes following delivery the heart undergoes remarkable changes in function. Pressures and flows in the RV drop while conversely increasing in the LV which is promoted to be the dominant ventricle by workload. LV afterload increases as the placental circulation is removed. The circulation becomes dynamically responsive to the changes in workload required by postnatal activities, LV output doubling from 150 to around 400 mL/kg/min and systemic blood pressure (BP) rising.[6 7] This produces a significant increase on the metabolic demand of the heart, coronary blood flow and oxygen delivery to the LV increases.[8] The heart is now far more like an adult heart, mechanically very efficient but metabolically more fragile. These changes appear seamless in the term infant but may be more challenging to the preterm where compromised CO has been clearly documented in the few hours following birth. The adaptive mechanisms that allow the heart to withstand this rapid change in function offer possible avenues for clinical intervention.

CARDIAC FUNCTION AND HAEMODYNAMICS AFTER BIRTH

Although the evolving cardiac dynamics throughout childhood are well described, we have only recently come to appreciate the changes that occur over the first few days of life. The advent of bedside ultrasound and neonatologist performed scans have furnished this information in the premature infant. The term infant is not considered a clinical problem and therefore only very recently starting to receive attention.[9]

In the compromised preterm, infant BP declines over the first 6 hours of life and then recovers after 12–24 hours of age.[10] This has been linked to clinical adverse outcomes including death, peri/intraventricular haemorrhage (P/IVH) and neurodevelopmental delay.[11] There has been little evidence that standard treatment with volume or pressor agents have improved outcomes, some studies suggesting worsening outcome if pressor agents are used.[11–14] Point-of-care clinical ultrasound has permitted insights as CO can be directly measured. A methodology that reflects cerebral perfusion and is independent of cardiac shunts (DA and FO) is superior vena cava flow (SVCf).[15] Although the pattern of SVCf over the first 24 hours of life mirrors that previously demonstrated with BP, there is growing awareness that the relationship between CO and BP is not

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tight as there is also considerable variation in systemic vascular resistance (SVR) and in the fetal cardiac shunts.[16] Low SVCf is a better predictor of P/IVH than BP[16 17] and also correlates with adverse neurodevelopmental outcomes.[18] The relationship between cerebral perfusion, CO and BP is complex and extends beyond early concepts of BP-dependent cerebral autoregulation. We are now aware of significant changes in oxygen extraction at lower cerebral perfusion and regional variations in cerebral blood flow that serve to protect the brain from injury.[7 19] It is only when these mechanisms are exhausted that the brain suffers hypoxic damage (uncompensated shock).[20]

Clinical measures of cardiac performance at this stage implicate a failure of the immediately post-transitional myocardium to adequately respond to increasing afterload induced by increases in SVR.[21 22] CO therefore diminishes before BP.[23] The addition of inotropic agents may induce a rise in SVR without compensatory increases in output further impairing organ perfusion.[24 25] Non-invasive measures of inherent myocardial function are difficult in clinical settings. Velocity of contraction in relation to wall stress (MVFS/WS) has been one such measure. In a study of infants exhibiting low SVCf and later increased risk of P/IVH, Osborn *et al* demonstrated a steeper MVFS/WS than in controls with normal SVCf,[26] implying the at-risk infants were less able to cope with increasing afterload. Lee *et al* demonstrated a clear reduction in the velocity of tissue Doppler measurements for both ventricles over the first few hours of life with recovery by 24 hours of age.[27] A greater understanding of underlying cardiac contractility may be available from the more sophisticated echo techniques that are now being adopted.[9 28 29]

While the clinical picture is now established, the pathophysiology underpinning these observations is not well understood and we are yet to fully comprehend the drivers of this transient haemodynamic compromise or introduce effective prevention or management. The following candidates are considered.

Myocardium and the contractile unit

The fundamental structure of the contractile unit is conserved throughout development. Repeating mirrored patterns of a honeycomb arrangement of six actin strands anchored by a Z disc give muscle its characteristic striated appearance. Myosin heavy chain proteins, from which hinged light chains project, are housed in opposing actin tubules. Binding between the head units of the myosin light chains and actin generates the longitudinal force of contraction. This force is proportional to intracellular Ca^{++} concentration which acts on the complex troponin protein to remove tropomyosin from the myosin/actin-binding site.[30] The contractile sarcomeres are held in an extracellular matrix containing the giant elastic molecule titin, this molecule facilitates passive diastolic recoil and filling.[31] Varying isoforms of the components of the contractile unit are present in development but are not clearly associated with significant alterations in function, the rate at which these changes occur is likely too slow to influence functional change around transition. More important changes occur in the intracellular development of the sarcoplasmic reticulum (SR) which serves as an intracellular Ca^{++} store. In the embryonic stages, the SR is poorly developed and the intracellular rise in Ca^{++} is predominantly across the cell membrane. With maturation, the SR grows to envelop the contractile units with Ca^{++} channels[32 33] and calcium-induced calcium release from the SR predominates.[34 35] Later in development, SR transverse tubules form to ensure the action potential initiated Ca^{++} release penetrates rapidly throughout the enlarging myocyte.[36]

Maturational changes occur both in the myocardial cells and their arrangement within the cardiac muscle. Embryonic myocardial cells are globular containing few contractile units, over time the cells elongate and become almost completely filled with contractile units and mitochondria.[37] These changes improve contractile efficiency and increase the compliance of the ventricles to enhance diastolic filling. The orientation of the cells within the LV develops into a complex of longitudinal, circumferential and spiral elements that combine to produce an efficient wringing motion during systole.[38]

Metabolic

The fetal heart is almost exclusively fuelled by glucose.[39] In the relatively hypoxic uterine environment only a fraction of the glucose is completely oxidised, the remainder being converted to lactate. After birth, oxygen availability increases and the heart more completely oxidises glucose improving energy production and ATP availability.[40] Over the first week of life, the heart switches to metabolism of fat via the fatty acid oxidation (FAO) pathway.[40] There is a complex signalling mechanism that orchestrates these changes.[41] In utero hypoxia-inducible factors (HIF-1α) promote the glucose transporter GLUT-1 and favour glucose metabolism. After birth, HIF-1α falls and releases inhibition of peroxisome proliferator-activated receptors (PPAR) and their cofactors which serve as transcription factors to upregulate the FAO pathways. Oestrogen-related receptors play a direct role in upregulation of the mitochondria at birth and feedforward with PPAR to promote FAO.[42] It is thought that the rise in circulating fats associated with the first milk feed also induces upregulation of myocyte FAO.[43] These changes are associated with the terminal differentiation of the myocyte as described above, and the forced maturation associated with premature birth may limit cardiomyocyte number[44] and alter cardiac function in later life.[45]

Dawes *et al* first described the deposition of cardiac glycogen in the fetus and the role this plays in surviving hypoxic ischaemic injuries at birth.[46] Shelley later described the depletion of these stores in the newborn facing a hypoxic insult.[47] We are still unclear whether the premature newborn heart can be compromised by lack of glucose supply over the first few hours of life.[48]

Endocrine

Early animal work demonstrated a marked increase in circulating catecholamines associated with birth and fetal adrenalectomy showed this rise necessary for the normal transition.[49] Furthermore, in the premature infant, the catecholamine rise is even more pronounced though the effect on promoting transition is blunted.[50] The seminal work of Liggins described a late gestational rise in cortisol that orchestrates the maturation of fetal organs in preparation for delivery, in hypophysectomised animals he showed poor transition despite a significant catecholamine response.[51 52] These findings have since been explained by cortisol-induced upregulation of α and β adrenergic receptors.[53] Liggins' observations paved the way for antenatal steroids for lung maturation, but the hormonal control of development is equally important for cardiac function and transition. Antenatal steroids have consistently been proven to improve neonatal survival and reduce the risk for P/IVH,[54] more specifically the need for BP support is reduced.[55 56] In a baboon model, a rise in fetal BP was demonstrated within 6 hours of maternal steroid administration, it is unclear whether this is mediated through increased catecholamine sensitivity or more fundamental myocardial changes.[57]

Thyroid hormone secretion increases slowly in late gestation and plays a role in maturing adrenergic receptors, a significant rise in thyroid-stimulating hormone-stimulated thyroxine release with birth has not been shown to facilitate the normal transition.[58] Trials of antenatal thyroid-releasing hormone, in addition to steroids, failed to yield significant improvements and were associated with increased risks for neurodevelopmental delay.[59 60]

In summary, the fetal heart has a relatively high-volume low-resistance circulation. At birth, the LV must cope with an increase in afterload and greater variability of demand, the RV output must mirror the LV but at a much lower afterload. The fetal heart is mechanically less efficient than in later life but metabolically resilient and able to withstand the hypoxic challenges of delivery. Postnatally, the heart rapidly becomes mechanically more efficient but metabolically more vulnerable, dependent on continuous oxygen and fuel delivery. These changes occur less rapidly in the preterm infant creating a period of vulnerability during the first few hours of life. Knowledge of this physiology can inform support of the circulation during this transition.

CLINICAL IMPLICATIONS

Prevention, as always, is the best strategy with avoidance of preterm birth and antenatal sepsis where possible. Antenatal steroids should be given to promote maturation of the heart as well as the lungs to diminish the postnatal consequences of early reductions in CO,[11 20] as well as potentially improving cardiac function in utero.[57] Can the premature heart be 'primed' for delivery? While there has been much published on the impact of alterations in late gestational physiology and long-term cardiovascular and metabolic programming,[61] less attention has been paid to the potential for such programming to influence cardiac function during the transition. It is tempting to think that in utero stressors may prepare the heart for extrauterine life. This is, however, unlikely to mirror the advantages seen in pulmonary development. Intrauterine growth restriction has been extensively studied and undernutrition can result in maturational changes in the cardiac myocytes,[62] this does not however translate into a clinical functional advantage.[63] Furthermore, premature maturation may diminish the total myocyte count into adult life.[44] Inflammation has also been considered and studied with intra-amniotic lipopolysaccharide administration in animal models. Inflammation has deleterious effects on the heart and also increases the risk of metabolic injury and infarction.[64] With current knowledge, it seems unlikely that we could promote the contractility of the heart without a concomitant increase in the metabolic vulnerability.

In infants who are perceived to have circulatory compromise in the first few hours of life, BP alone is insufficient to delineate pathophysiology or determine management. These infants are not a homogeneous group, clinical context and early echocardiographic assessment should define the underlying physiology and inform appropriate management. It is important to separate those infants with a physiological decline in LV function from those who have other defined problems. Sepsis, for instance, predominately presents as high output with a decreased SVR and may require volume and pressor agents[65]; rare cases of congenital heart disease should be evident on echocardiography and managed in conjunction with paediatric cardiologists. Infants with apparent physiologically low CO generally recover by 24 hours of age and 'permissive hypotension' may be a reasonable approach.[12] It is fair to say we know more about what does not help in this situation and are still unsure of any positive interventions. Inotropes appear more likely to do harm and may even decrease CO. Inodilators (milrinone) seem ineffective in this age group, possibly because the receptors are not yet developed.[66] We need to pay careful attention to ventilation so as not to impair LV preload. This may involve reducing mean airway pressures, if possible, and managing pulmonary hypertension with alternative ventilation modes and/or the addition of nitric oxide. While space does not permit a discussion of the controversies surrounding management of the DA, varying from possible closure if torrential left to right shunt to maintaining patency if significant pulmonary hypertension, these are options to consider. Toyoshima has developed an algorithm for managing these infants based on LV wall stress with considerable personal success but not widely reproduced.[67] Postnatal steroid therapy is being rediscovered with some encouraging trials.[68] None have specifically addressed early CO.

An understanding of the physiological mechanisms around immediate transition and the influence of management of the umbilical cord on cardiac function offers potential for intervention. In the lamb model, early clamping of the cord before the pulmonary circulation has been established significantly compromises LV function. The LV suffers from reduced preload as FO shunting decreases with cessation of umbilical venous return, at the same time afterload increases as the compliant placental circulation is removed.[69] If the placental circulation remains intact until pulmonary blood flow is established, physiologically-based cord clamping (PBCC), then haemodynamic compromise is minimised and insult to the LV reduced.[70] PBCC has also been shown to confer advantages in the asphyxiated animal model.[71] The translation of these findings to clinical practice has been hampered by a focus on a placental transfusion and delayed cord clamping without emphasis on establishing a pulmonary circulation; nevertheless, results are encouraging with a reduction in mortality and a trend towards reduced P/IVH and needs for circulatory support.[72] A large study in term infants from Tanzania demonstrated a significant negative relationship between mortality and the time from onset of respiration to cord clamping.[73] Two small studies of PBCC, one in term infants[74] and the other in preterm,[75] have confirmed the feasibility of this approach.

In conclusion, the challenges facing the transitioning preterm heart are complex and as yet not fully understood. It is likely the greatest improvements in care and outcomes for these infants will be derived from a more thorough understanding of their physiology and the subsequent application of management specifically targeted to their needs.

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REFERENCES

1 DAWES GS, MOTT JC, WIDDICOMBE JG. The foetal circulation in the lamb. *J Physiol* 1954;126:563–87.
2 Rudolph AM, Heymann MA. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ Res* 1967;21:163–84.
3 Prsa M, Sun L, van Amerom J, *et al*. Reference ranges of blood flow in the major vessels of the normal human fetal circulation at term by phase-contrast magnetic resonance imaging. *Circ Cardiovasc Imaging* 2014;7:663–70.
4 Hecher K, Campbell S. Characteristics of fetal venous blood flow under normal circumstances and during fetal disease. *Ultrasound Obstet Gynecol* 1996;7:68–83.
5 Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. *Physiol Rev* 2010;90:1291–335.

6 Heymann MA, Iwamoto HS, Rudolph AM. Factors affecting changes in the neonatal systemic circulation. *Annu Rev Physiol* 1981;43:371–83.
7 Smolich JJ, Soust M, Berger PJ, *et al*. Indirect relation between rises in oxygen consumption and left ventricular output at birth in lambs. *Circ Res* 1992;71:443–50.
8 Fisher DJ, Heymann MA, Rudolph AM. Regional myocardial blood flow and oxygen delivery in fetal, newborn, and adult sheep. *Am J Physiol* 1982;243:H729–H731.
9 Jain A, Mohamed A, Kavanagh B, *et al*. Cardiopulmonary adaptation during first day of life in human neonates. *J Pediatr* 2018.
10 Batton B, Li L, Newman NS, *et al*. Evolving blood pressure dynamics for extremely preterm infants. *J Perinatol* 2014;34:301–5.
11 Faust K, Härtel C, Preuß M, *et al*. Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F388–F392.
12 Dempsey EM, Al Hazzani F, Barrington KJ. Permissive hypotension in the extremely low birthweight infant with signs of good perfusion. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F241–F244.
13 Batton B, Li L, Newman NS, *et al*. Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F201–F206.
14 Synnes AR, Chien LY, Peliowski A, *et al*. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal intensive care units. *J Pediatr* 2001;138:525–31.
15 Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed* 2000;82:182F–7.
16 Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr* 1996;129:506–12.
17 Miletin J, Dempsey EM. Low superior vena cava flow on day 1 and adverse outcome in the very low birthweight infant. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F368–F371.
18 Hunt RW, Evans N, Rieger I, *et al*. Low superior vena cava flow and neurodevelopment at 3 years in very preterm infants. *J Pediatr* 2004;145:588–92.
19 Schwaberger B, Pichler G, Binder-Heschl C, *et al*. Cerebral blood volume during neonatal transition in term and preterm infants with and without respiratory support. *Front Pediatr* 2018;6.
20 Noori S, Seri I. Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates. *Semin Fetal Neonatal Med* 2015;20:232–7.
21 Friedman WF. The intrinsic physiologic properties of the developing heart. *Prog Cardiovasc Dis* 1972;15:87–111.
22 Eiby YA, Lumbers ER, Headrick JP, *et al*. Left ventricular output and aortic blood flow in response to changes in preload and afterload in the preterm piglet heart. *Am J Physiol Regul Integr Comp Physiol* 2012;303:R769–R777.
23 Groves AM, Kuschel CA, Knight DB, *et al*. Relationship between blood pressure and blood flow in newborn preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F29–F32.
24 Rozé JC, Tohier C, Maingueneau C, *et al*. Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;69:59–63.
25 Shah D, Paradisis M, Bowen JR. Relationship between systemic blood flow, blood pressure, inotropes, and aEEG in the first 48 h of life in extremely preterm infants. *Pediatr Res* 2013;74:314–20.
26 Osborn DA, Evans N, Kluckow M. Left ventricular contractility in extremely premature infants in the first day and response to inotropes. *Pediatr Res* 2007;61:335–40.
27 Lee A, Nestaas E, Liestøl K, *et al*. Tissue Doppler imaging in very preterm infants during the first 24 h of life: an observational study. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F64–F69.
28 Alvarez SV, Fortin-Pellerin E, Alhabdan M, *et al*. Strain rate in children and young piglets mirrors changes in contractility and demonstrates a force-frequency relationship. *J Am Soc Echocardiogr* 2017;30:797–806.
29 James AT, Corcoran JD, Breatnach CR, *et al*. Longitudinal assessment of left and right myocardial function in preterm infants using strain and strain rate imaging. *Neonatology* 2016;109:69–75.
30 Katrukha IA. Human cardiac troponin complex. Structure and functions. *Biochemistry* 2013;78:1447–65.
31 LeWinter MM, Granzier H. Cardiac titin: a multifunctional giant. *Circulation* 2010;121:2137–45.
32 Sulkin MS, Yang F, Holzem KM, *et al*. Nanoscale three-dimensional imaging of the human myocyte. *J Struct Biol* 2014;188:55–60.
33 Pinali C, Kitmitto A. Serial block face scanning electron microscopy for the study of cardiac muscle ultrastructure at nanoscale resolutions. *J Mol Cell Cardiol* 2014;76:1–11.
34 Mahony L. Calcium homeostasis and control of contractility in the developing heart. *Semin Perinatol* 1996;20:510–9.
35 Hatem SN, Sweeten T, Vetter V, *et al*. Evidence for presence of $^{Ca2+}$ channel-gated $^{Ca2+}$ stores in neonatal human atrial myocytes. *Am J Physiol* 1995;268:H1195–H1201.
36 Olivetti G, Anversa P, Loud AV. Morphometric study of early postnatal development in the left and right ventricular myocardium of the rat. II. Tissue composition, capillary growth, and sarcoplasmic alterations. *Circ Res* 1980;46:503–12.
37 Anderson PA. The heart and development. *Semin Perinatol* 1996;20:482–509.
38 Al-Naami GH. Torsion of young hearts: a speckle tracking study of normal infants, children, and adolescents. *Eur J Echocardiogr* 2010;11:853–62.
39 Lopaschuk GD, Spafford MA. Energy substrate utilization by isolated working hearts from newborn rabbits. *Am J Physiol* 1990;258(5 Pt 2):H1274–H1280.
40 Lopaschuk GD, Jaswal JS. Energy metabolic phenotype of the cardiomyocyte during development, differentiation, and postnatal maturation. *J Cardiovasc Pharmacol* 2010;56:130–40.
41 Vega RB, Kelly DP. Cardiac nuclear receptors: architects of mitochondrial structure and function. *J Clin Invest* 2017;127:1155–64.
42 Alaynick WA, Kondo RP, Xie W, *et al*. ERRgamma directs and maintains the transition to oxidative metabolism in the postnatal heart. *Cell Metab* 2007;6:13–24.
43 van der Lee KA, Vork MM, De Vries JE, *et al*. Long-chain fatty acid-induced changes in gene expression in neonatal cardiac myocytes. *J Lipid Res* 2000;41:41–7.
44 Bensley JG, Moore L, De Matteo R, *et al*. Impact of preterm birth on the developing myocardium of the neonate. *Pediatr Res* 2018;83:880–8.
45 Lewandowski AJ, Augustine D, Lamata P, *et al*. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation* 2013;127:197–206.
46 Dawes GS, Mott JC, Shelley HJ. The importance of cardiac glycogen for the maintenance of life in foetal lambs and newborn animals during anoxia. *J Physiol* 1959;146:516–38.
47 Shelley HJ. Carbohydrate reserves in the newborn infant. *Br Med J* 1964;1:273–5.
48 Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *Arch Dis Child* 1992;67:357–65.
49 Padbury J, Agata Y, Ludlow J, *et al*. Effect of fetal adrenalectomy on catecholamine release and physiologic adaptation at birth in sheep. *J Clin Invest* 1987;80:1096–103.
50 Padbury JF, Ludlow JK, Ervin MG, *et al*. Thresholds for physiological effects of plasma catecholamines in fetal sheep. *Am J Physiol* 1987;252:E530–E537.
51 Liggins GC. The role of cortisol in preparing the fetus for birth. *Reprod Fertil Dev* 1994;6:141–50.
52 Liggins GC. The role of the hypothalamic-pituitary-adrenal axis in preparing the fetus for birth. *Am J Obstet Gynecol* 2000;182:475–7.
53 Fletcher AJ, Forhead AJ, Fowden AL, *et al*. Effects of gestational age and cortisol treatment on ovine fetal heart function in a novel biventricular Langendorff preparation. *J Physiol* 2005;562(Pt 2):493–505.
54 Roberts D, Brown J, Medley N, *et al*. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017;3:CD004454.
55 Moïse AA, Wearden ME, Kozinetz CA, *et al*. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. *Pediatrics* 1995;95:845–50.
56 Demarini S, Dollberg S, Hoath SB, *et al*. Effects of antenatal corticosteroids on blood pressure in very low birth weight infants during the first 24 hours of life. *J Perinatol* 1999;19:419–25.
57 Koenen SV, Mecenas CA, Smith GS, *et al*. Effects of maternal betamethasone administration on fetal and maternal blood pressure and heart rate in the baboon at 0.7 of gestation. *Am J Obstet Gynecol* 2002;186:812–7.
58 Breall JA, Rudolph AM, Heymann MA. Role of thyroid hormone in postnatal circulatory and metabolic adjustments. *J Clin Invest* 1984;73:1418–24.
59 Crowther C, Hillier J, Haslam R, *et al*. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995;345:877–82.
60 Crowther CA, Hiller JE, Haslam RR, *et al*. Australian collaborative trial of antenatal thyrotropin-releasing hormone: adverse effects at 12-month follow-up. ACTOBAT Study Group. *Pediatrics* 1997;99:311–.
61 Kelishadi R, Poursafa P. A review on the genetic, environmental, and lifestyle aspects of the early-life origins of cardiovascular disease. *Curr Probl Pediatr Adolesc Health Care* 2014;44:54–72.
62 Lock MC, Botting KJ, Tellam RL, *et al*. Adverse intrauterine environment and cardiac miRNA Expression. *Int J Mol Sci* 2017;18:2628.
63 Fouzas S, Karatza AA, Davlouros PA, *et al*. Neonatal cardiac dysfunction in intrauterine growth restriction. *Pediatr Res* 2014;75:651–7.
64 Tare M, Bensley JG, Moss TJ, *et al*. Exposure to intrauterine inflammation leads to impaired function and altered structure in the preterm heart of fetal sheep. *Clin Sci* 2014;127:559–69.
65 de Waal K, Evans N. Hemodynamics in preterm infants with late-onset sepsis. *J Pediatr* 2010;156:918–22.
66 Paradisis M, Evans N, Kluckow M, *et al*. Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr* 2006;148:306–13.
67 Toyoshima K, Kawataki M, Ohyama M, *et al*. Tailor-made circulatory management based on the stress-velocity relationship in preterm infants. *J Formos Med Assoc* 2013;112:510–7.
68 Baud O, Maury L, Lebail F, *et al*. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet* 2016;387:1827–36.

69 Bhatt S, Alison BJ, Wallace EM, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol* 2013;591:2113–26.
70 Hooper SB, Binder-Heschl C, Polglase GR, *et al*. The timing of umbilical cord clamping at birth: physiological considerations. *Matern Health Neonatol Perinatol* 2016;2:4.
71 Polglase GR, Blank DA, Barton SK, *et al*. Physiologically based cord clamping stabilises cardiac output and reduces cerebrovascular injury in asphyxiated near-term lambs. *Arch Dis Child Fetal Neonatal Ed* 2017:fetalneonatal-2017-313657.
72 Fogarty M, Osborn DA, Askie L, *et al*. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018;218.
73 Ersdal HL, Linde J, Mduma E, *et al*. Neonatal outcome following cord clamping after onset of spontaneous respiration. *Pediatrics* 2014;134:265–72.
74 Katheria AC, Sorkhi SR, Hassen K, *et al*. Acceptability of bedside resuscitation with intact umbilical cord to clinicians and patients' families in the United States. *Front Pediatr* 2018;6.
75 Duley L, Dorling J, Pushpa-Rajah A, *et al*. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2018;103.