Section 1 General Principles

Chapter 1

The Rationale for Fetal Therapy

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Introduction

In 1982, a group of subspecialists in fetal medicine, pediatric surgery, pediatrics, radiology, genetics, and bioethics reported on a meeting that discussed the emerging field of 'fetal therapy' [1]. Their summary statement laid down the foundation and principles for the treatment of prenatally diagnosed congenital anomalies where the natural history of the disease can potentially be influenced by intervention before birth (Table 1.1). In principle, this document defines the criteria of candidate conditions for fetal therapy, the goals of fetal treatment, and the appropriate setting for where fetal therapy should be performed. Since this original publication there have been significant advances in prenatal diagnostic and prognostic assessments of the fetus, the scope of treatments, and the care settings where fetal therapy is offered that require consideration [2].

Table 1.1 Criteria for the advancement of fetal therapy: 1982

Topic	Viewpoint
Nature of the disorder	The disorder must be of a significant nature and should be a simple structural defect that interferes with organ development, whose alleviation might allow fetal development to proceed normally
Appropriateness criteria	The fetus should be a singleton without concomitant anomalies according to advanced ultrasonographic examination and amniocentesis for karyotype, α-feto protein, and cultures
Candidate diseases	Selection for treatment must be based on careful clinical evaluation and sound knowledge of the natural history of the fetal disease; intervention can be ethically justified only if there is reasonable probability of benefit
Goals of treatment	The family should be fully counseled about risks and benefits and should agree to treatment, including long-term follow-up to determine efficacy
Maternal safety and autonomy	*Implied but not stated:* maternal risks should be minor and acceptable to mother and family
Center infrastructure	There should be access to a level III high-risk obstetric unit and bioethical and psychosocial counseling
Checks and balances	A multidisciplinary team, including a perinatal obstetrician experienced in fetal diagnosis and intrauterine transfusion, an ultrasonographer experienced in the diagnosis of fetal anomalies, and a pediatric surgeon and neonatologist who will manage the infant after birth, should concur on the plan for innovative treatment and obtain approval of an institutional review board
Reporting requirements	All case material should be reported, regardless of outcome, to a fetal treatment registry or in the medical literature (or both)

Prenatal Diagnosis and Prognostic Assessment – Defining Candidate Conditions for Fetal Treatment

Fetal therapy targets specific conditions that carry significant risk for the fetus where prenatal intervention can be anticipated to significantly improve outcome. In order to be certain that a disease meets these fundamental criteria, a precise prenatal diagnosis and prognostic assessment is required. The principle diagnostic tools include a combination of ultrasound modalities, magnetic resonance imaging (MRI), or specialized computerized tomography (CT) imaging [3]. Following the formulation of a primary and differential diagnosis a major determining factor for eligibility for fetal treatment is the presence of any underlying untreatable conditions that affect outcome. Major advances have been made in genetic testing since the inception of fetal therapy. The range of prenatal genetic studies now ranges from traditional karyotyping to microarray analysis, targeted single gene testing, and exome sequencing [4, 5]. Another significant advance since the inception of fetal therapy is the transition of infection testing to polymerase chain reaction (PCR) for viral particles or viral culture from amniotic fluid [6, 7]. This contemporary approach to prenatal genetic testing and infection testing increases the diagnostic yield for significant underlying genetic or other abnormalities, and can now more deliberately identify fetuses that may benefit from prenatal

interventions and exclude those who do not. The importance of this approach is illustrated by the outcomes of shunting for fetal hydrocephaly, which was abandoned in an era where the exclusion of diseases with no anticipated benefit was not uniformly applied. Now that a group of fetuses with isolated aqueductal stenosis is more likely to be identified, fetal therapy for this specific subset of patients may need to be re-explored [8].

Concurrently with rendering a precise diagnosis of the fetal condition, assessing the severity of the fetal condition is part of identifying suitable candidates for fetal therapy. It is important to recognize that despite the prominent role of ultrasound in evaluating physical abnormalities of the fetus, MRI is complementary in many conditions, including spina bifida and congenital diaphragmatic hernia, in delineating the abnormality as well as its prognosis [9, 10]. Since most fetal conditions that are currently offered fetal therapy are considered severe, most prognostic assessments measure the mortality or irreversible damage that is associated with a particular condition rather than morbidity. To render a prognosis, several specific parameters have been described that offer disease-specific quantification of severity. These include the traditional [11] and observed to expected lung-to-head ratio [12] for congenital diaphragmatic hernia and the cyst-volume ratio [13] for cystic adenomatoid malformations of the lung. In addition to individual measurements, combinations of several parameters in scoring or staging systems have been described to grade the severity of fetal cardiovascular disease [14, 15], hydrops [16], or twin-twin transfusion syndrome (TTTS) [17, 18, 19]. The utilization of standardized prenatal prognostic markers is of critical importance from several perspectives. The relationship with outcome forms the basis of the risk-benefit assessment and the selection of appropriate candidates for fetal therapy. Uniform assessment of conditions allows the study of natural disease evolution and a more consistent case selection facilitates a more robust evaluation of the impact of fetal therapies. The ability to re-evaluate defining key prognostic indicators also allows appropriately targeted monitoring for resolution following fetal treatment.

The evaluation of any prenatal abnormality should ideally reach the highest level of certainty about the condition, any underlying contributors to lifelong health impacts, and the severity of the condition in terms of its anticipated prenatal and postnatal outcome if left untreated. Only when this level of information is available can the risks of the natural disease be weighed against the risks of the therapy and parents be provided with the opportunity to select the appropriate scope of treatment. At any point in these decisions it is the obligation of the fetal medicine provider to put safeguards in place to protect the pregnant women from undue risk. For conditions not meeting intervention criteria longitudinal observations at the appropriate surveillance intervals are often required in order to ensure that deterioration to a degree that meets treatment criteria is detected. This is often required for complicated monochorionic multiple gestation [20], or fetal anemia due to red cell alloimmunization [21].

The Scope and Goals of Fetal Therapy

Fetal therapy may involve medical and surgical treatments that are performed before separation of the fetus from the placenta during birth. Within this scope, fetal therapy can be divided into medical or surgical approaches that aim to achieve either a complete prenatal resolution, alleviate severe pediatric developmental or functional deficiencies, or optimize the fetal transition to extrauterine life. In the latter two instances, treatment requires completion after birth and therefore relies on an appropriate pediatric subspecialty setting (Figure 1.1).

Fetal interventions carry different levels of complexity both in terms of required operator training and experience and the systems requirement to safely administer the treatment. At the most basic level, ultrasound-guided needle procedures have been adapted from the sampling of amniotic fluid or chorion villus tissue. Fetal therapy techniques based on this approach include fetal blood sampling, intrauterine transfusions [22], shunt placements for renal or thoracic abnormalities [23], balloon valvuloplasty for cardiac lesions [24], and interstitial coagulation techniques utilizing laser, radiofrequency ablation or microwave technology [25, 26]. A greater level of complexity exists for diagnostic or operative fetoscopic procedures. While the insertion of the instrumentation relies on ultrasound guidance, the instrumentation required is more complex and most optimally used in an operative room setting. Fetoscopic techniques now encompass laser ablation of communicating vessels in TTTS [27], umbilical cord occlusion [28], tracheal balloon occlusion and reversal [29], amniotic band release [30], laser ablation for lower urinary tract obstruction [31], and more complex surgical procedures such as myelomeningocele (MMC) repair [32].

The highest level of complexity involves open fetal surgery that is performed through a hysterotomy through the muscular portion of the myometrium or the *ex utero* intrapartum treatment (EXIT), which is a specialized delivery technique that enables securing of the fetal airway on a placental bypass. These types of procedures require a specific approach guided by the anatomy of the fetus and have high system requirements for monitoring of maternal and fetal well-being at the time of the procedure and afterwards, as well as the ability to immediately respond to complications such as obstetric hemorrhage or maternal cardiopulmonary collapse [33]. Open fetal surgeries are most frequently performed for MMC repair [34] and less often for resection of lung masses or teratomas [35]. The EXIT delivery technique is specifically intended for the management of anomalies that compromise the newborn's airway at birth [36, 37, 38].

These treatment techniques evolved following the consideration of the fetal, neonatal and lifelong risks of the untreated condition as well as the potential fetal benefits of treatment and the risks to the mother and the fetus. With regards to the fetal benefits, treatments may achieve prenatal cure or alleviation of damage. Examples for approaches that aim to achieve a prenatal cure include fetal blood transfusions for anemia [22] and

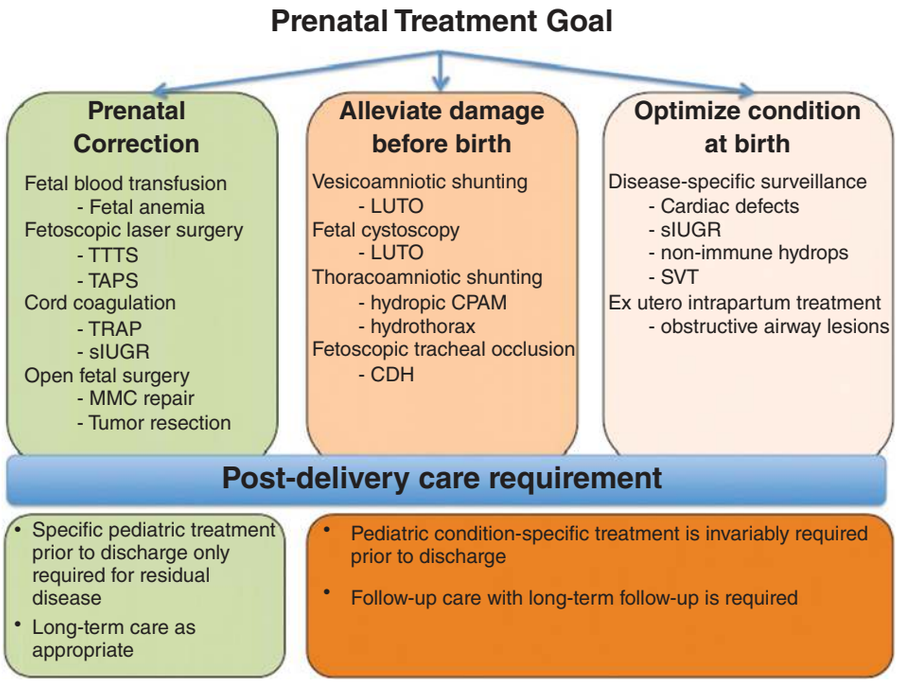

Figure 1.1 Treatment goals in fetal therapy. The schematic represents the prenatal treatment goals for various fetal interventions and their associated postnatal care needs. TTTS, twin-twin transfusion syndrome; TAPS, twin anemia polycythemia sequence; TRAP, twin reversed arterial perfusion; sIUGR, selective intrauterine growth restriction; MMC, myelomeningocele; LUTO, lower urinary tract obstruction; CPAM, cystic pulmonary airway malformation; CDH, congenital diaphragmatic hernia; SVT, supraventricular tachycardia.

fetoscopic laser dichorionization of the placenta in TTTS [39]. In addition to the appropriate care setting, the ability to achieve the intended outcome with these low- to medium-complexity therapies relies on operator experience and ongoing caseload [40–44]. Because the mortality of the underlying conditions in the absence of treatment is high, thresholds for the establishment of treatment centers are lower than for more complex treatments. A treatment that is also aimed at prenatal correction is fetal MMC repair. However, irrespective of whether an open or fetoscopic approach is chosen the multidisciplinary nature of the treatment team requires an appropriate resource setting to achieve the desired outcomee [45]. Since fetal MMC is not a lethal condition and treatment is also complex because of the maternal care requirements, prenatal repair can only be offered in an appropriately resourced setting. In fact it is the significant maternal risk with open fetal MMC repair that is one of the driving forces to transition to a viable fetoscopic technique that maintains the fetal benefits [46].

An example for a treatment that does not achieve prenatal cure, but rather alleviates prenatal damage until definitive postnatal repair can occur, is fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia (CDH) [12]. After successful FETO, delivery of the neonate at a center with expertise in the management of CDH is required to complete the treatment. It is important to recognize that caseload and operator experience improve outcomes in both the prenatal and postnatal components of FETO followed by post-delivery surgical CDH management [47, 48]. The ideal setting for a FETO program with an experienced fetal team would therefore be at a facility with a coexisting high-volume experienced pediatric CDH program [49]. The importance of the appropriate pediatric care setting at delivery is particularly evident for anomalies such as cardiac defects, where the primary contribution of the fetal medicine specialist is to optimize delivery circumstances to facilitate post-delivery surgical repair [50]. Accordingly, as the management goal of fetal therapies shifts from prenatal cure to alleviation of damage the emphasis on delivery in an appropriate pediatric care setting increases. With the exception of fetal therapies carried out prior to viability the need for a high-level neonatal intensive care unit (NICU) is universal for all fetal therapy centers [1, 2, 45].

Risk-Benefit Assessment for Fetal Therapy

Fundamental to the endeavor of fetal treatment is the construction of a risk-benefit assessment that considers potential benefits to the fetus, newborn and mother balanced against the risks to these parties. Since all fetal therapy, medical and surgical, must pass through the mother it cannot be performed without her informed consent, given with the necessary safeguards in place and full consideration of maternal and fetal risks. Assuming an accurate prenatal diagnosis, this assessment

rests on a reasonable degree of certainty about the natural history of the condition, the likelihood of treatment success, and the preparedness for the potential of unintended consequences. Fetal therapy is unique in that the potential complications for a given procedure may include the mother or fetus. For surgical interventions the potential for unintended consequences depends on the complexity of the procedures as well as operator experience and caseload. The correct risk-benefit estimate therefore relies on all of these factors.

The neonatal risks relate to the likelihood of premature delivery and the additional outcome impact of the underlying condition, and are partly mitigated when delivery occurs at a facility with the appropriate level of neonatal care [1]. For conditions that require surgical correction after birth risks may arise from the combination of residual morbidity after fetal therapy and superimposed neonatal complications. As prematurity is a risk factor associated with many fetal treatments, accurate representation of institution-specific, disease-specific outcomes of centers that perform fetal therapy is most pertinent to gauge the overall impact on outcome [1, 2, 45]. Over time advances in any of the subspecialties involved in the care of the fetal patient potentially alter outcome, and therefore ongoing reappraisal of the risk-benefit ratio is required whenever such developments occur. Examples include the transition from open fetal surgery to maternal steroid use as a primary treatment of congenital pulmonary airway malformations [51], or reappraisal of the relative safety of CO_2 insufflation for operative fetoscopy [52]. Once a risk-benefit assessment for a fetal treatment has been completed administration in the appropriate care setting is essential to mitigate some of the adverse effects.

Care Settings for Fetal Therapy

Since all fetal therapies pass through the mother the need to establish the most appropriate maternal care setting is universal for all fetal therapies. The resources required to ensure maternal safety may range from obstetric care facilities, including obstetric anesthesia, all the way to medical and intensive care facilities [38]. These requirements depend on the complexity of the fetal treatments performed. Ultrasound-guided procedures such as amniocentesis and chorion villous sampling have a negligible miscarriage rate and overall procedure-related risks ranging from 0.4% to 1% in high-risk populations [53, 54]. Fetal blood sampling and transfusion require a higher level of operator skill and carry a 5–10% risk of fetal bradycardia and a pregnancy loss rate of up to 25% in complex fetal conditions [55, 56, 57]. Fetal shunt procedures and fetoscopic laser ablation for TTTS involve larger diameter uterine instrumentation and accordingly can carry an up to 40% risk of obstetric complications, including preterm premature rupture of membranes (PPROM), preterm labor, and preterm birth [58, 59]. If intervention for fetal status is appropriate as part of the management plan or significant obstetric risks are recognized complications such fetal treatments should be performed in the vicinity of a Labor and Delivery unit to ensure that obstetric management, including delivery if appropriate, can be achieved in a timely fashion. Procedures that are performed at viability, carry significant obstetric risks, or require multidisciplinary effort may benefit from a dedicated intervention suite near Labor and Delivery. Fetal cardiac interventions have fetal mortality rates of 10–30% and may require additional treatment of complications such as bradycardia and hemopericardium in 27–52% of procedures [60, 61]. FETO with subsequent balloon removal is associated with a 47% rate of PPROM and the need for emergency balloon removal in over 50% of cases. Inability to remove the balloon prior to birth in the latter setting may lead to neonatal death in almost 5% of patients [29]. Hybrid or open fetal surgeries, including fetoscopic spina bifida repair [62] and EXIT, naturally require an appropriately staffed operation room setting [6, 63]. The significant risk for healing complications of the uterotomy with partial or complete dehiscence in 2.3% of patients, and the need for blood transfusion at delivery in 8%, emphasize the importance of follow-up dedicated obstetric care [34]. As integration of subspecialties is one of the core achievements that drives a fetal treatment center, the complete integration of the required level of maternal care is necessary. For the highest risk procedures this requires the in-house availability of an appropriate level of maternal care services, including intensive care and adult medical specialty availability.

As all neonates that are delivered after fetal therapy require post-delivery assessment, stabilization and potentially further management, a high-level NICU is recommended for all fetal therapy centers offering treatment after viability [1, 2, 45]. This level of care is recommended since most conditions targeted by fetal therapy have neonatal care requirements that reach beyond prematurity-related complications, and management of anomalies and associated problems is required [64, 65]. Specifically for neonates with congenital abnormalities such as CDH, MMC or cardiac defects, the in-house presence of the appropriate pediatric surgical specialties is highly desirable. In the US the 'Task Force for Children's Surgical Care' defines the highest level of center by its ability to manage congenital anomalies in an in- and outpatient setting [66]. The improved outcome for neonates cared for in such centers has been documented for several conditions, including CDH and MMC, and is in part attributable to infrastructure, higher surgical volumes and an enhanced ability to triage, recognize and manage complications compared with lower volume centers [67–69].

Requirements for a Fetal Therapy Center

A Fetal Therapy Center is ethically obliged to consider both maternal and fetal well-being and complications of *any* fetal intervention that may be offered. In order to provide safe care the appropriate infrastructure, dedicated institutional support and oversight are required. The level of infrastructure and support are dictated by the level of the maternal, fetal and neonatal care needs that arise as a consequence of the fetal

intervention. Once the appropriate multidisciplinary care context has been established the monitoring and reporting of outcomes allows for effective oversight monitoring at the institutional level. It has been considered essential for centers that perform invasive fetal procedures to report their maternal, fetal, and newborn outcomes as transparently as possible to allow for ongoing scientific scrutiny [1, 2, 45]. This can be in the form of institutional, national, regional, or international registries or trials. Examples include treatment registries for FETO for severe CDH [29] or fetal cardiac interventions [24] as well as randomized trials for laser therapy for TTTS [27, 70] and open fetal MMC repair [34]. Particularly for procedures that are still considered as innovative or under research a multidisciplinary institutional oversight committee is important, and ideally includes individuals not directly involved in the clinical care of patients. Such committees may sometimes also serve as reviewing bodies for the purposes of institutional or ethical review board submissions.

An important obligation of a Fetal Therapy Center is also to provide education for physicians and other healthcare personnel to train the next generation of fetal therapists. While there are currently no formal training programs for fetal therapy it is only a matter of time before a curriculum will be formalized and an appropriate training model developed in which junior faculty are gradually allowed to develop the necessary skill set to operate independently.

Conclusion

As both diagnostic and surgical techniques continue to evolve so does the role of fetal therapy in conditions that can be prenatally diagnosed. With advances in fetal treatment techniques and the management of maternal risks the focus is likely to shift from just enabling survival to improving quality of life (e.g. fetal MMC repair). The formalization of appropriate care settings and potentially levels of care is likely to not only ensure the safety of the mother and fetus but also expand the rationale for fetal therapy in the future.

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Section 1 General Principles

Chapter 2

A Fetal Origin of Adult Disease

Mark Hanson and Lucy Green

Introduction

There is a worldwide epidemic of non-communicable diseases (NCDs), including cardiovascular disease (CVD), type 2 diabetes, chronic lung disease, and some forms of cancer; predisposition to these is linked to obesity. This is despite efforts by individuals to modify their diet and lifestyle, and government and global programs aimed at promoting healthy eating or increased physical activity. Some initiatives have begun to target childhood eating and activity. But a strong and international body of scientific and epidemiological data suggests that health interventions should be focused on a much earlier period of development: pregnancy. Expectant couples are often focused on the immediate result of their pregnancy – a viable baby. It may come as a surprise to many of them to hear that the finer details of building a baby are in fact the foundation of lifelong health.

A number of potentially serious clinical conditions originate during fetal life, and these include neurological handicap, premature birth, fetal growth restriction (FGR), and pulmonary hypoplasia. These are often viewed as 'pathophysiological' conditions where normal development (or physiology) has been disrupted by a challenge *in utero* that has had immediate and longer-term damaging effects. But, current concepts suggest that the developing organism may respond to cues (e.g. nutrient supply, maternal stress) from the environment and that its development is 'channelled' (rather than disrupted) to give a phenotype optimized for the subsequent postnatal environment. However there may be limits to the responses that the developing organism (e.g. fetus) can make or the postnatal environment may not turn out to be what was expected. Either or both of these circumstances may lead to an increased disease risk in adulthood [1]. In this chapter we will explore human and animal studies that investigate how cues from the environment (e.g. nutrient supply) before and during gestation invoke one or several fetal adaptive strategies involving the timing of birth, fetal growth, metabolism, and cardiovascular control. These strategies are not simply linked to immediate survival but may put the offspring at a disadvantage in terms of health in later life.

An Early Origin for the Epidemic of Adult Non-communicable Disease

The Problem

CVD affects more than 40% of adults in the UK. Despite the fall in death from coronary heart disease (CHD) in the second half of the twentieth century, the combination of unhealthy lifestyle in the young and an ageing population is expected to increase the number of people suffering CVD such as heart failure. Globally, it is estimated that 17.9 million people died from CVD in 2016 and, without intervention, this number is projected to rise [2]. The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014 [3]. Obesity is a component of metabolic syndrome and is considered to be an intermediate risk factor for CVD, even in the young. The speed with which the incidence of these diseases has escalated has been attributed to changing lifestyles, especially the consumption of high glycemic index foods with a high fat and salt content and a sedentary lifestyle. However, not all individuals have the same risk of developing pathological conditions, even in the same environment. In the last 30 years it has emerged that the developmental environment (periconceptionally through early postnatal life) influences an individual's response to their adult environment and lifestyle, hence determining in part their risk of disease.

The DOHaD Concept

Epidemiological studies show that small size at birth and during infancy is associated with a greater risk of CHD, hypertension and stroke in later life [4]. Importantly, the degree of these changes, and hence disease risk, is graded across the normal range of size at birth, i.e. it is not just a consequence of FGR. The Developmental Origins of Health and Disease (DOHaD) concept suggested that the low birth weight-disease risk association may underestimate the true influence of the early environment effect. Birth size is one measure of fetal environment and DOHaD might be better viewed as a later consequence of a normal developmental response to environmental cues. The risk of adult CHD is particularly increased if small size at birth and during infancy is followed by rapid childhood weight gain [5]. Recent proposals suggest that the developing organism responds to its environment to develop a phenotype optimal for survival to reproduce in the postnatal environment in which it predicts that it will live, and that a mismatch between the *in utero* and childhood nutritional environments increases risk of CVD [1, 6]. The degree of mismatch will be increased by an unhealthy lifestyle (unbalanced diet, reduced physical activity, smoking, and excessive alcohol consumption) and this is of particular concern in light

of the rising incidence of childhood obesity and the links between obesity and CVD.

Human and Animal Evidence

There is potential for the embryo and fetus to be exposed to a range of such cues, including environmental toxins, 'maternal constraint' (from e.g. body composition, stature, nutrition, age, and parity), maternal stress, umbilical-placental complications (including resultant hypoxia/asphyxia), and maternal diseases. Environmental factors such as maternal nutrition can channel development (i.e. influence developmental plasticity). The adaptations that are made might be of immediate adaptive value and help survival, or could confer little or no immediate benefit but nonetheless be predictive of the postnatal environment. If the postnatal environment is not as predicted this may increase the risk of disease [1]. But studies attempting to investigate DOHaD should distinguish these sort of adaptive responses from pathophysiological effects of the environment (disrupting development, e.g. toxins or umbilical-placental complications) with no obvious adaptive value at any point in the life course. This is important since these simply disrupt the normal pattern of development and do not necessarily lead to an increased risk of disease.

There are a few key human cohorts in which the DOHaD concept has been investigated [7]. In addition a number of experimental animal models have been developed in a range of species. Ascertaining the risk of disease is usually not possible in animal models, but making sure that the challenges are of physiological rather than pathophysiological magnitude and of a type relevant to DOHaD remains crucial to progress in this field. In this chapter, we focus primarily on maternal constraint-type cues for which a cohesive and persuasive body of evidence exists.

Many women in the UK consume unbalanced or 'imprudent' diets, including during pregnancy. The influence of a poor intrauterine environment on later CVD was highlighted in the Dutch winter famine cohort [8]. Maternal body composition and metabolism provide the backdrop against which more acute changes in diet act and influence the compartmentalization of nutrients between the mother, placenta, and fetus. In England 15.6% of women are obese (body mass index (BMI) $\geq$30 kg/m^2) at the start of pregnancy and a smaller proportion (2.88%) are underweight (BMI $<$ 18.5 kg/m^2) [9]. In the Southampton Women's Survey by the Institute of Medicine Standards (2009), excessive (49%) and inadequate (21%) weight gain in pregnancy are prevalent [10]. Both extremes of maternal weight profile are thought to pose a significant threat to maternal and fetal/neonatal well-being and may have substantial ramifications for cardiovascular health in later life. Excessive weight gain is linked to offspring obesity [10, 11] and to higher systolic blood pressure into early adulthood (21 years [12]). Human data suggest that whilst gestational weight gain is associated with adverse cardiovascular risk factors at 9 years, pre-pregnancy weight has a greater overall impact [11]. Slimness in mothers is linked to CHD and raised blood pressure, while high maternal weight/adiposity is linked to CHD [13, 14]. In this regard, new guidelines on pregnancy weight management were issued in 2010 [9] and their implementation may serve to break the cycle of obesity and reduce the incidence of CVD.

Numerous studies in animal models (rodents, guinea pigs, sheep, and non-human primates) corroborate the idea that maternal diet during gestation and breastfeeding are very important in determining adult propensity to obesity, cardiovascular and renal dysfunction [15–23], and left ventricular hypertrophy [23, 24], in ways that mimic predisposition to CVD with increasing age. The phenotypic effects of an altered early environment include altered adult growth, glucose intolerance and insulin resistance [15, 25, 26] and changes in sympathoadrenal function and hypothalamic-pituitary-adrenal (HPA) axis responses [20, 24, 27, 28], and these may constitute part of the mechanism by which cardiovascular control is affected. There is emerging evidence that the nature of the response is sex dependent [15, 23]. It is striking that, without further dietary challenges in the F1 pregnancy, features of the cardiovascular dysfunction in adult guinea pig offspring following F0 maternal diet challenge can persist into the F2 generation [24, 29]. In sheep, maternal obesity abolishes the normal leptin spike in their neonatal offspring (important for development of hypothalamic appetite circuitry) and this effect is also observed in their granddaughters [30]. Importantly, maternal dietary restriction even before conception can induce effects on vascular function in adult offspring [31], which emphasizes the importance of life-long good nutrition. Maternal body composition can be reliably manipulated through diet in sheep and it can induce long-term adverse metabolic effects and skeletal muscle structural alterations, along with cardiovascular and renal effects, in offspring [32, 33]. This underlines the concept that these effects are part of a coordinated strategy affecting development of a range of tissues, as opposed to a pathological effect.

A comparatively small number of animal studies have tested directly the concept that a mismatch between the *in utero* and childhood nutritional environments increases risk of CVD. In sheep, cardiovascular dysfunction in offspring exposed to either prenatal or postnatal undernutrition alone was not seen when pre- and post-weaning environments were similar (Figure 2.1) [23]. Also, undernutrition in early-mid gestation was associated with more renal lipid deposition in young adult obese sheep [34]. Late gestation undernutrition in sheep increased the neonatal appetite for fat, changed the pattern of fat deposition [35], and predisposed adult sheep offspring to hypercholesterolemia in an obesogenic environment [36]. In rats, dietary manipulation to minimize the mismatch between pre- and post-weaning nutrition minimizes endothelial dysfunction and the disruption of mechanisms regulating appetite and energy expenditure in offspring [17, 37]. In rats, a greater pre- and postnatal dietary mismatch worsened liver function [38] and decreased life span [39]. In pigs, the coronary atherosclerotic effects of a high-fat diet were prevented by prior feeding of a similar diet to the pregnant mother [40].

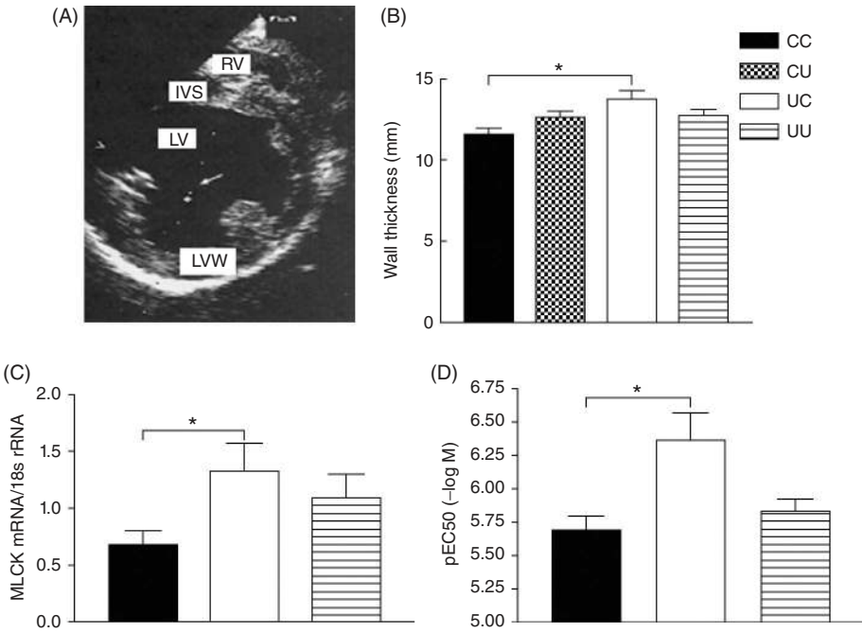

Figure 2.1 Altered cardiac morphology and coronary function in male adult sheep are absent when the mismatch of pre- and postnatal nutrition is minimized. Sheep were fed a control diet throughout pre- and postnatal life (CC), or they were exposed to moderate undernutrition either during early gestation (1–31 days' gestation, where term is 147 days; UC), during early postnatal life (12–25 weeks; CU), or both (UU). (A) An echocardiograph showing the right ventricle (RV), interventricular septum (IVS), left ventricle (LV), and left ventricular wall (LVW) of the ovine heart. (B) Thickness of the intraventricular septum; CC (n = 14), CU (n = 10), UC (n = 14), and UU (n = 14). Also shown are myosin light chain kinase (MLCK) relative mRNA expression in the coronary artery of male sheep as measured by real-time PCR [CC (n = 7), UC (n = 7), and UU (n = 4)] (C) and vascular response to acetylcholine in the coronary artery [CC (n = 10), UC (n = 9), and UU (n = 7)] (D). *, P <0.05, significantly different from CC (by one-way ANOVA). Values are mean ± SEM. Insufficient PCR and myography data were obtained from CU animals. Reproduced, with permission, from Cleal et al. [23]

The Fetus Responds to Its Environment

Adaptive or Disruptive?

Early detection of individuals who are at risk of disease is a cornerstone of predictive and personalized medicine. Children can show early signs of CVD, including atherosclerosis, and lower birth weight is associated with impaired endothelial function [41] and altered cardiac structure [42] in 8–9 year olds. In sheep, elevated blood pressure and HPA axis responsiveness were observed in 3-month-old offspring of ewes fed 85% total requirements for the first half of gestation [20]. However the fetus offers the potential for detection of an individual's risk of disease even earlier in life, and may provide future early routes for intervention. But, rather than being viewed as the start of a pathological process, current thinking suggests that some of these fetal changes might be of immediate adaptive value (prioritize and conserve energy use) and optimize a phenotype for better chance of survival over the life course [1]. Such prenatal physiological adaptive responses may operate over a broader range of normal development (Figure 2.2).

The cardiovascular system is a key part of a coordinated adaptive response, designed to get nutrients where they are really needed. Any redistribution of the cardiovascular resources might preserve the growth of some organs at the expense of others. There are also likely to be limits to the extent that the fetus can cope through cardiovascular or growth adaptations (stretched to the limit by duration or severity of challenge), at which point the cue from the maternal environment becomes 'disruptive' [1], or if the adaptations that it has made do not suit the postnatal environment this may lead to impaired function after birth and longer-term health problems. An alternative strategy would be for the fetus to be born early, and this may be a good course of action when the *in utero* environment is so hostile that life outside the womb confers a greater chance of survival. The effect of maternal adiposity and gestational weight gain on fetal blood pressure, blood flow and tissue perfusion is less well investigated.

These sorts of environmental challenges from modern western diets are relatively recent problems and ones that humans are unlikely to have evolved protective mechanisms against [1]. Unlike undernutrition, they are thought to disrupt development (nonadaptive fetal responses) in a way that might prove to be of some immediate benefit to the fetus but could lead to profound defects or perinatal death. In this section we summarize some of the evidence of fetal phenotypic changes (fetal CV homeostasis, organ perfusion, organ growth and function) in response to a suboptimal intrauterine environment (with occasional reference to overfeeding or obesity studies) and it will be obvious that with ethical restrictions on human fetal investigations, animal models have been crucial in advancing this area of research.

Bench to Bedside, and Back Again

Imaging of the fetus by ultrasound is now commonplace in developed countries as an obstetric tool to assess fetal growth and identify structural abnormalities of the fetus and blood flow anomalies through the major fetal organs, the umbilical cord, and uteroplacental circulation. Major technological advances have extended the application of this tool to the assessment of fetal movement and blood flow. Power Doppler is most commonly used to evaluate blood flow through vessels within solid organs, while color and spectral Doppler both reveal the direction of blood flow. This information, combined