Chapter 12
Physical and Mental Health in FASD

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Introduction

In addition to the well-documented effects on the developing brain, exposure to prenatal alcohol is known to be associated with a range of co-morbid conditions [1]. Some of these may be evident very early in life, including the facial dysmorphology and heart defects, and can be attributed to the teratogenic effects of alcohol at particular stages of development. However, more recently it has become apparent that prenatal alcohol exposure may be associated with a large range of chronic health conditions that are not readily apparent in childhood but emerge during adolescence and adult life. A recent community survey developed by three adults with FASD examined the health of more than 500 adults with FASD. They concluded that FASD was a "whole-body diagnosis" and that: "…*individuals with FASD have higher frequencies of a wide range of health conditions and develop these earlier than individuals in the general population"* [2]. It is particularly important to establish the links between prenatal alcohol and adult health to allow early intervention measures to be implemented that may prevent or at least delay the onset of secondary health conditions.

The concept that early life exposures may contribute to chronic disease in later life has been extensively examined through studies testing the Developmental

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O. A. Abdul-Rahman, C. L. M. Petrenko (eds.), *Fetal Alcohol Spectrum Disorders*,
https://doi.org/10.1007/978-3-031-32386-7_12

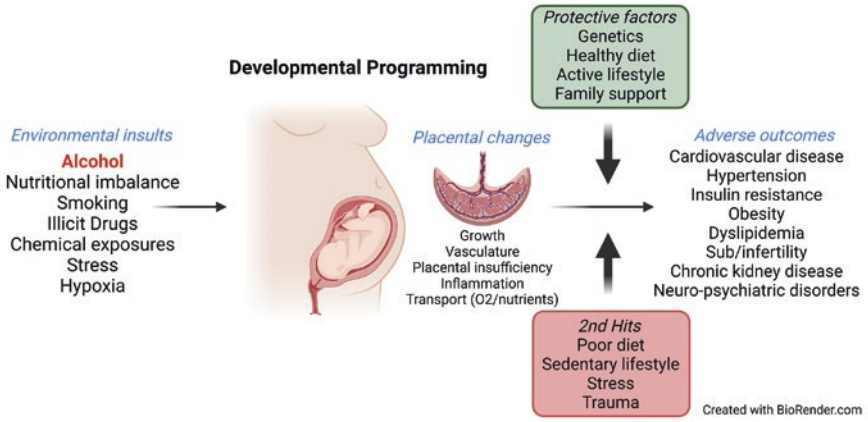

Fig. 12.1 The Developmental Origins of Health and Disease (DOHaD) hypothesis through which prenatal factors influence long-term health

Origins of Health and Disease (DOHaD) hypothesis (for review see Gluckman et al. [3]; Fig. 12.1). This hypothesis put forward by Barker and colleagues in the late 1980s suggests that exposures that occur in early life, particularly during fetal development in the womb, may contribute to altered development of organs and hormonal systems. This may result in babies being born of a low birth weight, with individuals then at increased risk of developing conditions such as high blood pressure, diabetes, cardiovascular disease, and osteoporosis. These alterations in normal development are not considered teratogenic effects (that is, causing birth defects or congenital abnormalities) but rather more subtle changes in growth and homeostatic mechanisms that are likely not immediately obvious at birth.

This chapter will focus on the evidence that prenatal alcohol contributes to physical and mental health outcomes as well as behavioral changes in children and adults. Given in some areas there are relatively few studies examining these outcomes in cohorts, we shall draw on findings from animal models and integrate these with the clinical data. The use of animal models can give insights in the timing and doses of alcohol that may impact health in later life and additionally provide information on the mechanisms involved and potential treatments that may be beneficial. We will also consider the supports and barriers in the health system to obtaining care for the physical and the mental health needs of people affected by prenatal alcohol exposure and finally, the areas where future research could provide beneficial strategies for prevention and intervention.

Early Life Links to Physical and Mental Health Outcomes: The DOHaD Hypothesis

Overview of the DOHaD Hypothesis

The DOHaD hypothesis has predominantly examined how maternal nutrition impacts fetal growth and contributes to long-term health and risk of chronic disease. Focus for many years was on inadequate maternal intake of calories or deficiencies in specific dietary components (e.g., iron, vitamin A). More recently, studies have also examined the impacts of excess dietary intake of calories that contribute to maternal obesity and/or diabetes during pregnancy. Another major factor investigated is the impact of inadequate oxygen supply to the fetus (fetal hypoxia) that can occur due to a poorly functioning placenta, maternal smoking, high altitude or maternal health conditions such as asthma. Finally, the impact of maternal stress, mediated through increased concentrations of hormones such as cortisol, has been examined. All of these exposures during pregnancy have been linked to an increased risk of chronic health conditions in adulthood [3]. The strongest evidence supporting this hypothesis relates to the development of metabolic dysfunction, in particular insulin resistance and type II diabetes, and cardiovascular disease, including coronary heart disease and stroke. It must be noted that outcomes are in part dependent upon the timing and severity of the exposure as well as the sex of the fetus. This "developmentally programmed" predisposition for chronic health conditions may be further exacerbated by factors after birth including poor nutrition (e.g., diets high in sugar, fats, and salt), lack of exercise, stress, and adverse childhood experiences.

The mechanisms contributing to developmental programming include changes in placental function (discussed further below, see Fig. 12.1), altered structural development of organs (leading to suboptimal organ function) and changes in hormone production and regulation. Epigenetic changes (such as DNA methylation or histone modifications) may also be involved. Many organs and hormonal systems have been shown to be affected, with organs such as the kidney shown to be particularly susceptible [4]. The hypothalamic–pituitary–adrenal (HPA) axis has also been shown to be especially susceptible to programming by prenatal events. Given the well-established associations between HPA function and neuropsychiatric disorders as well as metabolic/cardiac function, programming of the fetal HPA may be a common pathway linking early-life events to adult-onset chronic diseases.

Role of the Placenta

An important component of the DOHaD hypothesis is the role played by the placenta. As the placenta supplies all the nutrients and oxygen required by the fetus, maternal conditions that result in poor placental development (placental insufficiency) can contribute to fetal growth restriction. In relation to alcohol, there is evidence that prenatal alcohol exposure during pregnancy can contribute to increased rates of miscarriage and stillbirth, probably via mechanisms involving poor implantation and/or placental function. A recent systematic review and meta-analyses demonstrated that prenatal alcohol consumption caused a reduction in placental weight and increased the likelihood of placental abruption [5]. Detailed analysis of the placenta showed prenatal alcohol consumption caused structural changes in the placenta including alterations in blood vessel development and changes in expression of genes regulating processes such as placental growth and development. Together, these results suggest that in addition to the direct effects of alcohol on the fetus, prenatal alcohol may contribute to reduced placental function and therefore, may cause a degree of placental insufficiency. Recent studies using animal models support this concept. For example, in rats that consumed alcohol around the time of conception, placental development was impaired by the middle of pregnancy and by late pregnancy, expression of genes that regulate glucose and nutrient transfer was altered, likely contributing to the fetal growth restriction [6, 7].

Considerations of Prenatal Alcohol Exposure (PAE) in the Context of DOHaD

PAE has well-documented teratogenic effects, but consideration of the role PAE plays in the context of the DOHaD hypothesis has not historically been considered. More recently, the relationship between prenatal alcohol exposure and the risk of chronic disease has become particularly relevant since more widespread understanding and screening/assessment for FASD over the last 20–30 years has led to increased childhood diagnosis. Many of these individuals first diagnosed in the 1980s and 1990s are now entering their 30–40s and are reporting a range of health problems [2]. In many cases, these health issues are not considered related to the FASD diagnosis or are thought to be side-effects of other medications that an individual with FASD is taking. This can result in concerns being ignored or downplayed by health professionals and may lead to under-reporting of secondary health conditions experienced by people living with FASD.

A major challenge in understanding the contribution of PAE to the development of chronic disease in adulthood is in delineating the effects of the PAE from other exposures during pregnancy (such as maternal smoking/drug use and nutrition) as well as current lifestyle factors (e.g., drug and alcohol use, diet, and exercise). The prevalence of FASD varies with maternal poverty, nutritional deficiencies as well as

socio-historical factors, such as the impacts of colonialism on indigenous people. Indeed, it has previously been stated that: *"…fetal alcohol syndrome is not an equal opportunity birth defect"* [8]. Studies examining patterns of maternal alcohol consumption suggest that women from upper socioeconomic status (SES) groups are more likely to drink alcohol during pregnancy but have significantly lower rates of FASD than women in lower SES groups. This suggests the adverse developmental effects of prenatal alcohol exposure may be amplified by factors linked with poverty such as other substance use, nutritional deficiencies, stressful social circumstances, and poor prenatal care [9]. This is also true regarding the influence of postnatal experiences for children with FASD. Previous research has documented that children who are biologically vulnerable as a result of prenatal alcohol exposure are often also exposed to postnatal environmental risks (e.g., poverty, trauma) and therefore are at "double jeopardy" for poor outcomes [10]. Interactions between multiple stressors both during pregnancy and in early postnatal life are well recognized in the DOHaD field and have led to the concept of a "second" or "multiple-hit" hypothesis (see Fig. 12.1 below).

Physical Health Outcomes

Since the first diagnosis of fetal alcohol syndrome (FAS) and the associated diagnoses that make up FASD, there have been numerous case reports and small clinical studies reporting on a wide range of health outcomes. A number of recent systematic reviews have examined the comorbid conditions associated with FASD [1] or have focused on particular physical health outcomes associated with PAE including metabolic disorders and body composition [11], cardiovascular and renal conditions [12], immune function [13], and reproductive health [14] (Table 12.1). These reviews report that clinical evidence is scarce or lacking for many health outcomes, with studies either containing small numbers of participants or only examining young children or adolescents where chronic conditions may not yet have emerged. Further evidence of impacts of PAE on physical health comes from two recent health surveys; one undertaken by caregivers reporting on children/adolescents (average age 12 years, Reid et al. [15]) and the other, a health survey completed by over 500 adults with FASD or related diagnoses (average age 27.5 years, Himmelreich et al. [2]). Both surveys identified a range of disorders in people with FASD occurring at rates significantly higher than the general population and/or with an earlier onset (discussed in more detail below). However, at this time, the strongest evidence for PAE impacting physical health comes from preclinical studies in models where the dose and timing of alcohol exposure can be controlled, and animals can be studied over their entire life. Preclinical studies have also shed light on the biological mechanisms through which alcohol alters developmental processes, as well as enabled intervention strategies to be investigated.

Clinical Studies of Physical Health Outcomes Associated with FASD

Metabolic Outcomes (Including Diabetes and Plasma Hormones/Lipids)

A small number of studies have examined metabolic outcomes in people with FASD. A study of young children (aged 6–7 years) with FAS reported normal glucose but increased fasting insulin concentrations and evidence of glucose intolerance and insulin resistance (see Table 12.1 and the review of Akison et al. [11]). More recent studies have found altered insulin levels in adults with FASD [16] and

Table 12.1 Physical health outcomes in children and adults following PAE and/or a FASD diagnosis

Study cohort	Health domain	Outcome (age)
Children/adults with FAS/FASD (data derived from systematic reviews)	Metabolic Body composition Cardiovascular Renal Immune	Glucose intolerance/insulin resistance (6–7-year-olds) Altered insulin concentrations (adults) ↓ HDL and elevated triglycerides (adults) ↑ Rates of type II diabetes (adults) ↓ BMI and body fat (children, especially males) ↑ Rates of hypertension (adolescents and young adults) Impaired ability to concentrate urine/altered electrolyte excretion (6-year-olds) ↑ Rates of major/minor infections (all ages)
Children/adults with FAS/FASD (data from health surveys)[a]	Bone Cardiovascular Immune Other (eye)	Bone and muscle problems (e.g., stiff, painful, swollen joints; lack of flexibility; hypermobility of joints in adults) Heart conditions (e.g., cardiomyopathy in adults) ↑ Rates of infection (especially ear and kidney infections in both children and adults) ↑ Prevalence (and often earlier onset) of autoimmune disorders in adulthood ↑ Rates of dermatitis/eczema and psoriasis (both children and adults) Eye conditions (both children and adults)
Longitudinal birth cohorts[a]	Body composition Renal	↑ BMI and rates of obesity in adolescent girls but not boys ↑ Rates of kidney disease at 30 years of age
Documented PAE but no FAS/FASD diagnosis[a]	Immune	↑ Risk of infections and sepsis (newborns) ↑ Rates of asthma/dermatitis in some but not all studies (young children)

Data summarized from systematic reviews [11–14] and health surveys [2, 15] or cited in text (e.g., longitudinal birth cohorts). PAE in these cohorts was variable or unrecorded

[a]Includes only outcomes or details not captured in the systematic reviews

increased rates of type II diabetes [17]. One of these studies [17] also found lower levels of the high density lipoprotein (HDL) and elevated triglyceride levels in people with FASD, both of which are associated with an increased risk of cardiovascular problems such as stroke and heart attack. The adult health survey found that rates of type 1 diabetes were 5 times higher in adults with FASD and episodes of hypoglycemia, unrelated to diabetes, occurred in nearly a third of those with FASD compared to rates of less than 1% in the general population [2]. Of note, clinically evident hypothyroidism was present in approximately 5% of those with FASD, a rate more than 180 times that of the general population. In the caregiver survey, elevated rates of thyroid problems were also reported in children and adolescents [15]. Given hypothyroidism is an important metabolic cause of reversible cognitive impairment, alterations in thyroid function warrant further investigation in young people with FASD.

Body Composition (Including Risk of Underweight/Overweight/Obese and Changes in Bone Health)

Body mass index (BMI), used to detect people who are either underweight or overweight/obese, was found to be lower in children with FASD prior to puberty, particularly in males [18]. Similarly, percentage body fat was also lower in children with FAS/pFAS compared to non-exposed children or those exposed to prenatal alcohol but not displaying signs of FAS [19]. Both health surveys showed increased rates of underweight in those with FASD. Conversely, a more recent study using a large longitudinal cohort of children from the general population found BMI and rates of obesity were increased in adolescent girls exposed to prenatal alcohol exposure [20]. These studies suggest outcomes related to body composition will depend on the level of alcohol exposure but also may change with age. Puberty is likely to be a key time where differences may emerge, and this may involve not only hormonal changes but social changes including alterations to physical activity. With regard to bone health, there is some evidence that PAE may disrupt fetal bone development; however, studies examining bone densitometry are lacking in children with FASD. One recent study found that PAE was associated with increased rates of fractures in childhood [21] although the mechanism contributing to this outcome was unclear. Bone and joint problems were common conditions reported by adults with FASD, with rates of osteoarthritis increased 3.7-fold. In both health surveys, many respondents reported more generalized problems such as chronic joint pain and/or swelling.

Cardiovascular and Renal Outcomes (Including Heart Defects, High Blood Pressure, and Kidney Disease)

With regard to cardiovascular and kidney health following PAE, clinical evidence is limited (for review, see Reid et al. [12]). A recent study has shown that adolescents and young adults with FASD were more likely to be hypertensive after accounting for factors including age, sex, race/ethnicity, medication use, and obesity status [22]. Other outcomes in children with FASD included changes in heart rate and heart rate variability, particularly in response to minor physical challenges [13]. The health surveys showed increased rates of congenital heart defects, including the need for cardiac surgery in early childhood. However, the adult health survey also found increased rates of many other conditions including cardiomyopathy, high blood pressure, and valvular heart disease. Many of these emerged relatively early in life compared to the general population where they are more often considered diseases of middle/old age.

A series of studies has examined renal function in a small cohort of young children with FAS and found they presented with episodes of excess urine production and dehydration likely due to an inability to concentrate urine (see Reid et al. [13]). This may be a contributing factor to the increase rates of urinary incontinence that has been reported by caregivers of children with FASD [15]. In adults with FASD, the rates of diagnosed kidney disease were almost 5 times higher than the general population. Effects of relatively modest amounts of alcohol may also impact renal function; in a longitudinal study of women where PAE was well documented, alcohol consumption during early and late pregnancy was associated with mild to moderate chronic kidney disease in adults at approximately 30 years of age [23].

Immune Function (Including Infections, Allergies, and Asthma)

A recent systematic review identified 12 clinical studies where outcomes focused on allergy and infection in individuals with PAE, although only one study included a group with diagnosed FAS/FASD [12]. In newborns, PAE has been reported to increase the risk for sepsis and infections. In neonates and children, some but not all studies reported an increased risk of dermatitis, skin rashes, and/or eczema. Some studies concluded that PAE may have exacerbated a predisposition to dermatitis or asthma rather than being a causal factor. Children and adolescents with PAE may have increased risk of infection and be hyper-responsive to stress (for review see Reid et al. [15]). Alcohol consumption has also been shown to alter immune function in the mother, which has been linked to adverse neurodevelopment in children [24]. The health surveys provided strong evidence that children and adults with

FASD have a much greater incidence of immune disorders. In children, chronic infections were reported in over 20% of respondents and in adults, rates of infections were up to 200-fold higher than the general population for conditions such as sinusitis, chronic ear infections, and kidney infections. Skin conditions such as eczema/dermatitis and psoriasis were reported at increased rates in children with FASD and this trend continued in adults. Autoimmune diseases, which routinely occur in 5–7% of the general population, were reported in 35% of adults with FASD, with high rates of rheumatoid arthritis and fibromyalgia. Some other less common autoimmune disorders/conditions (e.g., lupus, Crohn's disease, sarcoidosis), were also more prevalent and often developed at a younger age in adults with FASD.

Reproductive Outcomes (Including Onset of Puberty and Fertility)

In one study, adolescent girls who were exposed to high levels of alcohol prenatally had delayed puberty onset (age at first menarche), although other studies have shown no effect (for review see Akison et al. [11]). In boys, there was a tendency for delayed pubertal development and in men, decreased sperm volume and concentration. In both sexes, there was increased salivary testosterone in adolescents with PAE. These outcomes may relate to effects of alcohol on the development of the hypothalamic–pituitary–gonadal (HPG) axis which have been explored in more detail in animal models (see below). Reproductive health problems were not reported in the child health survey but in the adult survey, women with FASD had much higher rates of premature menopause and recurrent miscarriages while men had a higher incidence of undescended testicles.

Other Health Conditions

The systematic review of Popova et al. [1] identified over 400 co-morbid conditions in people with a FASD diagnosis, with many related to the teratogenic effects of alcohol (such as congenital malformations) or those conditions noted above. The health surveys captured a range of other conditions experienced by people living with FASD including eye/vision problems, increased rates of infections, and gastrointestinal problems. The child health survey also reported that children with FASD were likely to have more than one other diagnosed health condition, with over 20% having three or more.

Preclinical Studies of Physical Health Outcomes Associated with PAE

Animal models of PAE have been used to explore the long-term health outcomes that may result from prenatal alcohol exposure (see Akison et al. [11, 14], Reid et al. [12, 13] for review; Table 12.2). Generally, rodents (rat and mice) have been given alcohol at various levels during particular stages of development and the fetus or offspring studied to determine the impacts on organ development and health outcomes. In interpreting animal studies, differences in exposure levels and how animals metabolize alcohol, as well as timing of organ development compared to

Table 12.2 Examples of physical health outcomes in animal models of prenatal alcohol exposure

Dose of alcohol (~BAC if known)	Timing of exposure (human pregnancy trimester equivalent)	Species	Outcome
High dose			
8 g/kg/day via gavage, ~280 mg/dL	Throughout pregnancy (first, second, third trimester)	Guinea pig	↑ Adiposity in adults ↔ Fasting blood glucose
Moderate to high dose			
12.5% (vol:vol) in liquid diet, ~120–240 mg/dL	Periconceptional: 4 days prior to GD4 (first trimester)	Rat	Glucose intolerance and insulin resistance, exacerbated by HFD ↑ Adiposity males most affected
10% Ethanol in saccharin solution	Early-mid gestation until PD10 (first, second, third trimester)	Rat	Precocious puberty onset in males and reduced mating performance/motivation
Moderate dose			
25–30% (vol:vol) in drinking water or ~35% ethanol-derived calories (EDC) in liquid diet	Preconception (4 weeks) and throughout pregnancy (first and second trimester)	Rat	Insulin resistance in juveniles, persisting into adulthood Altered glucose and fatty acid metabolism Delayed puberty onset in females Behavioral signs of feminization in males
1.25–3.75 g/kg via IP injection	Early gestation "binge" (GD7 only) (first trimester)	Mouse	↓ Electrolyte (Ca^{2+}, P^{3-}) excretion in adult males
30% EDC in liquid diet	Early-mid gestation (GD5–11) (first trimester)	Mouse	Delayed puberty onset in females
3 g/kg/day via gavage, ~100–150 mg/dL	Mid-late gestation (GD12–17) (second trimester)	Mouse	↔ Adiposity ↔ Glucose control or metabolic rate ↑ Heart rate but no evidence of hypertension
0.75 g/kg/day IV infusion, ~120 mg/dL	Late gestation (GD95–133) (third trimester)	Sheep	↓ Nephron # in late gestation fetus ↔ Kidney/fetal growth

Table 12.2 (continued)

Dose of alcohol (~BAC if known)	Timing of exposure (human pregnancy trimester equivalent)	Species	Outcome
4 g/kg/day via gavage or 35% EDC in liquid diet, ~100–150 mg/dL	Various timings: throughout, mid-late gestation to birth (first and/or second trimester)	Rat	Some studies found glucose intolerance and insulin resistance but others no change ↑ Estrogen levels, shortened reproductive lifespan and/or delayed puberty onset in females; other studies no reproductive changes Delayed spermatogenesis when PAE in first tri Diuresis and defective renal tubular transport ↑ Water intake ↑ Heart rate Nephrotic syndrome, indicative of kidney damage
Low dose			
10% (vol:vol) in drinking water	Early pregnancy (to GD8) (first trimester)	Mouse	↑ Adiposity in adult males
5–6% (vol:vol) in liquid diet, ~30–50 mg/dL	Throughout pregnancy (first and second trimester)	Rat	↔ Body composition Sex-specific effects on glucose control Structural and functional deficits in cardiovascular system in aged offspring (↑ blood pressure, heart weight, fibrosis)
1 g/kg/day via gavage, ~50 mg/dL	Mid-late gestation (GD13.5–14.5) (second trimester)	Rat	Insulin resistance in adult males only ↔ Plasma lipids ↔ Female puberty onset or fertility ↓ Nephron # in juveniles; sex-specific impairments in glomerular filtration rate and hypertension in adults

Data summarized from systematic reviews [11, 12, 14]) and Nguyen et al. [25] and McReight et al. [26]
GD gestational day, *HFD* high fat diet, *PD* postnatal day

humans, must be carefully considered (Fig. 12.2). Rats are often given very high doses of alcohol, but they metabolize alcohol considerably faster than humans and thus comparable blood alcohol levels may be achieved to a person consuming relatively lower amounts. For example, a dose of 3 g of ethanol per kg body weight in a rat typically results in a peak blood alcohol level of ~100–150 mg/dL, while a similar dose in humans would be equivalent to >18 standard drinks for an average weight woman.

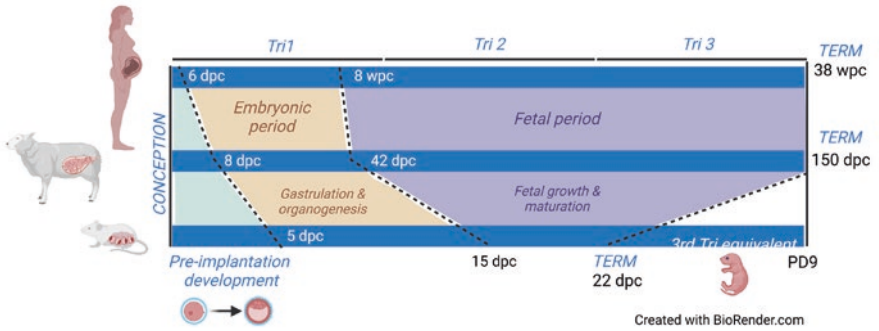

Fig. 12.2 Differences in timing of embryo and fetal development between different species. *dpc* days post conception, *wpc* weeks post conception, "term" refers to the timing of delivery in a normal pregnancy

With respect to timing of development, the processes that occur in the human brain (and other organs, including the kidney and ovary) during the third trimester of pregnancy occur during the first week after birth in the rat (Fig. 12.2). Also, definitions of human disease including "hypertension" and "diabetes" do not apply in animals so instead differences in measurable outcomes are compared to a non-alcohol exposed ("control") group.

Metabolic Outcomes (Including Glucose Intolerance, Insulin Resistance, and Plasma Hormones/Lipids)

Our systematic review identified nearly 30 publications examining metabolic outcomes in animal models [11]. These studies provide strong evidence that PAE at nearly any stage of pregnancy may result in adult rats with elevations in fasting blood glucose and/or insulin compared to non-alcohol exposed animals. These alterations to glucose homeostasis were typically demonstrated by performing a glucose tolerance test or insulin challenge in PAE and control animals. However, in many cases these outcomes only occurred when the dose of alcohol was high, and was often sex-specific, with male offspring appearing to be particularly vulnerable. Metabolic dysfunction was also sometimes only apparent when the PAE was combined with another adverse lifestyle factor, such as a "second hit" of a postnatal high fat diet. These physiological changes occurred together with changes in other hormones, such as leptin, which are known to control hunger. In addition, expression of genes in the liver, fat, and muscle that regulate blood glucose concentrations was affected by PAE. In terms of lipids, low-dose alcohol throughout pregnancy did not affect blood lipids in the offspring but higher doses, including when alcohol was

limited to the time around conception, resulted in elevated triglycerides and, in some cases, total cholesterol concentrations.

Body Composition (Including Fat Mass and Bone Density)

Studies where PAE occurred at relatively high levels around conception or throughout pregnancy resulted in male offspring with increased fat mass. This did not occur in female offspring or where alcohol exposure was relatively low (for review see Akison et al. [14]). As many of these studies used dual-energy X-ray absorptiometry, it was also possible to assess bone density and other measures of bone health. In most studies these were unaltered, although PAE has been shown to affect fetal bone development in rats [27].

Cardiovascular and Renal Outcomes (Including Organ Development)

Animal studies have examined heart and cardiovascular outcomes including heart function (measured by echocardiography), blood pressure, heart structure, and cardiovascular responses to various stressors (for review see Reid et al. [12]). A high-dose 2 day "binge" model of PAE resulted in elevated blood pressure in adult offspring, however low-dose alcohol or alcohol around conception either had no effect or slightly decreased blood pressure [28, 29].

One study in sheep found that prenatal alcohol exposure resulted in impaired vasodilation function and increased vascular stiffness in fetuses in late gestation although it is unknown if these changes persist in offspring [30]. A couple of studies have also identified PAE as contributing to left ventricular hypertrophy and impaired cardiac function, such as reduced cardiac output and contractility, as well as markers of cardiac fibrosis (see Reid et al. [12]).

In response to PAE, animal studies have described impaired kidney growth and development. This has resulted in less nephrons (the filtering unit) in the kidney, alterations in renal function (changes in the glomerular filtration rate and urinary responses to challenges such as dehydration), and signs of kidney disease such as renal fibrosis. However, these outcomes were not consistent and depended upon the timing and dose of alcohol. In particular, the early stages of development of the permanent kidney seem especially susceptible. Using in vitro culture of fetal kidneys from the rat, alcohol has been shown to directly impact the rate at which the cells within the kidney could grow and divide. Excitingly, these effects could be prevented by the addition of retinoic acid (a metabolite of vitamin A).

Immune Function (Including Markers of Inflammation and Immune-Related Conditions Such as Arthritis)

In terms of the impact of PAE on the immune system, most preclinical studies have used rat models of PAE (>80%), with moderate high doses over the first and/or second trimester equivalent period of pregnancy (see Reid et al. [13] for review). These studies have examined the effect of PAE on cell-mediated immune responses, particularly splenic or thymic lymphocyte proliferation in response to an immune challenge. Most studies reported that PAE attenuated immune responses to an experimental infection and therefore had an immunosuppressive effect, perhaps explaining the increased rates of infection seen in individuals with PAE in clinical studies. In addition, there was evidence of an attenuated febrile response in response to infection in PAE offspring, which may explain the reduced resistance to infection observed in animals and humans following PAE. Although PAE-induced alterations in immune responses have been reported at all ages, in many instances, the altered immune response was transient, with younger offspring exhibiting alterations that were normalized by adulthood.

Numerous studies have demonstrated changes in cytokine production either in circulating levels or within the brain. In some studies, when challenged with infection, animals exposed to PAE had an attenuated response. In a model of adjuvant-induced arthritis, female offspring exposed to PAE were found to have more severe inflammation and a prolonged course of disease compared to controls [31]. More recently, a study in rats has shown that peripheral inflammation, as measured by circulating and tissue-specific immune cells and cytokines, can show sex-specific changes in response to PAE [32]. Importantly, this study found that immune status was a predictor of glucose intolerance and neurobehavioral dysfunction in adult PAE offspring.

Reproductive Outcomes (Including Onset of Puberty and Fertility)

Animal studies demonstrate numerous impacts of PAE on both the male and female reproductive systems (see Akison et al. [11] for review). This is perhaps not surprising, given the importance of the hypothalamic–pituitary regulation of the gonads and the known impacts of prenatal alcohol on the developing brain. PAE has been shown to alter gonadotropin hormone secretion, activity, and responsiveness in both males and females (see Weinberg et al. [33] for review), and this can result in altered estrogen production from the ovaries in females and testosterone production from the testes in males.

PAE at any stage of pregnancy, but particularly in late gestation, results in an increased age at vaginal opening in female offspring during adolescence, indicative

of delayed puberty onset. However, very few other reproductive outcomes have been examined in females. A more recent study has examined ovarian reserve (i.e., primordial follicle numbers in neonates), estrous cyclicity, and pregnancy success in 6-month-old rat offspring and found no effects from a low-dose, acute exposure in late gestation [26].

A greater range of reproductive defects have been reported in male offspring with PAE. At birth, there is often evidence of a reduced anogenital distance compared to controls, suggestive of feminization. There is also evidence for reduced weight of the testes and accessory organs (e.g., prostate and seminal vesicles), reduced testosterone levels, delayed spermatogenesis, and altered mating behavior, resulting in reduced motivation and performance. However, there are inconsistencies in development of these adverse reproductive outcomes, with no clear links to the timing or level of alcohol exposure.

Other Health Outcomes (Including Impacts on the Lung, Gastrointestinal Tract)

Aside from the health outcomes described above, there are also a few studies reporting impacts of PAE on liver and gastrointestinal tract structure and function in offspring (see Akison et al. [14] for review). Aside from the impacts on liver function that manifest in altered regulation of glucose metabolism (described above), PAE has also been shown to increase susceptibility to development of fatty liver disease later in life, particularly in females. In the intestine, PAE has been shown to reduce absorption and transport of nutrients, such as folic acid, and alters the intestinal brush border enzymes of the intestinal villi, which are important for digestion. There is also one study that describes impacts on the structure of the lung in a low-dose, chronic exposure model in the rat [34]. This showed pulmonary fibrosis (i.e., increased collagen deposition) and reduced surfactant proteins, specifically in adult males, in these PAE animals.

Mental Health and Behavioral Outcomes (Including Sleep)

Mental health conditions are recognized as one of the most prevalent comorbidities with FAS or FASD, occurring in up to 70% of adults [1]. This includes psychiatric conditions such as depression, anxiety, and mood disorders as well as behavioral changes including conduct and externalizing disorders and hyperactivity. These conditions and behaviors contribute to challenges with social interactions (for review see Burgess and Moritz [35]; Table 12.3) as well as sleep.

A wide variety of animal models have been used to investigate behavior associated with PAE but extrapolating animal behavior to a defined clinical mental

Table 12.3 Mental health and behavioral outcomes associated with PAE

Timing and dose of alcohol	Study cohort	Outcome
Various timing throughout pregnancy	Children/adults with FAS/FASD diagnosis	Behavioral difficulties Externalizing disorders (including hyperactivity) Anxiety and mood disorders Psychiatric illness (including depressive disorders) Conduct and emotional disorders
>5 Drinks on one or occasions during pregnancy	Children with documented PAE but no FASD diagnosis	Externalizing disorders in boys Psychiatric illness Behavioral difficulties Difficult temperament Sleeping problems (infants, <2 years) Conduct disorders Disinhibited behaviors
~1 Drink/day, first trimester of pregnancy	Children and adults with documented PAE FASD diagnosis	Attention disorder (children) Alcohol use disorder (adults at 22 years) Anxiety and depression Conduct disorder Increased emotional and conduct difficulties Hyperactivity and inattention
<2 Drinks per occasion or 1–2 units per week throughout pregnancy	Children with documented PAE but no FASD diagnosis	Depressive symptoms Conduct and emotional symptoms
Various doses and timing throughout pregnancy	Adults with FAS/FASD (health surveys)[a]	↑ Rates of schizophrenia, psychosis, bipolar disorder ↑ Rates of attempted suicide

Adapted from Burgess and Moritz [35] and Himmelreich et al. [2]. Children refers to people under 12 years of age

[a]Includes only outcomes or details not captured above

illness has limitations. The experimental paradigms used have subjective interpretation and are often inconsistent in the ways they measure and report animal behaviors. Also as noted above, much of the later stages of brain development (the equivalent of the third trimester in humans) occur postnatally in rats and mice. Therefore, results need to be interpreted very carefully. However, animal models have been very useful to explore effects of alcohol on specific areas of brain development and have enabled researchers to investigate potential treatments.

Clinical Studies of Mental Health Outcomes Associated with FASD

Mental Health

Mental health issues are highly prevalent in people with prenatal alcohol exposure and/or FASD. Some of these conditions may present in early childhood. For example, in a small study of children prenatally exposed to alcohol, more than 85% developed a psychiatric illness, with the majority being mood disorders such as major depressive disorder [36]. Other mental health conditions associated with PAE may only become apparent and/or diagnosed during adolescence or adulthood. These most commonly include anxiety and depression. However, the adult health survey found a large range of mental health issues also occurred at much higher rates in individuals with FASD than the general population including panic attacks (17-fold higher), schizophrenia (4–5 times higher), bipolar disorder (sixfold higher), and psychosis (tenfold higher). Alcohol and substance abuse disorders also occurred at higher rates in adults diagnosed with FASD. These serious mental health conditions likely contributed to the survey identifying almost 30% of adults with FASD attempting suicide.

Behaviors (Including Hyperactivity)

Behavioral disorders including conduct disorders, disruptive behaviors, hyperactivity, and impulse control are common in children with a FASD diagnosis (see Table 12.3). However, studies have determined that even occasional or relatively low levels of alcohol during pregnancy may impact behaviors, irrespective of a FAS or FASD diagnosis. For example, a single occasion of binge drinking during the first trimester was associated with childhood emotional and conduct difficulties. A similar outcome was observed in children exposed to a low amount of alcohol (1 drink/day) during pregnancy or even when the exposure was only in the first trimester. The health survey found that almost 80% of adults with FASD also had attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD). Other common issues included personality disorders, oppositional defiant disorder, and obsessive-compulsive disorder, which occurred in people with FASD at 2–4 times the prevalence rates in the general population.

Sleep (Including Circadian Rhythms)

Caregivers of children with FASD commonly report sleeping problems in affected children including difficulty falling and staying asleep, early waking, and an overall reduction in total sleep time compared to non-affected children. A systematic review highlighted that these sleep issues may contribute to sleep deprivation and contribute to the cognitive and behavioral problems characteristic of FASD [37]. Indeed, a study has demonstrated that in families with a school age child with FASD, the sleep problems were associated with increased behavioral issues, increased caregiver anxiety and negative impacts on caregiver and family quality of life [38]. A recent study in children with FASD found more than 90% had disrupted circadian rhythm sleep disorders and insomnia, but during the day, experienced sleepiness as well as hyperactive behaviors [39]. The health survey identified sleep as a major issue for adults living with FASD, suggesting this is not just a problem that occurs in childhood. Difficulties in falling and staying asleep occurred in 50–70% of adults with FASD, who also reported many other sleep-related issues including nightmares, night sweats, and a general feeling of being tired all the time.

Changes in sleep patterns suggest that prenatal alcohol may induce changes in control of circadian rhythms. Circadian rhythms control biological processes including hormone secretion, sleep/wake cycles, body temperature, glucose homeostasis, and immune function that oscillate over a 24-h period. Children with FASD were observed to have increased salivary cortisol levels in the afternoon and at night, thereby implicating changes in the circadian regulation of the hypothalamic–pituitary–adrenal (HPA) axis [40]. Given the importance of sleep for normal circadian rhythms, including hormonal balance, sleep issues likely contribute to many other conditions including high blood pressure, diabetes, and obesity.

Animal Studies of Mental Health Outcomes Associated with PAE

Anxiety and Depressive-Like Outcomes

Animal studies using high doses of alcohol throughout pregnancy provide strong evidence that offspring exposed to prenatal alcohol display a range of altered behaviors. Rats and mice are most commonly used, and offspring exposed to prenatal alcohol display increased anxiety and depression (see Table 12.4). As shown in Fig. 12.2, much of brain development that takes place in the third trimester of a human pregnancy takes place in the first week after birth in rodent species. To examine effects of alcohol during this period, some studies have administered alcohol to the rat throughout pregnancy and then given alcohol directly to the pup for the first 10 days after birth. Outcomes were similar, with offspring showing signs of anxiety and depression. Studies using much lower doses of alcohol throughout

Table 12.4 Examples of mental illness-like and behavioral outcomes in animal models of prenatal alcohol exposure

Dose of alcohol (~BAC if known)	Timing of exposure (human pregnancy trimester equivalent)	Species	Mental illness-like phenotype (age and sex examined)
High dose			
~4 g/kg in liquid diet, ~155–225 mg/dL	All of pregnancy and lactation: GD1-PD10 (first, second, third trimester)	Rat	↑ Anxiety-like behavior ↑ Depressive-like behavior
20% (vol:vol) in liquid diet	"Binge" at GD7 (first trimester)	Rat	↑ Social interaction (males)
Moderate to high dose			
2–4 g/kg in sucralose solution, ~170–250 mg/dL	All of pregnancy (first, second, third trimester)	Guinea pig	↑ Locomotor activity (hyperactivity) ↓ Learning and memory
12.5% (vol:vol) in liquid diet, ~120–240 mg/dL	Periconceptional: 4 days prior to GD4 (first trimester)	Rat	↑ Anxiety (females) ↓ Anxiety (males)
2–4 g/kg in liquid diet (~36% ethanol-derived calories), ~130–190 mg/dL	All of pregnancy (first and second trimester)	Rat	↑ Depressive-like behavior (often males only) ↑ Anxiety-like behavior Hyperactivity Altered social interaction (often ↓ in males, ↑ in females) ↓ Recognition memory (males) ↓ Engaging and responding to playful interactions
Low dose			
5–6% (vol:vol) in liquid diet, ~30–50 mg/dL	All of pregnancy (first and second trimester)	Rat	↑ Anxiety-like behavior No effect on memory and learning ↓ Social interaction (females)

Adapted from Burgess and Moritz [35]
GD gestational day, *PD* postnatal day

pregnancy found evidence of anxiety and depression both in relatively young animals and in aged animals, indicating that the effects persist throughout life. Interestingly, the low dose alcohol throughout pregnancy did not cause significant changes in memory and learning, suggesting impacts on mental health may occur at lower doses of alcohol than other common outcomes related to prenatal alcohol exposure. Alcohol given only around conception (periconceptional exposure) caused changes in measures of anxiety but effects were dependent upon sex; female offspring showed increased levels of anxiety-like behaviors, but male offspring tended to have decreased levels.

Social Interactions and Hyperactivity

Rodent models have explored the effects of prenatal alcohol exposure on social behaviors using a range of different experimental situations. Most often this involves placing an animal exposed to prenatal alcohol in an environment with a control animal (not exposed to alcohol) and observing interactions including non-aggressive (sniffing, licking, playing) and aggressive (fighting, rearing, biting) behaviors as well as avoidance/non-social behaviors. High doses of alcohol throughout pregnancy (first and second trimester equivalent) commonly reduced the social interactions of offspring, including engaging and responding to playful interactions, especially in male offspring. In some studies, hyperactivity in rat and guinea pig offspring was noted together with changes in social behaviors aligning with clinical observations in children with FASD.

Sleep and Circadian Rhythms

In a rat model of prenatal alcohol exposure throughout pregnancy, young offspring, both before and during puberty, spent less total time asleep and more time awake compared to control animals [39]. Similarly, when alcohol was administered postnatally to male rats (days 4–9, third trimester human equivalent) and they were studied as adults, it was found they took longer to enter rapid eye movement (REM) sleep and that the amount of time spent in REM sleep was considerably less [41]. Changes in circadian rhythms such as altered diurnal changes in body temperature and locomotor activity have been observed in rat offspring following prenatal alcohol exposure throughout pregnancy [42]. These outcomes have been associated with changes in the genes that control circadian rhythms (“clock” genes) in the brain [42, 43].

Barriers to Care in Physical and Mental Health Care Systems

While awareness of the impacts of PAE, including acknowledgment of FASD, has been increasing in many countries, individuals with FASD still face substantial barriers to accessing appropriate care for their developmental, physical, and mental health needs. Many of these barriers occur at a system level and stem from a lack of knowledge around FASD, both within the health sector (e.g., general practitioners, speech pathologists, physiotherapists etc.) and across other sectors (including

education and the justice system; see Petrenko et al. [44] for review). This lack of knowledge inevitably results in delayed assessment, diagnosis, and appropriate supports being provided. Many parents and caregivers report seeing a large number of health care professionals before FASD is even considered, let alone diagnosed. Along the way, many children will have received an incorrect diagnosis and, in some cases, inappropriate treatment. Even when FASD is suspected, waiting lists to specialist diagnostic services are often extremely long or prohibitively expensive to access.

Once diagnosed, children with FASD may experience challenges qualifying for services, as FASD is not as well recognized as other conditions such as autism spectrum disorder and ADHD. From a health perspective, following diagnosis, the focus is usually then centered on the neurobehavioral aspects of the condition and other aspects of health are often dismissed or considered side-effects of other medications. Additionally, mental health interventions are often not targeted or adjusted to the neurodevelopmental needs of individuals with FASD and are therefore less effective, which can result in frustration and distress for individuals with FASD at not being able to meet the demands of the treatment program.

Individuals with FASD also face barriers due to the multiple systems of care required to meet their physical and mental health support needs (Fig. 12.3). The range of health conditions, comorbidities, and complexities associated with FASD requires the provision of support across a broad array of medical and allied health specialists that tend to be provided "in silos," often with little communication and coordination of care across service providers. Navigating these separates services can be difficult for caregivers, who also report frustration at continually needing to initiate and lead conversations about FASD and the impacts of prenatal alcohol exposure with health providers [46, 47]. This can also be relevant when interacting with other formal support services that are often required, for example, in the education or legal systems.

Stigmatization associated with FASD can also be a significant barrier to care whereby affected individuals and their caregivers may experience external shame in the form of feeling judged or blamed for the challenges associated with the disability. This can lead to a reluctance to seek support and/or disclose prenatal alcohol exposure when accessing services [45, 48].

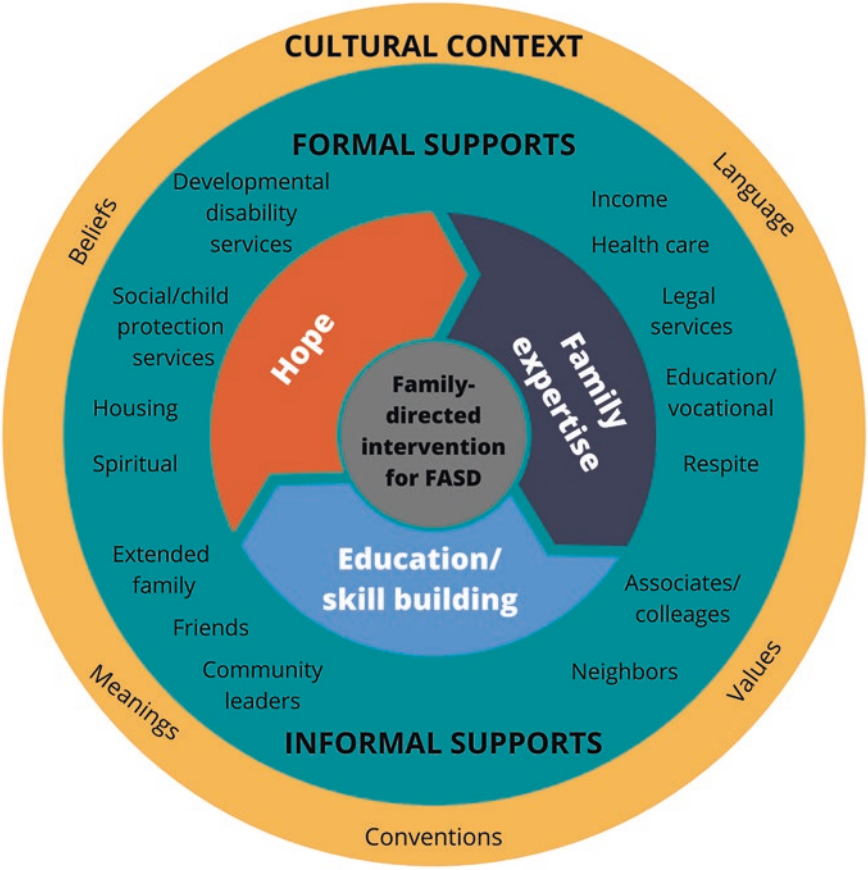

Fig. 12.3 Summary of the formal and informal supports and services that require navigation by caregivers and individuals diagnosed with FASD. (Reproduced with permission from [45])

Historical and Future Trends

Since FAS was first recognized as a condition resulting from prenatal alcohol exposure in the mid 1970s, the emphasis has been on establishing clear criteria for diagnosis as well as focusing on prevention of further alcohol-exposed pregnancies. The initial criteria included the facial features as a key component, but the last 20 years has seen a move to consider the presentation of an individual exposed to prenatal alcohol on a spectrum, with the facial features absent in the majority of cases. Some early studies included a focus on identifying and reporting some of the physical health impacts (e.g., congenital heart defects, the range of physical anomalies).

Although this has continued, overwhelmingly the focus has moved to "proving" the teratogenic effects of alcohol on the developing brain. However, given that

alcohol can freely cross the placenta into all cells of the developing fetus, it is surprising that there has been little focus on investigating the impact of prenatal alcohol on development of other fetal organs. With a large number of people who were diagnosed with FAS or FASD as young children now reaching their 30s and 40s, they are experiencing a wide range of conditions not previously considered part of the spectrum.

Recent interest in other aspects of FASD has provided important direction for researchers and the need for education for clinicians and other health professionals in how to provide more effective care for individuals with FASD. The application of a more integrated model of care that brings together professionals across multiple disciplines will ensure the diverse developmental, physical and mental health needs of individuals with FASD are met. Importantly, taking an interprofessional approach provides an opportunity to deliver client-centered, FASD-informed collaborative care for individuals and their families. One example of an integrated and holistic approach that is yet to be widely considered in the care of individuals with FASD is the International Classification of Functioning, Disability and Health (ICF) Framework. The ICF provides an interprofessional, strengths-based, participation and context specific approach to assessing and supporting individuals with FASD. While in the past, there was a need to focus on deficits to evidence the teratogenic effects of alcohol, effective care requires a strength-based approach that incorporates a person's individual strengths and interests and focuses on improving outcomes that are meaningful to individuals with FASD and their families. Interventions and supports that increase participation in school, social, and work activities, for example, are important for improving quality of life and are likely to have long-term flow-on benefits for physical and mental health [45, 49, 50].

Finally, there is increasing recognition that FASD is not necessarily a condition associated with exposure at levels consistent with an alcohol use disorder during pregnancy. Given there are high rates of alcohol consumption in women of reproductive age in most countries around the world, it is perhaps not surprising that there is alcohol exposure during pregnancy [51]. This can partly be explained by the fact that approximately 50% of pregnancies are unplanned, with some women consuming alcohol prior to pregnancy recognition but then stopping or reducing their consumption for the remainder of their pregnancy [52]. However, there is also the misconception that only "strong" alcohol, or alcohol in large quantities is harmful during pregnancy [53].

While abstinence is the only solution to prevent FASD, this is not feasible on a population basis. Therefore, there has been much interest in developing effective intervention strategies to ameliorate the adverse outcomes of PAE. One potential intervention is supplementation with choline, an essential nutrient that contributes to multiple important processes in the body including formation of cell membranes and brain function. Given these roles, the requirement for choline consumption during pregnancy is high but many women fail to consume a diet that provides recommended levels [54]. Additionally, alcohol has been shown to reduce circulating choline levels in both preclinical [5, 7] and clinical studies. There is currently abundant preclinical and clinical evidence to suggest that choline supplementation,

either in the mother during pregnancy or of the offspring in early life, can ameliorate some of the brain, growth, and placental deficits from prenatal alcohol exposure [55–58]. However, the integration of this supplement into prenatal care needs to be considered carefully, so that the over-arching message of avoiding alcohol when pregnant or planning a pregnancy is not dismissed.

Conclusions

Broadening the focus on the full range of health issues experienced by people exposed to prenatal alcohol has led to a more inclusive view of a whole-body approach to FASD. Much of the renewed interest in the effects of alcohol on organs other than the brain has emerged due to the insights and experiences of people with FASD. On-going research to fully understand the full range of health problems faced by individuals exposed to prenatal alcohol is important to enable them to access appropriate healthcare throughout their lives and for healthcare professionals to be able to advise of potential prevention or intervention measures.

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