Fetal alcohol spectrum disorder

A pervasive burden

DOUG SHELTON MB BS, DipPaed, FRACP

Fetal alcohol spectrum disorder (FASD) is a pervasive neurodevelopmental disorder that appears under-diagnosed in Australia. It should be considered in all children with developmental delay or behaviour problems. A new Australian guide to diagnosis of FASD may help improve recognition and treatment of patients with FASD.

Fetal alcohol spectrum disorder (FASD) is a significant public health issue in Australia that is poorly understood, chronic and costly. The exact prevalence is currently unknown. Health promotion and education about FASD is only just beginning; 10 years ago, only 16% of health professionals knew the essential features of FASD.[1]

FASD is caused by diffuse prenatally acquired brain injury secondary to alcohol exposure. Prenatal alcohol exposure is frequently unintended, occurring before a woman is aware she is pregnant, as about half of pregnancies in Australia are unplanned.[2,3] Overall, about 60% of pregnancies are exposed to some alcohol, no matter how little.[2]

KEY POINTS

- Fetal alcohol spectrum disorder (FASD) is a severe pervasive neurodevelopmental disorder that is often, but not always, accompanied by sentinel facial features.
- Although FASD has a high prevalence in some Indigenous populations, it is estimated to affect six times as many non-Indigenous as Indigenous people in Australia.
- A safe lower limit of alcohol use during pregnancy has not been established; the safest option for women who are pregnant or planning a pregnancy is not to drink alcohol.
- Despite high alcohol consumption in Australia, health promotion about FASD has been scant, and FASD diagnostic and informed treatment services are few.
- The recently published Australian guide to diagnosis of FASD may improve recognition and treatment of patients with FASD.

History of FASD

FASD has probably occurred since alcoholic beverages were first consumed, and numerous reports in the literature imply a historical awareness of a link between maternal alcohol use and adverse child outcomes. For example, during the 18th century 'gin epidemic' in the UK, a letter to the British Parliament expressed concern about the gin problem, stating that it is 'too often the cause of weak, feeble, and distempered children, who must be, instead of an advantage and strength, a charge to their country'.[4]

The earliest recorded medical journal article on FASD appeared in 1899, noting higher stillbirth rates in alcoholic prisoners, which contradicted the prevailing heredity view at the time.[5] Dr Paul Lemoine in France published a study in 1968 about the connection between prenatal alcohol exposure and dysmorphology.[6] The term 'fetal alcohol syndrome' was coined in 1973 by doctors at the University of Washington in the USA. The term FASD is now used diagnostically in Australia.[7]

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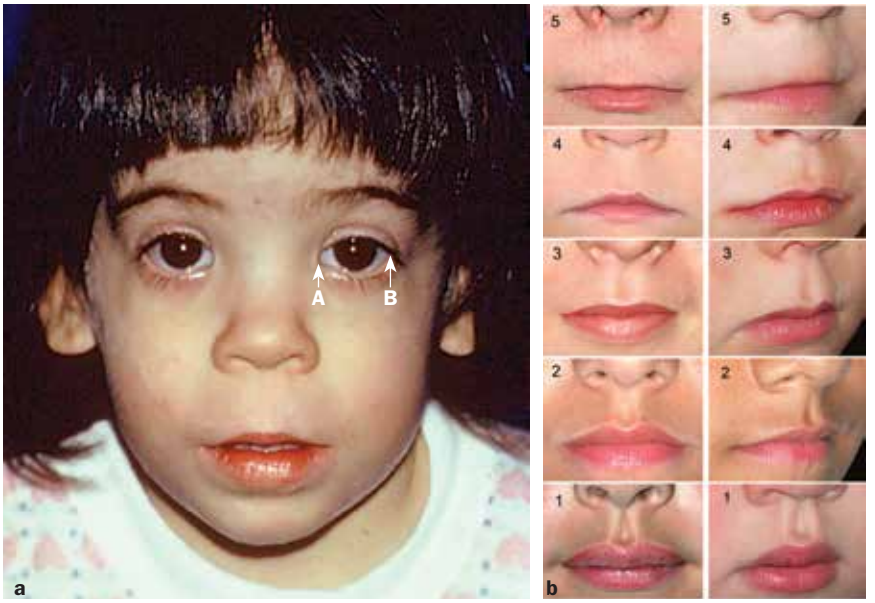


Figures a and b. Fetal alcohol spectrum disorder (FASD) facial features. a (left). The three diagnostic facial features of FAS are: short palpebral fissure lengths (distance A to B); a smooth philtrum groove between the nose and mouth (rank 4 or 5 on the Lip-Philtrum Guide); and a thin upper lip (rank 4 or 5 on the Lip-Philtrum Guide). b (right). The Lip-Philtrum Guide is used to rank upper lip thinness and philtrum smoothness for Caucasians and other ethnic groups with similar lips. The guide reflects the full range of lip and philtrum shapes, with rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterise the FASD sentinel facial phenotype. Another guide is available for African Americans and other ethnic groups with similar lips.

Definition and nomenclature

FASD is a brain-based disorder with a behavioural phenotype, with or without three sentinel facial features (short palpebral fissures, smooth philtrum and thin vermillion border on the upper lip, Figure). The behavioural phenotype is a severe pervasive neurodevelopmental disorder, defined as functional impairments of more than two standard deviations below the mean in at least three specific brain domains. Diagnostic criteria for FASD recommended for use in Australia are shown in the Table.[8]

The nomenclature around FASD has changed significantly over time, contributing to confusion. The term 'fetal alcohol syndrome' (FAS), coined in 1973, denoted the presence of all the sentinel facial features and severe neurodevelopmental impairment. Some children also had microcephaly and other physical birth defects. The term 'partial fetal alcohol syndrome' (pFAS) was later added to denote a child who had some, but not all, of the facial features while still having severe neurodevelopmental impairment. Additional categories included 'alcohol-related neurodevelopmental disorder' and 'alcohol-related birth defects'.

The term was altered to 'fetal alcohol spectrum disorder' (FASD) when it was realised that neurodevelopmental impairment can occur in the absence of sentinel facial and other physical features.[9] FASD was initially used as an umbrella term encompassing the four diagnoses outlined above, but in Australia has been adopted as a diagnostic term.[8]

Prevalence of FASD

The prevalence of FASD in the general population in Australia is unknown as there has been only one prevalence study reporting on FAS and pFAS, and that was in a sample of children living in remote Australia.[10] The active case ascertainment used in that study was methodologically excellent but too complex and expensive to be used at a population level. An alternative to case ascertainment is clinic-based studies, which are prone to referral bias, and in any case there are few established FASD clinics in the country. Other alternatives are passive surveillance and record review systems, which are hampered by the absence of accurate consistent data, although the publication of the *Australian Guide to the Diagnosis of Fetal Alcohol Spectrum Disorder (FASD)* in 2016 should begin to address this.[8] Nevertheless, there are no national legislative requirements to report FASD and only intermittent studies of alcohol use in pregnancy.[11]

The paucity of Australian data has led to extrapolations from studies conducted in similar Western societies. In studies published in 2009 and 2014, the prevalence of FASD was estimated using active case ascertainment as between 2% and 5% in school cohorts, albeit using the US Institute of Medicine criteria, which are more inclusive than criteria in Australian guidelines.[12-14] If these rates were applied to the Australian population then between 463,000 and 1.15 million individuals would be affected by FASD. The data support the assertion that FASD is a significant public health problem worldwide.[15]

Some Indigenous communities have higher rates of FASD than the general population, but FASD should not be regarded solely as an Indigenous problem. Prevalence rates of FAS/pFAS of up to 12% have been found in some Indigenous communities in Australia.[10] Applying this rate to the Indigenous population of Australia would suggest that up to 80,000 Indigenous people might have FASD. Assuming the lower rate described above for the non-Indigenous population (463,000 people with FASD) would still give a non-Indigenous to Indigenous ratio of around 6:1.

Aetiology of FASD

FASD is a diffuse brain injury caused by the teratogenic effects of alcohol on the developing brain. Alcohol is one of the most

potent teratogens in common use and readily crosses the placenta and blood–brain barrier.

Prenatal exposure to alcohol is thought to cause brain injury via epigenetic changes to methylation switches, microRNA signalling and histone residues, all of which control gene expression.[16] Animal evidence also suggests that alcohol exposure before conception can cause changes in stress regulatory genes in multiple areas of the brain of offspring.[17] Similarly, alterations in gene methylation occur in the sperm of alcoholic men and can be transmitted through the male germline.[18-20] These findings suggest aetiology may be more complex than previously thought.

A safe lower limit of alcohol consumption during pregnancy has not been established. Hence, the NHMRC currently recommends that not drinking alcohol is the safest option for women who are pregnant or planning a pregnancy.[21] However, about half of Australian pregnancies are unplanned, and prenatal alcohol exposure often occurs inadvertently in these cases.

Whether prenatal alcohol exposure causes FASD in an individual pregnancy depends on various factors, including:

- the amount, type, duration and frequency of drinking
- the trimester of pregnancy (exposure in the first trimester is more likely to result in facial dysmorphism)
- the mother's size
- maternal and fetal genetics, which may influence alcohol metabolism.

Binge drinking, defined in Australia as five or more standard drinks in a single session (where one standard drink is 10 g of alcohol), is likely to be the most teratogenic pattern of alcohol use because it leads to higher blood alcohol concentrations. Continued binge drinking after a woman becomes aware of the pregnancy predicts an adverse outcome.[22,23]

Prevention of FASD

The Australian Government has developed an action plan to reduce the impact of FASD. This recommends a whole-of-government population approach, with emphasis on targeted approaches to prevention and management for populations at greatest risk.[24]

For clinicians, several brief interventions, including motivational interviewing and referral to a dietitian, have been shown to reduce or eliminate alcohol consumption in pregnant women and result in better birth outcomes.[25,26] Ideally, these interventions should be embedded within antenatal care and youth health services.[27] GPs should refer patients to their local services if additional support is required.

TABLE. FETAL ALCOHOL SPECTRUM DISORDER (FASD): DIAGNOSTIC CRITERIA AND CATEGORIES[8]

Diagnostic criteria	Diagnostic categories	
	FASD with 3 sentinel facial features	**FASD with <3 sentinel facial features**
Prenatal alcohol exposure	Confirmed or unknown	Confirmed
Neurodevelopmental domains • Brain structure/neurology • Motor skills • Cognition • Language • Academic achievement • Memory • Attention • Executive function, impulse control and hyperactivity • Affect regulation • Adaptive behaviour, social skills or social communication	Severe impairment in at least 3 neurodevelopmental domains	Severe impairment in at least 3 neurodevelopmental domains
Sentinel facial features • Short palpebral fissure • Smooth philtrum • Thin upper lip	Presence of 3 sentinel facial features	Presence of 0, 1 or 2 sentinel facial features

Reproduced with permission from Bower et al. *Australian guide to the diagnosis of fetal alcohol spectrum disorder (FASD).*[8]

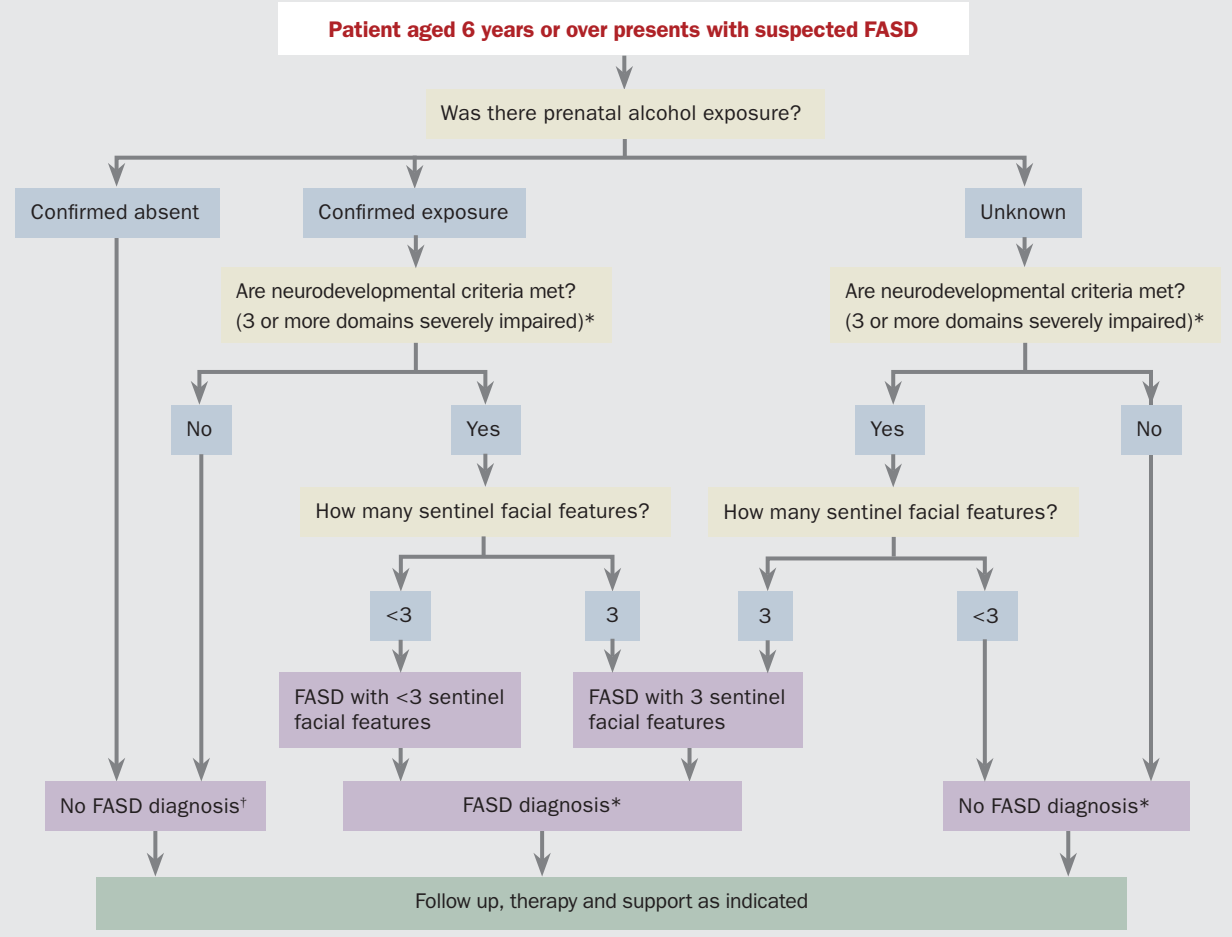
Presentation

Children with FASD can present with heterogeneous symptoms of developmental or learning delay as well as behavioural and mental health concerns. A history of prenatal alcohol exposure may not be readily available, especially if the child is in foster care. The child with a long list of previous diagnoses who remains problematic should alert the clinician to ask careful questions about prenatal exposures. Alternatively, if prenatal alcohol exposure is already established then the child should be considered at risk. Careful monitoring of their development, learning and mental health is required until early adolescence.

Individuals with FASD may have a wide range of comorbidities. A recent study identified 428 comorbid conditions, spanning more than 18 of 22 chapters of the *International Classification of Diseases* (ICD-10).[28] In particular, children with FASD may have microcephaly.

FASD is not just a problem of childhood but also of adolescence and adulthood. Adults with FASD are likely to be present in all caseloads, especially among patients with mental health problems and disability. International data suggest that most cases are either undiagnosed or misdiagnosed.[29] Clinicians should be vigilant for adult patients with a string of previous diagnoses, none of which adequately explains their predicament.

1. SUGGESTED DIAGNOSTIC ALGORITHM FOR FASD IN PATIENTS AGED 6 YEARS OR OLDER[8]



Abbreviation: FASD = fetal alcohol spectrum disorder.

* Assuming assessment is fully completed and current, and other diagnoses have been considered.

† In the presence of confirmed prenatal alcohol exposure, reassessment of neurodevelopmental domains can be considered as clinically indicated (e.g. if there is a decline in the individual's functional skills or adaptive behaviour over time).

Modified from: Bower et al. *Australian guide to the diagnosis of fetal alcohol spectrum disorder (FASD)*, 2016 (https://alcoholpregnancy.telethonkids.org.au).[8]

Diagnosis

A diagnosis of FASD requires a clear history of prenatal alcohol exposure and severe impairment in at least three of 10 specific brain domains (Table).[8] Suggested algorithms for diagnosis of FASD in children of different ages are shown in Flowcharts 1 and 2.[8]

GPs should ask carefully, and more than once, about prenatal alcohol exposure for all children presenting with developmental delay or behaviour problems and also for adults with mental health, intellectual and learning problems or chronic offending. If GPs suspect the diagnosis of FASD and discover prenatal alcohol exposure in a child with developmental or behavioural problems then they should refer the child to a paediatrician, child development service or FASD service.

Assessing prenatal alcohol exposure

When taking an alcohol history from the mother, it is important to ask the following three questions, embedded within the context of the usual clinical interview.

- Was your pregnancy planned or unplanned?
- How many weeks were you when you realised you were pregnant?
- What lifestyle changes did you make then?

The final question about lifestyle changes should open a discussion of alcohol, cigarettes, folate, foods and antenatal care. If the response is 'I stopped drinking as soon as I found out' then as well as congratulating

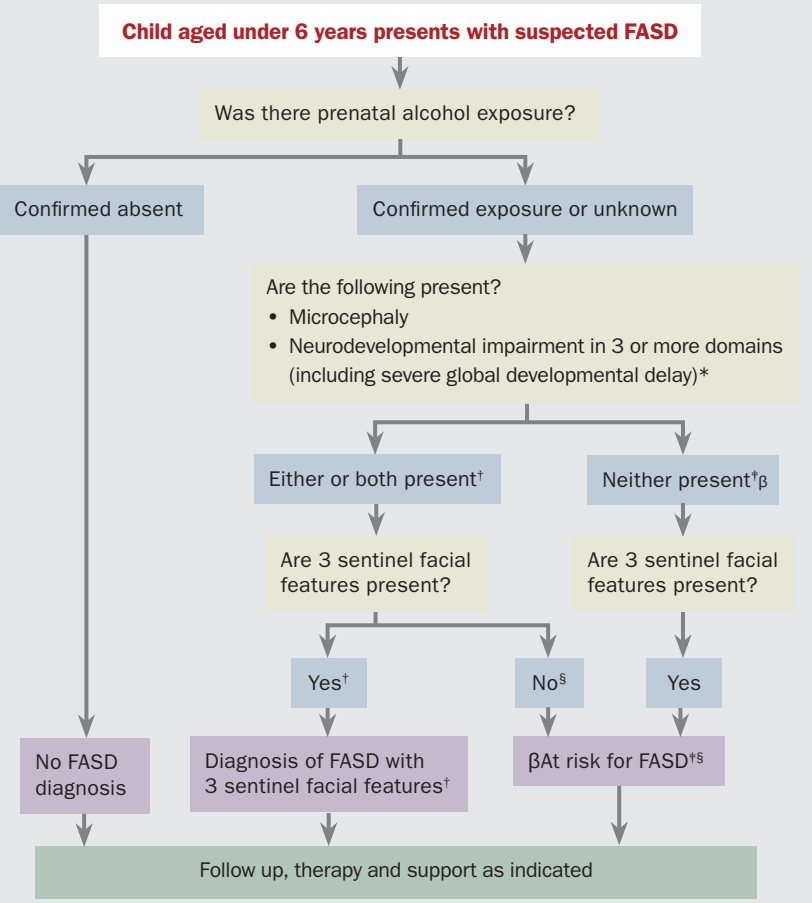
the patient for ceasing or minimising alcohol intake, clinicians should ask questions about the amount and frequency of alcohol consumption, including:[30]

- usual patterns and amounts of drinking
- special occasion drinking, either for celebration or sadness (important information that may not be volunteered)
- binge drinking in the weeks before the pregnancy was recognised (crucial information)
- continued drinking, especially binge drinking, after the pregnancy was recognised (very significant).

A useful standardised tool for assessing alcohol use is the AUDIT-C (Alcohol Use Disorders Identification Test – Consumption). This standardised measure is available in the *Australian Guide to the Diagnosis of FASD* and can be completed by the mother or someone who has directly observed the pregnancy.[8]

If significant prenatal alcohol exposure is identified then the clinician should carefully assess the index child, as well as any siblings. A plan is also needed to prevent recurrence in subsequent pregnancies and to address alcohol use disorders in the mother and family if possible.

2. SUGGESTED DIAGNOSTIC ALGORITHM FOR FASD IN PATIENTS AGED UNDER 6 YEARS[8]



Abbreviation: FASD = fetal alcohol spectrum disorder.

* Assuming assessment is fully completed and current, and other diagnoses have been considered.

† To diagnose FASD in children under 6 years of age, three sentinel facial features are required, in addition to confirmed or unknown prenatal alcohol exposure and either microcephaly or neurodevelopmental impairment in three or more domains (including severe global developmental delay) or both.

†βf neurodevelopmental criteria are not met (e.g. no microcephaly or severe global developmental delay) then the child remans 'at risk of FASD' and requires follow up and reassessment after 6 years of age.

§ If prenatal alcohol exposure is confirmed and three or more neurodevelopmental domains are impaired but there are fewer than three sentinel facial features then the child remains 'at risk of FASD' and requires follow up and reassessment after 6 years of age.

Modified from: Bower et al. *Australian guide to the diagnosis of fetal alcohol spectrum disorder (FASD),* 2016 (https://alcoholpregnancy.telethonkids.org.au).[8]

Assessing the patient

FASD is a brain-based problem, so ideally requires a multidisciplinary assessment directed at facial dysmorphology and brain function. At present, there are only four specialist FASD diagnostic clinics in Australia, on the Gold Coast and the Sunshine Coast and in Sydney and Perth. Many areas do not, and perhaps never will, have access to such teams. To fill this need, services with existing expertise in child development should upskill their teams. Provision of FASD services within a child development service has been shown to be highly acceptable to families, as well as emphasising the need for more diagnostic options and ongoing support.[31]

Between 2000 and 2014, the Gold Coast child development service diagnosed one child with FASD. Since appropriate training was provided in 2013, the service has diagnosed approximately 80 children with FASD, referral biases not withstanding. However, diagnostic expertise for FASD needs to be widened beyond specialised teams, to include GPs, specialists, nurses, midwives and allied health professionals, and to become as mainstream as that for type 2 diabetes to have any appreciable effect.

The recently published *Australian Guide to the Diagnosis of FASD* aims to give clinicians the skills, knowledge and information required to diagnose, refer and manage individuals with FASD.[8] Clinicians with a working knowledge of these guidelines or additional training in assessment methods can develop the skills necessary to undertake this with confidence.

A common misconception among clinicians is that a child must have 'the face'

of FASD to have the disorder. The three sentinel facial features of short palpebral fissures, smooth philtrum and thin upper lip are specific to prenatal alcohol exposure but occur in only about 20% of children with FASD. Most affected individuals have normal facial features and are diagnosed through psychometric and clinical assessments. Therefore, a normal facial appearance in a child or adult with prenatal alcohol exposure does not preclude the possibility of FASD.

Differential diagnoses for FASD with three sentinel facial features include:

- genetic disorders (e.g. Aarskog, Brachman-deLange or Cornelia deLange, Dubowitz, Noonan and Williams syndromes and many other chromosome deletion and duplication syndromes)
- fetal anticonvulsant syndrome
- toluene embryopathy
- maternal phenylketonuria.

Individuals with FASD sometimes have comorbidities, such as a genetic disorder or syndrome, trauma, neglect or other prenatal exposure causing neurodevelopmental problems. These comorbidities do not necessarily preclude a diagnosis of FASD, and although their relative contributions to the child's predicament may be impossible to quantify, they are all part of the diagnostic formulation.

Sequelae of FASD

FASD is a disability with two components. The first component, the primary brain injury, is permanent. However, secondary disabilities can develop as a result of the brain injury, especially if FASD remains undiagnosed and untreated. To illustrate, a longitudinal study of a US cohort of people with FAS found high rates of:[32]

- depression, anxiety and suicide (94%)
- school failure, expulsion or drop out (70%)
- unemployment (80%)
- crime (60%)
- incarceration (40%)
- self-medication with alcohol or substances (50 to 70%)
- dependent living (80%).

FASD is over-represented among individuals in the corrections and foster care systems, with up to 34% of children with disabilities in care found to have FASD in a Canadian study.[33] FASD may well also be common in individuals in the health, mental health, justice, corrections, disability and Centrelink systems in Australia.

Early identification, provision of services, stable home care and protection from violence are thought to provide a two to fourfold reduction in secondary disabilities.[22]

Cost to the community

The cost of FASD to the community is significant. The annual cost to the Canadian economy in 2013 was approximately C$1.8 billion.[34] In the same year, the annual cost to the New Zealand economy was calculated at NZ$200 million per year, representing 0.09% of gross domestic product (GDP); this comprised lost productivity alone and would have been even higher if the costs to the health, education and justice systems were also included.[35] The report concluded 'The estimated productivity losses associated with FASD further reinforces that effective FASD prevention as a primary public health strategy may be of significant value'. New Zealand has recently announced NZ$12 million in funding for FASD.

It is worth noting that 0.09% of Australia's 2013 GDP was $1.4 billion. Following a national enquiry into FASD, the Australian Government has allocated approximately $20 million to the diagnosis, management and prevention of FASD in Australia.

Interventions

A systematic review of FASD interventions across the lifespan did not recommend any specific intervention for individuals with FASD but rather suggested a broader ecological approach targeting multiple domains of functioning.[36] An ecological approach places the individual at the centre and emphasises the need for central coordination across health, home and school, continuing across the lifespan. Many services and professionals have the appropriate backgrounds to contribute to such an ecological approach but few have any specific training in FASD. It is hoped that access to quality intervention will steadily improve as clinicians increase their familiarity with FASD and more resources become available for this vulnerable population.

It is beyond the scope of this article to provide detailed recommendations for intervention across the lifespan and across service or professional groups. However, a range of evidence-based interventions for specific impairments can be helpful in children with FASD, including speech therapy for speech and language problems, occupational therapy for fine motor problems, cognitive behavioural therapy and medication for attention deficit hyperactivity disorder, and remedial education for specific learning and academic difficulties.

Why don't we know more about FASD in Australia?

Knowledge about FASD is firmly embedded within the systems of many other countries, promoting seamless conversations across the health, education, disability and justice systems. Australia is only beginning to have such conversations about FASD. Why are we so far behind in this area when we are at parity, or better, in so many others?

Have our current knowledge and beliefs about alcohol been skewed by vested interests in the alcohol industry?[37] Or are they a result of increasing affluence? For example, rates of alcohol consumption in South Korean women have increased in direct proportion to income.[38] In Australia, rates of medium and high-risk drinking have increased for both sexes in recent years, and the gender gap for alcohol consumption has narrowed.[39] The average alcohol consumption per capita aged over 15 years was 12.2 L in the years 2008–2010.[40] This puts Australia in the second tier of alcohol consumption worldwide, eclipsed only by Russia and some other European countries.

Alcohol use during pregnancy in Australia, however, appears to be declining, with a study finding a decrease in alcohol consumption by pregnant women over the period 2007 to 2011, although rates of high-risk drinking remained stable.[41] There appears to be an association between alcohol consumption during pregnancy and higher income and education in Australia. A recent study found that women with a tertiary degree were more than twice as likely to continue drinking throughout pregnancy at moderate to high levels.[30] The same study noted that higher household income (more than $100,000 per year) not only increased the likelihood of drinking throughout pregnancy but also predicted drinking at binge levels before the woman was aware of her pregnancy.

The landscape is complex at best. I believe we need a careful nuanced consideration of the relative contribution, good and bad, of alcohol to our community in general and to unborn babies in particular, followed by the question 'How can we do it better?'

Conclusion

FASD is a significant public health issue in Australia that is poorly understood, chronic and costly. FASD is almost certainly more common than previously suspected and exists within all caseloads. Clinicians are becoming more aware of diagnostic criteria, referral and management options. The *Australian Guide to the Diagnosis of FASD* is an excellent resource for all clinicians. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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References

1. Payne J, France K, Henley N, et al. Changes in health professionals' knowledge, attitudes and practice following provision of educational resources about prevention of prenatal alcohol exposure and fetal alcohol spectrum disorder: fetal alcohol education. Paediatr Perinat Epidemiol 2011; 25: 316-327.
2. Colvin L, Payne J, Parsons D, Kurinczuk JJ, Bower C. Alcohol consumption during pregnancy in nonindigenous west Australian women. Alcohol Clin Exp Res 2007; 31: 276-284.
3. Mazza D, Harrison C, Taft A, et al. Current contraceptive management in Australian general practice: an analysis of BEACH data. Med J Aust 2012; 197: 110-114.
4. Cooper EF. Alcohol use and abuse by women. CRS Report for Congress. Washington DC: Library of Congress; 1991. Available online at: http://www.come-over.to/FAS/congress.htm (accessed February 2017).
5. Sullivan WC. A note on the influence of maternal inebriety on the offspring. J Mental Sci (now Br J Psychiatry) 1899; 45: 489-503.
6. Lemoine P, Harousseau H, Borteyru JB, Menuet JC. Les enfants de parents alcooliques. Anomalies observées, à propos de 127 cas. Quest Medicale 1968; 21: 476-482.
7. Jones KL, Smith DW, Ulleland CN, Streissguth AP. Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 1973; 1: 1267-1271.
8. Bower C, Elliott EJ; on behalf of the Steering Group. Australian guide to the diagnosis of fetal alcohol spectrum disorder (FASD). Report to the Australian Government Department of Health. Perth: Telethon Kids Institute; 2016. Available online at: https://alcoholpregnancy.telethonkids.org.au/alcohol-pregnancy-and-breastfeeding/diagnosing-fasd/australian-guide-to-the-diagnosis-of-fasd/ (accessed February 2017).
9. Sokol R, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. JAMA 2003; 290: 2996-2999.
10. Fitzpatrick JP, Latimer J, Carter M, et al. Prevalence of fetal alcohol syndrome in a population-based sample of children living in remote Australia: the Lililwan Project. J Paediatr Child Health 2015; 51: 450-457.
11. Burns L, Breen C, Bower C, O' Leary C, Elliott EJ. Counting fetal alcohol spectrum disorder in Australia: the evidence and the challenges: counting FASD. Drug Alcohol Rev 2013; 32: 461-467.
12. May PA, Gossage JP, Kalberg WO, et al. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev 2009; 15: 176-192.
13. May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics 2014; 134: 855-866.
14. Stratton KR, Howe C, Battaglia F; Institute of Medicine. Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment. Washington DC: National Academies Press; 1996.
15. Popova S, Chambers C. Fetal alcohol spectrum disorders must be recognized globally as a large public health problem [editorial]. Int J Alcohol Drug Res 2014; 3: 1-3.
16. Kobor MS, Weinberg J. Focus on: epigenetics and fetal alcohol spectrum disorders. Alcohol Res Health 2011; 34: 29-37.
17. Jabbar S, Chastain LG, Gangisetty O, Cabrera MA, Sochacki K, Sarkar DK. Preconception alcohol increases offspring vulnerability to stress. Neuropsychopharmacology 2016; 41: 2782-2793.
18. Abel E. Paternal contribution to fetal alcohol syndrome. Addict Biol 2004; 9: 127–133; discussion 135–136.
19. Ouko LA, Shantikumar K, Knezovich J, Haycock P, Schnugh DJ, Ramsay M. Effect of alcohol consumption on CpG methylation in the differentially methylated regions of H19 and IG-DMR in male gametes: implications for fetal alcohol spectrum disorders. Alcohol Clin Exp Res 2009; 33: 1615-1627.
20. Govorko D, Bekdash RA, Zhang C, Sarkar DK. Male germline transmits fetal alcohol adverse effect on hypothalamic proopiomelanocortin gene across generations. Biol Psychiatry 2012; 72: 378-388.
21. NHMRC. Australian guidelines to reduce health risks from drinking alcohol. Canberra: NHMRC; 2009.
22. Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. Am J Psychiatry 2006; 163: 1061-1065.
23. Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. Alcohol Clin Exp Res 2014; 38: 214-226.
24. Australian Government. Responding to the impact of fetal alcohol spectrum disorders in Australia. A Commonwealth action plan. Canberra: Commonwealth of Australia; 2014.
25. O'Connor MJ, Whaley SE. Brief intervention for alcohol use by pregnant women. Am J Public Health 2007; 97: 252-258.
26. Project CHOICES Intervention Research Group. Reducing the risk of alcohol-exposed pregnancies: a study of a motivational intervention in community settings. Pediatrics 2003; 111(5 Pt 2): 1131-1135.
27. Grant TM, Ernst CC, Streissguth A, Stark K. Preventing alcohol and drug exposed births in Washington state: intervention findings from three parent-child assistance program sites. Am J Drug Alcohol Abuse 2005; 31: 471-490.

28. Popova S, Lange S, Shield K, et al. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. Lancet 2016; 387: 978-987.
29. Chasnoff IJ, Wells AM, King L. Misdiagnosis and missed diagnoses in foster and adopted children with prenatal alcohol exposure. Pediatrics 2015; 135: 264-270.
30. Muggli E, O'Leary C, Donath S, et al. 'Did you ever drink more?' A detailed description of pregnant women's drinking patterns. BMC Public Health 2016; 16: 683.
31. Chamberlain K, Reid N, Warner J, Shelton D, Dawe S. A qualitative evaluation of caregivers' experiences, understanding and outcomes following diagnosis of FASD. Res Dev Disabil 2016; pii: S0891-4222(16)30122-6. (Epub ahead of print.)
32. Streissguth AP, Barr HM, Kogan J, Bookstein FL. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Final report to the Centers for Disease Control and Prevention (CDC), August, 1996. Tech. rep. no. 96-06. Seattle: University of Washington, Fetal Alcohol and Drug Unit; 1996.
33. Popova S, Lange S, Burd L, Rehm J. Canadian children and youth in care: the cost of fetal alcohol spectrum disorder. Child Youth Care Forum 2014; 43: 83-96.
34. Popova S, Lange S, Burd L, Rehm J. The burden and economic impact of fetal alcohol spectrum disorder in Canada. Toronto: Centre for Addiction and Mental Health; 2015.
35. Easton B, Burd L, Rehm J, Popova S. Productivity losses associated with fetal alcohol spectrum disorder in New Zealand. N Z Med J 2016; 129: 72-83.
36. Reid N, Dawe S, Shelton D, et al. Systematic review of fetal alcohol spectrum disorder interventions across the life span. Alcohol Clin Exp Res 2015; 39: 2283-2295.
37. Martino FP, Miller PG, Coomber K, Hancock L, Kypri K. Analysis of alcohol industry submissions against marketing regulation. PLoS ONE 2017; 12: e0170366.
38. Kim W, Kim S. Women's alcohol use and alcoholism in Korea. Subst Use Misuse 2008; 43: 1078-1087.
39. Yusuf F, Leeder SR. Making sense of alcohol consumption data in Australia. Med J Aust 2015; 203: 128-130.
40. WHO. Global status report on alcohol and health 2014. Geneva: WHO; 2014.
41. Cameron CM, Davey TM, Kendall E, Wilson A, McClure RJ. Changes in alcohol consumption in pregnant Australian women between 2001 and 2011. Med J Aust 2013; 199: 355-357.