Fetal Alcohol Syndrome
A Literature Review

National Alcohol Strategy 2001 to 2003-04
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Executive Summary

Concerns have surrounded the consumption of alcohol during pregnancy since biblical times. However research and academic interest in the teratogenic effects of alcohol on the developing embryo is relatively recent. Since Jones first described Fetal Alcohol Syndrome (FAS) in the 1970s considerable interest and conflicting evidence have emerged in the areas of FAS and its less severe form, Fetal Alcohol Effects (FAE) or Alcohol Related Neurodevelopmental Disorder (ARND).

The diagnosis of Fetal Alcohol Syndrome is based on a set of criteria comprised of abnormalities in three main categories: growth retardation, characteristic facial features, and central nervous system anomalies (including intellectual impairment). The intellectual impairment associated with FAS is permanent and FAS is now regarded as the leading, preventable cause of non-genetic intellectual handicap.

The literature supports the biological plausibility of alcohol as a teratogen and a number of potential mechanisms have been described. The impact of heavy alcohol consumption will vary depending upon the timing of exposure on embryonic development. It is during the first eight weeks of embryogenesis that the primary teratogenic effects occur while exposure later in pregnancy may affect growth and behavioural and cognitive disorders.

Epidemiological research supports an association between the excessive consumption of alcohol by women who are pregnant and the risk of FAS or FAE/ARND. There appears to be little doubt that the expression of full FAS is found in children whose mothers had a history of chronic heavy alcohol use or frequent heavy intermittent alcohol use during pregnancy.

However, controversy surrounds the debate about the quantity and frequency of alcohol consumption that is required to produce FAE/ARND. The dilemma stems from difficulties surrounding the area of research and surveillance of FAS and related disorders. These include accurate diagnosis, methodological problems such as recall bias, quantification of alcohol consumption, case ascertainment, and analysis of alcohol consumption averaged to daily or weekly intake. Research that analyses alcohol consumption by averaging alcohol intake over time masks the importance of the pattern and quantity of alcohol necessary for the expression of teratogenic effects of alcohol. Overall, there appears to be no sound evidence that low levels of alcohol consumption produce FAS and FAE/ARND.

The incidence or prevalence of FAS varies across populations. It is reported to be highest for African American groups in the United States, indigenous groups in the US, Canada, and Australia, and coloured/mixed races in South Africa. Exposure to heavy alcohol intake does not result in FAS in every case. The occurrence of FAS has been shown to vary between communities of the same racial group while within high-risk populations only a small number of women will produce affected children. A number of component causes appear to increase the risk of FAS occurring, in particular low socio-economic status, pattern of drinking, age or duration of drinking, genetic predisposition, maternal nutrition and health, smoking and loss of traditional culture.
The issue of FAS has not been the subject of extensive research or policy development in Australia to date. Initial Australian case-series reports of children diagnosed with FAS found a maternal history of heavy/binge drinking or chronic alcoholism to be present. The Western Australian Birth Registry data identify indigenous Australians as a high-risk group for FAS within that State, although under-ascertainment of cases may have clouded the true level of FAS in both the high-risk groups and the general community.

Research has shown that knowledge is a necessary, although not sufficient, factor for eliciting behaviour change. The knowledge of women, both in the general community and within high-risk groups, of the risks associated with alcohol consumption during pregnancy and of FAS in particular is limited. This lack of awareness is compounded by a lack of counseling by physicians on the risks associated with maternal alcohol consumption. Studies indicate that many physicians do not feel confident making a diagnosis of FAS and have identified a need for the issue of FAS to be more fully covered in medical schools and through continuing medical education programs.
Introduction

This paper provides a review of the published scientific literature on Fetal Alcohol Syndrome (FAS) and Alcohol Related Neurodevelopmental Disorder (ARND) with the aim of giving the reader an understanding of FAS and the surrounding issues.

The National Expert Advisory Committee on Alcohol (NEACA) instigated the review to examine the situation regarding FAS in Australia. The NEACA is an advisory committee to Australian governments on issues related to the reduction of alcohol related harm. The committee had become aware of the generation of new population data showing a high rate of FAS in indigenous communities, the efforts of FAS lobby groups, and the development of local prevention and education responses to FAS in a range of communities across Australia.

The draft review was also provided as a background paper to participants attending the National Fetal Alcohol Syndrome Workshop in May 2002. The Australian National Council on Drugs in conjunction with the NEACA convened this Workshop in order to bring together researchers, clinicians, service providers and individuals with an interest and/or expertise in FAS spectrum disorders to explore issues and strategies to respond to FAS in the Australian context. Workshop participants were given the opportunity to provide further comment on the draft review.

Scope of the Review

The areas covered by the review include:

- historical perspective of FAS;
- the biological plausibility of alcohol as a teratogen;
- the diagnosis of FAS and the difficulties with rendering such a diagnosis;
- the epidemiology of FAS, the prevalence/incidence of FAS;
- Australian and International data; and
- knowledge of FAS among women and physicians.

Search Strategy

The following search strategy was used to identify relevant research findings. The literature was searched using the keywords: pregnancy and alcohol and fetal alcohol syndrome on Medline, Expanded Academic ASAP Index, SwetsNet and PubMed databases and the World Wide Web.
Historical Perspective of Fetal Alcohol Syndrome

Concern about the effect alcohol has on the unborn child is not a recent phenomenon. It has been recorded that pregnant women were advised not to drink during pregnancy as long ago as Biblical times. In 1899, W.C. Sullivan compared the children of alcoholic mothers to the children of the mother’s non-drinking relatives and found the offspring of the alcoholic mothers were twice as likely to die in the first two years. Sullivan believed the cause to be a combination of the toxic effects of alcohol and the poor social environment. He also observed that the likelihood of a normal child was increased when the mother was incarcerated and unable to access alcohol during pregnancy (Overholser, 1990, Streissguth et al., 1980).

The first descriptions of a pattern of physical malformations in eight children of alcoholic mothers was described by Lemoine (Lemoine et al., 1968) in 1968 in France and five years later independently by Jones (Jones et al., 1973) in 1973 in the United States. It is this latter group who first referred to the abnormal features as Fetal Alcohol Syndrome (FAS). It is important to realize that although it has become universally accepted, the name chosen is misleading. Technically the main effect of alcohol appears to occur during embryonic development (conception to 3 months) with the effects visible in the fetus (from 3 months gestation until birth) and in the infant after birth.

The syndrome described by Jones and colleagues included the following features:
- Developmental delay – social and motor performance related to mental, not chronological age
- Microcephaly – with no significant catch-up through early childhood
- Prenatal growth deficiency – length reduced proportionately more than for weight
- Postnatal growth deficiency – lack of catch-up growth in spite of adequate nutrition
- Short palpebral fissures
- Maxillary hypoplasia with relative prognathism
- Epicanthal folds
- Joint anomalies
- Cardiac anomaly

The eight children examined were from three different ethnic groups, diverse backgrounds, and all families were on welfare. Two of the children were raised from an early age in foster homes however there was no suggestion that a more stable home environment resulted in better progress in functioning. The authors did however recognize that the socioeconomic environment could have exacerbated the poor developmental progress resulting from exposure to alcohol.

Interest in the impact of maternal alcohol consumption on the developing fetus has increased significantly since the description of FAS by Jones and Lemoine three decades ago. Research
conducted since 1973 has shown that although a number of the facial features diminish over
time, central nervous system dysfunction including the long-term intellectual and behaviour
problems and psychological and social maladjustment remain through life. FAS is now
recognized as the foremost, non-genetic cause of intellectual impairment (Abel and Sokol,
1986a, Abel and Hannigan, 1995), one which is potentially preventable.
Toxicity of Alcohol – Mechanism of Action

In order for a substance to cause harm, exposure must occur prior to the outcome and the association must be biologically plausible. This section aims to provide the reader with information on the ways alcohol has been shown to, or postulated to affect the developing embryo/fetus. The mechanisms of the effects of alcohol as a teratogen have been studied extensively using experimental animals, in vitro models, and epidemiological human studies. Reviews of the literature have been utilized here in order to present an overview of the evidence of how alcohol is thought to affect human development.

The first 8 weeks of embryonic development is a time of rapid development with the formation of major organ systems and limbs occurring from gestation day 20 to day 55 (Overholser, 1990, Michaelis and Michaelis, 1994, Abel, 1998a). The formation of the premature subdivisions of the brain is complete by 12 weeks, and this is followed by a second brain growth spurt in the final two months of pregnancy and continued maturation for the first two years of life (Abel, 1998a). The effect of alcohol will therefore depend upon the timing of exposure on fetal development.

The toxic effects of alcohol may impact on conception as well as embryonic development affecting the quality of the egg and sperm prior to conception. Alcohol’s toxic effects can damage early development and neural tube elaboration occurring during the first three weeks after conception resulting in spontaneous abortion (miscarriage) (Overholser, 1990) (Kesmodel et al., 2002). Exposure between the fourth and ninth weeks is the critical period for malformations of the brain and other cranial structures. Alcohol can result in craniofacial anomalies, organ malformations, microcephaly or a normal sized brain with decreased cells. Alcohol exposure later in pregnancy may affect pre- and post-natal growth and/or behavioural and cognitive disorders (Overholser, 1990, Michaelis and Michaelis, 1994, Abel, 1998a, Gabriel et al., 1998).

It is well accepted that the small molecular size of alcohol allows it to freely cross the placenta attaining nearly equal concentrations in both the mother and fetus. Although it has been questioned whether alcohol affects the fetus directly or indirectly through the production of acetaldehyde, in vitro and in vivo studies have shown that fetal damage occurs even in the absence of acetaldehyde (Overholser, 1990, Michaelis and Michaelis, 1994). The effect of alcohol is considered to occur through a reduction in cell populations either through cell death or decreased cellular proliferation (Abel, 1998a).

Alcohol is thought to affect fetal and cell growth through malnutrition by inhibiting the uptake of nutrients from the gastrointestinal tract (Fisher et al., 1981, Lin, 1981, Overholser, 1990, Michaelis and Michaelis, 1994, Abel, 1998a). The mechanisms contributing to malnutrition include inhibition of the transport of glucose, vitamin B6 (Michaelis and Michaelis, 1994) (Abel, 1998a) and amino acids across placental tissue (Fisher et al., 1981, Lin, 1981, Michaelis and Michaelis, 1994) (Abel, 1998a), and by influencing maternal diet (Abel, 1998a). The maternal and fetal endocrine systems are also reported to be affected by alcohol in a number of ways, and the maternal-fetal endocrine balance may also be disrupted (Michaelis and Michaelis, 1994, Gabriel et al., 1998).
Hypoxia causing developmental delays and malformations is considered to be a likely effect of alcohol although the exact mechanism of action has not been determined. Possible mechanisms of action include constriction of placental and umbilical blood vessels (Michaelis and Michaelis, 1994); reduction of blood flow within the fetus, particularly the brain; maternal hepatic metabolism resulting in reduction of oxygen available to the fetus (Abel, 1998a); and the formation of toxic free radicals (Michaelis and Michaelis, 1994, Abel, 1998a).

The blood concentrations of alcohol required for high levels of free radicals have been reported to be associated with chronic, binge-like consumption of alcohol. Smoking has also been shown to increase free radical formation (Abel, 1998a) and may potentiate the effect of alcohol (Poskitt, 1984). Free radicals result in the accumulation of calcium in cells resulting in the release of neurotransmitters, such as glutamic acid, which have the potential to interrupt the migration of some nerve cells (Michaelis and Michaelis, 1994, Abel, 1998a). Alcohol also results in an increase in prostaglandins. The evidence for involvement of prostaglandins in oxygenation is conflicting though, with some reviews reporting that increased levels lead to hypoxia through constriction of blood vessels (Michaelis and Michaelis, 1994), while others report that they are protective resulting in vasodilation (Abel, 1998a).
Fetal Alcohol Syndrome Diagnosis

Definitions

The term “possible fetal alcohol effects” (FAE) was developed to describe the wide range of alcohol effects on the developing embryo and fetus in the absence of full FAS (Rosett, 1980). Although FAE is still used by some researchers, its definition is considered ambiguous and use has been discouraged (Sokol and Clarren, 1989). Instead, the use of the term Alcohol Related Birth Defect (ARBD), or alternatives such as Alcohol Related (Neuro) Developmental Disorder/Effect (ARND), have been encouraged since the late 1980s as these are terms were considered to denote attribution of the outcomes to the impact of alcohol (Sokol and Clarren, 1989).

Some researchers are concerned that fetal alcohol effects (FAE) and related terms such as alcohol related birth defects (ARBD) and alcohol related neurodevelopmental disorder (ARND) are poorly defined, particularly when history of maternal alcohol use in pregnancy is unknown, and should not be used (Astley and Clarren, 2000). More recently new terms to describe fetal alcohol effects have emerged in the literature including Partial FAS (PFAS) (Moore et al., 2002) and Fetal Alcohol Spectrum Disorders (FASD) which include FAS (Barr and Streissguth, 2001).

Diagnosis

To date there is no objective laboratory test for diagnosing FAS. Instead, the diagnosis of FAS relies on a pattern of abnormalities that make up the syndrome and reports (generally self-reports) of alcohol use/misuse by the mother during pregnancy and around the time of conception. The emphasis is on the occurrence of a set of criteria as each of the individual abnormalities are often subtle, difficult to detect, and may occur in situations where alcohol is not a factor (Aase, 1994).

Over the years a number of paradigms have been described for diagnosing FAS, but each has retained the following key features which occur in a majority of cases: growth retardation, characteristic facial features and central nervous system anomalies (including mental retardation). A number of associated anomalies that occur more frequently with FAS have been documented, but none have been reported to occur in the majority of cases (Clarren and Smith, 1978). Abnormalities in each of the three main categories exclude most other birth defect syndromes (Clarren and Smith, 1978, Rosett, 1980, Sokol and Clarren, 1989, Aase, 1994), while confirmation of diagnosis requires a history of maternal alcohol use during pregnancy (Aase, 1994).

Diagnosis is generally made on infants and young children, as the features of FAS often change with age (Streissguth et al., 1991, Streissguth, 1994, Larkby and Day, 1997). Central nervous system dysfunction and the facial morphology may be difficult to assess prior to 2 years of age (Rosett, 1980, Larkby and Day, 1997). Longitudinal studies have also found that with adolescence the FAS facial morphology becomes less distinctive and the weight approaches the mean. The other manifestations of FAS, intellectual problems, poor age-appropriate life skills, and behaviour problems do not attenuate but continue to be pervasive throughout adulthood (Streissguth et al., 1991, Streissguth, 1994).
The developmental changes occurring in adolescents diagnosed with FAS were investigated in forty-four FAS patients in Germany (Spohr et al., 1994). Their findings may help with diagnosing FAS during late childhood and adolescence. The typical FAS facial features are known to change with puberty, but a number of symptoms persist including microcephaly, short palpebral fissures, indistinct philtrum, a thin upper lip and mild micrognathia. Nasal features change with the development of a large nose and a “distinctive nasal bridge” (page 22). Physical height and head circumference both remained below the norm with 60% and 42% (respectively) remaining 2 SD below the population mean. Weight varied between the sexes with 54% of males 2 SD below the population mean, while only 19% of females fell within this category. The intelligence level of seventy-five percent of these adolescents remained in the borderline categories with low intelligence. The authors also identified the presence of a number of psychiatric disorders in the adolescents.

Institute of Medicine – 1996 Diagnostic Criteria for FAS

The recent paradigm developed by the Institute of Medicine (IOM) in 1996 described five categories for FAS and partial FAS (Abel, 1998a, Weinberg, 1997):

- Category 1 – FAS with confirmed maternal alcohol exposure (Table 1)
- Category 2 – FAS without confirmed maternal alcohol exposure (Table 1 without A)
- Category 3 – Partial FAS with confirmed maternal alcohol exposure (Table 1)
- Category 4 – Alcohol-related birth defects with confirmed maternal alcohol exposure and presence of consistent physical anomalies
- Category 5 – Alcohol-related neurodevelopmental disorder with confirmed maternal alcohol exposure and neurodevelopmental abnormalities and/or behavioural or cognitive deficits

The second category recognizes the fact that information on maternal drinking behaviour may not be present or is unreliable, as many children with FAS are in adoptive or foster homes (Abel, 1998a). This lack of data thereby prevents confirmation of diagnosis and the benefits of that diagnosis.

Criticism has been leveled at both the new IOM guidelines and the preceding paradigms for lacking objective, quantitative scales thereby increasing the risk of diagnostic misclassification. The preceding paradigms also allow diagnosticians to place subjective weights to the features when making a diagnosis. This is of particular importance when assessing the facial features and growth retardation, both of which vary between ethnic populations. The absence of race-standardized norms increases the likelihood of misclassification (Abel, 1995).

The 4-Digit Diagnostic Code

Researchers have recently developed a new diagnostic code in an attempt to overcome the use of a gestalt approach of diagnosis and provide a more accurate and reliable diagnostic system (Astley and Clarren, 2000). Astley and Clarren (2000) have developed the 4-Digit Diagnostic Code, which encompasses quantitative, objective measurement scales and specific case-definitions. A new nomenclature has been developed replacing FAE and ARND with more elaborate diagnostic categories enabling a more comprehensive case description.
Table 1
Institute of Medicine’s 1996 Diagnostic Criteria for FAS: Category 1

A. Confirmed Maternal Alcohol Consumption
   Excessive drinking characterized by considerable, regular, or heavy episodic consumption.

B. Characteristic Facial Feature Include:
   - Short palpebral fissures (small eye openings)
   - Characteristic premaxillary features:
     - Flat upper lip
     - Flattened philtrum (an absent or elongated groove between the upper lip and nose)
   - Flat midface

C. Growth Retardation
   - Decreased birth weight for gestational age
   - Failure to thrive postnatally not related to nutrition
   - Disproportionate ratio of weight to height

D. CNS Abnormalities, including at least one of the following:
   - Small head size
   - Structural abnormalities
     - Small brain
     - Partial or complete absence of corpus callosum
     - Decreased size of cerebellum
   - Neurological hard or soft signs (age appropriate), such as impairment of fine motor skills
   - Neurosensory hearing loss
   - Incoordination
   - Impaired eye-hand coordination

Institute of Medicine’s 1996 Diagnostic Criteria for FAS: Category 3
‘Partial FAS with confirmed maternal alcohol exposure’

A. Confirmed Maternal Alcohol Consumption (as for Category 1)

B. Same facial features as for previous categories. Either C, or D, or E:

C. Same growth retardation as for previous categories

D. Same CNS abnormalities as for previous categories

E. Evidence of complex pattern of behavioural or cognitive dysfunction unrelated to developmental maturity, or to family or home environment including:
   - Difficulties in learning
   - Poor in school performance
   - Poor impulse control
   - Problems in relating to others
   - Deficits in language (understanding and speaking)
   - Poor ability for abstract thinking
   - Poor arithmetic skills
   - Problems in memory, attention, or judgement
Nine diagnostic outcome categories replace the five diagnostic outcome categories used in the gestalt method of diagnosis. The magnitude of expression of the four key diagnostic features of growth deficiency, FAS facial phenotype, central nervous system damage/dysfunction and gestational alcohol exposure, are ranked independently reducing the likelihood of misclassification. Anthropometric and psychometric measures can be developed within this model to assist diagnosis across age, gender, and race.

The 4-Digit Diagnostic Code has been tested over three years in both prospective and retrospective studies of over 1,000 patients and has been reported to have more precision, reliability, and power over the traditional ‘gestalt’ method of diagnosis. When the gestalt and 4-Digit Diagnostic Code outcomes for 454 patients were compared, the gestalt method produced a heterogeneous FAS population with 69 patients diagnosed as FAS, 41 as atypical FAS and 344 as probable FAE. The 4-Digit system on the other hand produced a more specific and exact diagnosis. The new method identified 11 patients with FAS, 16 with atypical FAS and 367 fell into categories that would previously have been defined as FAE/ARND while the remaining patients fell into new 4-Digit categories.

When a random selection of twenty patient files were reanalysed by the authors separately, the 4-Digit Diagnostic Code was found to have a 100% inter- and intra-rater reliability (Kappa = 1.0, p = 0.000). The inter-rater reliability between centres was 94% for the four digits (Kappa = 0.93, p = 0.000) and 100% for matching the diagnostic category (Kappa = 1.0, p = 0.000).

Other research teams are also working to develop a diagnostic-screening test based on craniofacial anthropometric measurements to enable a more reliable diagnosis of FAS facial phenotype and partial FAS to be made. Moore (2002) reported on a method using 21 craniofacial anthropometric measurements that enhances the ability to diagnose individuals with FAS and also those exhibiting the less severe end of the spectrum of disorders in the field (Moore et al., 2002). The authors suggest that this method has the potential to be used as a screening tool, which will enable high-risk children to be identified and referred for further investigation.

The use of magnetic resonance imaging to describe the effect of alcohol on the brain has recently been described although the literature is limited and relates almost entirely to case or group studies. The results of these studies have shown that the basal ganglia, cerebellum, and corpus callosum are sensitive to prenatal alcohol exposure however the full significance of these findings is yet to be determined (Mattson and Riley, 1995).
Epidemiology of FAS and FAE/ARND

Since the early description of FAS three decades ago the association between alcohol consumption and FAS has become widely accepted and as discussed earlier, the features have been clearly documented. Results from early studies clearly identified that the full FAS phenotype was expressed only in patients whose mothers had a history of chronic heavy alcohol use or frequent heavy intermittent alcohol use (Jones et al., 1973, Clarren and Smith, 1978, Rosett, 1980, Sokol and Clarren, 1989). Major risk to the fetus was reported to require an alcohol intake of at least 5-6 drinks per occasion (Clarren and Smith, 1978, Rosett, 1980), with a monthly intake of at least 45 drinks (Rosett, 1980) or daily consumption (Clarren and Smith, 1978).

An important principle of the effect of a teratogen is that it produces a variability of severity in outcomes (Clarren and Smith, 1978). The effects of alcohol can also be seen in a milder, although often clinically significant form, affecting physical, learning, and behavioural outcomes termed Alcohol Related Neurodevelopmental Disorders (ARND) or Fetal Alcohol Effects (FAE). It is a continuum of alcohol related effects that are generally presented in research papers. The quantity of alcohol required to produce ARND has been difficult to establish and is surrounded in controversy.

Alcohol is clearly the necessary factor for the development of FAS and related disorders but as not all children exposed to heavy alcohol consumption during pregnancy are affected or are affected to the same degree, expression of the anomalies appears to require component causes. Other factors, such as the pattern and quantity of alcohol consumption, timing of intake, the stage of development of the fetus at the time of exposure, and socio-behavioural risk factors such as poverty and smoking may act as permissive influences (Abel and Hannigan, 1994, Michaelis and Michaelis, 1994). An overview of prospective epidemiological studies, human morphological studies, and reviews investigating FAS and ARND is presented below.

Pattern of Dysmorphology

A range of brain malformations and disorders have been documented in the embryos of chronic, alcoholic mothers including microcephalus, hydrocephalus, hydroaencephalia and disorders in the migration of cellular elements. Konovalov et al. (1997) undertook a case-control study, in Russia, examining 44 embryos (5-12 weeks) and three fetuses (14-15 weeks) of alcoholic mothers who had undergone termination of pregnancy.

The results showed a high rate of brain dysmorphogenesis and a positive correlation between the amount and frequency of maternal alcohol consumption. Sixty percent of the fetuses of women in the highest intake group, 800-3500 ml. ethanol/week (12.5 mls ethanol = 1 Standard Drink), had major malformations compared to 33% of fetuses of mothers with an intake of 100-200 ml. ethanol/week. An episodic pattern of alcohol consumption (35-100 ml. ethanol) was associated with minor malformations in two/seven cases with no dysmorphogenesis seen in fetuses of non-drinking controls. The type of dysmorphogenesis seen indicates that the initial 3-6 weeks of brain development is likely to be a critical time for the teratogenic effects of heavy alcohol consumption to occur (Konovalov et al., 1997).
Dose Relationship

There is evidence that children exposed to high levels of alcohol during pregnancy and who do not exhibit full FAS remain at risk of significant cognitive deficits. Mattson (1997) reported a reduction of IQ in both children with FAS and children without FAS exposed to high levels of alcohol during pregnancy compared with controls exposed to minimal or no alcohol. Reductions in IQ scores were found for both groups of children (cases) compared to controls with marginally higher IQ scores in the nondysmorphic group (Mattson et al., 1997).

The Seattle Longitudinal Study on Alcohol and Pregnancy is a population-based, prospective, longitudinal study on-going since 1974 (Streissguth et al., 1994, Olson et al., 1997). This study is unique in that the cohort (n=500) involves middle class, Caucasian women considered to be low risk for competing causes (confounders) of poor developmental outcomes.

The results of this longitudinal study demonstrated a relationship between dose and outcome, with a positive relationship between the number of drinks per occasion and the risk of learning problems and attention/memory deficits at 14 years of age (Streissguth et al., 1994, Olson et al., 1997). A correlation was found between the pattern of deficits found in adolescence and those identified during the first seven years of life (Streissguth et al., 1994). Adolescent antisocial behaviour, school problems, and self-perceived learning difficulties were associated with binge drinking in early pregnancy, although not all individuals exposed to high alcohol levels during pregnancy had poor outcomes in these areas (Olson et al., 1997).

Larroque (1995) found consumption of three drinks or more per day during pregnancy to be related to a reduction of psychomotor development in a French cohort study (n=160) but did not find evidence of a significant trend. The relationship was similar, although less significant, for alcohol consumption prior to conception (Larroque et al., 1995). A Pittsburgh cohort study of 595 women found each additional drink per day during the second trimester to be significantly associated with deficits in reading, spelling, and arithmetic, and in the third trimester in spelling (Goldschmidt et al., 1996).

A study by Brown (1991) (cited in Jacobson and Jacobson 1999) found continued drinking throughout pregnancy to be associated with poorer social competence and more aggressive and destructive behaviour. Another study found a relationship between prenatal alcohol exposure and teacher ratings of students’ social, attention, and aggression problems with greater inattention and impulsivity, after controlling for potential confounding factors (Jacobson et al., 1998a). Clinically significant aggressive behaviour problems were found in 33% of children exposed prenatally to moderate or heavy levels of alcohol, compared with 4-5% of the general population (Jacobson and Jacobson, 1999).

A Detroit Study examining 382 Black, mostly lower socioeconomic, inner city infants (12-13 months old) investigated the effect of alcohol consumption during pregnancy and around conception on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) (Jacobson et al., 1993).

The effect of alcohol on the PDI, which assesses walking and balance, was not dose-related with reductions seen only with levels of exposure of 4 drinks/day during pregnancy and 8 drinks/day around conception. Most of these women showed evidence of alcohol related problems (positive MAST score).
The MDI, which assesses simple fine motor and prehensile coordination, showed a dose-dependent linear trend with subtle decrements at lower drinking levels during pregnancy. The study found that at least one drink per day (0.5 oz Absolute Alcohol /day) during pregnancy was required to produce clinically significant impairment. There was an interaction between volume and frequency for MDI, with poorer outcomes seen in infants whose mothers consumed a high volume per occasion and who drank frequently. For drinking at conception no clear threshold was demonstrated.

The study found an increased prevalence of impairment in infants of women greater than 30 years of age, and it was thought that heavy drinking over several years may result in physiological changes affecting metabolism of alcohol (Jacobson et al., 1993, Jacobson et al., 1996). Children of women over 30 years of age who drank at least one drink per day during pregnancy were more than four times as likely to be in the bottom tenth percentile of the MDI test than other children of older women (Jacobson et al., 1993).

In 1999 the data from a sub-sample of the Detroit cohort whose mothers drank greater than one drink per day was reanalyzed to examine the effects of dose and frequency on developmental outcome (Jacobson and Jacobson, 1999). The authors have previously noted that consumption of alcohol by pregnant women does not tend to occur on a daily basis, so averaging alcohol intake and analysing weekly or daily consumption by pregnant women may not accurately reflect the true relationship between alcohol and fetal harm. The results of the re-analysis show the importance of detailing both the quantity and pattern of drinking.

The re-analysis found that the principal determinant of functional deficit was dose of alcohol, and that a history of alcohol related problems (positive MAST score) was not related to functional deficit (Jacobson et al., 1993). The results showed that 80% of the functionally impaired infants had been exposed to a binge pattern of alcohol consumption during pregnancy.

In the group of mothers who drank alcohol on at least four days per week, there was evidence of a threshold with an average of five drinks per occasion required for functional impairment to occur in the fetus. The incidence of functional impairment from heavy drinking per occasion was found only when the heavy drinking occurred at least once a week. The authors warn that this threshold may be too high for many women due to individual metabolic and fetal differences, and that a safety factor should be introduced when determining a “safe” drinking level for pregnant women. As in the original study, the effects of moderate and heavy drinking during pregnancy were more severe in the children whose mothers were over 30 years of age (Jacobson et al., 1998, Jacobson and Jacobson, 1999).

The significance of the pattern of alcohol consumption continues to be overlooked by some authors, adding confusion in determining a ‘safe’ threshold of alcohol consumption. A recent paper by Sood (2001) reports an increased risk of externalizing and aggressive behaviours in children six to seven years of age who were exposed prenatally to as little as one drink per week during pregnancy (Sood et al., 2001). The authors averaged maternal alcohol consumption “across visits to generate a summary measure of alcohol exposure (per day) throughout pregnancy”, thereby overlooking the pattern of drinking and quantity consumed per session. Jacobson has clearly demonstrated the importance of these factors in ascertaining the relationship between maternal alcohol consumption during pregnancy and harm to the developing child.

The studies reported above all surveyed relatively small numbers of pregnant women therefore limiting the statistical power of each study. A meta-analysis of studies examining the relationship between moderate alcohol consumption during pregnancy and the occurrence of fetal
malformations was undertaken to increase statistical power (Polygenis et al., 1998). The authors analysed seven studies with 130,810 pregnancy outcomes, 24,007 in the moderate alcohol group and 106,803 controls and found no increase in fetal malformations with moderate (>2 drinks per week to 2 drinks per day) alcohol consumption during the first three months of pregnancy.

**Issues Relating to Study Bias**

In studies examining the relationship between alcohol consumption during pregnancy and FAS and FAE, bias can arise from inaccurate estimation of the quantity of alcohol consumed and inaccurate diagnosis (refer to section on FAS diagnosis). The impact of the bias will depend upon how it is distributed across the study participants. If the misclassification is random then the study results will underestimate the true association. On the other hand, if the misclassification differs according to the individual’s exposure status, called nonrandom or differential misclassification, the effect of differential misclassification will vary according to the study. In some cases it will have no effect on the result, while in other studies it can overestimate or underestimate the risk from exposure. It is therefore important to consider the potential impact of misclassification on studies investigating the relationship between the level of alcohol consumption during pregnancy and the impact on the developing embryo.

Underreporting of alcohol consumption, particularly where alcohol consumption is perceived to be socially unacceptable, is a problem for alcohol research. The difficulty in collecting accurate data on alcohol consumption is clearly shown by comparison of the per capita level of alcohol consumption based on alcohol sales data and that based on survey data. The estimation of per capita alcohol consumption obtained through surveys is between 40% and 60% of that obtained from sales data. A number of reasons are given for these discrepancies, including seasonal variations in the pattern of drinking behaviour, inaccurate estimates of drink sizes, selective reporting or intentional under-reporting of alcohol consumption and differences in the methods used for collecting data on self-reported alcohol consumption (Stockwell et al., 2000).

**Changes in Pattern of Alcohol Consumption During Pregnancy**

The Seattle Longitudinal Study obtained data on pre-pregnancy and pregnancy drinking (oz. absolute alcohol consumed/day and the pattern of consumption) in the fifth month of pregnancy. Women reported that their pattern of drinking changed once pregnancy was recognized. Decreases were observed in the average number of drinks consumed per occasion from 2.5 to 2, in the average number of drinking occasions per month from 17 to 8, and in the proportion of women drinking five or more drinks on at least one occasion, from 39% to 24% (Streissguth et al., 1994).

Changes in the pattern of alcohol consumption have also been reported by other studies (Plant, 1984, Day et al., 1989). Day (1989) followed a cohort of 650 women of low socioeconomic status in Pittsburgh. They found a decrease in alcohol use (>0.89 drinks/day) between the first to the third months of pregnancy (36.6% to 13.6%), with the greatest decrease following recognition of pregnancy. In a Scottish cohort 70% of women reduced alcohol consumption after becoming aware of their pregnancy (Plant, 1984). Heavy drinkers have been reported to continue heavy drinking during pregnancy, although variability in the quantity consumed was reported (Rosett, 1980).
These results identify an area of concern as the effect of alcohol exposure on the developing embryo/fetus has been shown to depend upon the timing of alcohol exposure. Therefore surveys of alcohol consumption during pregnancy should be conducted at multiple times, including pre-pregnancy levels of consumption, as a single survey point during pregnancy or following delivery would be unlikely to provide a precise estimate.

The Australian Institute of Health and Welfare recently analysed data from the 2001 National Drug Strategy Household Survey (NDSHS) relating to alcohol consumption by pregnant and breastfeeding women. Their results showed a large reduction in consumption of alcohol during pregnancy, with 59% of women reducing their alcohol consumption from pre-pregnancy levels, and 36% of women abstaining compared to 21% of women abstaining from alcohol in the general population. Reductions in alcohol consumption for breastfeeding women showed the same trends with 66% decreasing their consumption and 28% abstaining from alcohol (2001 NDSHS unpublished data).

Recall Bias

Recall bias in alcohol research can happen when alcohol consumption is reported differently by a person exposed to one level of consumption compared to those with a different level of consumption. If it occurs among pregnant women who have a moderate to high level of alcohol consumption resulting in their misclassification as light to moderate drinkers, there is the potential for a dose-response relationship to appear where one does not truly exist (Verkerk, 1992).

Estimation of Alcohol Consumption

Research commonly uses the term ‘standard unit’ or ‘standard drink’ when conducting surveys about alcohol consumption. However there is considerable evidence that these terms are not an accurate measure of the amount people drink. A number of issues impact on the precision of measurement of alcohol intake using the term standard drink, including knowledge of the term, country and region, drinking venue, strength of beverage, drinking vessel and style of drinking (Carruthers and Binns, 1992, Lemmens, 1994, Banwell, 1999, Kaskutas and Graves, 2000, Stockwell et al., 2000, Kaskutas and Graves, 2001).

Many survey participants do not understand what constitutes a standard drink (Carruthers and Binns, 1992, Lemmens, 1994, Stockwell et al., 2000, Banwell, 1999, Kaskutas and Graves, 2000, Kaskutas and Graves, 2001), and the definition of a standard drink is not uniform throughout the world. There is up to a 6 gram variation in quantities defined as a standard serve from 8 grams in the UK, 10 grams of alcohol in Australia and New Zealand, 13.6 grams in Canada and 12-14 grams in the USA (Stockwell et al., 2000).

The quantity of alcohol served as a drink also varies according to venue. In licensed premises, legislation determines the standard size of a serve of some beverages such as spirits (Stockwell et al., 2000), but not for wine which has been shown to have considerable variation in a standard serve. In studies investigating the serving size of wine in urban hotels in Australia, serving sizes were on average 160mls (range 110-230 mls) or 60% more (Banwell, 1999) up to 70% more (range 100-250+ mls) (Stockwell, 1992) than a standard drink of wine (100 mls). Research has also found a glass of wine consumed in a private setting to have a volume in excess of a standard drink (Carruthers and Binns, 1992, Banwell, 1999).

The variation in the size of a serve of alcohol in private settings has been supported by other studies (Carruthers and Binns, 1992, Lemmens, 1994, Kaskutas and Graves, 2000, Kaskutas...
and Graves, 2001). A Dutch study found that self-reported drinks were higher than a standard
drink of 10 grams and varied by beverage type ranging from an increase of 26% for spirits,
14% for fortified wines and 4% for wine (Lemmens, 1994).

A US researcher interviewed a sample of pregnant Native American and African American
women. The studies investigated a ‘graduated frequency’ method for estimating drink size
(Kaskutas and Graves, 2001) and a vessels methodology (Kaskutas and Graves, 2000), and
compared the responses to estimates obtained using the term ‘standard drink’. The results
showed that drinkers consumed larger-than-standard drink sizes and that the variation was
greater for some types of drinks (eg spirits) than other types of alcoholic beverages. Although
the numbers surveyed in these two studies were small, the results support those reported
elsewhere, and identify the need for surveys to include questions on type of beverage and
drink size in order to obtain a precise measurement of alcohol consumption. The estimates can
also be undermined by the pattern of drinking, which in some indigenous communities consists
of sharing a bottle with a number of other people (Kaskutas and Graves, 2001).

The evidence suggests that using the term ‘standard drink’ in surveys underestimates the true
level of consumption in many cases and may result in spurious estimates. Reliable and consistent
methods for estimating alcohol consumption are needed in order to compare the findings of
studies and determine the true relationship between low to moderate alcohol consumption and
FAE/ARND.

**Socio-Behavioural Component Causes**

**Maternal Age**

The early report by Jones (1973) described FAS in eight children of whom only two had
mothers less than 30 years of age. Recent studies found functionally significant deficits occurred
most strongly in children of older mothers (Jacobson et al., 1996, Jacobson et al., 1998). Children
of moderate-to-heavy (at least five drinks/occasion on an average of at least once/week) drinking
mothers 30 years of age and over were 2 to 5 times more likely to have functional impairment
than those with younger moderate-to-heavy drinking mothers (Jacobson et al., 1998). The
authors state that the increased risk may be due to either age-related physiological changes
and/or duration of drinking. The physiological changes include increases in maternal body fat-
to-water ratio and an increased rate of alcohol metabolism in women with a pattern of chronic
drinking (Jacobson et al., 1996, Jacobson et al., 1998).

**Socio-Economic Status**

As discussed earlier, low socioeconomic status was identified as being associated with FAS in
the early study by Jones (1973), although the extent of the relationship was unknown to the
authors. Since the early studies, ascertainment of populations for the study of FAS has generally
focused on inner city hospitals and low socioeconomic groups (Abel and Hannigan, 1995).

When chronic alcoholic mothers were divided into upper middle and lower class, a significant
increase was seen in the incidence of FAS offspring in lower class alcoholic mothers (Bingol
et al., 1987). The authors noted that that the women in the lower socioeconomic group were
much younger in age at first delivery (6.5 years younger on average) and had started drinking
at a younger age. It is difficult to interpret the importance of age as a contributing factor as
duration of drinking may be a confounding factor (Abel and Sokol, 1986b) and is not always
accounted for.
Bingol (1987) found a significant increase in the incidence of FAS in children whose mothers were of low socioeconomic status (SES) and of either Black or Hispanic origin. The parameters of mean weight, length and head circumference at birth were all significantly lower in the offspring of lower socioeconomic alcoholic mothers compared with the offspring of both upper middle class alcoholic mothers (all Caucasian) and lower socioeconomic, non-drinking controls. The rate of congenital malformation, failure to thrive, and mental retardation were also significantly increased in this group of children. An increased prevalence of attention deficit disorder (ADD) in school age children was found in both the offspring of upper middle class alcoholic and lower socioeconomic alcoholic women compared to the general population (4 and 14 times respectively). The authors proposed that the socioeconomic differences in the incidence of FAS and ARND were due to an interaction of poor nutrition, genetic, and social factors along with the cumulative effect of intergenerational maternal alcoholism in the impoverished group (Bingol et al., 1987).

Other factors pertaining to low SES include environmental pollutants such as lead, which can directly affect central nervous system damage, psychological stress or physical abuse, nutrition and smoking. Stress and abuse can work directly on maternal physiology and health, indirectly to enhance the biological potency of alcohol, and by contributing to the initiation and continuation of alcohol consumption by pregnant women. The review by Abel and Sokol (1986) reported a high correlation between smoking, alcohol consumption, and low SES, which combine to elicit an increased susceptibility to the teratogenic effects of alcohol.

Race

The importance of race as a contributing factor is confounded by socioeconomic status since the two are highly linked (Abel and Hannigan, 1995). The review by Able and Hannigan (1995) found that there is no evidence that the increased risk of FAS in African- and Native-American alcoholic women is due to biological factors, as genetic studies have found greater intra-group than inter-group genetic variability in African-Americans and Caucasians. The authors suggest that cultural factors, such as drinking patterns, amount consumed per occasion, low socioeconomic status and differences in diet contribute to the racial differences seen in the incidence of FAS.

Concern has been voiced that associating FAS within a minority race or social class could propagate discrimination. Public attention and effort to address FAS would be likely to be greater if the issue is perceived to impact on the general community but this approach has been shown to have some problems. It may serve to instill panic, reduce the attention on social inequality, and result in the blaming of individual mothers, as has occurred in the US where a pregnant women who was intoxicated was charged with child abuse (Armstrong and Abel, 2000).

Genetic Factors

Genetic factors may play a role in the individual fetal response to alcohol. Differences in individual sensitivity to alcohol are thought to contribute to the impact of alcohol on the fetus with twin studies the basis of support. A high correlation has been shown for FAS among monozygotic twins, while dizygotic twins show differential sensitivity to FAS suggesting a genetic basis for these differential sensitivities (Abel and Hannigan, 1995).
‘Other’ Drugs

Research investigating the effect of alcohol and other non-pharmaceutical drugs on pregnancy outcomes, is generally segregated by the type of substance. There is evidence that tobacco, marijuana, and cocaine individually reduce fetal oxygenation through effects on uterine blood flow resulting in hypoxia and increased free radical formation, while smoking and caffeine are also thought to reduce the levels of certain nutrients. These effects may enhance the teratogenic effects of alcohol (Young, 1997).

The literature reports show conflicting findings on individual substances, which in part can be attributed to methodological issues. Some studies have found a high correlation between women who use alcohol during pregnancy and the use of other substances including marijuana, tobacco, and other illicit drugs (Day et al., 1989, Abel and Hannigan, 1995). On the other hand, a prospective study found no increased risk of FAS with prenatal drug exposures including cigarettes, opiates, cannabis and cocaine (Sokol et al., 1993). The literature assessing the impact of inhalants on fetal development is primarily limited to descriptive studies lacking in scientific rigor. A recent case-control study however did not find evidence of a physical phenotype associated with fetal solvent syndrome (Tenenbein, 2000). Overall there have been too few longitudinal studies analyzing the interactive effects of prenatal polydrug exposure to draw a conclusion.

Antiepileptic drugs during pregnancy have been demonstrated to have a teratogenic effect on the developing fetus which may exhibit features similar to FAS (Fonager et al., 2000, Holmes et al., 2001, Dean et al., 2002, Holmes, 2002). Abnormalities include midface hypoplasia, developmental delay, microcephaly and growth retardation, although the evidence for growth retardation is conflicting.

Incidence or Prevalence of FAS, FAE/ARND

Australian Data

Initial case reports of FAS in Australia were published in the early 1980s identifying a total of 27 children with FAS of whom 18.5% had Aboriginal parents. All the mothers of these children had a history of heavy or binge drinking during the pregnancy or a history of chronic alcoholism (Lipson et al., 1983, Walpole and Hockey, 1980).

An Australian prospective cohort study conducted between 1982-84 examined the relationship between low to moderate alcohol, averaged to daily intake, and FAS in infants within one to three days following birth (Walpole et al., 1990, Walpole et al., 1991). As discussed earlier, diagnosis of FAS prior to two years of age is difficult and likely to underestimate the prevalence of alcohol-related problems.

The importance of using multiple sources for FAS surveillance has been demonstrated recently in Western Australia (WA). The prevalence of FAS on the Births Defects Registry in WA increased 38% with the addition of data from the Rural Pediatric Service (RPS) database. Since the addition of the RPS data, the prevalence of FAS (1980-97) increased from 0.13 to 0.18/1,000 and is now recorded as 0.02/1,000 for non-Aboriginal children and 2.76/1,000 for Aboriginal children in WA. The authors suggest that these results may be an under-estimate of the true prevalence due to under-diagnosis, under-ascertainment, or both and that further investigation of ascertainment and baseline prevalence is warranted (Bower et al., 2000).
International Data

Estimates for the incidence and prevalence of FAS vary between countries, between ethnic groups within those countries, and over time. Two reviews that critique population-based studies that have published the incidence of FAS are reported here (Abel, 1995, Sampson et al., 1997) (Table 2).

The review by Abel (1995) reports the U.S. incidence of FAS from 1973-1992 as 1.95/1,000 births; 0.26/1,000 when restricted to middle/upper class Caucasians, 2.29/1,000 for African/Native Americans, and the European incidence as 0.8/1,000 births. The author reports that low SES rather than racial characteristics, is responsible for the observed differences. However, the variation between the studies in the criteria used for diagnosing FAS and for case ascertainment should not be discounted and may account for some of the reported variation in estimates.

The review by Sampson (1997) reported the incidence of FAS for different time periods at two U.S. sites and one site in France. At each of these centres the mothers of children with FAS were characterised by poverty and alcoholism, and in the U.S. centres the mothers belonged to racial minorities, while in France the mothers were Caucasian. The diagnostic criteria used in France divides the diagnosis of FAS into three categories, moderate FAS (Type I), full FAS (Type II), and severe FAS (Type III), a diagnostic method that varies from that used at the U.S. sites. The reported incidence in France varies depending upon the diagnostic criteria used from 1.3/1,000 live births for severe FAS (Type III) to 4.8/1,000 births for all three FAS Types combined. This range encompasses the estimates reported for both U.S. studies, 2.8/1,000 live births in Seattle to 4.6/1,000 in Cleveland (Table 2). When the authors applied the US diagnostic criteria to the data from France an estimated incidence of FAS of 2.3/1,000 live births. When the prevalence of both FAS and ARND in the Seattle data are reported together, the result is considerably higher (9.1/1,000 births).

These studies demonstrate some of the inherent difficulties encountered when trying to get a clear picture of the incidence/prevalence of FAS. They also present evidence for a strong relationship between alcohol, poverty, and the incidence of FAS.

Indigenous Populations

Indigenous people are reported as having a higher incidence/prevalence of FAS that the wider community, but, as stated above, this association may be determined more by socio-cultural variables such as SES and drinking patterns rather than racial characteristics.

A study by May (1991) reported rates of FAS in three major Indian cultural groups (Navajo, Pueblo, and SW Plains) for two periods in time, 1969-1977 and 1978-1982 (May, 1991). Considerable effort was extended in case ascertainment and where ascertainment was incomplete, the community was excluded. The results show a high variation in the prevalence of FAS between cultural groups (1.0, 1.3, and 17.5 /1,000 births respectively) and an increase in the prevalence of FAS over time, most notably in the two groups with initial low rates (5.2, 5.7, and 20.5 /1,000 respectively) in the 1978-1982 birth cohort (Table 2; Figure 1).

The variations between cultural groups in the earlier time frame reflect the high rate of abusive drinking in the SW Plains Indians that was not found in the other two groups. The increase in the prevalence in FAS over time in the Navajo and Pueblo groups reflects an increase in the prevalence of drinking in these groups, while no significant change in drinking patterns was
seen for the SW Plains group. In these communities only a small proportion of women gave birth to children with FAS (maternal rate 6.1/1,000), and unless these women totally abstained from alcohol during subsequent pregnancies, all their future children were also born with FAS or FAE. Of the mothers who gave birth to children with FAS or FAE, 23% died prior to their children being diagnosed. Therefore the target group for tertiary prevention is relatively small and easily identifiable.

Sixteen data sources were used to investigate the prevalence of FAS in Alaska during the time period 1977 through 1992. Potential cases were identified through private and public pediatric practices, native health services and corporations and were screened to ensure they met the full criteria for FAS (diagnosis by physician, alcohol exposure, facial features, growth deficiency, and CNS impairment). Of the 630 potential cases identified, 23% (n=145) met the full FAS criteria. Native Alaskan children comprised 83% of the cases and 67% of the children with known custody status were either in foster care or adopted. The prevalence reported when the strict criteria were used was 3.0/1,000 among Alaska Natives during 1977 through 1992 and for the non-native population it was 0.2/1,000. The prevalence of FAS in the native population fluctuated when the sixteen years were divided into four-year time periods (Table 2). The authors believe the reliance on medical chart notations for case ascertainment may have under-represented the prevalence of FAS in Alaska (Egeland et al., 1998).

A retrospective study conducted in Canada, of which 86% of the study population was indigenous, reported a lower prevalence of FAS (0.585/1,000 during 1973-1992) than that reported by May in his study of the Navajo, Pueblo, and SW Plains group (Habbick et al., 1996). This may reflect either the true prevalence in this population or result from incomplete ascertainment of cases (Table 2). Retrospective studies may not provide an accurate estimate of the incidence of FAS, as untrained observers frequently do not fully detail the facial anomalies making the diagnosis of FAS difficult (Clarren and Smith, 1978). The Canadian study found no significant difference in the prevalence of FAS between the two time periods investigated.
(1973-1977 and 1988-1992), but the inherent difficulties with retrospective studies could have clouded the true prevalence.

A review of three studies of FAS by Bray and Anderson (1989) found considerable discrepancy in the prevalence of FAS in Native Canadian children (Bray and Anderson, 1989). The results varied from a reported ratio of 9.9:1 FAS cases in indigenous people to non-indigenous, 46/1,000 in Native children in the Yukon and 25/1,000 in Native children in Northwest British Columbia. The authors identify methodological issues that may partially account for the wide variation including selection bias, lack of non-Native comparison groups, and lack of control for potential confounders.

A more recent review of studies of the prevalence of FAS in Canadian and American indigenous people concluded that the high rates reported for FAS among these populations are consistent between the studies reviewed although the true estimate is difficult to determine. This is in spite of methodological inconsistencies including differences in ascertainment of cases, diagnostic criteria, and selection bias in relation to choice of communities for inclusion used between studies (Burd and Moffatt, 1994).

The highest rate of FAS documented for any racial group was reported in a case-control study conducted in the Western Cape Province of South Africa by May et al (2000) where 89% of the study population was of coloured or mixed-ancestry (Table 2) (May et al., 2000). The occurrence of FAS was found more frequently in the rural compared to the urban schools and reflects the risk from residence on grape-growing, wine-producing farms where regular and heavy alcohol consumption is the pattern by workers. These workers have a binge pattern of drinking occurring mostly on weekends. The study found a significant difference in the mean number of drinks consumed on Saturday, the pattern of drinking during pregnancy, and the proportion smoking during pregnancy between the mothers of children with FAS and the mothers of control children. The authors identify a number of social and economic conditions that may result in extreme alcohol misuse in developing communities. These include low SES and education, early stage of increasing economic development, increased access to alcohol and loss of traditional culture.

**Surveillance**

The Australian Paediatric Surveillance Unit commenced active surveillance of FAS in January 2001, with monthly reporting by over one thousand paediatricians in Australia. This, the first prospective national study of FAS in Australia, will continue for three years and aims to document the incidence of FAS. All reported cases to date had high alcohol exposure in utero and the indigenous population was over-represented. Non-parental care was common with a high rate of referral to the Department of Community Service and developmental and disability services (personal communication, Bower C. for Australian Paediatric Surveillance Unit FAS Study Group).

The U.S. Centers for Disease Control and Prevention have been conducting population-based surveillance of the prevalence of FAS and FAE since 1979 (Table 2) (Cordero et al., 1994, Centers for Disease Control & Prevention, 1995, Centers for Disease Control & Prevention, 1997). The changes in prevalence over time are considered to reflect improved ascertainment of cases rather than a true increase in the incidence of FAS and FAE (Cordero et al., 1994). The National Birth Defects Monitoring Program (BDMP) is not specific for FAS and is based on a diagnosis of FAS in newborn infants while the Metropolitan Atlanta Congenital Defects Program (MACDP) uses multiple sources to diagnose FAS during the first year of life. Neither of these
methods are reliable and both methods may underestimate the true incidence, since FAS is most frequently diagnosed in older children (Streissguth et al., 1991, Streissguth, 1994, Larkby and Day, 1997)

A more complete, multiple-source method of FAS surveillance is conducted using the MACDP and the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP), the latter of which identifies children aged 3-10 years of age receiving special services due to impairments including mental retardation (Table 2). Diagnosis of FAS or partial FAS is based on the Institute of Medicine’s diagnostic paradigm. Although this latter method of surveillance utilizes existing sources of data and results in more complete case finding, a number of difficulties with this method of surveillance remain. These include a lack of confirmation of diagnosis by a dysmorphologist and underascertainment of cases (Cordero et al., 1994).
Table: 2 Incidence/Prevalence of FAS or FAS & ARND

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Years Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.A. May 1991</td>
<td>Pilot project to produce accurate prevalence statistics – surveillance case-finding with diagnosis by a trained dysmorphologist</td>
<td>1979-1983</td>
</tr>
<tr>
<td>J.F. Cordero 1994</td>
<td>Review reporting the prevalence of FAS reported by the National Birth Defects Monitoring Program (BDMP) and Metropolitan Atlanta Congenital Defects Program (MACDP).</td>
<td>1979, 1992</td>
</tr>
<tr>
<td></td>
<td>Population-based surveillance</td>
<td>1979-92</td>
</tr>
<tr>
<td>E.L. Abel 1995</td>
<td>Review of 35 studies reporting the incidence of FAS and overall estimate calculated</td>
<td>Articles from 1973-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centers for Disease Control &amp; Prevention, 1997</td>
<td>National Birth Defects Monitoring Program (BDMP), based on ICD-9 code 760.71</td>
<td>1979, 1993</td>
</tr>
<tr>
<td></td>
<td>Population-based surveillance</td>
<td>1979-1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1973-1992</td>
</tr>
<tr>
<td>Centers for Disease Control &amp; Prevention, 1997</td>
<td>Multiple data source, population-based surveillance – CDC linked data from Metropolitan Atlanta Congenital Defects Program (MACDP) and Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)</td>
<td>1981-1989</td>
</tr>
<tr>
<td>G.M. Egeland et al 1998</td>
<td>Multiple data source surveillance in Alaska – 16 data sources were used</td>
<td>1977-1992</td>
</tr>
<tr>
<td>H. Grinfeld et al 1999 (Short Report)</td>
<td>Cross-sectional study of FAS reported in four genetic services linked to universities in Sao Paulo, Brazil</td>
<td>1997</td>
</tr>
<tr>
<td>P.A. May et al 2000</td>
<td>Case-control design with active case ascertainment in a community in the Western Cape Province of South Africa of 6-7 year olds included 12/13 primary schools</td>
<td>Not Stated</td>
</tr>
<tr>
<td>Population studied or number of FAS &amp; ARND cases</td>
<td>Incidence/Prevalence/1,000 births</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------</td>
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</tr>
<tr>
<td>All SW Indians: FAS</td>
<td>2.0 per 1,000 births</td>
<td>Rates varied by cohort and community.</td>
</tr>
<tr>
<td>FAS &amp; ARND</td>
<td>3.1 per 1,000 births</td>
<td>* Maternal rates of production of a child with FAS or ARND were 6.1/1,000 in all SW Indians ranging from 4.6 – 30.5/1,000.</td>
</tr>
<tr>
<td>FAS &amp; ARND: Navajo Indians</td>
<td>4 &amp; 5.2 / 1,000</td>
<td></td>
</tr>
<tr>
<td>Pueblo Indians</td>
<td>4.1 &amp; 5.7 / 1,000</td>
<td></td>
</tr>
<tr>
<td>SW Plains Indians</td>
<td>17.5 &amp; 20.5 / 1,000</td>
<td></td>
</tr>
<tr>
<td>BDMP: based on ICD-9 code 760.71</td>
<td>0.1 per 1,000 births</td>
<td>These programs were not designed for surveillance of FAS. BDMP not evaluated for sensitivity and P.V.P. ICD – 9 code includes birth-defects in Atlanta</td>
</tr>
<tr>
<td>MACDP: Monitors all birth-defects in Atlanta</td>
<td>4.1 per 1,000 births</td>
<td>FAS but is not specific. and may reflect improved ascertainment of cases.</td>
</tr>
<tr>
<td>Both:</td>
<td>0.33 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>U.S. incidence</td>
<td>1.95 per 1,000 births</td>
<td>The author states that the major determinant for FAS is poverty, not racial background.</td>
</tr>
<tr>
<td>Low SES African/Navajo Indians</td>
<td>2.29 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Middle / Upper SES Pueblo Indians</td>
<td>0.26 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>European incidence</td>
<td>0.08 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Not given</td>
<td>1.0 per 1,000 births</td>
<td>ICD – 9 code 760.71 includes FAS, but is not specific to FAS. Increases may reflect improved ascertainment of cases.</td>
</tr>
<tr>
<td>126 / 188,905 births</td>
<td>0.67 per 1,000 births</td>
<td></td>
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<tr>
<td>2023 / 9,434,560 births</td>
<td>0.22 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Denominator not given</td>
<td>0.515 per 1,000 births</td>
<td>Specialist physicians examined all but 15 cases. 86% (178) Aboriginal, 4.3% unknown, 9.7% (20) Caucasian. Full FAS only examined.</td>
</tr>
<tr>
<td>40 cases Full FAS</td>
<td>0.589 per 1,000 births</td>
<td></td>
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<tr>
<td>47 “ “</td>
<td>0.585 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>194 “ “</td>
<td>0.585 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Full FAS:29 / 285,538 births</td>
<td>0.10 per 1,000 births</td>
<td>Multiple-source method of FAS surveillance, more complete &amp; enables comparison of rates between (US) states.</td>
</tr>
<tr>
<td>Partial FAS: 41 / 285,583 births</td>
<td>0.25 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Seattle – FAS</td>
<td>2.8 per 1,000 births</td>
<td>Rate for France depends upon diagnostic criteria used. (Refer text).</td>
</tr>
<tr>
<td>Cleveland – FAS</td>
<td>4.6 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>France - FAS</td>
<td>1.3-4.8 / 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Seattle FAS &amp; ARND</td>
<td>9.1 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Alaska total population</td>
<td>4.1 per 1,000 births</td>
<td>Prevalence of FAS reported for cases meeting 5-criteria case definition. Rates higher when strict criteria not used. Multiple data sources gave more accurate case ascertainment.</td>
</tr>
<tr>
<td>Alaska Natives</td>
<td>3.0 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>“ “</td>
<td>1.4 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>“ “</td>
<td>3.8 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>“ “</td>
<td>4.1 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>“ “</td>
<td>2.5 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>17/16,440 (referred births)</td>
<td>1.0 per 1,000 births</td>
<td>No mention of criteria used for FAS diagnosis. The authors comment that FAS could be under-reported and under-diagnosed.</td>
</tr>
<tr>
<td>18 Urban &amp; 28 Rural</td>
<td>46.4 per 1,000 births</td>
<td>Stable community. (89%) Coloured /mixed ancestry. (5%) Black African. (6%) White. Highest documented rate of FAS.</td>
</tr>
<tr>
<td>46 Total/992 in schools</td>
<td>46.4 per 1,000 births</td>
<td></td>
</tr>
<tr>
<td>Community wide age-specific rate for 6-7 year olds (48 cases)</td>
<td>39.2 per 1,000 births</td>
<td></td>
</tr>
</tbody>
</table>

*This reflects the increased probability of a mother with a FAS child having subsequent children with FAS (Day, 1992) (May, 1991)
Knowledge of FAS

The patterns of drinking in young women indicate the need for this group to understand the risks associated with heavy alcohol consumption during pregnancy. A study conducted in the U.S. found that 4% of young women aged 18-20 years of age continued their use of alcohol and tobacco during pregnancy, and that this use was associated with a lower level of education (Henderson, 2000). These findings raise significant concern as 38% of Australian women report consuming three or more drinks and 15.5% consume five or more drinks per occasion with 24% and 10% (respectively) consuming this quantity at least weekly (Australian Institute of Health and Welfare, 1999).

Women’s knowledge of the risks associated with alcohol consumption during pregnancy appears to be limited. A study conducted in Perth found that a minority (22%) of women knew about FAS, while 30% thought it was safe to drink above recommended guidelines during pregnancy, and around 30% intended to drink during future pregnancy. There was a positive relationship between knowledge of FAS and the level of education attained. The study found that medical advice on consumption of alcohol during pregnancy was received by less than a third of women who had been recently pregnant and less than a quarter of women pregnant more than four years prior to the study (Corti et al., 1990).

The provision of information on FAS is a necessary step in health promotion and prevention strategies but knowledge alone may not be enough to change behaviour. In 1990, three cases of FAS were identified out of 119 Aboriginal pregnancies in Port Augusta, South Australia. Health messages about refraining from alcohol consumption during pregnancy were available, but there was no indication of the degree that this knowledge was internalized and acted upon by indigenous women (Brady, 1991).

A low level of knowledge of FAS was found in indigenous communities in Northern Manitoba where 51% of indigenous women report consuming alcohol during pregnancy. Thirty-six percent of the women had heard of FAS, but there appeared to be a weak relationship between knowledge of FAS and alcohol use during pregnancy. The use of alcohol and other drugs during pregnancy was highest in young women, although they were the most knowledgeable about FAS (Williams and Gloster, 1999).

A recent Canadian study evaluated physician’s knowledge of maternal drinking patterns and their ability to diagnose FAS (Nevin et al., 2002). The study found that although the majority of physicians surveyed reported counseling pregnant women about the use of alcohol, none used a recognized screening method to determine maternal alcohol use. In relation to making a diagnosis of FAS, most of the physicians surveyed did not feel comfortable or competent at diagnosing FAS. The study identified the need for increased education about FAS in medical schools and in-service education for practicing physicians.
References


Abel, E. L. and Sokol, R. J. (1986a) Fetal alcohol syndrome is now leading cause of mental retardation, Lancet, 2, 1222.

Abel, E. L. and Sokol, R. J. (1986b) Maternal and fetal characteristics affecting alcohol’s teratogenicity, Neurobehavioural Toxicology and Teratology, 8, 329-334.


Henderson, C. W. (2000) Younger women less likely to stop using alcohol and tobacco during pregnancy, Medical letter on the CDC & FDA.


Glossary

Anencephaly
Congenital absence of the cranial vault, with cerebral hemispheres completely missing or reduced to small masses attached to the base of the skull.

Binge drinking
Generally considered as consumption of at least five or more drinks per occasion for women.

Cerebellum
Part of the brain concerned with the coordination of movements.

Corpus Callosum
An arched mass of white matter which connects the cerebral hemispheres.

Dysmorphogenesis
Malformation of the development of form, in this case the fetus.

Epicanthal folds
A vertical fold of skin on either side of the nose, sometimes covering the inner canthus (of the eye). It is present as a normal characteristic in persons of certain races and sometimes occurs as a congenital anomaly in others.

Hydrocephalus
A condition characterized by abnormal accumulation of fluid in the cranial vault, accompanied by enlargement of the head, prominence of the forehead, atrophy of the brain, mental deterioration, and convulsions. It may be congenital or acquired and have a sudden onset.

ICD-9-CM, 760.71 –
This code of the International Classification of Diseases, Ninth Revision, comprises noxious influences affecting the fetus or newborn through placenta or breast milk, specifically alcohol, and includes FAS. The code however is not specific for FAS.

Metropolitan Atlanta Congenital Defects Program (MACDP)
Monitors infants born to residents of five metropolitan Atlanta counties using multiple sources to identify diagnoses of FAS in newborns and infants through the first year of life. Abstractors visit all birth hospitals, neonatal intensive-care units, and genetics clinics to identify and document possible cases.

Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)
Identifies children aged 3-10 years of age living in the same five metropolitan Atlanta counties who have mental retardation, cerebral palsy, hearing impairment, or vision impairment. These children are primarily enrolled in public special education programs or receiving other special services.

Microcephalus
An individual with a very small head.

Microcephaly
Abnormal smallness of the head, usually associated with mental retardation.

Micrognathia
Failure of development of the lower jaw resulting in a receding chin.
Morphogenesis
The evolution and development of form as for example, the development of the shape of a particular organ or part of the body.

National Birth Defects Monitoring Program (BDMP)
Monitors reported hospital discharge diagnoses of newborns that use the ICD-9-CM. This program relies on the diagnosis and recording of FAS on the newborn’s hospital admission and/or discharge records.

Palpebral
Pertaining to an eyelid. Short palpebral fissures are small eye openings.

Philtrum
The vertical groove in the median portion of the upper lip.