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Alcoholis

THE BULLETIN OF THE MEDICAL COUNCIL ON ALCOHOL

Committed to improving medical understanding of alcohol-related problems

FROM THE EDITOR

Dr Dominique Florin

Fetal alcohol syndrome

In this issue we have published two articles about very different aspects of fetal alcohol syndrome (FAS). Denis Viljoen from the Foundation for Alcohol Related Research in South Africa has written about the shockingly high rates of FAS in South Africa, apparently due to historical and sociological factors. At the other end of the spectrum, Peter Hepper has written about some of the detailed studies into the effects of alcohol on the behaviour of the fetus *in utero*. We have accompanied these pieces with an excellent entry to our National Alcohol Awareness Day poster competition, which gives a striking warning about the effects of alcohol in pregnancy. FAS will be the subject of a symposium at the MCA's AGM on 25 November, and we will be publishing more pieces on this fascinating and crucial topic in subsequent issues of *Alcoholis*.

Evidence for policies to reduce alcohol-related harm

Two recent publications provided summaries of the evidence for reducing alcohol-related harm. New NICE guidelines came out in June and were widely reported in the media.[1] The most extensive coverage was given to the recommendation to introduce minimum pricing for alcohol. This action is of course strongly supported by many authoritative medical voices. However, the idea of minimum pricing is not universally popular, and has been described as potentially penalising the sensible, moderate majority. The NICE guidelines cover both population-wide policy changes, such as minimum pricing and reducing availability, and individual interventions by local health professionals. NICE do, however, comment that policy change (such as minimum pricing) is likely to be more effective and cost-efficient than individual interventions. In summary, the NICE guidelines make a total of 12 recommendations, ranging from policy (action on pricing, availability and marketing) to practice (action on licensing, screening and brief interventions). These guidelines are part of a group of three on alcohol use disorders. Earlier this year NICE published guidelines on the diagnosis and clinical management of alcohol-related physical complications, and in February 2011 publication is expected of guidelines on the diagnosis and management of harmful drinking and alcohol dependence.

Another publication of relevance to alcohol policy is the second edition of *Alcohol: no ordinary commodity* by Babor *et al*.[2] This is an excellent and comprehensive review of international data on the full range of population-wide and individual interventions to reduce alcohol harm. The authors report that the strongest evidence is for pricing interventions, restrictions on the physical availability of alcohol, drink-driving measures, and brief interventions and treatment of at-risk and dependent drinkers. The effectiveness of voluntary marketing codes and education and persuasion strategies is much lower.

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Michael Frowen Memorial Essay Prize

In this issue we announce the winners of the annual Michael Frowen Memorial Essay Prize. The winning essay will be published in the 2010 Annual Report. We also announce the title of the essay for next year and hope that students will be encouraged to apply.

Fetal alcohol syndrome – an epidemic in South Africa?

Professor Denis Viljoen, chairman, Foundation for Alcohol Related Research; professor, Faculties of Health Sciences, Universities of the Witwatersrand (Johannesburg) and University of Stellenbosch (Cape Town)

Fetal alcohol spectrum disorder (FASD) is a recently defined condition affecting the unborn child, which is brought about by the noxious effects of alcohol consumed by mothers during pregnancy. FASD is considered the most common cause of mental retardation and childhood behavioural disorders in the world. It was first defined by Lemoine in France in 1968, but the first reports in the English medical literature were by Jones and Smith in 1973.

Fetal alcohol syndrome (FAS) is the most severe of the disorders characterised in the FASD group of conditions. It comprises both antenatal and postnatal growth failure, and neurological deficits including developmental delays, poor concentration span, hyperactive behaviours, low IQ and a recognisable gestalt. Unfortunately, there are no biomarkers that can identify FASD, and the diagnosis is solely reliant on the maternal history of alcohol abuse during pregnancy and the clinical findings outlined above. The latter can be mistaken by the uninformed or inexperienced clinician, leading to stigmatisation of the family, particularly the mother, who is in danger of being labelled as an alcohol abuser when an erroneous diagnosis is made on her child. It is therefore strongly advised that a clinician, preferably one trained in dysmorphology and abnormal pattern recognition in children, and one experienced in the field of FASD, be approached to confirm the diagnosis.

In South Africa, an unfortunate combination of historical events has conspired to create circumstances in which FASD is a relatively common birth defect in its citizens. The Foundation for Alcohol Related Research (FARR), a non-governmental organisation, was registered in 1997 with the aim of evaluating the aetiology, social circumstances, pathology and impact of the disorder in our country. Since that time, and with the collaborative assistance of many local and international funding agencies and universities, more than 40 scientific articles have been published on numerous aspects of FASD in South Africa. This has led to a deepening national awareness of the problems associated with the condition, and has awakened interest in other countries of the severity of the immense psychosocial and financial burdens within their own populations.

Historically, South Africa has evolved through a complex and convoluted past. In the mid-fifteenth and sixteenth centuries, the sea-faring nations of Europe opened the Cape sea route around the southernmost part of South Africa for trading purposes to the East (the so-called spice trade). This led to the settlement of the Cape by the Dutch, German, Portuguese, French Huguenot, English and others, firstly creating a refurbishing station for seafarers, but later resulting in the colonisation of southern Africa.

Viticulture, particularly in the communities of French Huguenot refugees, became an established agricultural activity, which continues to expand to this day. In the early days, agricultural workers employed on wine farms were given 'dop' (alcohol) as part of their wages, thereby starting the so-called 'dop system' or 'tot system'. Unfortunately, the practice became so ingrained in the culture of the poorer segments of society that 'binge drinking' became a normal social activity, particularly over weekends. The dop system was outlawed in South Africa in the 1920s and, due to non-adherence by farmers, president Nelson Mandela made a passionate plea to wine farmers to desist from the practice soon after his 1994 inauguration. This, together with punitive action of wine cooperatives on farmers practising the dop system, has led to a remarkable decline in these activities. So much so that in the many studies of women who have mothered a FASD-affected child, only 3% have ever been exposed to the dop system. Nevertheless, the legacy of this practice is that significant sectors of society still binge drink.

Other risk factors which have been identified in evaluations of women who have had FASD-affected offspring include poverty and poor social circumstances; lack of education; single parent families; low religiosity; other substance abuse (especially cigarette smoking); informal housing (shack dwellers); and other factors. Challenges to change these circumstances have been bedevilled by the coexistence of the HIV/AIDS epidemic, high prevalences of tuberculosis infection, and malnutrition in susceptible communities. All these factors, together with abuse of alcohol and other drugs, are instrumental in working as a 'wheel of misfortune' in large sectors of the South African population.

Prevalence studies have been undertaken by FARR since its inception. Whole populations were studied, and frequency of FAS calculated in a strictly scientific manner amongst school-entry children in those communities. In comparison with developed nations (USA, France and Sweden) the prevalence rates in our at-risk communities are mind-blowingly high. Unprecedented figures of 20–120 per 1,000 school-entry children have been found in

Table 1 International prevalence of FAS

Country	Prevalence of FAS	
	Per 1,000	%
USA	1–3	0.1–0.3
France	1.20	0.1
Sweden	1.33	0.1
Certain sectors of American Indian population	8	0.8
South Africa		
Wellington (2002)	88	8.8
De Aar (2002)	120	12
Upington (2003)	69	6.9
Johannesburg (2000)	27	2.7
Witzenberg Region (2010)	73	7.3

major studies in the Johannesburg area, in two towns in the Northern Cape Province, and in a study repeated on three occasions among children from a rural setting in the Western Cape Province. These are the highest figures reported anywhere in the world (Table 1). A further community from the Witzenberg area of the Western Cape has recently been studied, and tentative figures for FAS and PFAS have been calculated at approximately 73 per 1,000 school-entry children.

Other findings from FARR's research have been the subject of some 40 manuscripts and congress presentations which have appeared in the local and international medical literature. These are briefly summarised below and appear on our website.

Maternal risk factors associated with FASD

These have been elucidated, and include binge drinking of large amounts of alcohol, poor socio-economic circumstances, cigarette smoking, low religiosity, limited education, single parenthood, and maternal depression (see May *et al* 2005[1] and Viljoen *et al* 2002).[2] These risk factors will be different for every community.

Photogrammetry

This technique has been employed for the rapid diagnosis of FASD, and has been demonstrated to be remarkably specific and sensitive. The evaluation of several hundred children has been reported in many publications from FARR's collaborations with the Medical Imaging Unit at the University of Cape Town (eg Douglas *et al* 2003).[3] Such methodologies may form the basic of surveillance in whole populations in the future.

Cognitive and motor development

This has been evaluated in children in high-risk South African populations. Children have demonstrated deficiencies in several neurological domains including speech and hearing, performance, practical reasoning and eye–hand coordination. Surprisingly, locomotor subscales were relatively unaffected (Adnams *et al* 2001).[4]

Genetic effects

Genetic effects have been demonstrated in families spared FAS; polymorphisms of the ADH2*2 molecule were significantly more common in controls than amongst FAS affected persons of mixed ancestry in the Western Cape Province of South Africa. This finding suggests that susceptibility in mothers and their offspring with FAS is increased because metabolism of alcohol is slower in these persons, leading to higher blood alcohol concentrations compared with control subjects without FAS. These studies were the first reported in the literature to assist in understanding susceptibility to FAS amongst different populations (see Viljoen *et al* 2001).[5]

New biomarkers

A new biomarker of fetal exposure to alcohol was reported in a study of meconium (first stools passed by the baby after delivery), where ethyloleate concentrations were much higher in newborns exposed to recent alcohol use in their mother. This is a highly sensitive and specific indicator of maternal alcohol exposure during the latter stages of pregnancy (see Bearer *et al* 2003).[6]

Infant visual acuity

The effects of prenatal alcohol exposure on infant visual acuity was demonstrated among children exposed to alcohol in a South African collaborative study. This was assessed by Teller Acuity Cards at 6 months post-delivery. The finding was consistent with clinical and annual evidence of alcohol related disruptions of the visual pathways (see Carter *et al* 2005).[7]

Other research articles are available through contact with staff at FARR.
web: www.farr-sa.co.za
email: info@farrsa.org.za

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Alcohol and the behaviour of the human fetus

Peter G Hepper, School of Psychology, Queen's University Belfast

Introduction

Prenatal exposure to alcohol may have long-term consequences for the neurobehavioural functioning of the individual. Manifested as behavioural, social or cognitive deficits, these are a result of alcohol influencing the development and functioning of the individual's brain and nervous system. These adverse consequences are often only detected some years after birth. If the effects of alcohol could be observed during the prenatal period when exposure is causing these effects, a greater understanding of how alcohol influences the developing brain could be achieved. One possible means to achieve this is through the study of the behaviour of the fetus, which offers the opportunity to document the effects of alcohol in real-time (in acute exposure) and at the time when alcohol is influencing brain and neural function.

The behaviour of the human fetus

The behaviour of the fetus, defined as any observable action or reaction (to an external stimulus),[1] can be observed using ultrasound, which provides detailed observations of even the smallest movements, eg the opening and closing of the pupil of the eye. The first spontaneous movements of the fetus occur after around 7–8 weeks of gestation. These begin in the back or spine, appear slow, and may result in the passive displacement of the arms and legs. Over the course of the next few weeks, a wide range of movements develop (Table 1) and by about 20 weeks of gestation, most of the individual movements that the fetus produces will have emerged. As the fetus develops, movements become organised into periods of activity and inactivity, which culminate towards the end of pregnancy in the emergence of behavioural states: quiet sleep, active sleep, quiet awake and active awake,[2] similar to those seen in the newborn infant. After 36 weeks' gestation, these individual states persist for relatively long periods of time, with the transition from one state to the next being rapid and organised, and as such the fetus spends very little time in 'no state'. The development of movements and behavioural states represents the advancing maturation, integration and functioning of the fetus's brain.

As behaviour is a product of central nervous system functioning, examining behaviour enables brain function to be assessed.[1] In conditions where the fetus has been compromised (eg growth retardation), exposed to maternal illness (eg diabetes), or has chromosomal or neural anomalies, atypical behaviour is observed. If alcohol exerts an effect on the brain of the fetus, this may be reflected in changes in the normal behavioural repertoire of the fetus.

Maternal alcohol consumption and human fetal behaviour

Whilst there have been few studies, three broad strategies have been adopted in attempting to observe the effects of alcohol on the fetus. First, mothers have been asked to drink a small amount of alcohol and its effect on the behaviour of their fetus has been observed. Second, the behaviour of fetuses of mothers who drink alcohol has been compared with the behaviour of fetuses whose mothers do not drink alcohol. These two approaches also differ in as much as the former entails observation of the fetus whilst alcohol is present in the mother's system, providing an opportunity to observe the acute effects of alcohol exposure, whereas the latter involves observations when there is no alcohol in the mother's system, and documents more chronic effects. These studies have focused on low levels of alcohol consumption. The third strand has been opportunistic, and has documented the behaviour of fetuses of individual women who are alcoholic and under extreme alcohol intoxication at the time of observation, a case study approach.

Studies observing the behaviour of the fetus following maternal alcohol consumption have been performed after 36 weeks' gestation. Reports are

In the last issue, we showed you the top three entries to the National Alcohol Awareness Day poster competition. Here we feature another entry, which was commended as highly original and thought-provoking, by Rhi Lewis, Hannah Walsh, James Hansell and Annabelle Lee, from the University of Cardiff. The poster is particularly relevant to this issue's theme of fetal alcohol syndrome.

consistent in that fetal breathing movements decrease almost immediately upon maternal consumption of alcohol, and have disappeared totally by 30–40 minutes after consumption.[3] Studies have used small amounts of alcohol, eg two glasses of white wine. Breathing movements were still absent after 2–3 hours, despite maternal blood ethanol levels reading zero at this time. Two glasses of white wine also disrupted the organisation of the fetus's behavioural states organisation.[4]

Studies examining the acute effects of maternal alcohol consumption on the behaviour of the fetus all indicate that alcohol suppresses the behavioural repertoire of the fetus, and this suppression persists even after alcohol levels in the maternal blood stream are negligible. The question remains, however, as to what levels and duration of consumption are required before a permanent effect on the nervous system occurs.

To address this, some studies have examined the behaviour of fetuses exposed to low – medium levels of alcohol at a time when no alcohol was present in the mother's system. These may reveal any chronic (permanent) effect of fetus exposure to alcohol.

The incidence of spontaneous startles at 18–20 weeks' gestation was much higher in a group of fetuses whose mothers drank low levels of alcohol (approximately 2.5 units per week) than in fetuses of mothers who did not drink alcohol.[5]

Spontaneous startles first appear around 8 weeks of gestation, peak around week 9, and then decrease in incidence. Startles are a reflection of the 'primitive' stage of neural system development, and as the fetus's nervous system matures, more complex and integrated behaviour patterns emerge. The development of inhibitory pathways may be a major factor in the reduction of startles. By 18–20 weeks, spontaneous startle behaviour is rare, and the increased incidence of startles at this stage in fetuses exposed to alcohol may reflect a permanent effect on the fetus's nervous system or a delay in its maturation.

A longitudinal study attempted to tease out these two factors, and observed startle behaviour in fetuses from 20 to 35 weeks of gestation.[6] The incidence of spontaneous startles was higher in fetuses exposed to alcohol (just over four units per week) at all ages. However, with advancing gestation, the incidence of startles in fetuses exposed to alcohol decreased and approached the level exhibited by fetuses not exposed to alcohol. However, there still remained a significant difference at 35 weeks, with more startles exhibited by fetuses exposed to alcohol. This suggests that there is both a developmental delay caused by alcohol exposure in the fetus, and perhaps a permanent effect on the fetus's nervous system.

Case studies

Observations of a fetus at 37 weeks' gestation, when its mother was severely intoxicated (blood alcohol level of 322 mg/dl), revealed decreased body and breathing movements compared with observations 24 hours later (blood alcohol level <10 mg/dl). When born, this baby presented facial dysmorphology consistent with fetal alcohol syndrome. Behavioural states were found to be disorganised in a fetus of a mother who drank '10 glasses of beer or more' during the first 12 weeks of pregnancy, and between 'two and 10 glasses of beer a day' during the following months. Fetuses usually exhibit a smooth transition through different states from quiet sleep through active sleep to active awake, however this fetus jumped directly from quiet sleep to active awake. These case studies again indicate that exposure to alcohol affects the behaviour of the fetus.

Two routes of alcohol-mediated effects

It is widely accepted that alcohol, or its breakdown products, exert a teratogenic effect on the fetus. Observations of the fetus in response to exposure to alcohol suggest a secondary route by which alcohol may exert its effect on the fetus's brain. The behaviour of the fetus is important for its normal development.[1] The actions, reactions, motor behaviour and sensory experiences of the fetus contribute to, and are essential for, the complex neurobehavioural developmental processes of the prenatal period. As alcohol, even at low doses, disrupts behaviour, this may adversely affect the expression and experience of behaviour, and the feedback derived from behaviour, also necessary for normal development. A single unit of alcohol affects behaviour for over 2 hours. Continual disruption of behaviour on a daily basis, for example through a single drink every day, may adversely affect the normal developmental processes and

Table 1 The gestational age at which behaviours are first observed in the fetus

Behaviour	Gestational age (weeks)
Just discernible movement	7
Startle	8
General movement	8
Hiccup	9
Isolated arm movement	9
Isolated leg movement	9
Isolated head retroflexion	9
Isloated head rotation	9–10
Isolated head anteflexion	10
Breathing movements	10
Arm twitch	10
Leg twitch	10
Hand–face contact	10
Stretch	10
Rotation of fetus	10
Jaw movement	10–11
Yawn	11
Finger movement	12
Sucking and swallowing	12
Clonic movement: arm or leg	13
Rooting	14
Eye movements	16

consequently lead to impairment. Whether such low dose exposure does have a permanent effect is unknown, but it is an issue that needs to be explored further.

Summary

- Small amounts of alcohol (one or two units) exert an immediate, suppressing, effect on the behaviour of the fetus.
- This effect is long-lasting and persists after the alcohol has been cleared from the mother's system.
- Chronic low levels of exposure (two to five units per week) result in a delay in the development of the fetus's behavioural repertoire and possibly a permanent effect.
- As behaviour reflects neural function, the effects are most likely to be mediated by the effect on alcohol on the fetus's brain.
- The level at which these effects become permanent is unknown, but they do allow one statement to be made: 'one unit of alcohol exerts an effect on the fetus's behaviour and brain'.

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Michael Frowen Memorial Essay Prize

Competition winners 2009–10

Winner: Adam Walton, University of Southampton

Second place: Ross Elledge, University of Birmingham

Third place: Nicole McGrath, University of Leicester

With grateful thanks to the judges: Dr D Florin, Dr H Kholi and Dr G Ratcliffe

Michael Frowen Memorial Essay Prize 2011

Awarded for a paper not exceeding 3,000 words (excluding references and title)

'Is drinking alcohol during pregnancy a form of child abuse?'

First prize £500 • Second prize £300 • Third prize £200

Closing date 31 March 2011

The winning essay will be published in the MCA Annual Report and possibly elsewhere. Open to current medical students within the UK only.

The Medical Council on Alcohol is a small national charity committed to improving the medical understanding of alcohol-related problems

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