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The International Medical e-Network devoted to
Fetal Alcohol Spectrum Disorders

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INTRODUCTION

Once again we are privileged to have contributions from some of the leading FASD experts around the world. Our first original article is from Dr Therese Grant, Director of the Fetal Alcohol and Drug Unit at the University of Washington, Seattle, Washington, USA.

In 1991, with Dr. Ann Streissguth, Dr Grant established the award winning Parent-Child Assistance Program (PCAP), which she still runs today. Dr Grant shares her experience of the ground breaking PCAP project for FASD prevention and intervention.

From Northwest Australia, Penny Bridge describes the Ord Valley Aboriginal Health Services (OVAHS), community driven comprehensive strategy for FASD prevention and intervention developed to meet the unique needs of Aboriginal men as well as women. We can learn and adapt much from the OVAHS project.

We are also highlighting the innovative work of UK biomedical scientist, Jean Deenmamode and the CDT (Carbohydrate Deficient Transferrin) test, which can trace alcohol consumption in pregnant women in the fortnight prior to meetings with their midwives.

The contribution from Sung-Gon Kim introduces a ground-breaking Korean study to be published this summer. Canadian PhD, Catherine Lebel, discusses her team’s findings in a recent study identifying prenatal alcohol effects on key brain regions for maths deficits.

The FETAL ALCOHOL FORUM is now divided into four sections:
1. ORIGINAL ARTICLES BY FASD EXPERTS, written exclusively for the FORUM
2. RESEARCH ABSTRACTS of the most recent international studies in the past six months
3. NEWS AND PRESS
4. FULL ARTICLES

The FETAL ALCOHOL FORUM network is rapidly growing. Please pass it on to colleagues, download the FORUM from our website (www.nofas-uk.org) or contact us if you would like to contribute an original article or refer us to new research. To join the FORUM network, click here.

Thank you for your interest.

Susan Fleisher
Publisher
Vandana Alimchandani
Editor/Technical Support Supervisor
Elizabeth Mitchell
Associate Editor
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I first heard the term Fetal Alcohol Syndrome when I was a young teacher living and working on an Indian Reservation in Washington State, but it wasn't until I met Benny that I understood what FAS meant. Benny's mother was an alcoholic and he lived with his grandma on the reservation. He was a sweet and dear student in my fourth grade classroom, and he always sat in front so I could keep a close eye on him because he couldn't sit still for long. He would look long and hard at me with his eyes squinting and his head tilted to one side as he tried --really tried--to absorb what I was saying or to follow what was going on in the busy classroom. When he couldn’t comprehend, his attention would wander and so would he. Benny and I would set goals, and when he succeeded one of the things he liked best was to eat lunch together, just the two of us, and I would bring his favorite peanut butter cookies. When I left teaching to go to graduate school, I often thought about Benny. I knew his prognosis was not good --there was no special education teacher at his rural school, and he was viewed by most as a problem student. As I learned more about FAS it was clear to me that Benny surely had this disorder, and it made me worry for him even more. It’s to Benny that I owe my first interest in FAS intervention and prevention.

In 1983 I finished my master’s degree, moved to Seattle, and had the great fortune to meet Dr. Ann Streissguth, a pioneer in the FAS field, and the woman who became my mentor. Cocaine was at the height of popularity then, and Ann hired me to work on a research grant studying the effects of prenatal cocaine exposure on young children. My job included enrolling high-risk cocaine-using mothers, interviewing them, and bringing their babies into the lab for neuropsychological testing. I learned a lot from these women as I sat in their cramped apartments listening to stories of family dysfunction that seemed horrific to me, but were “just the way it is” to them. These mothers were giving their babies the same kind of upbringing they had experienced as children. They didn’t know any other way.

As the cocaine study came to an end, I realized that for me a more compelling challenge than studying effects of prenatal substance exposure would be to work in a meaningful way with the high-risk mothers who delivered these babies--- to help them take care of the children they already had, and avoid future births of exposed and affected children. Thus began the Parent-Child Assistance Program (PCAP), a home visitation/case management intervention originally...
developed with the aim of preventing subsequent alcohol and drug exposed births among high-risk pregnant or parenting mothers (Ernst et al., 1999; Grant et al., 2003; Grant et al., 2005).

Although PCAP did not begin as an FASD intervention, it became apparent that many of the mothers enrolled may have been affected. About 25% of the women we worked with reported that their own mothers were alcoholic and had been heavy drinkers during pregnancy with them; many of these had signs of FASD (e.g., impulsiveness, poor judgment), and had the kinds of troubled life circumstances that people with FASD often experience, such as failure in school and trouble with the law.

We decided to expand PCAP’s formal eligibility criteria to enroll a sample of women who had confirmed or suspected FASD, and we conducted a 12-month pilot study to examine more specifically how these women could be helped within the existing framework of PCAP’s intensive case management. In standard PCAP, trained and supervised case managers each work with 15-16 mothers for 3 years, beginning during pregnancy or within six months postpartum. Based on a strong theoretical framework, the PCAP model incorporates well-known aspects of effective case management: workers develop a positive, trusting rapport with their clients, offer regular home visitation, and help their clients address a wide range of problems including obtaining alcohol and drug treatment and staying in recovery. They connect the families with community services, coordinate services among this multidisciplinary network, and assist clients in following through with provider recommendations.

We enrolled a total of 19 clients with FASD (n = 11) or suspected FASD (n = 8) in our pilot study. Their average age was 22 years, most were unmarried (84%), poorly educated (47% had a 9th grade education or less), and had been physically or sexually abused as young children (94%). Among the 15 who were mothers, the mean number of children was 2.3 (range 1-6); on average, only half of the children were living with their biologic mother. Among the 11 young women with a diagnosis of FASD, the mean IQ was 82 and six had a formal psychiatric diagnosis: bipolar disorder (4), depression (1), or schizophrenia (1). All reported having poor linkages to even the basic community services and amenities.

“Best practices” clinical recommendations for FASD patients call for coordinated, sustained, multi-systemic management. But best practices recommendations rarely reflect reality. As we began our work, we found that even here in Seattle where FAS was first named, most clinicians knew very little about FASD, and few had direct experience with people who had FASD. With that in mind, we began talking to service providers about FASD, and found a small group who not only expressed interest in the problem, but were also willing to work with a client with FASD as a case study, in close collaboration with her PCAP case manager. We conducted FASD training with these providers at 15 major medical and mental health clinics or agencies, and offered ongoing consultation as questions arose.

By combining education with follow-up hands-on experience, we attempted to demystify FASD for these providers, who were then able to deliver services more appropriately tailored to the specific needs of FASD patients. In addition, the pilot resulted in relatively stable and enduring relationships between clients and providers. While the pilot project did not necessarily result in FASD clients developing the ability to access services independently, it did result in the clients’ increased use of necessary and appropriate services (Grant et al., 2004; Grant et al., 2005).

A PCAP Case Study

Claire’s drugs of choice during her fifth pregnancy were methamphetamine and alcohol. She was referred to PCAP late in the pregnancy, and by that time she had lost permanent custody of
four older children. When she delivered this new baby boy, child welfare services allowed her to keep custody because she was making good progress. It was clear from the beginning of Claire’s participation in PCAP that she had multiple problems. At intake the PCAP clinical supervisor suspected FASD and met with Claire’s mother to interview her about her pregnancy drinking. Claire’s mother initially denied alcohol use, but readily admitted to using heroin. When the supervisor asked if it were possible that she drank before she knew she was pregnant the mother said yes, she had “partied just like everybody else, and loved Bloody Marys.” With prenatal alcohol exposure verified, Claire then had a neuropsychological evaluation. Her IQ was 73 and she had significant problems with memory and processing information.

Within a year and a half of her son’s birth, Claire gave birth to a sixth child, a girl. By this time Claire had completed treatment and was no longer using alcohol or drugs. Her PCAP case manager located a clean and sober home for women in recovery where Claire and her two young children went to live. Problems arose, not because Claire was abusive or purposely neglectful, but because she couldn’t manage the two children simultaneously; her young son disappeared on several occasions. A child welfare report was made and she lost custody of the children. PCAP arranged to have Claire evaluated at a brain injury clinic, where they formulated a treatment plan including occupational therapy and memory tools. Claire was able to recognize her own improvement, stating, “Hey! I can multitask now!”

Claire’s two youngest children were eventually allowed to have longer visits with her at her home, and she was able to track their activities. She did not regain custody of them because of her past history, however, the children’s foster parents allowed liberal visitation and Claire was able to be an active part of their lives. Claire made the decision to have a tubal ligation because she could not bear the grief of relinquishing a future child, and because she knew that she would be able to stay in contact with her two youngest.

Our small pilot study demonstrated that an experienced and clinically supported case manager, working with her client in collaboration with a network of educated providers, might reasonably expect to accomplish a number of important steps over a 12-month intervention. These steps include:

• Securing safe, stable placements for the children;
• Assisting clients in obtaining inpatient or outpatient treatment and supportive aftercare, for those abusing alcohol or drugs;
• Assisting clients in evaluating family planning needs and choosing a contraceptive method, keeping in mind that a long-term, more reliable method may be the best option because of memory and judgment impairment.
• Establishing an educated network of service providers who will continue to work with clients after the case manager’s services are no longer available.

These interventions may not only improve the client’s current quality of life, but may also establish an enduring foundation for preventing crises long after an intervention program is no longer available, thereby mitigating the social and familial burden associated with the long term care of these individuals. Caregivers who have become exhausted or alienated may be willing to resume a supportive mentoring role after a case manager has helped the client stabilize.

The PCAP model has been replicated or adapted in dozens of urban, rural, and reservation communities in the United States, Canada, and New Zealand. Our team works closely with interested organizations to train on the model, or consult on adapting the model to complement programs that are already in place. General information about PCAP and additional study citations are available at http://depts.washington.edu/pcapuw/
For information about training please contact Stacy Dimmich at the University of Washington: 
mailto:sdimmich@u.washington.edu

References:


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II. AN ABORIGINAL COMMUNITY TAKES CONTROL: FOETAL ALCOHOL SPECTRUM DISORDERS PROGRAM KUNUNURRA, WESTERN AUSTRALIA

PENNY BRIDGE
FASD Project Coordinator
Ord Valley Aboriginal Health Service (OVAHS)

The Ord Valley Aboriginal Health Services (OVAHS) is a comprehensive Primary Health Care facility servicing Aboriginal people in the remote township of Kununurra and surrounding communities. Kununurra is situated in the far north west of Western Australia in the Kimberley region. The town has a population of approximately 7,500 people and of these approximately fifty percent are Aboriginal.

The OVAHS Foetal Alcohol Spectrum Disorders (FASD) Program was developed in response to the incidence of alcohol consumption during pregnancy in the Kimberleys and the suspected
high incidence of FASD. Funding for this program was provided by local Aboriginal people through the Miriuwung Gajerrong Ord Enhancement Scheme (MG OES).

Current international research indicates alcohol is the most commonly ingested teratogen yet there is no safe amount of alcohol that can be consumed during pregnancy (Streissguth 1997). Unfortunately, awareness in Australia about the risks of consuming alcohol during pregnancy and its connection with FASD is often poor or misguided, not only within the general population but also amongst many health professionals (Telethon Institute for Child Health Research 2009). Elliott (2008) indicated that only 12% of health professionals gave information and advice to their clients that was consistent with Australia’s National Guideline on safe levels of alcohol in pregnancy. Comprehensive education, diagnosis and management of FASD in Australia is virtually non-existent, and at present there are no national standards of accurately assessing and identifying children with FASD (Walker 2008). As a result, health professionals rely primarily on the assumption that where there is a high level of alcohol abuse (in particular ‘binge drinking’) combined with large numbers of unplanned pregnancies it is likely that a significant number of children will be born with FASD.

To date, health professionals in Australia are not routinely screening women for alcohol use during pregnancy, and therefore pregnant women are not being adequately provided with the necessary information and support they need to make healthy alcohol-free choices. In fact, many women continue to drink throughout the gestation period, unaware of the possible consequences for their children (Telethon Institute for Child Health Research 2009).

In an effort to address this problem, and to combat the lack of culturally appropriate services providing FASD education to Aboriginal communities in the Kununurra region, local traditional owners, the Miriuwung and Gajerrong peoples through MG OES agreed to provide funding for a 12-month program run through OVAHS. This began in earnest in August 2009. The FASD program team is made up of a Registered Nurse and an Aboriginal Program Worker who are part of the OVAHS Social Support Unit (SSU). The SSU offers case management, counselling and education to Aboriginal individuals and groups on issues related to alcohol, drugs, mental health, domestic violence, relationship problems and youth support. The FASD team also work closely with antenatal clients who access the OVAHS Aboriginal Child and Maternal Health Unit. The main aim of the program is to gain an understanding of the situation locally, establish what is needed, and consider what can be done to meet those needs by supporting both the individual and the family to make valuable changes.

At the onset of the program, the team recognised there was a lack of culturally appropriate FASD health promotion material, and so set about developing a number of resources in consultation with the local Aboriginal population. These have included posters, pamphlets, a DVD and a radio advertisement targeting education and awareness of FASD for both men and women.

Considering there is invariably a connection between the individual, the family, the community, the environment and alcohol, the FASD program takes a holistic approach towards dealing with these issues. What is more, there is also a clear recognition that prenatal alcohol and other drug taking behaviours are often directly tied to peer/partner relationships, including the culture of the household and the community as a whole. This in turn is compounded by issues of addiction and the multiple social challenges that inevitably impact on pregnant woman within the Kununurra community. These variables may impact on women’s ability to make positive behavioural changes during pregnancy.
To date there have been, both nationally and locally, a number of challenges to the implementation of this program. Nationally, as stated above, knowledge and recognition of FASD is often poor, and the information about safe levels of alcohol during pregnancy is generally ambiguous. There is no integrated national strategy and virtually no funding available for research, either into the condition itself or to provide support for those affected. Locally, apart from the many social issues of concern already mentioned, Kununurra is geographically remote (almost 4,000 km from the state’s capital city, Perth) which impacts on the accessibility and integration of services. Despite these many challenges, OVAHS and MG OES have developed a five-point plan aimed at tackling these issues.

The program primarily provides FASD education, AOD (alcohol and other drug) screening and counseling on a one-to-one basis to each antenatal client, and then extends its multi-pronged approach to include partners, families and the community as a whole. Brief interventions and motivational interviewing are key features of the program. This involves viewing an appropriate DVD and encouragement to discuss any issues or concerns. A survey has also been developed to establish pre-and-post conception alcohol-related behaviors, while also gaining an awareness of the client’s understanding of FASD. The intention of the survey is not only to guide the education required for each antenatal client, but also to become a tool for data collection and program evaluation at a later point. In addition, all FASD education during the antenatal period incorporates contraception education and advice, which is then followed up during the post natal period. The FASD project, and indeed OVAHS, views this as a significant way for women, and in particular young women in the region, to gain greater control over the possibility of any future unplanned pregnancy.

Secondly, the FASD program targets all women of childbearing age (13-45 years) through OVAHS and local centres such as the schools, the crisis centre and weekly community stalls and events, all of which form a significant part of the team’s out-reach program. There is recognition that local Aboriginal women may start families as young as 13 years of age and some of these will continue having children into their 40’s. In addition, there is evidence that binge drinking among teenage women is high and increasing in incidence in Australia. This is especially concerning given the link between unplanned pregnancy and high levels of alcohol consumption (Walker 2008). As a consequence, contraceptive advice to this group is an integral part of the FASD education provided. Special emphasis is placed on targeting at-risk women who may not access community, education or health services. Teaching the elderly women about FASD is also providing an important means of support for the younger women in the community.

The third aim of this program is to provide FASD education and training to all OVAHS staff on alcohol awareness, FASD and contraception. Developing skills in motivational interviewing and providing brief interventions are key aspects of this process. Particular emphasis is placed on recognising the important role of the Aboriginal staff at OVAHS as they are seen as vital contributors to raising public awareness of FASD in the community. Along with the Aboriginal FASD Program worker, the Aboriginal staff are imperative in ensuring the cultural appropriateness of all aspects of the program. Many of the nursing and medical staff at OVAHS have completed an online FASD diagnostic training course through Washington University in the USA (4-Digit Diagnostic Code Training). The course aims at increasing the capacity of the staff to identify FASD by reflecting on the true extent of the diagnostic process. Suspected cases are to be referred to a paediatrician for further review.

The fourth directive is the implementation of out-reach programs and workshops targeting local Aboriginal men, who are viewed as possible key players in supporting their partners to make alcohol-free choices throughout pregnancy. While recognising that traditionally Aboriginal men are not involved in the antenatal process, the FASD program has broadened its scope to include
male partners. Moreover, the program aims to provide FASD education to all local Aboriginal men from the teenage years upwards, as the issue is seen as effecting the broad community. Fortunately, the opportunity to provide FASD education to local Aboriginal men has been greatly increased in recent months with the expansion of the OVAHS Men’s Health Program to include education sessions. The men who have received FASD education have mostly welcomed this information. Aboriginal knowledge and stories relies heavily on oral tradition and therefore memory. Consequently there is a recognition that this knowledge has the potential to be lost if many of the next generation suffer neurological damage as a result of pre-natal alcohol exposure. Men within the local community also understand that too many of their young men are leaving school without even a basic education, and rates of imprisonment are high among Aboriginal men. According to Krieg (2006), Aboriginal people currently make up 22% of the total number of Australian prisoners, yet only comprise 2.5% of Australia’s population (Australian Bureau of Statistics 2008). The local men are concerned that FASD could be a contributing factor. In the early stages, overcoming resistance to discussing pre-natal alcohol exposure as “Women’s Business” was a challenge, but this has since been resolved following the provision of FASD education to many senior men in the community.

Lastly, continual community consultation is paramount to the success of the project, and strong links continue to be expanded within the local Aboriginal population. Similarly, developing links with national and international FASD networks has been vital to the progress and establishment of the FASD program. There is strong recognition of the importance of a unified and consistent approach at all levels of health promotion, research and policy development, and a need for ongoing and targeted lobbying of various government bodies. Importantly, growing interest across the various sectors is contributing to the growing impetus for addressing the issues of FASD in Australia.

Program work planned for the year ahead is aimed at continuing with further promotion of education and awareness of FASD within the local community. In conjunction with visiting paediatricians, the OVAHS Child and Maternal Health Unit and all other staff, the feasibility of setting up a pilot FASD screening unit based at OVAHS will also be explored. This process will become even more dynamic as community acknowledgement and recognition of the issues develops. However, the future of the program and its goals for greater expansion will be determined by the availability of sufficient funding either from government or non-government sources.

Decades after the recognition of the effects of alcohol on the unborn child were identified, FASD continues to present a number of significant challenges in Australia. Despite this, OVAHS, an Aboriginal controlled health service in remote north Western Australia along with funding from MG OES, has taken steps to tackle the suspected problem of FASD locally. The FASD program has developed a comprehensive strategy that is community driven and functions at a grass-roots level targeting a large number of local Aboriginal people through community awareness and education. The success of the program to date can be attributed to both community ownership and the willingness of the Aboriginal community of Kununurra to take control and embrace change.

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“Local Aboriginal women receive FASD education while they wait for their Child Health check up”
I must admit that I became aware of FASD/FAS only in the latter part of last year when the chief executive of NOFAS UK met the specialist midwife at Homerton Hospital.

I certainly did not anticipate that a combination of our diagnostic service, a midwife’s project, a homemade information leaflet and an invitation to present our service to midwives attending NOFAS workshops in London would result in a front page article of the Times (6/3/10) and then literally lead to an internet wildfire globally.

Unlike the rest of mainland Europe, quantitative assessment of alcohol abuse using CDT and EtG are still in the stages of infancy. It is surprising that currently in the UK, only three laboratories (including Homerton) offer the %CDT service by capillary electrophoresis. This might be due to laboratories not fully adapted to the methodology of capillary electrophoresis and the possible cost implications of infrequent CDT and/or EtG testing.

Our service is available to any individual. The results are validated with the use of internal quality control. The laboratory’s performance is evaluated by participation in an external quality assessment scheme for CDT.

Locally, we have been informed by general practitioners, of the positive outcomes of both %CDT and EtG testing because in a number of instances, individuals (irrespective of social class) were unaware that they were at risk of chronic alcohol abuse and altered their drinking habits.

The most important factor has been this ability to present a quantitative result to the individual as self disclosure might most likely have been inaccurate.

My views of the applications of serum %CDT and urine EtG in pregnancy branch in two directions.

Post conception, it might be too late to prevent FASD/FAS or perhaps more optimistically, the tests might provide a guide to help reduce the degree of FAS as the foetus develops and the mother abstains from alcohol.

Evaluation of possible alcohol consumption by both self disclosure and the use of such biomarkers would be most relevant at the first antenatal visit. There is a degree of uncertainty about the accuracy of CDT as gestation progresses (third trimester in particular) because of hormonal changes. However, previous reports referred more to absolute CDT and not %CDT.

A significant outcome that the midwife’s project could clarify would be unfortunate FASD outcomes which are associated with CDT and/or EtG. Furthermore, the possible prognostic
information could be further enhanced by the outstanding ultra sound foetal response work done in Northern Ireland.

I firmly believe that, from a diagnostic laboratory viewpoint, CDT and EtG and other future biomarkers of alcohol abuse would greatly help to minimise or even eliminate the incidence of alcohol related birth defects and challenges at preconception, with a good collaborative educational programme in place.

In the UK alone, this might be an uphill journey because of the current uncontrolled drinking habits of individuals of child bearing age. The programme should incorporate the more graphic realities of FAS and offer biomarkers of alcohol abuse together with self disclosure as a drinking lifestyle assessment and attach less the label of being an alcohol misuser.

The lifestyle assessment approach has been most effective locally.

Moreover, irrespective of FAS, testing should not be limited to expectant mothers, but both partners should be given the opportunity to assess their drinking habits.

This issue was highlighted in more than one instance with the case studies discussed during both NOFAS workshops. While the participants (midwives) were focusing on the baby’s and mother’s presentations, the laboratory’s approach was focused on easily overlooked but critical evidence which clearly highlighted alcohol related issues. In fact, in every case study, serum %CDT and/or urine EtG would have most likely been beneficial to the investigator irrespective of pregnancy or post partum.

Appropriate assessment of alcohol abuse would be best performed over a two week period. Serum %CDT, urine EtG and blood alcohol should be measured on days 1 and 12. Urine EtG and blood alcohol should be measured on days 3, 5, 8 and 10 to monitor recent or binge sessions.

There seems to be a greater need (in the UK) for services offered by some specialist disciplines and the diagnostic laboratory to integrate further. My ultimate desire would be to offer a rapid turnaround of alcohol assessment service on one blood and one urine sample providing a quantitative profile of binge and/or chronic alcohol abuse risk.

A slight alteration of an anonymous quote, “To find an individual’s true alcohol intake, double what they say and halve what the partner or relative says”.

While at Homerton we may be some way ahead of other UK laboratories there is always room for improvement. We have successfully evaluated the urine EtG methodology and platform for serum samples. The correlations with the HPLC method from a German laboratory were perfect. In order to finalise the method evaluation and set a cut off level, a number of positive and negative EtG matched sets of urine and serum samples should be processed. We are not able to generate such numbers readily locally.

I am happy to welcome any potential collaborative work from any centres.

**CDT and EtG Tests**

Established markers of alcohol abuse, blood alcohol (direct biomarker of recent drinking), gamma glutamyl transpeptidase, alanine aminotransferase, mean corpuscular volume (indirect biomarkers of chronic abuse) are offered by most diagnostic pathology departments.
Following the publication of the then Darzi report, recommending improved laboratory assessment of alcohol abuse, our laboratory was already equipped with the instrumentation (Capillarys and Minicap of Sebia, France) and methodology (Capillary electrophoresis) to include recent markers of alcohol abuse.

From late 2008, carbohydrate deficient transferrin (CDT), an indirect biomarker, was offered as part of our service for the assessment of individuals who might unknowingly be at risk of chronic alcohol abuse. During 2009, urine Ethyl glucuronide (EtG, Microgenics-Thermo), a direct biomarker, was offered on our routine analyser (Abbott Architect) as a marker of binge drinking.

Transferrin
Transferrin is a protein synthesized mainly in the hepatocytes. It is the most important iron transporter through the bloodstream to the bone marrow where red blood cells are synthesized, as well as to the liver and spleen.

In 1976, Stibler and Kjellin first reported the presence of transferrin isoforms in cerebrospinal fluid and serum from alcoholic patients. Increased amounts of these isoforms appeared with a high prevalence in serum from alcoholics and disappeared after abstinence, with a half life of about fourteen days.

Carbohydrate deficient transferrin (CDT)
Monosaccharide carbohydrates (sialic acid residues) are attached to transferrin. Differing levels of sialylation result in the existence of various isoforms of transferrin. The most common isoform is tetrassertransferrin (4 sialic residues attached).

Consumption of significant quantities of alcohol (50-80g daily for one week) leads to eventual increase of transferrin with 2, 1 or 0 sialic side chains. These are collectively referred to as CDT. The pathomechanisms for raised CDT isoforms in alcohol abuse is not completely understood. It is possible that alcohol and/or its metabolite acetaldehyde could affect N-glycan chain synthesis in the Golgi apparatus. Possibly, diminished messenger RNA concentration and glycoprotein glycosyltransferase activities involved in Transferrin N-glycan synthesis and increased sialidase activity could account for ethanol-induced increase in CDT.

Of the different methodologies (ELISA, EIA, RIA, turbidimetry, HPLC) available for CDT in diagnostic laboratories, capillary electrophoresis reports %CDT.

A level of >1.6% is regarded to be positive, while <1.3% is negative. There is a borderline zone, 1.3 – 1.6%, where if individuals have maintained abstinence from alcohol, further measurements 3 to 4 weeks later should yield negative results. There is increasing interest perhaps, for CDT levels to be either positive or negative only with a single cut off for the relevant methodology.

Possible other known causes of raised CDT are genetic variants of transferrin where CDT fractions are masked and a less reliable result calculated by the software. Congenital disorders of glycosylation (CDG) and advanced cholestatic liver disease where CDT removal is impaired leading to false positive results. Instances of absent CDT can be related to severe liver disease (cirrhosis), anorexia or atransferrinaemia.

Factors such as, aged, improperly stored samples, anticoagulated blood bottles, serum haemolysis, high polyclonal immunoglobulins and monoclonal proteins can interfere with CDT results.
CDT is the only test approved by the FDA for the assessment of heavy alcohol use (Das et al, 2008)

**Ethyl Glucuronide (EtG)**

EtG and ethyl sulphate (EtS) are direct biomarkers of recent drinking (binge). They are more stable than ethanol and are detectable in urine, blood, hair, saliva, post mortem tissue and meconium. EtG is a direct metabolite of alcohol, which is formed by enzymatic conjugation of ethanol with glucuronic acid.

EtG accounts for a very small, but important percentage of ethanol metabolism and is still detectable in urine even when the alcohol has been completely eliminated from the body. Urinary alcohol is normally detectable for a few hours after consumption whereas EtG is detectable in urine up to 3-5 days depending on the amount of alcohol consumed.

Methodologies include EIA, GC/MS, LC/MS, LC/tandem MS (LC/MS/MS). The methodology used in our laboratory is the first fully automated EtG immunoassay (Microgenics-Thermo) on the market and installed on our current routine Abbott Architect analyser.

Fermentation of urine containing sugars (diabetes) and yeast or bacteria (Ecoli beta glucuronidase infection) can lead to spontaneous production of ethanol. Since this ethanol produced is not metabolised by the liver, EtG will be undetectable in such urine samples. EtS can be used to support EtG results in these situations.

There is essentially no EtG in urine unless alcohol has been present in vivo. EtG is produced whenever an individual is exposed to alcohol containing products. EtG cannot determine the source of ethanol.

When abstaining from alcohol, it is important for individuals to avoid products, such as, over the counter medications, mouthwash, foods (vanilla extract), and communion wine and hand sanitisers, that could contain any alcohol. This would minimise false positive results.

Urinary EtG concentration is normalised to creatinine concentration to eliminate the effects of consumption of large amounts of water which could cause a decrease in urinary EtG.

**CDT/EtG and the Antenatal Clinic**

The use of these new biomarkers is being further evaluated as part of an ongoing project by the substance misuse specialist midwife at Homerton. In addition to the completion of self disclosure investigative tools, serum CDT and urine EtG are being evaluated with client consent (on first ante natal visit). Combination of these investigations would perhaps further improve the accuracy of alcohol consumption in pregnant women.

The biomarkers would be used to monitor abstinence between clinic attendances. Investigations in the later stages of pregnancy would be a ‘grey area’ because of hormonal influences which could likely affect CDT.

**References**

Introduction: Recently, women who drink alcohol have increased consistently in Korea and childbearing-aged young women show the highest drinking rate (Korean Ministry of Health and Welfare, 2008). Drinking alcohol during pregnancy can result in various negative consequences including fetal alcohol spectrum disorder, malformation of the fetus, diverse behavioural problems in newborns, attention deficit hyperactivity disorder and learning disorder (Sokol RJ et al., 2003; Sood B et al., 2001). Nevertheless, few studies have been conducted in Korea to investigate alcohol consumption and factors influencing drinking behaviour during pregnancy in Korean women. Therefore, a survey was conducted on pregnant women to investigate whether they drank alcohol and to identify factors predictive of drinking behaviour during pregnancy.

Method: Pregnant women at less than 30 days before expected delivery who visited 3 types of Obstetrics and Gynecology hospitals (a university hospital, a specialized hospital, and a clinic) were asked to complete a self-report questionnaire. Demographic (age, education, job, income, religion etc.) and obstetric characteristics (primipara or multipara, whether they wanted the pregnancy or not), and smoking history (cigarette smoking before and after the realization of pregnancy, frequency of smoking, average amount smoked and family history of smoking) were investigated, as were alcoholic history (consumption of alcohol before and after the realization of pregnancy, frequency of drinking, average amount consumed, and awareness that consuming alcohol during pregnancy is harmful).

Results: 1) 695 subjects of average age 30.8 years were enrolled (Table 1). 141 subjects visited to a university hospital, 496 subjects visited a specialized clinic, and 58 subjects visited to a clinic. 3) Of these subjects, 25.7% had completed up to high school education and 37.6% had
a job. 67.9% were primiparous, and 99.4% were aware that consuming alcohol during pregnancy is harmful (Table 1). 4) 578 (83.2%) and 173 subjects (24.9%), respectively, consumed alcohol before becoming pregnant and after they were aware of being pregnant. 5) 97 (14.2% of 685 subjects) and 20 subjects (2.9% of 689 subjects), respectively, smoked before becoming pregnant and after they were aware of being pregnant. 6) Those that had consumed alcohol before becoming pregnant ($\chi^2=107.21$, $p<0.001$, OR=68.85), those that smoked before becoming pregnant ($\chi^2=4.98$, $p=0.025$, OR=3.31) and those with a family history of smoking ($\chi^2=8.06$, $p=0.004$, OR=2.29) were found to be more likely to drink alcohol when pregnant (Table 2).

**Conclusion:** This study shows that a quarter of pregnant Korean women aware of their status consume alcohol, and that 3 factors, alcohol drinking before becoming pregnant, cigarette smoking before becoming pregnant and family history of cigarette smoking, are predictive of drinking behaviour during pregnancy. These results strongly suggest that an anti-drinking educational strategy should be devised to target women of childbearing potential, in particular, those at high risk.

Table 1. Demographic characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Mean±SD or Number(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>695</td>
<td>30.8 ± 3.8</td>
</tr>
<tr>
<td>Completed up to high school education</td>
<td>689</td>
<td>512 (74.3)</td>
</tr>
<tr>
<td>Job (yes)</td>
<td>686</td>
<td>258 (37.6)</td>
</tr>
<tr>
<td>Primiparous</td>
<td>689</td>
<td>468 (67.9)</td>
</tr>
<tr>
<td>Being aware that consuming drinking during pregnancy is harmful (yes)</td>
<td>691</td>
<td>687 (99.4)</td>
</tr>
<tr>
<td>Family history (over 15 day per month)</td>
<td>690</td>
<td>130 (18.8)</td>
</tr>
<tr>
<td>Intended pregnancy</td>
<td>688</td>
<td>611 (88.8)</td>
</tr>
</tbody>
</table>

Table 2. Factors associated with drinking behaviour during pregnancy in Korean women

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>Wald $X^2$</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol drinking before becoming pregnant</td>
<td>68.854</td>
<td>30.901-153.39</td>
<td>107.21</td>
<td>1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cigarette smoking before becoming pregnant</td>
<td>3.310</td>
<td>1.156-9.478</td>
<td>4.98</td>
<td>1</td>
<td>.025</td>
</tr>
<tr>
<td>Family history of cigarette smoking</td>
<td>2.286</td>
<td>1.291-4.047</td>
<td>8.06</td>
<td>1</td>
<td>.004</td>
</tr>
</tbody>
</table>

OR: Odds Ratio
I first became interested in brain imaging during several undergraduate research projects focused on magnetic resonance imaging (MRI) techniques. Then, after volunteering for several months at a school in Canada’s Northwest Territories where I worked with many children with FASD, I was excited to combine the two during my PhD research. Brain imaging techniques such as magnetic resonance imaging (MRI) have greatly widened the possibilities for non-invasive assessment of the teratogenic effects of alcohol in-vivo. Conventional MRI produces images with excellent contrast among the major brain tissues (white matter, cortical gray matter and deep gray matter) and allows for measurements of structure volume, thickness, and density, all of which have been shown to be abnormal in children with fetal alcohol spectrum disorder (FASD).

Diffusion tensor imaging (DTI) is an advanced MRI technique that provides an excellent way of further studying brain tissue, as it provides quantitative measures of tissue microstructure not available via conventional imaging methods. One of the most common DTI parameters is fractional anisotropy (FA), which provides a measure of white matter integrity within the brain. DTI studies have revealed widespread brain abnormalities (as indicated by lower FA values) in individuals with FASD, highlighting many of the same regions identified by autopsy and conventional MRI studies and suggesting even more widespread damage than seen in conventional MRI.

In addition to structural brain damage, many studies have shown that children, adolescents, and adults with FASD have learning difficulties in a wide range of areas. These may include reading, memory, executive functioning, attention, and mathematics. Despite this diverse range of cognitive deficits, mathematics seems to be more affected than other cognitive skills. However, little is known about the relationship between brain structure, cognition and behavior in FASD, or even in the general population. Only two DTI studies had previously examined the relationship between mathematics and brain structure – one study looked at healthy children (van Eimeren et al, Neuroreport 2008) and one at children with a rare genetic disorder (Barnea-Goraly et al, Brain
Res Cogn Brain Res 2005). Since white matter forms the brain connections necessary for proper and efficient cognitive function, it is logical that weaker connections would be associated with cognitive deficits, and brain regions where correlations occur may indicate some degree of specificity related to a certain cognitive task.

In our recent study, we examined correlations between FA and mathematical ability across the brains of 21 children with FASD aged 5-13 years old. Four regions with significant correlations were observed: two positively correlated clusters in the left parietal region, one positive cluster in the left cerebellum, and a negatively correlated cluster in the brainstem. Two of these regions in the left parietal area are very similar to the findings of the only two previous DTI studies of mathematical ability. These convergent results suggest that the parietal areas are key brain regions for math ability across populations with diverse abilities, including children with FASD who have substantial math deficits. Furthermore, it is well known from functional MRI that the parietal area is functionally important for mathematical tasks, but now three DTI studies have shown that parietal structure is also related to math abilities. The two other regions of correlations observed by our study – the cerebellum and the brainstem – might be unique to children with FASD in terms of math-structure relationships, as previous studies have not identified them.

Clearly, connecting diffusion abnormalities with cognitive difficulties in FASD is an important area of research and very little is currently known. Ultimately, further studies of mathematics and other cognitive skills in subjects with FASD will elucidate the important links between specific structural brain abnormalities in FASD and the widespread cognitive, behavior, and emotional difficulties. Potentially, this will provide clues as to the causes of certain deficits and may lead to more effective treatments of such difficulties in the future, as well as giving insight into structure-function relationships in the general population.

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RESEARCH ABSTRACTS

Wiley InterScience - Public Health Nursing. Volume 27 Issue 3, Pages 240-247
Published Online: 14 April 2010

1. EVALUATION OF A SUCCESSFUL FETAL ALCOHOL SPECTRUM DISORDER COALITION IN ONTARIO, CANADA
Donna M. Clarke-McMullen
B.Sc., R.N., M.N., is Clinical Educator, Mental Health Program, Hotel Dieu Hospital, Kingston, Ontario, Canada.

ABSTRACT
Leading a successful coalition that benefits both the members and the community is a difficult task. Coalitions are complex and require a great deal of skill to initiate, lead, and evaluate. This article examines a successful coalition, developed to build community capacity to address fetal alcohol spectrum disorder (FASD). FASD is a complex, multidimensional health issue common in many communities. Coalitions can be effective in tackling these types of issues and fit with community capacity-building approaches to health promotion. The Internal Coalition Outcome Hierarchy (ICOH) model (Cramer, Atwood, & Stoner, 2006a, 2006b) is used to retrospectively examine the internal constructs of the FASD Action Network and provide useful lessons learned for other coalition leaders and public health nurses. This hierarchical model demonstrates that sound internal processes lead to more successful outcomes and ultimately an increased impact on community issues. The usefulness of ICOH as a tool in evaluating the FASD Action Network and its application to other health-promotion situations with community capacity goals is described in this article.


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Wiley InterScience - Public Health Nursing. Volume 27 Issue 3, Pages 240-247
Published Online: 14 April 2010

2. RESULTS OF A NURSE-LED WORKSHOP DESIGNED TO PREVENT FETAL ALCOHOL SPECTRUM DISORDER
Linda M. Caley1, Sara Riemer2, and Helen S. Weinstein3
1 Ph.D., R.N., is Assistant Professor, School of Nursing, University at Buffalo, Buffalo, New York
2 M.S., R.N., is a Doctoral Student, University at Buffalo, Buffalo, New York
3 B.S. Education, CPP, is Program Coordinator, Fetal Alcohol and Drug Effects, The Erie County Council for the Prevention of Alcohol and Substance Abuse, Buffalo, New York

ABSTRACT
Preventing the negative consequences of prenatal exposure to alcohol remains an unmet challenge. This paper presents the results of a workshop, designed to increase the implementation of fetal alcohol spectrum disorders (FASD) prevention interventions in 8 counties of New York. The workshop was based on constructivist learning theory and used the Population-Based Public Health Nursing Intervention Model as the structure for discussing potential interventions. The number and type of FASD interventions implemented were determined by surveys sent out postworkshop to 167 participants. At 4 months postworkshop, 37
participants reported implementing 226 primary, secondary, and tertiary interventions in 74 different worksites. The results indicate that incorporation of constructivist learning theory shows promise for future public health and continuing education programs aimed at changing or enhancing practice.


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3. ASSOCIATIONS OF LIGHT AND MODERATE MATERNAL ALCOHOL CONSUMPTION WITH FETAL GROWTH CHARACTERISTICS IN DIFFERENT PERIODS OF PREGNANCY: THE GENERATION R STUDY
Bakker R, Pluimgraaff LE, Steegers EA, Raat H, Tiemeier H, Hofman A, Jaddoe VW. The Generation R Study Group, Erasmus Medical Centre, Rotterdam, The Netherlands, Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands, Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, The Netherlands, Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands, Department of Child & Adolescent Psychiatry, Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, The Netherlands and Department of Paediatrics, Erasmus Medical Centre, Rotterdam, The Netherlands.

ABSTRACT
Background: Excessive alcohol consumption during pregnancy has adverse effects on fetal growth and development. Less consistent associations have been shown for the associations of light-to-moderate maternal alcohol consumption during pregnancy with health outcomes in the offspring. Therefore, we examined the associations of light-to-moderate maternal alcohol consumption with various fetal growth characteristics measured in different periods of pregnancy.

Methods: This study was based on 7333 pregnant women participating in a population-based cohort study. Alcohol consumption habits and fetal growth were assessed in early (gestational age <17.9 weeks), mid- (gestational age 18-24.9 weeks) and late pregnancy (gestational age >/=25 weeks). We assessed the effects of different categories of alcohol consumption (no; less than one drink per week; one to three drinks per week; four to six drinks per week; one drink per day and two to three drinks per day) on repeatedly measured fetal head circumference, abdominal circumference and femur length.

Results: In total, 37% of all mothers continued alcohol consumption during pregnancy, of whom the majority used less than three drinks per week. We observed no differences in growth rates of fetal head circumference, abdominal circumference or femur length between mothers with and without continued alcohol consumption during pregnancy. Compared with mothers without alcohol consumption, mothers with continued alcohol consumption during pregnancy had an increased fetal weight gain [difference 0.61 g (95% confidence interval: 0.18, 1.04) per week]. Cross-sectional analyses in mid- and late pregnancy showed no consistent associations between the number of alcoholic consumptions and fetal growth characteristics. All analyses were adjusted for potential confounders.
Conclusions: Light-to-moderate maternal alcohol consumption during pregnancy does not adversely affect fetal growth characteristics. Further studies are needed to assess whether moderate alcohol consumption during pregnancy influences organ growth and function in postnatal life.

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ABSTRACT

Objectives: The purposes of this investigation were to determine the frequencies of and associations between different neurodevelopmental disorders and to study the potential lasting effects of alcohol on children adopted from eastern Europe.

Methods: In a population-based, prospective, observational, multidisciplinary, cross-sectional, cohort study of 71 children adopted from eastern Europe, children were assessed 5 years after adoption, from pediatric, neuropsychological, and ophthalmologic perspectives.

Results: Fetal alcohol spectrum disorders, that is, fetal alcohol syndrome (FAS), partial FAS, and alcohol-related neurodevelopmental disorders, were identified for 52% of children; FAS was found for 30%, partial FAS for 14%, and alcohol-related neurodevelopmental disorders for 9%. Alcohol-related birth defects were found for 11% of children, all of whom also were diagnosed as having FAS. Mental retardation or significant cognitive impairment was found for 23% of children, autism for 9%, attention-deficit/hyperactivity disorder for 51%, and developmental coordination disorder for 34%.

Conclusions: Fetal alcohol spectrum disorders and neurodevelopmental disorders were common in this long-term follow-up study of children adopted from orphanages in eastern Europe. Maternal alcohol consumption during pregnancy has long-lasting adverse effects, causing structural, behavioral, and cognitive damage despite a radically improved environment.

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http://pediatrics.aappublications.org/cgi/content/abstract/peds.2009-0712v1?maxtoshow=&hits=10&RESULTFORMAT=1&author1=landgren&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&fdate=1/1/2010&resourcetype=HWCIT

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5. **EARLY EXPOSURE TO ETHANOL OR RED WINE AND LONG-LASTING EFFECTS IN AGED MICE. A STUDY ON NERVE GROWTH FACTOR, BRAIN-DERIVED NEUROTROPIC FACTOR, HEPATOCYTE GROWTH FACTOR, AND VASCULAR ENDOTHELIAL GROWTH FACTOR**


**ABSTRACT**

Prenatal ethanol exposure produces severe changes in brain, liver, and kidney through mechanisms involving growth factors. These molecules regulate survival, differentiation, maintenance, and connectivity of brain, liver, and kidney cells. Despite the abundant available data on the short and mid-lasting effects of ethanol intoxication, only few data show the long-lasting damage induced by early ethanol administration.

The aim of this study was to investigate changes in nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) in brain areas, liver, and kidney of 18-mo -old male mice exposed perinatally to ethanol at 11% vol or to red wine at the same ethanol concentration. The authors found that ethanol per se elevated NGF, BDNF, HGF, and VEGF measured by ELISA in brain limbic system areas. In the liver, early exposure to ethanol solution and red wine depleted BDNF and VEGF concentrations. In the kidney, red wine exposure only decreased VEGF.

In conclusion, the present study shows that, in aged mice, early administration of ethanol solution induced long-lasting damage at growth factor levels in frontal cortex, hippocampus, and liver but not in kidney. Otherwise, in mice exposed to red wine, significant changes were observed in the liver and kidney but not in the hippocampus and frontal cortex. The brain differences in ethanol-induced toxicity when ethanol is administered alone or in red wine may be related to compounds with antioxidant properties present in the red wine.

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macrophage contributes to the observed cellular dysfunction in the ethanol-exposed newborn mouse. Control alveolar macrophage differentiation was characterized by increased expression of CD32/CD11b (p ≤ 0.05) and increased in vitro phagocytosis of Staphylococcus aureus (p ≤ 0.05) compared to interstitial macrophage. After in utero ethanol exposure, both alveolar and interstitial macrophage lacked the acquisition of CD32/CD11b (p ≤ 0.05) and displayed impaired in vitro phagocytosis (p ≤ 0.05). Ethanol significantly increased TGFbeta(1) in the bronchoalveolar lavage fluid (p ≤ 0.05), as well as in both interstitial and alveolar macrophages (p ≤ 0.05). Oxidant stress contributed to the ethanol-induced changes on the interstitial and alveolar cells, since maternal supplementation with the glutathione precursor S-adenosylmethionine during ethanol ingestion normalized CD32/CD11b (p ≤ 0.05), phagocytosis (p ≤ 0.05) and TGFbeta(1) in the bronchoalveolar lavage fluid and macrophages (p ≤ 0.05). Contrary to our hypothesis, fetal ethanol exposure did not solely impair interstitial to alveolar macrophage differentiation. Rather, fetal ethanol exposure impaired both neonatal interstitial and alveolar macrophage phagocytic function and differentiation. Increased oxidant stress and elevated TGFbeta(1) contributed to the impaired differentiation of both interstitial and alveolar macrophage.

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7. PATERNAL GENETIC CONTRIBUTION INFLUENCES FETAL VULNERABILITY TO MATERNAL ALCOHOL CONSUMPTION IN A RAT MODEL OF FETAL ALCOHOL SPECTRUM DISORDER
Sittig LJ, Redei EE.
Asher Center, Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States of America.

ABSTRACT
Background: Fetal alcohol exposure causes in the offspring a collection of permanent physiological and neuropsychological deficits collectively termed Fetal Alcohol Spectrum Disorder (FASD). The timing and amount of exposure cannot fully explain the substantial variability among affected individuals, pointing to genetic influences that mediate fetal vulnerability. However, the aspects of vulnerability that depend on the mother, the father, or both, are not known.

Methodology/Principal Findings: Using the outbred Sprague-Dawley (SD) and inbred Brown Norway (BN) rat strains as well as their reciprocal crosses, we administered ethanol (E), pair-fed (PF), or control (C) diets to the pregnant dams. The dams’ plasma levels of free thyroxine (T4), triiodothyronine (T3), free T3 (T3), and thyroid stimulating hormone (TSH) were measured to elucidate potential differences in maternal thyroid hormonal environment, which affects specific aspects of FASD. We then compared alcohol-exposed, pair fed, and control offspring of each fetal strain on gestational day 21 (G21) to identify maternal and paternal genetic effects on bodyweight and placental weight of male and female fetuses.

Conclusions: SD and BN dams exhibited different baseline hypothalamic-pituitary-thyroid function. Moreover, the thyroid function of SD dams was more severely affected by alcohol
consumption while that of BN dams was relatively resistant. This novel finding suggests that genetic differences in maternal thyroid function are one source of maternal genetic effects on fetal vulnerability to FASD.

The fetal vulnerability to decreased bodyweight after alcohol exposure depended on the genetic contribution of both parents, not only maternal contribution as previously thought. In contrast, the effect of maternal alcohol consumption on placental weight was consistent and not strain-dependent. Interestingly, placental weight in fetuses with different paternal genetic contributions exhibited opposite responses to caloric restriction (pair feeding).

In summary, these novel findings demonstrate both maternal and paternal genetic contributions to in utero vulnerability to alcohol, refining our understanding of the genetically-based heterogeneity seen in human FASD.

Link to the Article,

8. THE IMPACT OF AN ADHD CO-MORBIDITY ON THE DIAGNOSIS OF FASD
Carmen Rasmussen, Jennifer Benz, Jacqueline Pei, Gail Andrew, Gail Schuller, Lynne Abele-Webster, Connie Alton, Lindsay Lord

ABSTRACT
Objective: Many children with Fetal Alcohol Spectrum Disorders (FASD) also have co-morbid ADHD. The goal of this study was to examine the impact of having a co-morbid ADHD diagnosis on FASD diagnostic results. We compared children with FASD to those with FASD and co-morbid ADHD across the neurobehavioral domains recommended by the Canadian Guidelines in the diagnosis of FASD.

Methods: We retrospectively analyzed data from 52 children, aged 4 to 17 years, diagnosed with an FASD at a hospital FASD clinic. Thirty-three of these children had a co-morbid diagnosis of ADHD and 19 did not. Children with FASD and those with FASD and co-morbid ADHD were compared on the following neurobehavioral domains: sensory/motor, cognition, communication, academic achievement, memory, executive functioning, attention, and adaptive behavior.

Results: Children with FASD and ADHD performed significantly worse than those without ADHD on attention but better on academic achievement. No other group differences were significant.

Conclusions: Having an ADHD co-morbidity had little effect on the FASD diagnosis. The results of this project will inform the diagnostic process for FASD and have implications for standardizing diagnostic processes across clinics.

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http://www.cjcp.ca/pubmed.php?articleId=259

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9. THE REMARKABLY HIGH PREVALENCE OF EPILEPSY AND SEIZURE HISTORY IN FETAL ALCOHOL SPECTRUM DISORDERS
Stephanie H. Bell, Brenda Stade, James N. Reynolds, Carmen Rasmussen, Gail Andrew, Paul A. Hwang, and Peter L. Carlen
From the Department of Pharmacology and Toxicology (SHB, JNR), and Centre for Neuroscience Studies, Queens University, Kingston, ON; Department of Pediatrics (BS), St. Michael's Health Centre, Toronto, ON; Department of Pediatrics (CR, GA), University of Alberta and Glenrose Rehabilitation Hospital; University Health Network (PLC), Toronto, ON; Toronto Western Research Institute (PLC), University of Toronto, Toronto, ON; North York General Hospital (PAH), Toronto, ON; University of Toronto Epilepsy Research Centre (PAH, PLC), Toronto, ON; The Applied Health Research Centre of the Keenan Research Centre (BS), Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

ABSTRACT
Background: Fetal alcohol spectrum disorder (FASD) is the umbrella term that describes the range of adverse developmental outcomes that may occur in the offspring of mothers who drink alcohol during pregnancy. FASD is associated with several comorbidities including epilepsy. The objective of the study was to evaluate the prevalence of epilepsy or a history of seizures in subjects with FASD and the contribution of relevant risk factors.

Methods: A retrospective chart review was conducted on all active charts (N = 1063) at two FASD clinics. After exclusion of subjects without a confirmed diagnosis, a total of 425 subjects between the ages of 2–49 were included in the analysis. The relationships between FASD diagnosis and other risk factors for co-occurrence of epilepsy or a seizure disorder (e.g., extent of exposure to alcohol and other drugs, type of birth, and trauma) were examined using chi-square and multivariate multinomial logistic regression.

Results: Twenty-five (5.9%) individuals in the study population had a confirmed diagnosis of epilepsy, and 50 (11.8%) had at least one documented seizure episode, yielding an overall prevalence of 17.7% in this population. Importantly, a history of epilepsy or seizures was not different across the three diagnostic subgroups. In those subjects with available maternal drinking histories, first trimester exposure or drinking throughout all three trimesters were the predominant forms of fetal exposure. None of the other risk factors were associated with a greater prevalence of epilepsy or seizures.

Conclusions: There is a remarkably high prevalence of epilepsy/seizures in the FASD population.


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10. SENSORY PROCESSING AND ADAPTIVE BEHAVIOR DEFICITS OF CHILDREN ACROSS THE FETAL ALCOHOL SPECTRUM DISORDER CONTINUUM
Joshua L. Carr, Sabrina Agnihotri, and Michelle Keightley
From the Department of Occupational Science and Occupational Therapy (JLC), University of Toronto, Vancouver, BC; Graduate Department of Rehabilitation Science (SA), University of Toronto; and Department of Occupational Science and Occupational Therapy (MK), Graduate Department of Rehabilitation Science & Department of Psychology, University of Toronto, Toronto, ON, Canada.

ABSTRACT
Background: Prenatal alcohol exposure can have detrimental effects on a child's development of adaptive behaviors necessary for success in the areas of academic achievement, socialization, and self-care. Sensory processing abilities have been found to affect a child's ability to successfully perform adaptive behaviors. The current study explored whether significant differences in sensory processing abilities, adaptive behavior, and neurocognitive functioning are observed between children diagnosed with partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), or children who were prenatally exposed to alcohol (PEA), but did not meet criteria for an FASD diagnosis. The influence of IQ on adaptive behavior as well as further exploration of the relationship between sensory processing and adaptive behavior deficits among these children was also examined.

Methods: A secondary analysis was conducted on some of the Short Sensory Profile (SSP) scores, Adaptive Behavior Assessment System—Second Edition (ABAS-II) scores, and Wechsler Intelligence Scale—Fourth Edition/Wechsler Preschool and Primary Scale of Intelligence—Third Edition (WISC- IV/WPPSI—III) scores of 46 children between 3 and 14 years of age with pFAS, ARND, or who were PEA.

Results: Greater sensory processing deficits were found in children with a diagnosis of pFAS and ARND compared to those in the PEA group. Children with an ARND diagnosis scored significantly worse on measures of adaptive behavior than the PEA group. Children with pFAS scored significantly lower than children with ARND or PEA on perceptual/performance IQ. No correlation was found between IQ scores and adaptive behaviors across the FASD diagnostic categories. A significant positive correlation was found between SSP and ABAS-II scores.

Conclusions: Regardless of the diagnosis received under the FASD umbrella, functional difficulties that could not be observed using traditional measures of intelligence were found, supporting guidelines that a broad range of standardized assessments be included when screening children for FASD.


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11. FAS PREVALENCE IN A SAMPLE OF URBAN SCHOOLCHILDREN IN CROATIA
Petković G, Barisić I.
Children's University Hospital Zagreb, Klaićeva, Zagreb, Croatia. gigi.petkovic@gmail.com

ABSTRACT
We present the results of active case ascertainment of fetal alcohol syndrome (FAS). This study included a sample of urban schoolchildren attending 1st to 4th grade elementary school and their mothers. Out of 912 mothers, 575 (63.04%) participated in the interview. Prenatal alcohol consumption was admitted by 15.47% and binge drinking by 3.13% of interviewed mothers. We evaluated 466 (51.09%) schoolchildren for signs of FAS or partial fetal alcohol syndrome (PFAS) using revised Institute of Medicine (IOM) diagnostic criteria. Nineteen students had features consistent with FAS or PFAS. The observed prevalence of FAS is 3 children and of PFAS is 16 children among 466 students, based on 51% participation rate. The estimated prevalence of FAS is 6.44/1000, of PFAS 34.33/1000 and overall prevalence of FAS/PFAS 40.77/1000. This is the first study of FAS prevalence in Croatia and as far as we are aware the second study in Europe.

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12. NEURODEVELOPMENTAL FUNCTIONING IN CHILDREN WITH FAS, PFAS, AND ARND
Chasnoff IJ, Wells AM, Telford E, Schmidt C, Messer G.
From the Children's Research Triangle, Chicago, IL.

ABSTRACT
Objective: The purpose of this article is to compare the neurodevelopmental profiles of 78 foster and adopted children with fetal alcohol syndrome (FAS), partial FAS (pFAS), or alcohol-related neurodevelopmental disorder (ARND).

Method: Seventy-eight foster and adopted children underwent a comprehensive diagnostic evaluation. By using criteria more stringent than those required by current guidelines, the children were placed in 1 of 3 diagnostic categories: FAS, pFAS, or ARND. Each child was evaluated across the domains of neuropsychological functioning most frequently affected by prenatal exposure to alcohol. Multivariate analyses of variance were conducted to examine differences in neuropsychological functioning between the 3 diagnostic groups. Descriptive discriminant analyses were performed in follow-up to the multivariate analyses of variance.

Results: The children in the 3 diagnostic categories were similar for descriptive and child welfare variables. Children with FAS had significantly decreased mean weight, height, and head circumference. Children with FAS exhibited the most impaired level of general intelligence, significantly worse language-based memory compared with children with ARND, and significantly poorer functional communication skills than children with pFAS. On executive functioning, the FAS group of children performed significantly worse on sequencing and shift than either the pFAS or ARND
groups. Children with pFAS and ARND were similar in all neurodevelopmental domains that were tested.

**Conclusion:** The children who met tightly defined physical criteria for a diagnosis of FAS demonstrated significantly poorer neurodevelopmental functioning than children with pFAS and ARND. Children in these latter 2 groups were similar in all neurodevelopmental domains that were tested.

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March 26, 2010

13. **PROFILE OF THE FIRST 1,400 PATIENTS RECEIVING DIAGNOSTIC EVALUATIONS FOR FETAL ALCOHOL SPECTRUM DISORDER AT THE WASHINGTON STATE FETAL ALCOHOL SYNDROME DIAGNOSTIC & PREVENTION NETWORK**
Susan J Astley

**ABSTRACT**

**Background:** An interdisciplinary approach to fetal alcohol spectrum disorder (FASD) diagnosis using rigorously defined diagnostic guidelines has been adopted as best practice. Diagnostic clinics are being established worldwide. If these clinics are to successfully compete for limited health care dollars, it is essential to document their value.

**Objective:** The primary objectives were to document the value of the largest and longest standing interdisciplinary FASD diagnostic program; the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FAS DPN). Now in its 17th year of operation, the WA FAS DPN is a statewide network of diagnostic clinics all using the 4-Digit Diagnostic Code and contributing to a centralized electronic database.

**Methods:** The clinical database was used to generate comprehensive profiles of all patients evaluated for FASD from 1993-2005. These profiles were used to answer a multitude of clinical, research, and public health questions including:-

What is the demand for FASD diagnostic services, who is referred to the clinics, and what are their FASD diagnostic outcomes? Can FAS/D prevalence estimates from this clinical population be used to estimate FAS/D prevalence estimates in the general population? Do FASD diagnostic outcomes vary by race, age or alcohol exposure? Does the presence of other adverse exposures/events lead to more severe outcomes? Does this approach to diagnosis meet the needs of families?

**Results:** Demand for diagnosis remains very high. Of 1,400 patients (newborn to adult) with confirmed prenatal alcohol exposure, 11% were diagnosed with FAS/PFAS, 28% with static encephalopathy, 52% with neurobehavioral disorder, and 9% with no evidence of CNS abnormality. FASD outcomes varied significantly by age, race, gender, alcohol exposure, and presence of other risk factors. Families reported high satisfaction with the diagnostic process, and receipt of information/services they were unable to obtain elsewhere.
Conclusions: This report documents the immense contribution of a statewide FASD diagnostic program, and underscores the extraordinary value of a comprehensive FASD clinical dataset.

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PubMed, Biofactors. 2010 Mar 23. [Epub ahead of print]

14. THE PLAUSIBILITY OF MATERNAL NUTRITIONAL STATUS BEING A CONTRIBUTING FACTOR TO THE RISK FOR FETAL ALCOHOL SPECTRUM DISORDERS: THE POTENTIAL INFLUENCE OF ZINC STATUS AS AN EXAMPLE
Department of Nutrition, University of California, Davis, Davis, CA 95616, USA.

ABSTRACT
There is increasing evidence that human pregnancy outcome can be significantly compromised by suboptimal maternal nutritional status. Poor diet results in a maternal-fetal environment in which the teratogenicity of other insults such as alcohol might be amplified.

As an example, there is evidence that zinc (Zn) can interact with maternal alcohol exposure to influence the risk for fetal alcohol spectrum disorders (FASD). Studies with experimental animals have shown that the teratogenicity of alcohol is increased under conditions of Zn deficiency, whereas its teratogenicity is lessened when animals are given Zn-supplemented diets or Zn injections before the alcohol exposure. Alcohol can precipitate an acute-phase response, resulting in a subsequent increase in maternal liver metallothionein, which can sequester Zn and lead to decreased Zn transfer to the fetus. Importantly, the teratogenicity of acute alcohol exposure is reduced in metallothionein knockout mice, which can have improved Zn transfer to the conceptus relative to wild-type mice. Consistent with the above, Zn status has been reported to be low in alcoholic women at delivery. Preliminary data from two basic science and clinical nutritional studies that are ongoing as part of the international Collaborative Initiative on Fetal Alcohol Spectrum Disorders support the potential role of Zn, among other nutritional factors, relative to risk for FASD.

Importantly, the nutrient levels being examined in these studies are relevant to general clinical populations and represent suboptimal levels rather than severe deficiencies. These data suggest that moderate deficiencies in single nutrients can act as permissive factors for FASD, and that adequate nutritional status or intervention through supplementation may provide protection from some of the adverse effects of prenatal alcohol exposure.

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15. EFFECTS OF THE COGNITION-ENHANCING AGENT ABT-239 ON FETAL ETHANOL-INDUCED DEFICITS IN DENTATE GYRUS SYNAPTIC PLASTICITY
Varaschin RK, Akers KG, Rosenberg MJ, Hamilton DA, Savage DD.
University of New Mexico, Department of Neurosciences;

ABSTRACT
Prenatal ethanol exposure causes deficits in hippocampal synaptic plasticity and learning. At present, there are no clinically effective pharmacotherapeutic interventions for these deficits.

Here, we examined whether the cognition-enhancing agent ABT-239, a histamine H(3) receptor antagonist, could ameliorate fetal ethanol-induced long-term potentiation deficits. Long-Evans rat dams consumed a mean of 2.82 g/kg ethanol during a four-hour period each day. This voluntary drinking pattern produced a mean peak serum ethanol level of 84 mg/dL. Maternal weight gain, offspring litter size and birthweights were not different between ethanol-consuming and control groups.

A stimulating electrode was implanted in the entorhinal cortical perforant path and a recording electrode in the dorsal dentate gyrus of urethane-anesthetized adult male offspring. Baseline input/output responses were not affected either by prenatal ethanol exposure or by 1 mg/kg ABT-239 administered two hours prior to data collection. No differences were observed between prenatal treatment groups when a ten tetanus train protocol was used to elicit LTP. However, LTP elicited by three tetanizing trains was markedly impaired by prenatal ethanol exposure compared to control. This fetal ethanol-induced LTP deficit was reversed by ABT-239. In contrast, ABT-239 did not enhance LTP in control offspring using the three tetanus train protocol.

These results suggest that histamine H(3) receptor antagonists may have utility for treating fetal ethanol-associated synaptic plasticity and learning deficits. Further, the differential effect of ABT-239 in fetal alcohol offspring compared to controls raises questions about the impact of fetal ethanol exposure on histaminergic modulation of excitatory neurotransmission in affected offspring.

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has been shown that the cleavage plane orientation is developmentally regulated and plays a crucial role in cell fate determination of neural progenitors or the maintenance of the proliferative ventricular zone during neocortical development. We tested if fetal exposure to ethanol, the most widely used psychoactive agent and a potent teratogen that may cause malformation in the central nervous system, alters mitotic cleavage orientation of the neural progenitors at the apical surface of the ventricular zone in the developing neocortex. Fetal exposure to ethanol on E10.5 and 11.5 increased the occurrence frequency of a horizontal cleavage plane that is parallel to the ventricular surface on E 12.5.

Administration of picrotoxin, a GABA(A) receptor antagonist, prior to ethanol administration canceled the effect of ethanol with the frequency of horizontal division similar to the control level, although picrotoxin itself did not show any effect on cleavage plane orientation. Phenobarbital, a GABA(A) receptor agonist, induced horizontal cleavage to an extent similar to that induced by ethanol administration. (+)MK801, an antagonist of NMDA receptor that is another major target of ethanol in neural cells, did not affect the cleavage plane of dividing progenitors. These results suggest that fetal ethanol exposure induced alterations in the cleavage plane orientation of neural progenitors in the ventricular zone of the neocortex via the enhancement of the function of GABA(A) receptors.


17. DIFFERENTIATING PRENATAL EXPOSURE TO METHAMPHETAMINE AND ALCOHOL VERSUS ALCOHOL AND NOT METHAMPHETAMINE USING TENSOR-BASED BRAIN MORPHOMETRY AND DISCRIMINANT ANALYSIS


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ABSTRACT

Here we investigate the effects of prenatal exposure to methamphetamine (MA) on local brain volume using magnetic resonance imaging. Because many who use MA during pregnancy also use alcohol, a known teratogen, we examined whether local brain volumes differed among 61 children (ages 5-15 years), 21 with prenatal MA exposure, 18 with concomitant prenatal alcohol exposure (the MAA group), 13 with heavy prenatal alcohol but not MA exposure (ALC group), and 27 unexposed controls. Volume reductions were observed in both exposure groups relative to controls in striatal and thalamic regions bilaterally and in right prefrontal and left occipitoparietal cortices. Striatal volume reductions were more severe in the MAA group than in the ALC group, and, within the MAA group, a negative correlation between full-scale intelligence quotient (FSIQ) scores and caudate volume was observed. Limbic structures, including the anterior and posterior cingulate, the inferior frontal gyrus (IFG), and ventral and lateral temporal lobes bilaterally, were increased in volume in both exposure groups. Furthermore, cingulate and right IFG volume increases were more pronounced in the MAA than ALC group. Discriminant function analyses using local volume measurements and FSIQ were used to predict group membership, yielding factor scores that correctly classified 72% of participants in jackknife analyses. These findings suggest that striatal and limbic structures, known to be sites of
neurotoxicity in adult MA abusers, may be more vulnerable to prenatal MA exposure than alcohol exposure and that more severe striatal damage is associated with more severe cognitive deficit.

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Wiley InterScience - Infancy.
Published Online: 10 March 2010

18. INFANT SYMBOLIC PLAY AS AN EARLY INDICATOR OF FETAL ALCOHOL-RELATED DEFICIT
Christopher D. Molteno1, Sandra W. Jacobson2, R. Colin Carter2 and Joseph L. Jacobson4
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2 Department of Psychiatry and Behavioral Neurosciences Wayne State University School of Medicine Departments of Human Biology and Psychiatry University of Cape Town Faculty of Health Sciences
3 Department of Pediatrics Children's Hospital Boston and Harvard Medical School
4 Department of Psychiatry and Behavioral Neurosciences Wayne State University School of Medicine Departments of Human Biology and Psychiatry University of Cape Town Faculty of Health Sciences

ABSTRACT
Infant symbolic play was examined in relation to prenatal alcohol exposure and socioenvironmental background and to predict which infants met criteria for fetal alcohol syndrome (FAS) at 5 years. A total of 107 Cape-Colored, South African infants born to heavy drinking mothers and abstainers/light drinkers were recruited prenatally. Complexity of play, sociodemographic and psychological correlates of maternal alcohol use, and quality of parenting were assessed at 13 months, and intelligence quotient and FAS diagnosis at 5 years.

The effect of drinking on spontaneous play was not significant after control for social environment. In contrast, prenatal alcohol and quality of parenting related independently to elicited play. Elicited play predicted 5-year Digit Span and was poorer in infants subsequently diagnosed with FAS/partial FAS and in nonsyndromal heavily exposed infants, compared with abstainers/light drinkers. Thus, symbolic play may provide an early indicator of risk for alcohol-related deficits. The independent effects of prenatal alcohol and quality of parenting suggest that infants whose symbolic play is adversely affected by alcohol exposure may benefit from stimulation from a responsive caregiver.

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http://www3.interscience.wiley.com/journal/123317033/abstract

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19. BRIEF SCREENING QUESTIONNAIRES TO IDENTIFY PROBLEM DRINKING DURING PREGNANCY: A SYSTEMATIC REVIEW

Ethel Burns ¹, Ron Gray ² & Lesley A. Smith ¹
1 School of Health and Social Care, Oxford Brookes University, Jack Straws Lane, Marston, Oxford, UK
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ABSTRACT

Aims: Although prenatal screening for problem drinking during pregnancy has been recommended, guidance on screening instruments is lacking. We investigated the sensitivity, specificity and predictive value of brief alcohol screening questionnaires to identify problem drinking in pregnant women.

Methods: Electronic databases from their inception to June 2008 were searched, as well as reference lists of eligible papers and related review papers. We sought cohort or cross-sectional studies that compared one or more brief alcohol screening questionnaire(s) with reference criteria obtained using structured interviews to detect 'at-risk' drinking, alcohol abuse or dependency in pregnant women receiving prenatal care.

Results: Five studies (6724 participants) were included. In total, seven instruments were evaluated: TWEAK (Tolerance, Worried, Eye-opener, Amnesia, Kut down), T-ACE [Take (number of drinks), Annoyed, Cut down, Eye-opener], CAGE (Cut down, Annoyed, Guilt, Eye-opener], NET (Normal drinker, Eye-opener, Tolerance), AUDIT (Alcohol Use Disorder Identification Test), AUDIT-C (AUDIT-consumption) and SMAST (Short Michigan Alcohol Screening Test). Study quality was generally good, but lack of blinding was a common weakness. For risk drinking sensitivity was highest for T-ACE (69-88%), TWEAK (71–91%) and AUDIT-C (95%), with high specificity (71– 89%, 73– 83% and 85%, respectively). CAGE and SMAST performed poorly. Sensitivity of AUDIT-C at score ≥3 was high for past year alcohol dependence (100%) or alcohol use disorder (96%) with moderate specificity (71% each). For lifetime alcohol dependency the AUDIT at score ≥8 performed poorly.

Conclusion: T-ACE, TWEAK and AUDIT-C show promise for screening for risk drinking, and AUDIT-C may also be useful for identifying alcohol dependency or abuse. However, their performance as stand-alone tools is uncertain, and further evaluation of questionnaires for prenatal alcohol use is warranted.


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20. VERBAL AND NONVERBAL MEMORY IN ADULTS PRENATALLY EXPOSED TO ALCOHOL

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School of Medicine, Atlanta; and Department of Neurology (FCG), Emory University School of Medicine, Atlanta, Georgia.

ABSTRACT
Background: Neurocognitive effects of prenatal alcohol exposure in adulthood are not well documented. Questions persist regarding the extent to which there are specific, measurable effects beyond those associated with global ability deficits, whether individuals without the full fetal alcohol syndrome (FAS) demonstrate alcohol-related cognitive impairments, and whether observed memory effects are specific to a particular modality, i.e., verbal vs. visual/spatial domains.

Methods: In this study, verbal and nonverbal selective reminding paradigms were used to assess memory function in 234 young adults (M age: 22.78, SD: 1.79). Alcohol exposure was quantified prenatally. Alcohol groups included: Individuals with physical effects of alcohol exposure (Dysmorphic group, n = 47); Exposed individuals without such effects (n = 74). Contrast groups included: Controls (n = 59) matched for ethnicity, socioeconomic status, and hospital of birth; Special Education contrast group (n = 54) included to control for disability status. Memory outcomes entailed total recall, delayed recall, and measures of encoding and retrieval, and learning over trials as indexed by slope.

Results: Results indicated that Dysmorphic individuals were significantly less efficient in memory performance than Controls on all of the outcomes measured, but they did not differ from those in the Special Education contrast group. The nondysmorphic, alcohol-exposed group was intermediate in their performance, suggesting a continuum of effects of prenatal exposure. Evaluation of the encoding and retrieval aspects of memory performance indicated that learning rather than forgetting accounted for the deficits associated with prenatal alcohol exposure. Finally, no interaction was found between modality of presentation (verbal and nonverbal) and effects of alcohol exposure on memory performance.

Conclusion: These findings indicate that prenatal alcohol exposure is associated with persistent and specific effects on memory performance, and these problems result from less efficient encoding of information across both verbal and nonverbal modalities. Education and training efforts with this clinical group should take these characteristics into account.

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http://www3.interscience.wiley.com/journal/123309053/abstract

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ABSTRACT
Background: Ethanol is the main addictive and neurotoxic constituent of alcohol. Ethanol exposure during embryonic development causes dysfunction of the central nervous system (CNS) and leads to fetal alcohol spectrum disorders. The cerebellum is one of the CNS regions that are particularly vulnerable to ethanol toxic effects. Retinoic acid (RA) is a physiologically active metabolite of vitamin A that is locally synthesized in the cerebellum. Studies have shown that RA is required for neuronal development, but it remains unknown if ethanol impairs RA signaling and thus induces neuronal malformations. In this study, we tested the hypothesis that ethanol impairs the expression and activation of RA receptors in cerebellum and in cerebellar granule cells.

Methods: The cerebellum of ethanol unexposed and exposed pups was used to study the expression of retinoic acid receptors (RARs or RXRs) by immunohistochemistry and by Western blot analysis. We also studied the effect of ethanol on expression of RA receptors in the cerebellar granule cells. Activation of RA receptors (DNA-binding activities) in response to high-dose ethanol was determined by electrophoretic mobility shift and supershift assays.

Results: Findings from these studies demonstrated that ethanol exposure reduced the expression of RARα/γ while it increased the expression of RXRα/γ in the cerebellum and in cerebellar granule neurons. Immunohistological studies further strengthened the expression pattern of RA receptors in response to ethanol. The DNA-binding activity of RARs was reduced, while DNA-binding activity of RXRs was increased in response to ethanol exposure.

Conclusion: For the first time, our studies have demonstrated that high-dose ethanol affects the expression and activation of RA receptors, which could impair the signaling events and induce harmful effects on the survival and differentiation of cerebellar granule cells. Taken together, these findings could provide insight into the treatment options for brain defects caused by excessive ethanol exposure, such as in Fetal Alcohol Spectrum Disorders.


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Wiley InterScience - Synapse. Volume 64 Issue 6, Pages 467–477. Published Online: 19-2-2010

22. NEUROPROTECTIVE EFFECT OF VITAMIN C AGAINST THE ETHANOL AND NICOTINE MODULATION OF GABAB RECEPTOR AND PKA-EXPRESSION IN PRENATAL RAT BRAIN
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ABSTRACT
Prenatal ethanol exposure has various deleterious effects on neuronal development and can induce various defects in developing brain, resulting in fetal alcohol syndrome (FAS). Aminobutyric acid (GABAB) receptor (R) is known to play an important role during the development of the central nervous system (CNS). Our study was designed to investigate the effect of ethanol (100 mM), nicotine (50 M) (for 30 min and 1 h), vitamin C (vitC, 0.5 mM),
ethanol plus vitC, and nicotine plus vitC on expression level of GABAB1, GABAB2R, and protein kinase A- (PKA) in prenatal rat cortical and hippocampal neurons at gestational days (GD) 17.5. The results showed that, upon ethanol and nicotine exposure, GABAB1 and GABAB2R protein expression increased significantly in the cortex and hippocampus for a short (30 min) and long term (1 h), whereas only GABAB2R subunit was decreased upon nicotine exposure for a long term in the cortex. Furthermore, PKA expression in cortex and hippocampus increased with ethanol exposure during short term, whereas long-term exposure results increased in cortex and decreased in hippocampus. Moreover, the cotreatment of vitC with ethanol and nicotine showed significantly decreased expression of GABAB1, GABAB2R, and PKA in cortex and hippocampus for a long-term exposure. Mitochondrial membrane potential, Fluoro-jade-B, and propidium iodide staining were used to elucidate possible neurodegeneration. Our results suggest the involvement of GABABR and PKA in nicotine and ethanol-mediated neurodevelopmental defects and the potential use of vitC as a effective protective agent for FAS-related deficits.

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http://www3.interscience.wiley.com/journal/123297024/abstract


23. PRENATAL EXPOSURE TO ETHANOL AFFECTS POSTNATAL NEUROGENESIS IN THALAMUS
Mooney SM, Miller MW.
Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY 13210, USA; Developmental Exposure Alcohol Research Center, State University of New York, Binghamton NY 13902; Cortland NY13054; Syracuse NY 13210, USA.

ABSTRACT
The number of neurons in the ventrobasal thalamus (VB) in the adolescent rat is unaffected by prenatal exposure to ethanol. This is in sharp contrast to other parts of the trigeminal-somatosensory system, which exhibit 30-35% fewer neurons after prenatal ethanol exposure. The present study tested the hypothesis that prenatal ethanol exposure affects dynamic changes in the numbers of VB neurons; such changes reflect the sum of cell proliferation and death. Neuronal number in the VB was determined during the first postnatal month in the offspring of pregnant Long-Evans rats fed an ethanol-containing diet or pair-fed an isocaloric non-alcoholic liquid diet. Offspring were examined between postnatal day (P) 1 and P30. The size of the VB and neuronal number were determined stereologically. Prenatal exposure to ethanol did not significantly alter neuronal number on any individual day, nor was the prenatal generation of VB neurons affected. Interestingly, prenatal ethanol exposure did affect the pattern of the change in neuronal number over time; total neuronal number was stable in the ethanol-treated pups after P12, but it continued to rise in the controls until P21. In addition, the rate of cell proliferation during the postnatal period was greater in ethanol-treated animals. Thus, the rate of neuronal acquisition is altered by ethanol, and by deduction, there appears to be less ethanol-induced neuronal loss in the VB. A contributor to these changes is a latent effect of ethanol on postnatal neurogenesis in the VB and the apparent survival of new neurons.

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24. OVEREXPRESSION OF SERUM RESPONSE FACTOR RESTORES OCULAR DOMINANCE PLASTICITY IN A MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS
Paul AP, Pohl-Guimaraes, Krahe TE, Filgueiras CC, Lantz CL, Colello RJ, Wang W, Medina AE
Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298-0709, USA.

ABSTRACT
Neuronal plasticity deficits underlie many of the neurobehavioral problems seen in fetal alcohol spectrum disorders (FASD). Recently, we showed that third trimester alcohol exposure leads to a persistent disruption in ocular dominance (OD) plasticity. For instance, a few days of monocular deprivation results in a robust reduction of cortical regions responsive to the deprived eye in normal animals, but not in ferrets exposed early to alcohol. This plasticity deficit can be reversed if alcohol-exposed animals are treated with a phosphodiesterase type 1 (PDE1) inhibitor during the period of monocular deprivation. PDE1 inhibition can increase cAMP and cGMP levels, activating transcription factors such as the cAMP response element binding protein (CREB) and the serum response factor (SRF). SRF is important for many plasticity processes such as LTP, LTD, spine motility, and axonal pathfinding. Here we attempt to rescue OD plasticity in alcohol-treated ferrets using a Sindbis viral vector to express a constitutively active form of SRF during the period of monocular deprivation. Using optical imaging of intrinsic signals and single-unit recordings, we observed that overexpression of a constitutively active form of SRF, but neither its dominant-negative nor GFP, restored OD plasticity in alcohol-treated animals. Surprisingly, this restoration was observed throughout the extent of the primary visual cortex and most cells infected by the virus were positive for GFAP rather than NeuN. This finding suggests that overexpression of SRF in astrocytes may reduce the deficits in neuronal plasticity seen in models of FASD.

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Epidemiology

25. DECLINE IN THE BIRTH PREVALENCE OF FETAL ALCOHOL SYNDROME IN ALASKA
Department of Health and Social Services - William H. Hogan, MSW, Commissioner
Division of Public Health - Ward Hurlburt, MD, MPH, CMO/Director
Editors - Beth Funk, MD, MPH, Bradford D. Gessner, MD, MPH

ABSTRACT
Background: Population-based estimates of fetal alcohol syndrome (FAS) birth prevalence are higher for Alaska than other states using similar and consistent surveillance methodology. Trend analysis is critical to evaluating FAS prevention programs but is problematic because diagnostic and surveillance factors that affect FAS case determination are often inconsistent. The objective of this study was to evaluate overall and population specific FAS birth prevalence trends in Alaska.

Methods: During 2009, medical record abstractions were completed for all potential FAS cases reported to the Alaska Birth Defects Registry (ABDR) for children who were at least 6 years of age (birth years 1996-2002). Data from these abstractions was linked to birth certificates and the
linked file was used to determine FAS prevalence estimates. Confirmed FAS cases met the following criteria: matched an Alaska birth certificate; were reported to the ABDR before age 6 years; and had at least one complete medical chart abstraction.

**Results:** During 1996-2002, Alaska experienced a 32% decrease in FAS birth prevalence from 19.9 to 13.5 per 10,000 live births (p=0.05) (Figure 1). Decline in the overall FAS prevalence was limited entirely to Alaska Native children who experienced a 49% decline from 63.1 to 32.4 per 10,000 live births (p=.003). The prevalence among non-Native children increased 64% from 3.7 to 6.1 per 10,000 live births (p=.18). The prevalence ratio of Alaska Native to non-Native infants fell from 17 (95% confidence interval [CI]: 8 to 36) in 1996-1998 to 5 (95% CI: 7 to 16) in 2000-2002.

![Graph showing FAS prevalence decrease](image)

**Discussion:** In Alaska, FAS prevalence fell because of a reduction in risk among Alaska Native infants. Despite these improvements, population-specific FAS rates remain higher for Alaska Native children, although some of this increased risk may result from ascertainment bias. The observed decline occurred in association with a number of prevention activities: development and sustainability of a network of community-based FASD Diagnostic Teams; development of university-level FASD curricula and statewide training programs for educators and providers; a statewide multi-media public awareness campaign; and increased substance use screening in primary care settings. The temporal association of declining FAS prevalence with these Prevention activities suggests that these interventions played a role. It is unclear why FAS prevalence has not declined among non-Native children.

**Recommendations:**
1. Health care providers should familiarize themselves with signs of alcohol abuse and provide patient education and appropriate referrals for pregnant and other women of childbearing age.
2. Health care providers should familiarize themselves with the clinical presentation of FAS and provide appropriate interventions to affected children. Providers should evaluate children for FAS using standardized diagnostic criteria or refer patients to FAS diagnostic teams.
3. All health care providers should comply with the state’s requirements for conditions reportable to public health.5
4. Specialists should record diagnostic information in the child’s medical record; including specific information on facial dysmorphia, growth delay and central nervous system development.

References:
3. AAP. Policy Statement. FAS and Alcohol-Related Neurodevelopmental Disorders. Available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics
4. ADHSS. Diagnosing FAS. Available at: http://www.faslink.org/diagnose.htm

Link to the Article, http://www.epi.alaska.gov/bulletins/docs/b2010_03.pdf

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Wiley InterScience - Congenital Anomalies. Published Online: 11 feb 2010

26. ALTERATION IN ANXIETY-RELATED BEHAVIORS AND REDUCTION OF SEROTONERGIC NEURONS IN RAPHE NUCLEI IN ADULT RATS PRENATALLY EXPOSED TO ETHANOL
Ken-ichi Ohta, Hiromi Sakata-Haga, and Yoshihiro Fukui
Department of Anatomy and Developmental Neurobiology, Institutes of Health Biosciences, the University of Tokushima Graduate School, Tokushima, Japan.

ABSTRACT
It is known that the developing serotonergic system is one of the targets of ethanol teratogenicity. Because serotonin has multiple functions in both mature and immature brains, disturbance of the serotonergic system by ethanol exposure in utero can be cause of a wide range of psychiatric problems in adulthood. In the present study, we observed serotonergic neurons in the midbrain raphe nuclei and anxiety-like behaviors which would be affected by an altered serotonergic system in adult rats prenatally exposed to ethanol. Pregnant rats were fed a liquid diet containing 2.5-5.0% (w/v) ethanol during gestational days 10-21. Their offspring was examined during 60-70 days of age. A significant decrease in the number of serotonergic cells in the midbrain raphe nuclei was shown in prenatally ethanol-exposed offspring. In an open field test, they spent more time in a central area compared to controls. Also in an elevated plus maze test, prenatally ethanol-exposed offspring spent more time on the open arms than controls. These behavioral results suggested that prenatally ethanol-exposed rats were less sensitive to anxiety. On the other hand, 44% of prenatally ethanol-exposed offspring exhibited freezing behavior on the open
arms of the elevated plus maze, causing strong anxiety, compared with 0% in intact control and 12.5% in isocaloric sucrose-fed control groups. These findings suggest that prenatal ethanol exposure decreases both susceptibility and resistance of anxiety. Insufficient serotonergic actions caused by reduced serotonergic neurons in the raphe nuclei might contribute to the alterations in anxiety-related behaviors observed in our prenatally ethanol-exposed rats.

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http://www3.interscience.wiley.com/journal/123279432/abstract


27. MANAGING FETAL ALCOHOL SPECTRUM DISORDER IN THE PUBLIC SCHOOL SYSTEM: A NEEDS ASSESSMENT PILOT  
Gal I Koren, Ellen Fantus, Irena Nulman

ABSTRACT  
Background: Published data and Canadian population reports suggest that approximately 1% of students in Toronto may have learning problems related to Fetal Alcohol Spectrum Disorders (FASDs). It is therefore imperative to understand how the needs of affected students are being met by various practitioners in their school environment. To date no comprehensive follow-up studies on FASD-affected children, families and educators in Toronto public schools are available. Documentation of school experiences associated with FASDs is needed to aid in developing appropriate and efficient intervention models for FASDs.

Objectives: Identify and document needs as related to school capacities and education practitioner capabilities with respect to their abilities to support children diagnosed with FASDs.

Methods: A qualitative approach using semi-structured interviews was utilized for this exploratory pilot study. Twelve practitioners from various disciplines, all of whom work for Toronto public schools participated.

Results: Participants represented approximately 3500 students enrolled amongst their schools and classrooms. Only one respondent reported having worked with a child diagnosed with an FASD during their career. Education practitioners commonly report a lack of knowledge of FASDs and how to appropriately plan for affected children.

Conclusions: Practitioners need additional supports in order to address FASDs in their schools. As this is the first pilot study on FASDs in the Ontario school system, further study is warranted.

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http://www.cjcp.ca/pubmed.php?articleId=254

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28. NORMAL DISTRIBUTION OF PALPEBRAL FISSURE LENGTHS IN CANADIAN SCHOOL AGE CHILDREN
Sterling K Clarren, Albert E Chudley, Louis Wong, Janis Friesen, Rollin Brant

ABSTRACT
Background: Fetal alcohol syndrome (FAS) includes the facial dysmorphic feature of short palpebral fissures (PFs) and short PFs are a key physical marker for identifying children with FAS and some other rarer conditions. There is concern that normative data on PFs now available may not reflect all racial/ethnic groups and might be inaccurate in general.

Objectives: To accomplish a large population based study that would accurately determine normative PF values across the full diversity of the Canadian school age population.

Methods: A normative sample of school age children was identified in Vancouver, British Columbia and Winnipeg, Manitoba to reflect the diversity of racial and national groups in Canada. The sample included students in grades 2, 4, 6, 8, and 10 from 17 schools in Vancouver and 31 schools in Winnipeg. Schools were selected based on racial diversity obtained from data from the 2001 Statistics Canada census. 1064 students in Vancouver and 1033 students in Winnipeg were photographed in a standardized way. Photographs were analyzed using a computerized method.

Results: Analysis demonstrated that PFs do grow with age and there is a slight but meaningful difference between boys and girls in each age group. It is possible to define Canadian standards without reference to racial or ethnic origin.

Conclusion: Mean results with norms and standard deviations are presented in figures for clinical use and are clinically smaller than those found in the most commonly used reference book.

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29. COGNITIVE FUNCTIONING IN CHILDREN PRENATALLY EXPOSED TO ALCOHOL AND PSYCHOTROPIC DRUGS
Dalen K, Bruarøy S, Wentzel-Larsen T, Laegreid LM.
Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway.
knut.dalen@psych.uib.no

ABSTRACT
Cognitive functioning was compared in 29 children diagnosed with fetal alcohol syndrome (FAS), 35 children with fetal alcohol effects (FAE), and 66 psychotropic drugs-exposed (PDE) children using Wechsler tests and the neuropsychological test battery NEPSY. In the FAS group, verbal IQ (VIQ=78), performance IQ (PIQ=77), and full scale IQ (FSIQ=75) were significantly lower as compared to the FAE and PDE groups. In the PDE group VIQ and FSIQ were significantly higher
than in the FAE group. In the FAS group, processing speed (PS) was significantly lower than the other three factors. In the FAE group, perceptual organization (PO) was significantly higher, whereas PS was significantly lower than the other factors. In the PDE group, verbal comprehension (VC) was significantly higher than the other factors. Attention subscales on the NEPSY were significantly lower in all the three groups. Prenatal alcohol exposure affects IQ levels more than exposure to psychotropic drugs. Attentional problems were found in all children when tested with the NEPSY in all groups. Georg Thieme Verlag KG Stuttgart New York.

Link to the Article,


30. ACUTE ALCOHOL EXPOSURE INDUCES APOPTOSIS AND INCREASES HISTONE H3K9/18 ACETYLATION IN THE MID-GESTATION MOUSE LUNG
Wang X, Gomutputra P, Wolgemuth DJ, Baxi LV.
Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, USA

ABSTRACT
Objective: Alcohol consumption causes cellular injury and excessive cell death. Recent studies indicate that ethanol can induce epigenetic alterations, particularly acetylation and methylation of histones and hypomethylation and hypermethylation of DNA. In the current study, we tested the hypothesis that acute exposure of pregnant mice to alcohol during mid-gestation can induce apoptosis and increase histone H3K9/18 acetylation in the fetal lung. The increased expression of histone H3K9/18 acetylation could alter the expression of genes that induce apoptosis.

Study Design: C57BL/6J mice at day 13.5 of gestation were injected intraperitoneally with 2 doses of 25% ethanol (experimental) or Ringer solution (control) at 4-hour intervals. The fetuses were retrieved at 1, 3, 12, and 24 hours after alcohol exposure. The lungs were processed for detection of apoptosis by the terminal deoxynucleotidyl transferase biotin- deoxyuridine triphosphate (dUTP) nick end labeling (TUNEL) assay and for levels of acetylated histone H3K9/18 by immunohistochemistry.

Results: In the control lungs, apoptosis was observed in 0.22% and 0.25% of the mesenchymal and epithelial cells, respectively. In contrast, at 24 hours after alcohol injection at E13.5, 3.4% of the mesenchymal and 4.0% of the epithelial cells in the lung were undergoing apoptosis (TUNEL-positive; P < .005). The number of positively stained cells and levels of acetylated histone H3K9/18 staining significantly increased 1 hour after alcohol injection (P < .05) and returned to basal levels after 12 hours.

Conclusions: Acute alcohol exposure of pregnant mice at mid-gestation results in increased apoptosis in the fetal lung, and elevated levels of acetylated histone H3K9/18 precede the observation of apoptosis.

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31. BRAIN MICROSTRUCTURE IS RELATED TO MATH ABILITY IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER
Lebel C, Rasmussen C, Wyper K, Andrew G, Beaulieu C.
Department of Biomedical Engineering, University of Alberta, Alberta, Canada.

ABSTRACT
Background: Children with fetal alcohol spectrum disorder (FASD) often demonstrate a variety of cognitive deficits, but mathematical ability seems to be particularly affected by prenatal alcohol exposure. Parietal brain regions have been implicated in both functional and structural studies of mathematical ability in healthy individuals, but little is known about the brain structure underlying mathematical deficits in children with FASD. The goal of this study was to use diffusion tensor imaging (DTI) to investigate the relationship between mathematical skill and brain white matter structure in children with FASD.

Methods: Twenty-one children aged 5 to 13 years diagnosed with FASD underwent DTI on a 1.5-T MRI scanner and cognitive assessments including the Woodcock-Johnson Quantitative Concepts test. Voxel-based analysis was conducted by normalizing subject images to a template and correlating fractional anisotropy (FA) values across the brain white matter with age-standardized math scores.

Results: Voxel-based analysis revealed 4 clusters with significant correlations between FA and math scores: 2 positively-correlated clusters in the left parietal region, 1 positively-correlated cluster in the left cerebellum, and 1 negatively-correlated cluster in the bilateral brainstem. Diffusion tractography identified the specific white matter tracts passing through these clusters, namely the left superior longitudinal fasciculus, left corticospinal tract and body of the corpus callosum, middle cerebellar peduncle, and bilateral projection fibers including the anterior and posterior limbs of the internal capsule.

Conclusions: These results identify 4 key regions related to mathematical ability and provide a link between brain microstructure and cognitive skills in children with FASD. Given previous findings in typically developing children and those with other abnormal conditions, our results highlight the consistent importance of the left parietal area for mathematical tasks across various populations, and also demonstrate other regions that may be specific to mathematical processing in children with FASD.

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32. [DIAGNOSTIC CRITERIA FOR FETAL ALCOHOL SYNDROME AND FETAL ALCOHOL SPECTRUM DISORDERS] ARTICLE IN SPANISH
Evrard SG.
Hospital Neuropsiquiátrico Braulio A. Moyano, Buenos Aires. sgevrard@yahoo.com.ar

ABSTRACT
Prenatal ethanol exposure, in our professional practice, is an almost neglected condition as an
important etiological factor for the induction of a wide spectrum of neuropsychiatric diseases that may appear during childhood, adolescence or adulthood. Children born to alcoholic mothers may show a profound mental retardation ranging to an apparent normality, and extending through epilepsy, attention deficit disorders with or without hyperactivity, autism and pervasive developmental disorders, and different types of learning disorders. When adolescents, they may develop different kinds of personality disorders and substance abuse disorders. Finally, in adulthood, they may suffer from different types of affective and psychotic disorders, among others. A great number of those children may not develop their full mental and social potentiality as free individuals. They usually have diverse types of cognitive, attentional, mnemonic and affective impairments. Not infrequently, they engage in antisocial behaviors or have school or work troubles. In this work, the present clinical classifications and diagnostic criteria for the disorders emerging from a prenatal ethanol exposure are reviewed in order to call attention to the medical pediatric and neuropsychiatric community about the increasingly, although underdiagnosed, frequency of these disorders in our country.

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33. [PSYCHOACTIVE SUBSTANCE USE DURING PREGNANCY: A REVIEW.]
[ARTICLE IN FRENCH]
Lamy S, Thibaut F.
CHU de Rouen, 76031 Rouen, France; Inserm CIC 0204, Inserm U 614, UFR de médecine, Rouen, France.

ABSTRACT
All around the world, the potential consequences of the increasing use of psychoactive substances during pregnancy are a major public health concern. It is estimated that 20 to 30% of pregnant women use tobacco, 15% use alcohol, 3 to 10% use cannabis and 0.5 to 3% use cocaine. The estimation of tobacco consumption during pregnancy is better known as compared with alcohol and substance use prevalence during pregnancy, which remains under estimated or unknown.
For example, in France, the prevalence of cannabis and cocaine use during pregnancy is unknown. In general, the prevalence of drug or alcohol use during pregnancy is estimated by extrapolating data from epidemiological studies conducted in the general population (in France or in other countries). However, drug or alcohol use in the general population may dramatically vary from one country to another. Even if some studies have reported the prevalence of alcohol or substance use in different countries around the world, most of them were based on the mother's interview. In most cases, the mother did not report exactly the amount of drugs or alcohol used. Further studies measuring alcohol or substance use in the mother's blood, hair or in the newborn's meconium are needed. In addition, different methodologies have been used in the literature (different types of interview, with or without biological measurements; different subjects included (in- or out-pregnant women, psychiatric comorbidities or not, different economic status, etc).
Despite these methodological biases, the prevalence of drug or alcohol use increases in pregnant women, and in most cases, several drugs are associated. Most of the studies have used structured or semi-structured interviews such as the addiction severity index (ASI) or the
alcohol use disorders identification test (AUDIT) to assess alcohol or drug consumption. In addition, the identification of risk factors for substance or alcohol use during pregnancy would allow the early detection of these high-risk pregnancies. Environmental factors such as low economic status or marital status may play an important role. Personality disorders may also contribute to substance or alcohol use during pregnancy. In fact, in most studies the quality of the obstetrical survey is lower in pregnant women using drugs or alcohol but it remains difficult to describe a specific at-risk profile in these pregnant women. Consumption of alcohol or of one or more psychoactive substances during pregnancy may have serious consequences on the pregnancy and on the child's development. Fetal alcoholism syndrome is the main etiology of mental retardation in France. We need to improve our knowledge of alcohol and substance use during pregnancy in order to target information for prevention campaigns and to implement specific mother and child medical care in high-risk populations.

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34. ALTERATION OF SELECTIVE NEUROTRANSMITTERS IN FETAL BRAINS OF PRENATALLY ALCOHOL-TREATED C57BL/6 MICE: QUANTITATIVE ANALYSIS USING LIQUID CHROMATOGRAPHY/TANDEM MASS SPECTROMETRY
Sari Y, Hammad LA, Saleh MM, Rebec GV, Mechref Y.
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ABSTRACT
We previously demonstrated that prenatal alcohol exposure results in brain defects at different embryonic stages. This study is aimed at characterizing the influence of prenatal alcohol exposure on the levels of several neurotransmitters at early embryonic stage 13 (E13). Pregnant C57BL/6 mice were exposed to either a 25% ethanol derived calorie diet (ALC) or pair-fed (PF) liquid diet from E7 to E13. At E13, fetal brains were collected from dams of the ALC and PF groups. Liquid chromatography/tandem mass spectrometry (LC-MS) was then used to evaluate neurotransmitter levels. This approach involved the use of an LC column in conjunction with multiple-reaction monitoring mass spectrometry. Quantitative analyses of catecholamines, idolamine, and amino acid neurotransmitters revealed significant reductions in the levels of dopamine (p=0.004), norepinephrine (p=0.0009), epinephrine (p=0.0002), serotonin (p=0.004), and GABA (p=0.002) in the ALC group compared to the PF group. However, there was no significant change in the levels of glutamate in E13 fetal brains. These findings demonstrate that prenatal alcohol exposure reduces the concentrations of some catecholamines, idolamine, and amino acid neurotransmitters in E13 fetal brains. This study suggests that alterations of selective neurotransmitters may be the cause of abnormalities in brain function and behavior found in fetal alcohol spectrum disorders.

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35. REVERSAL OF ALCOHOL-INDUCED LEARNING DEFICITS IN THE YOUNG ADULT IN A MODEL OF FETAL ALCOHOL SYNDROME
Incerti M, Vink J, Roberson R, Wood L, Abebe D, Spong CY.
Unit on Perinatal and Developmental Neurobiology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892-0925, USA. maddalena.incerti@gmail.com

ABSTRACT
Objective: To evaluate whether treatment with neuroprotective peptides to young adult mice prenatally exposed to alcohol reverses alcohol-induced learning deficits in a mouse model of fetal alcohol syndrome, whether the mechanism involves the N-methyl-d-aspartate (NMDA) and gamma-aminobutyric acid type A (GABAA) receptors, and whether it is related to glial cells.

Methods: C57Bl6/J mice were treated with alcohol (0.03 ml/g) or placebo on gestational day 8. On day 40, male mice exposed to alcohol in utero were treated daily for 10 days with D-NAPVSIPQ and D-SALLRSIPA (n=20) or placebo (n=13); and control offspring were treated with placebo (n=46), with the treatment blinded. Learning evaluation began after 3 days using the Morris watermaze and the T-maze. The hippocampus, cortex, and cerebellum were isolated. Expression of NR2A, NR2B, GABAAbeta3, GABAAalpha5, vasoactive intestinal peptide (VIP), activity-dependent neuroprotective protein, and glial fibrillary acidic protein was measured using calibrator-normalized relative real-time polymerase chain reaction. Statistical analysis included analysis of variance and Fisher's protected least significant difference.

Results: Treatment with D-NAPVSIPQ and D-SALLRSIPA reversed the alcohol-induced learning deficit in both learning tests as well as the NR2A and NR2B down-regulation in the hippocampus and the up-regulation of NR2A in the cortex and NR2B in the cortex and cerebellum (all P<.05). No significant differences were found in GABAA expression. Moreover, the peptides changed activity-dependent neuroprotective protein expression in the cortex (P=.016) but not the down-regulation of VIP (P=.883), probably because the peptides are downstream from VIP.

Conclusion: Alcohol-induced learning deficit was reversed and expression of NR2A and NR2B was restored in the hippocampus and cortex of young adult mice treated with D-NAPVSIPQ and D-SALLRSIPA. Given the role of NMDA receptors in learning, this may explain in part the mechanism of prevention of alcohol-induced learning deficits by D-NAPVSIPQ and D-SALLRSIPA.

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36. PRENATAL ALCOHOL EXPOSURE ALTERS PHOSPHORYLATION AND GLYCOSYLAION OF PROTEINS IN RAT OFFSPRING LIVER
Fofana B, Yao XH, Rampitsch C, Cloutier S, Wilkins JA, Nyomba BL.
Diabetes Research Group, Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

ABSTRACT
To gain more insights into the translational and PTM that occur in rat offspring exposed to alcohol in utero, 2-D PAGE with total, phospho- and glycoprotein staining and MALDI-MS/MS and database searching were conducted. The results, based on fold-change expression, revealed a down-regulation of total protein expression by prenatal alcohol exposure in 7-day-old and 3-month-old rats. There was an up-regulation of protein phosphorylation but a down-regulation of glycosylation by prenatal alcohol exposure in both age groups. Of 31 protein spots examined per group, differentially expressed proteins were identified as ferritin light chain, aldoketo reductase, tumor rejection antigen gp96, fructose-1,6-bisphosphatase, glycerol-3-phosphate dehydrogenase, malate dehydrogenase, and gamma-actin. Increased phosphorylation was observed in proteins such as calmodulin, glutathione S-transferase, glucose regulated protein 58, alpha-enolase, eukaryotic translation elongation factor 1 beta-2, riboprotein large P2, agmatinase, ornithine carbamoyltransferase, quinolinate phosphoribosyltransferase, formimidoyltransferase cyclodeaminase, and actin. In addition, glycosylation of adenosine kinase, adenosylhomocysteine hydrolase, and 3-hydroxyanthranilate dioxygenase was reduced. Pathways affected by these protein alterations include cell signaling, cellular stress, protein synthesis, cytoskeleton, as well as glucose, aminoacid, adenosine and energy metabolism. The activity of the gluconeogenic enzyme fructose-1,6-bisphosphatase was elevated by prenatal alcohol. The observations may have important physiological implications.

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37. IMPACT OF A SOCIAL SKILLS INTERVENTION ON THE HOSTILE ATTRAIBUTIONS OF CHILDREN WITH PRENATAL ALCOHOL EXPOSURE
Keil V, Paley B, Frankel F, O'Connor MJ.
Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California 92630, USA. vkeil29@gmail.com

ABSTRACT
Background: Prenatal alcohol exposure (PAE) has been linked to a wide array of developmental deficits, including significant impairments in social skills. Given the extensive body of evidence linking social information-processing patterns with social behavior, it is possible that social information-processing may represent one mechanism of behavioral change. The present investigation sought to answer the question of whether a well-established social skills intervention decreased the hostile attributions of children with PAE. Further, was there a differential impact of the intervention on hostile attributions in the context of peer provocation versus group entry scenarios?

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**Methods:** Participants consisted of 100 children (51% male) with PAE between the ages of 6 and 12 years. Participants were randomly assigned to either a social skills intervention, Children’s Friendship Training (CFT), or to a Delayed Treatment Control (DTC) condition. **Results:** Analyses indicated that the social skills intervention resulted in a significantly lower proportion of hostile attributions in peer group entry, but not peer provocation, scenarios. This decrease was maintained over a 3-month follow-up period. **Conclusions:** Deficits in social information-processing among individuals with PAE can be improved through social skills intervention, and these changes may lead to more positive developmental outcomes.


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Wiley InterScience - Electrophoresis Volume 31 Issue 3, Pages 483 - 496. Published Online 29 Jan 2010

38. **DIFFERENTIAL EXPRESSION OF PROTEINS IN FETAL BRAINS OF ALCOHOL-TREATED PREGNATALLY C57BL/6 MICE: A PROTEOMIC INVESTIGATION**

Youssef Sari 1, Min Zhang 2, Yehia Mechref 3

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3 METACyt Biochemical Analysis Center, Department of Chemistry, Indiana University Bloomington, IN, USA email: Youssef Sari (ysari@indiana.edu) Yehia Mechref (ymechref@indiana.edu)

**ABSTRACT**

Alcohol is known to impede the growth of the central nervous system and to induce neurodegeneration through cellular apoptosis. We have previously shown that moderate prenatal alcohol exposure results in brain defects at different stages of development. In this study, we further characterize the proteomic architecture underlying ethanol teratogenesis during early fetal brain development using chromatography in conjunction with a LC-MS/MS system. Pregnant C57BL/6 mice were exposed from embryonic day 7 (E7) to E13 with either a 25% ethanol derived calorie or pair-fed liquid diets. At E13, fetal brains were collected from five dams for each group. Individual brains were homogenized and the extracted proteins were then tryptically digested and analyzed by LC-MS/MS. Label-free quantitative proteomic analyses were performed on proteomes extracted from fetal brains of both alcohol-treated (ALC) and pair-fed groups.

These analyses demonstrated that prenatal alcohol exposure induced significant downregulation (p<0.001) of the expression of mitochondrial enzymes including ADP/ATP translocase 1, ATP synthase subunit and ubiquinol-cytochrome-c reductases. In addition, mitochondrial carrier homolog 1, which plays a role in apoptosis, was significantly downregulated (p<0.001) in the ALC group. Moreover, among the cytosolic proteins that were significantly downregulated (p<0.001) are Bcl-2, 14-3-3 protein and calmodulin.

Significant downregulation (p<0.001) of proteins that are critical for fetal brain development was observed such as prohibitin and neuronal migration protein doublecortin. These findings provide
information about possible mechanisms underlying the effects of prenatal alcohol exposure during early embryonic stage.

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http://www3.interscience.wiley.com/journal/123268168/abstract


39. PRENATAL ALCOHOL EXPOSURE ALTERS BIOBEHAVIORAL REACTIVITY TO PAIN IN NEWBORNS
Oberlander TF, Jacobson SW, Weinberg J, Grunau RE, Molteno CD, Jacobson JL.
From the Department of Pediatrics (TFO, REG), University of British Columbia, Vancouver, British Columbia, Canada; Department of Psychiatry and Behavioral Neurosciences (SWJ, JLJ), Wayne State University, Detroit, Michigan; Departments of Human Biology and Psychiatry (SWJ, JLJ), University of Cape Town, Cape Town, South Africa; Department of Cellular and Physiological Sciences (JW), University of British Columbia, Vancouver, British Columbia, Canada; Department of Psychiatry (CDM), University of Cape Town, Cape Town, South Africa; Department of Obstetrics and Gynecology (JLJ), Wayne State University, Detroit, Michigan.

ABSTRACT
Objectives: To examine biobehavioral responses to an acute pain event in a Cape Town, South Africa, cohort consisting of 28 Cape Colored (mixed ancestry) newborns (n = 14) heavily exposed to alcohol during pregnancy (exposed), and born to abstainers (n = 14) or light (</=0.5 oz absolute alcohol/d) drinkers (controls).

Methods: Mothers were recruited during the third trimester of pregnancy. Newborn data were collected on postpartum day 3 in the maternity obstetrical unit where the infant had been delivered. Heavy prenatal alcohol exposure was defined as maternal consumption of at least 14 drinks/wk or at least 1 incident of binge drinking/mo. Acute stress-related biobehavioral markers [salivary cortisol, heart rate (HR), respiratory sinus arrhythmia (RSA), spectral measures of heart rate variability (HRV), and videotaped facial actions] were collected thrice during a heel lance blood collection (baseline, lance, and recovery). After a feeding and nap, newborns were administered an abbreviated Brazelton Neonatal Behavioral Assessment Scale.

Results: There were no between-group differences in maternal age, marital status, parity, gravidity, depression, anxiety, pregnancy smoking, maternal education, or infant gestational age at birth (all ps > 0.15). In both groups, HR increased with the heel lance and decreased during the postlance period. The alcohol-exposed group had lower mean HR than controls throughout, and showed no change in RSA over time. Cortisol levels showed no change over time in controls but decreased over time in exposed infants. Although facial action analyses revealed no group differences in response to the heel lance, behavioral responses assessed on the Brazelton Neonatal Scale showed less arousal in the exposed group.

Conclusions: Both cardiac autonomic and hypothalamic-pituitary-adrenal stress reactivity measures suggest a blunted response to an acute noxious event in alcohol-exposed newborns. This is supported by results on the Brazelton Neonatal Scale indicating reduced behavioral arousal in the exposed group. To our knowledge, these data provide the first biobehavioral examination of early pain reactivity in alcohol-exposed newborns and have important implications
for understanding neuro-/biobehavioral effects of prenatal alcohol exposure in the newborn period.

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40. EFFECT OF PRENATAL STRESS ON ALCOHOL PREFERENCE AND SENSITIVITY TO CHRONIC ALCOHOL EXPOSURE IN MALE RATS  
Van Waes V, Enache M, Berton O, Vinner E, Lhermitte M, Maccari S, Darnaudéry M.  
Neurostress UPRES EA 4347 and CNRS UMR 8576, Université Lille Nord de France, University of Lille 1, 59655, Villeneuve d'Ascq, France, vincent.vanwaes@rosalindfranklin.edu.

ABSTRACT
Rationale: In rats, prenatal restraint stress (PRS) induces persistent behavioral and neurobiological alterations leading to a greater consumption of psychostimulants during adulthood. However, little is known about alcohol vulnerability in this animal model.

Objectives: We examined in adolescent and adult male Sprague Dawley rats the long-lasting impact of PRS exposure on alcohol consumption.

Methods: PRS rats were subjected to a prenatal stress (three daily 45-min sessions of restraint stress to the mothers during the last 10 days of pregnancy). Alcohol preference was assessed in a two-bottle choice paradigm (alcohol 2.5%, 5%, or 10% versus water), in both naïve adolescent rats and adult rats previously exposed to a chronic alcohol treatment. Behavioral indices associated with incentive motivation for alcohol were investigated. Finally, plasma levels of transaminases (marker of hepatic damages) and DeltaFosB levels in the nucleus accumbens (a potential molecular switch for addiction) were evaluated following the chronic alcohol exposure.

Results: Alcohol preference was not affected by PRS. Contrary to our expectations, stressed and unstressed rats did not display signs of compulsive alcohol consumption. The consequences of the alcohol exposure on locomotor reactivity and on transaminase levels were more prominent in PRS group. Similarly, PRS potentiated alcohol-induced DeltaFosB levels in the nucleus accumbens.

Conclusion: Our data suggest that negative events occurring in utero do not modulate alcohol preference in male rats but potentiate chronic alcohol-induced molecular neuroadaptation in the brain reward circuitry. Further studies are needed to determine whether the exacerbated DeltaFosB upregulation in PRS rats could be extended to other reinforcing stimuli.

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41. PRENATAL ALCOHOL EXPOSURE AND CHILDHOOD BALANCE: A SYSTEMATIC REVIEW
Rachel Humphrisss,a,b, Amanda Halla and John Macleodb
a Centre for Hearing and Balance Studies
b Department of Social Medicine, University of Bristol, Bristol, UK

ABSTRACT
Balance problems in childhood have known adverse psychosocial associations such as poorer quality of life and lower educational achievement. Previous longitudinal studies have documented an adverse effect of prenatal alcohol exposure on a variety of neurodevelopmental outcomes and so an effect on balance would seem plausible. This is supported by a previous laboratory study that found that rats exposed to ethanol in utero have dysfunctional balance and gait. The present study is a systematic review of the current evidence on the effects of maternal alcohol use during pregnancy on offspring balance in childhood.

A search strategy was devised and applied in the CENTRAL database (Cochrane Collaboration). Prospective longitudinal studies were then sought using databases including Medline, EMBASE, PsychInfo, CINAHL and AMED. In addition, citations in relevant published papers and books were followed up and experts in the field were contacted. No relevant human experimental studies were found. Four longitudinal studies were found to have assessed balance in preschool children. Only one of these studies suggested strong or substantial effects of alcohol exposure on balance-related outcomes. However, this study appeared the most methodologically robust. In conclusion, at present, there is limited evidence on the possible effects of alcohol exposure on childhood balance.

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http://www3.interscience.wiley.com/journal/123262599/abstract

42. PRENATAL ALCOHOL EXPOSURE AND CHRONIC MILD STRESS DIFFERENTIALLY ALTER DEPRESSIVE- AND ANXIETY-LIKE BEHAVIORS IN MALE AND FEMALE OFFSPRING
Kim G. C. Hellemans, Pamela Verma, Esther Yoon, Wayne K. Yu, Allan H. Young, and Joanne Weinberg
From the Department of Cellular and Physiological Sciences (KGCH, PV, EY, WKY, JW), University of British Columbia, Vancouver, British Columbia, Canada; Department of Psychology (KGCH), Institute of Neuroscience, Carleton University, Ottawa, Ontario, Canada; and Department of Psychiatry (AHY), University of British Columbia, Vancouver, British Columbia, Canada
ABSTRACT

Background: Fetal Alcohol Spectrum Disorder (FASD) is associated with numerous neurobehavioral alterations, as well as disabilities in a number of domains, including a high incidence of depression and anxiety disorders. Prenatal alcohol exposure (PAE) also alters hypothalamic-pituitary-adrenal (HPA) function, resulting in increased responsiveness to stressors and HPA dysregulation in adulthood. Interestingly, data suggest that pre-existing HPA abnormalities may be a major contributory factor to some forms of depression, particularly when an individual is exposed to stressors later in life. We tested the hypothesis that exposure to stressors in adulthood may unmask an increased vulnerability to depressive- and anxiety-like behaviors in PAE animals.

Methods: Male and female offspring from prenatal alcohol (PAE), pair-fed (PF), and ad libitum-fed control (C) treatment groups were tested in adulthood. Animals were exposed to 10 consecutive days of chronic mild stress (CMS), and assessed in a battery of well-validated tasks sensitive to differences in depressive- and/or anxiety-like behaviors.

Results: We report here that the combination of PAE and CMS in adulthood increases depressive- and anxiety-like behaviors in a sexually dimorphic manner. PAE males showed impaired hedonic responsivity (sucrose contrast test), locomotor hyperactivity (open field), and alterations in affiliative and nonaffiliative social behaviors (social interaction test) compared to control males. By contrast, PAE and, to a lesser extent, PF, females showed greater levels of "behavioral despair" in the forced swim test, and PAE females showed altered behavior in the final 5 minutes of the social interaction test compared to control females.

Conclusions: These data support the possibility that stress may be a mediating or contributing factor in the psychopathologies reported in FASD populations.


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Wiley InterScience - Alcoholism: Clinical and Experimental Research - Volume 34 Issue 4 - Pages 594-606
Published Online: 26 Jan 2010

43. ETHANOL ACUTELY INHIBITS IONOTROPIC GLUTAMATE RECEPTOR-MEDIATED RESPONSES AND LONG-TERM POTENTIATION IN THE DEVELOPING CA1 HIPPOCAMPUS
Michael P. Puglia and C. Fernando Valenzuela
From the Department of Neurosciences, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

ABSTRACT

Background: Developmental ethanol (EtOH) exposure damages the hippocampus, causing long-lasting alterations in learning and memory. Alterations in glutamatergic synaptic transmission and plasticity may play a role in the mechanism of action of EtOH. This signaling is fundamental for synaptogenesis, which occurs during the third trimester of human pregnancy (first 12 days of life in rats).
Methods: Acute coronal brain slices were prepared from 7- to 9-day-old rats. Extracellular and patch-clamp electrophysiological recording techniques were used to characterize the acute effects of EtOH on α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor (AMPAR)- and N-methyl-d-aspartate receptor (NMDAR)-mediated responses and long-term potentiation (LTP) in the CA1 hippocampal region.

Results: Ethanol (40 and 80 mM) inhibited AMPAR- and NMDAR-mediated field excitatory postsynaptic potentials (fEPSPs). EtOH (80 mM) also reduced AMPAR-mediated fEPSPs in the presence of an inhibitor of Ca2+ permeable AMPARs. The effect of 80 mM EtOH on NMDAR-mediated fEPSPs was significantly greater in the presence of Mg2+. EtOH (80 mM) neither affected the paired-pulse ratio of AMPAR-mediated fEPSPs nor the presynaptic volley. The paired-pulse ratio of AMPAR-mediated excitatory postsynaptic currents was not affected either, and the amplitude of these currents was inhibited to a lesser extent than that of fEPSPs. EtOH (80 mM) inhibited LTP of AMPAR-mediated fEPSPs.

Conclusions: Acute EtOH exposure during the third-trimester equivalent of human pregnancy inhibits hippocampal glutamatergic transmission and LTP induction, which could alter synapse refinement and ultimately contribute to the pathophysiology of fetal alcohol spectrum disorder.


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Wiley InterScience - Alcoholism: Clinical and Experimental Research - Volume 34 Issue 4 - Pages 617-627. Published Online: 26 Jan 2010

44. AN EVENT-RELATED POTENTIAL STUDY OF RESPONSE INHIBITION IN ADHD WITH AND WITHOUT PRENATAL ALCOHOL EXPOSURE
From the Wayne State University School of Medicine (MJB, JLJ, LHL, AM, NCD, SWJ), Detroit, Michigan; Children's Hospital Boston, Harvard Medical School (AW, CAN), Boston, Massachusetts; University of Rochester (RK), Rochester, New York; and Vanderbilt University (MJA), Nashville, Tennessee

ABSTRACT
Background: The attention and cognitive problems seen in individuals with a history of prenatal alcohol exposure often resemble those associated with attention deficit hyperactivity disorder (ADHD), but few studies have directly assessed the unique influence of each on neurobehavioral outcomes.

Methods: We recorded event-related potentials (ERPs) during a Go/No-go response inhibition task in young adults with prospectively obtained histories of prenatal alcohol exposure and childhood ADHD.

Results: Regardless of prenatal alcohol exposure, participants with childhood ADHD were less accurate at inhibiting responses. However, only the ADHD group without prenatal alcohol exposure showed a markedly diminished P3 difference between No-go and Go, which may reflect a more effortful strategy related to inhibitory control at the neural processing level.
Conclusion: This finding supports a growing body of evidence suggesting that the manifestation of idiopathic ADHD symptoms may stem from a neurophysiologic process that is different from the ADHD symptomatology associated with prenatal alcohol exposure. Individuals who have been prenatally exposed to alcohol and present with ADHD symptomatology may represent a unique endophenotype of the disorder, which may require different treatment approaches from those found to be effective with idiopathic ADHD.

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Wiley InterScience - American Journal of Medical Genetics - Volume 152A Issue 2, Pages 528 - 536. Published Online: 25 January 2010

45. A REVIEW OF FACIAL IMAGE ANALYSIS FOR DELINEATION OF THE FACIAL PHENOTYPE ASSOCIATED WITH FETAL ALCOHOL SYNDROME
Tania S. Douglas, Tinashe E.M. Mutsvangwa
MRC/UCT Medical Imaging Research Unit, Department of Human Biology, University of Cape Town, Observatory, South Africa
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ABSTRACT
The facial anomalies associated with fetal alcohol syndrome (FAS), some of which are also present in individuals with less severe forms of the broader category of fetal alcohol spectrum disorders (FASD), are typically identified with the aid of linear distance measurements taken between facial landmarks. Digital facial imaging methods are increasingly being used in syndrome delineation. Distance measurements derived from stereo-photogrammetry and facial surface imaging have been used to study the FAS facial anomalies. Geometric morphometric methods capture the spatial arrangement between landmarks, providing a statistical platform for comparison of facial shapes, and have been shown to hold promise for characterizing the FAS facial shape. We review the progression in the use of imaging and image analysis methods in studies on the facial phenotype associated with FAS.


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46. CINGULATE GYRUS MORPHOLOGY IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDERS
Bjorkquist OA, Fryer SL, Reiss AL, Mattson SN, Riley EP.
Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA, USA.
ABSTRACT
Alcohol consumption during pregnancy can lead to a variety of cognitive and other birth defects, collectively termed fetal alcohol spectrum disorders (FASD), and including the Fetal Alcohol Syndrome (FAS). This study examined the impact of gestational alcohol exposure on the morphology of the cingulate gyrus, given this region's role in cognitive control, attention, and emotional regulation, all of which are affected in children with FASD. Thirty-one youth (ages 8-16) with histories of heavy prenatal alcohol exposure (n=21) and demographically matched comparison subjects (n=10) underwent structural magnetic resonance imaging. The cingulate gyrus was manually delineated, and parcellated volumes of grey and white matter were compared across groups. Alcohol-exposed individuals had significantly smaller raw cingulate grey matter, white matter, and tissue volumes compared with controls. After adjustment for respective cranial tissue constituents, only white matter volumes remained significantly reduced, and this held regardless of whether or not the child qualified for a diagnosis of FAS. A correlation between posterior cingulate grey matter volume and the WISC-III Freedom from Distractibility Index was also observed in alcohol-exposed children. These data suggest that cingulate white matter is compromised beyond global white matter hypoplasia in alcohol-exposed individuals, regardless of FAS diagnosis. The observed volumetric reductions in the cingulate gyrus may contribute to the disruptive and emotionally dysregulated behavioral profile commonly observed in this population.


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47. PRENATAL ALCOHOL EXPOSURE REDUCES THE SIZE OF THE FORELIMB REPRESENTATION IN MOTOR CORTEX IN RAT: AN INTRACORTICAL MICROSTIMULATION (ICMS) MAPPING STUDY
Xie N, Yang Q, Chappell TD, Li CX, Waters RS.
Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, 38163, USA.

ABSTRACT
Children with fetal alcohol spectrum disorder (FASD) often exhibit sensorimotor dysfunctions that include deficits in motor coordination and fine motor control. Although the underlying causes for these motor abnormalities are unknown, they likely involve interactions between sensory and motor systems. Rodent animal models have been used to study the effects of prenatal alcohol exposure (PAE) on skilled reaching and on the development and organization of somatosensory barrel field cortex. To this end, PAE delayed the development of somatosensory cortex, reduced the size of whisker and forelimb representations in somatosensory barrel field cortex, and delayed acquisition time to learn a skilled reaching task. However, whether PAE also affects the motor cortex (MI) remains to be determined. In the present study, we investigated the effect of PAE on the size of the forelimb representation in rat MI, thresholds for activation, and the overlap between motor and sensory cortical forelimb maps in sensorimotor cortex. Pregnant Sprague-Dawley rats were assigned to alcohol (Alc), pair-fed (PF), and chow-fed (CF) groups on gestation day 1 (GD1). Rats in the Alc group (n=4) were chronically intubated daily with binge doses of alcohol (6g/kg body weight) from GD1 to GD20 that resulted in averaged blood alcohol levels measured on GD10 (mean=191.5+/−41.9mg/dL) and on GD17 (mean=247.0+/−72.4mg/dL). PF
(n=2) and CF (n=3) groups of pregnant rats served as controls. The effect of PAE on the various dependent measures was obtained from multiple male offspring from each dam within treatment groups, and litter means were compared between the groups from alcohol-treated and control (Ct: CF and PF) dams. At approximately 8 weeks of age, rats were anesthetized with ketamine/xylazine and the skull opened over sensorimotor cortex. A tungsten microelectrode was then inserted into the depths of layer V and intracortical microstimulation was used to deliver trains of pulses to evoke muscle contractions and/or movements; maximum stimulating < or =100microA. When a motor response was observed, the threshold for movement was measured and the motor receptive field projected to the cortical surface to serve as representative point for that location. A motor map for the forelimb representation was generated by systematically stimulating at adjacent sites until current thresholds reached the maximum and/or motor responses were no longer evoked. The major findings in this study were as follows: (1) PAE significantly reduced the area of the forelimb representation in the Alc offspring (6.01mm(2), standard error of the mean=+/-.278) compared with the Ct offspring (8.03mm(2)+/-0.586), (2) PAE did not significantly reduce the averaged threshold for activation of movements between groups, (3) PAE significantly reduced the percent overlap (Alc=31.1%, Ct=55.4%) between the forelimb representation in sensory and motor cortices, and (4) no significant differences were observed in averaged body weight, hemisphere weight, or age of animal between treatment groups. These findings suggest that the effects of PAE are not restricted to somatosensory barrel field cortex but also involve the MI and may underlie deficits in motor control and sensorimotor integration observed among children with FASD. 2010.

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48. MATERNAL ETHANOL CONSUMPTION ALTERS THE EPIGENOTYPE AND THE PHENOTYPE OF OFFSPRING IN A MOUSE MODEL
Kaminen-Ahola N, Ahola A, Maga M, Mallitt KA, Fahey P, Cox TC, Whitelaw E, Chong S.
Division of Genetics and Population Health, Queensland Institute of Medical Research, Herston, Australia.

ABSTRACT
Recent studies have shown that exposure to some nutritional supplements and chemicals in utero can affect the epigenome of the developing mouse embryo, resulting in adult disease. Our hypothesis is that epigenetics is also involved in the gestational programming of adult phenotype by alcohol. We have developed a model of gestational ethanol exposure in the mouse based on maternal ad libitum ingestion of 10% (v/v) ethanol between gestational days 0.5-8.5 and observed changes in the expression of an epigenetically-sensitive allele, Agouti viable yellow (A(vy)), in the offspring. We found that exposure to ethanol increases the probability of transcriptional silencing at this locus, resulting in more mice with an agouti-colored coat. As expected, transcriptional silencing correlated with hypermethylation at A(vy). This demonstrates, for the first time, that ethanol can affect adult phenotype by altering the epigenotype of the early embryo. Interestingly, we also detected postnatal growth restriction and craniofacial dysmorphology reminiscent of fetal alcohol syndrome, in congenic a/a siblings of the A(vy) mice. These findings suggest that moderate ethanol exposure in utero is capable of inducing changes in the expression of genes other than A(vy), a conclusion supported by our genome-wide
analysis of gene expression in these mice. In addition, offspring of female mice given free access to 10% (v/v) ethanol for four days per week for ten weeks prior to conception also showed increased transcriptional silencing of the A(vy) allele. Our work raises the possibility of a role for epigenetics in the etiology of fetal alcohol spectrum disorders, and it provides a mouse model that will be a useful resource in the continued efforts to understand the consequences of gestational alcohol exposure at the molecular level.

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49. PARENTING WITH FETAL ALCOHOL SPECTRUM DISORDER
Deborah Rutman1 and Marilyn Van Bibber2
(1) Research Initiatives for Social Change unit, School of Social Work, University of Victoria, Victoria, British Columbia, Canada
(2) Qualicum Beach, British Columbia, Canada

ABSTRACT
This paper focuses on issues associated with parenting and living with FASD. It is based on a larger research and video production project that examined the challenges, accomplishments and support needs of adults with FASD in relation to parenting, employment and the legal system. Using theoretical sampling techniques, in-depth, face-to-face interviews were conducted with a total of 59 people from 5 diverse communities in British Columbia; of these, 15 were adults with (suspected) FASD. Findings presented in this article relate to parents’ hopes, goals and accomplishments, parenting challenges, experiences with the child welfare system, and perceived barriers to support, including policy-related barriers. Findings also revealed prevailing ignorance about the nature of FASD and the day-to-day support needs of those living with FASD, which potentially have profound implications from both a health and a social justice perspective. For example, parents experienced reluctance to seek assistance for their secondary disabilities related to FASD (e.g., substance use or mental health problems), for fear of that their needs for support would be viewed as evidence of their parenting incapability. Highlighted will be directions for positive policy and practice-related change in working with parents with FASD.

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PubMed, Alcohol. 2010 Jan 7. [Epub ahead of print]

50. PRENATAL ALCOHOL EXPOSURE ALTERS THE PATTERNS OF FACIAL ASYMMETRY
ABSTRACT
Directional asymmetry, the systematic differences between the left and right body sides, is widespread in human populations. Changes in directional asymmetry are associated with various disorders that affect craniofacial development. Because facial dysmorphology is a key criterion for diagnosing fetal alcohol syndrome (FAS), the question arises whether in utero alcohol exposure alters directional asymmetry in the face.
Data on the relative position of 17 morphologic landmarks were obtained from facial scans of children who were classified as either FAS or control. Shape data obtained from the landmarks were analyzed with the methods of geometric morphometrics. Our analyses showed significant directional asymmetry of facial shape, consisting primarily of a shift of midline landmarks to the right and a displacement of the landmarks around the eyes to the left. The asymmetry of FAS and control groups differed significantly and average directional asymmetry was increased in those individuals exposed to alcohol in utero.
These results suggest that the developmental consequences of fetal alcohol exposure affect a wide range of craniofacial features in addition to those generally recognized and used for diagnosis of FAS.

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PubMed, Matern Child Health J. 2010 Jan 7. [Epub ahead of print]

51. INDEPENDENT AND INTERACTIVE ASSOCIATIONS OF PRENATAL MOOD AND SUBSTANCE USE WITH INFANT BIRTH OUTCOMES
Gyllstrom ME, Hellerstedt WL, McGovern PM.

ABSTRACT
The main objective of this work is to examine low prenatal mood, alcohol and tobacco use and rates of preterm (PTB) and low birth weight (LBW) births among women in Minnesota between 2002 and 2006. We examined the Minnesota version of the national, cross-sectional survey of postpartum women, the Pregnancy Risk Assessment Monitoring System (MN PRAMS). Of the 11,891 women sampled in 2002-2006, 7,457 had complete data for analysis; the weighted response rates averaged 76%. The major variables of interest were: LBW, PTB, maternal mood during pregnancy, prenatal alcohol use, prenatal tobacco use and interaction terms created from the mood and substance use variables. Women with low mood who used tobacco during pregnancy were twice as likely to have a LBW infant as women who did not smoke and reported high mood (AOR = 2.12, 95% CI: 1.35, 3.33, P = 0.001). Among women who abstained from alcohol during pregnancy, those with low mood were at an increased risk for PTB (AOR = 1.95, 95% CI: 1.54-2.45, P < 0.0001) compared to women with high mood. Low maternal mood was associated with increased risks for PTB, and LBW births among MN PRAMS respondents. Substance use and low prenatal mood co-occur and the combined effect on PTB and LBW birth outcomes warrants further investigation.

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52. FETAL ALCOHOL SYNDROME: KNOWLEDGE AND ATTITUDES OF FAMILY MEDICINE CLERKSHIP AND RESIDENCY DIRECTORS
Zoorob R, Aliyu MH, Hayes C.
Department of Family and Community Medicine, Meharry Medical College, Nashville, TN 37208-3599, USA.

ABSTRACT
Fetal alcohol spectrum disorders (FASD) are the leading preventable causes of developmental disabilities with serious permanent consequences. Regardless of the increased awareness of fetal alcohol syndrome (FAS), 13% of women in the United States drink alcohol during pregnancy. Health care professionals do not routinely assess the frequency and quantity of alcohol use by their patients. This study examined the knowledge, skills, and practices of family medicine residency and clerkship directors and assessed the time devoted and format of FAS curricula in the programs. A self-administered anonymous survey was sent to the residency and clerkship directors (N=571). Response rate of clerkship directors was 52% and residency directors 46%. Both groups showed high level of knowledge of FASD and of alcohol counseling practices for pregnant women. Although almost two thirds of the residency programs had FASD integrated in the curriculum, an equivalent fraction of predoctoral programs did not. More than half of the clerkship directors without FASD in their curriculum agreed that a need exists for its inclusion. These findings raise important medical education and policy issues and provide insight into the disparity in FASD content of curricula between predoctoral and family medicine residency programs in the United States. The role of physician counseling in primary prevention of FAS should continue to be stressed in predoctoral and residency education.


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53. TAU PHOSPHORYLATION AND CLEAVAGE IN ETHANOL-INDUCED NEURODEGENERATION IN THE DEVELOPING MOUSE BRAIN
Saito M, Chakraborty G, Mao RF, Paik SM, Vadasz C, Saito M.
Laboratory of Neurobehavior Genetics, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA. marsaito@nki.rfmh.org

ABSTRACT
Previous studies indicated that ethanol-induced neurodegeneration in postnatal day 7 (P7) mice, widely used as a model for the fetal alcohol spectrum disorders, was accompanied by glycogen synthase kinase-3beta (GSK-3beta) and caspase-3 activation. Presently, we examined whether tau, a microtubule associated protein, is modified by GSK-3beta and caspase-3 in ethanol-treated P7 mouse forebrains. We found that ethanol increased phosphorylated tau recognized by the paired helical filament (PHF)-1 antibody and by the antibody against tau phosphorylated at Ser199. Ethanol also generated tau fragments recognized by an antibody against caspase-cleaved tau (C-tau). C-tau was localized in neurons bearing activated caspase-3 and fragmented nuclei. Over time, cell debris and degenerated projections containing C-tau appeared to be engulfed by activated microglia. A caspase-3 inhibitor partially blocked C-tau formation. Lithium, a GSK-3beta inhibitor, blocked ethanol-induced caspase-3 activation, phosphorylated tau

54. ALCOHOL CONTENT IN DECLARED NON-OR LOW ALCOHOLIC BEVERAGES: IMPLICATIONS TO PREGNANCY
Y Ingrid Goh, Zulfikar Verjee, Gideon Koren

ABSTRACT
Background: Alcohol consumption in pregnancy may result in serious adverse fetal outcome. Non- or low alcoholic wines and beers may be a risk-reduction strategy to help alcohol-dependent individuals to prevent or limit ethanol consumption. The objective of this study was to quantify ethanol concentrations in Canadian beverages claiming to contain no or low alcohol content.

Methods: Forty-five different beverages claiming to contain no or low alcohol content in the Canadian market were tested for ethanol concentration using gas chromatography.

Results: Thirteen (29%) of the beverages contained ethanol levels higher than the declared concentration on their label. Six beverages claiming to contain no alcohol were found to contain greater than 1% ethanol.

Conclusion: Pregnant women seeking replacement to alcoholic beverages may be misled by these labels, unknowingly exposing themselves and their unborn babies to ethanol.

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PubMed, Alcohol. 2010 Jan 4. [Epub ahead of print]

55. VALIDITY OF THE T-ACE IN PREGNANCY IN PREDICTING CHILD OUTCOME AND RISK DRINKING
Chiodo LM, Sokol RJ, Delaney-Black V, Janisse J, Hannigan JH.
College of Nursing, Wayne State University, Detroit, MI 48202, USA.

ABSTRACT
Preventing fetal alcohol spectrum disorders (FASDs) requires detection of in-pregnancy maternal risk drinking. The widely used T-ACE screen has been applied in various ways, although the impact of those different uses on effectiveness is uncertain. We examined relations among
different T-ACE scoring criteria, maternal drinking, and child outcome. Self-reported across-pregnancy maternal drinking was assessed in 75 African-American women. The different T-ACE criteria used varied the level of drinking that defined tolerance (two or three drinks) and the total T-ACE score cut-points (two or three). Receiver operator curves and regression analysis assessed the significance of relations. Increasing the total T-ACE score cut-point to 3 almost doubled specificity in detecting risk drinking whereas maintaining adequate sensitivity, equivalent to that in the original report, and identified substantially more neurobehavioral deficits in children. Redefining tolerance at three drinks did not improve T-ACE effectiveness in predicting outcomes. This study is among the first to show the ability of an in-pregnancy T-ACE assessment to predict child neurodevelopmental outcome. In addition, increasing the total T-ACE score criterion (from 2 to 3) improved identification of non-drinking mothers and unaffected children with little loss in detection of drinkers and affected children. Efficient in-pregnancy screens for risk drinking afford greater opportunities for intervention that could prevent/limit FASDs.

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PubMed, Alcohol. 2010 Jan 4. [Epub ahead of print]

56. DIAGNOSIS OF FETAL ALCOHOL SPECTRUM DISORDERS: A VALIDITY STUDY OF THE FETAL ALCOHOL SYNDROME CHECKLIST
Burd L, Klug MG, Li Q, Kerbeshian J, Martsof JT.
Department of Pediatrics, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND, USA

ABSTRACT
Fetal alcohol spectrum disorders (FASD) are a common cause of developmental disability, birth defects, and mortality. The performance characteristics of current diagnostic tools for FASD are not adequately reported. This study examines the performance characteristics of the Fetal Alcohol Syndrome Diagnostic Checklist (FASDC). In a population of 658 subjects from North Dakota, we used the FASDC score to examine the agreement between FASDC score, clinical diagnosis, and the Institute of Medicine criteria for FASD. All subjects were seen for evaluation in the genetic/dysmorphology clinics, which are funded by the state to provide genetic diagnostic services for residents of North Dakota. We compared the clinical diagnosis and the FASDC scores to determine the performance characteristics of the FASDC in the categorical diagnosis of fetal alcohol spectrum (FAS), other-FASD, and a group with No-FASD. Comparisons were made using univariate and logistic models of outcomes using both the presence and the absence of alcohol exposure or FASDC phenotype data. The FASDC performance characteristics for differentiation of the FAS group from non-FASD were excellent (accuracy 99%, sensitivity 99%, and specificity 99%). Logistic models for subjects with scores in the FASD range were differentiated with an accuracy of 82%, sensitivity 85%, and specificity 80% using the data on phenotype and exposure. We were able to delineate subjects with scores in the No-FASD range with an accuracy of 78%, sensitivity 64%, and specificity 81% without including the exposure and phenotype data by use of the other descriptive data (maternal characteristics, birth records, and demographic data) from the FASDC. All diagnostic tools should have performance characteristics assessed and available before adoption for use in clinical settings. The FASDC scores produce diagnostic groupings that approximate expert clinical judgment. The tool may be
useful in other clinical settings for the diagnosis of FASD or as an FASD registry or research database.

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PubMed, Alcohol. 2010 Jan 4. [Epub ahead of print]

57. EFFECTS OF MODERATE DRINKING DURING PREGNANCY ON PLACENTAL GENE EXPRESSION
Rosenberg MJ, Wolff CR, El-Emawy A, Staples MC, Perrone-Bizzozero NI, Savage DD. Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM 87131, USA.

ABSTRACT
Many children adversely affected by maternal drinking during pregnancy cannot be identified early in life using current diagnostic criteria for fetal alcohol spectrum disorder (FASD). We conducted a preliminary investigation to determine whether ethanol-induced alterations in placental gene expression may have some utility as a diagnostic indicator of maternal drinking during pregnancy and as a prognostic indicator of risk for adverse neurobehavioral outcomes in affected offspring. Pregnant Long-Evans rats voluntarily consumed either a 0 or 5% ethanol solution 4 h each day throughout gestation.

Ethanol consumption produced a mean maternal daily intermittent peak serum ethanol concentration of 84 mg/dL. Placentas were harvested on gestational day 20 for gene expression studies. Microarray analysis of more than 28,000 genes revealed that the expression of 304 known genes was altered twofold or greater in placenta from ethanol-consuming dams compared with controls. About 76% of these genes were repressed in ethanol-exposed placentas. Gene expression changes involved proteins associated with central nervous system development; organ morphogenesis; immunological responses; endocrine function; ion homeostasis; and skeletal, cardiovascular, and cartilage development.

To date, quantitative real-time polymerase chain reaction analysis has confirmed significant alterations in gene expression for 22 genes, including genes encoding for three calcium binding proteins, two matrix metalloproteinases, the cannabinoid 1, galanin 2 and toll-like receptor 4, iodothyronine deiodinase 2, 11-beta hydroxysteroid dehydrogenase 2, placental growth factor, transforming growth factor alpha, gremlin 1, and epithelial growth factor (EGF)-containing extracellular matrix protein. These results suggest that the expression of a sufficiently large number of placental mRNAs is altered after moderate drinking during pregnancy to warrant more detailed investigation of the placenta as a biomarker system for maternal drinking during pregnancy and as an early indicator of FASD. Furthermore, these results provide new insights into novel mechanisms on how ethanol may directly or indirectly mediate its teratogenic effects through alterations in placental function during pregnancy.

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58. HIGH-THROUGHPUT CAVEOLAR PROTEOMIC SIGNATURE PROFILE FOR MATERNAL BINGE ALCOHOL CONSUMPTION
Ramadoss J, Liao WX, Chen DB, Magness RR.
Department of Obstetrics and Gynecology, Perinatal Research Laboratories, University of Wisconsin, Atrium-B Meriter Hospital, 202 South Park Street Madison, WI 53715, USA.

ABSTRACT
Currently, no single marker is sensitive and specific enough to be considered a reliable biomarker for prenatal alcohol exposure. To identify a proteomic signature profile for maternal alcohol consumption, we carried out high-throughput proteomics on maternal endothelial caveolae exposed to moderate binge-like alcohol conditions. In these specialized lipid-ordered microdomains that contain a rich assembly of proteins, we demonstrate that moderate binge-like alcohol resulted in a distinctive maternal caveolar proteomic signature with important proteins being dramatically decreased/knocked out in the alcoholic profile. These proteins span from histones and basic structural proteins like alpha tubulin to proteins involved in trafficking, deubiquitination, cell signaling, and cell-cell adhesion. The profile also suggests an important role for the mother and the uteroplacental compartment in the pathogenesis of fetal alcohol spectrum disorders (FASD). These data demonstrate that the caveolar proteomic signature created by alcohol shows a promising direction for early detection of FASD.

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59. PREVENTING FETAL ALCOHOL SPECTRUM DISORDERS: THE ROLE OF PROTECTION MOTIVATION THEORY
Cismaru M, Deshpande S, Thurmeier R, Lavack AM, Agrey N.
University of Regina, Regina, Saskatchewan, Canada.

ABSTRACT
This article examines health communication campaigns aimed at preventing alcohol consumption among women who are pregnant or attempting to become pregnant. Relevant communication materials were gathered and a qualitative review was conducted. A majority of the campaigns followed the tenets of protection motivation theory by focusing on the threat variables of severity and vulnerability, as well as emphasizing response efficacy. Few campaigns focused on costs or self-efficacy. Future fetal alcohol spectrum disorders prevention initiatives should attempt to reduce perceived costs, as well as include self-efficacy messages in order to increase women's confidence that they can carry out the recommended actions.

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60. EVIDENCE OF A COMPLEX ASSOCIATION BETWEEN DOSE, PATTERN AND TIMING OF PRENATAL ALCOHOL EXPOSURE AND CHILD BEHAVIOUR PROBLEMS

O'Leary, Colleen M. ¹; Nassar, Natasha ¹; Zubrick, Stephen R. ²; Kurinczuk, Jennifer J. ³; Stanley, Fiona ⁴; Bower, Carol ¹

ABSTRACT

Background: There is a lack of evidence regarding the effect of dose, pattern and timing of prenatal alcohol exposure and behaviour problems in children aged 2 years and older.

Methods: A 10% random sample of women delivering a live infant in Western Australia (1995-96) were invited to participate in an 8-year longitudinal survey (78% response rate n = 2224); 85% were followed-up at 2 years, 73% at 5 years and 61% at 8 years. Alcohol consumption was classified by combining the overall dose, dose per occasion and frequency to reflect realistic drinking patterns. Longitudinal analysis was conducted using generalized estimating equations (GEE) to investigate the association between child behaviour as measured by the Child Behaviour Checklist at 2, 5 and 8 years of age and prenatal alcohol exposure collected 3 months postpartum for each trimester separately, adjusting for a wide range of confounding factors.

Results: Low levels of prenatal alcohol were not associated with child behaviour problems. There were increased odds of internalizing behaviour problems following heavy alcohol exposure in the first trimester; anxiety/depression [adjusted odds ratio (aOR) 2.82; 95% confidence interval (CI) 1.07-7.43] and somatic complaints (aOR 2.74; 95% CI 1.47-5.12) and moderate levels of alcohol exposure increased the odds of anxiety/depression (aOR 2.24; 95% CI 1.16-4.34).

Conclusions: Prenatal alcohol exposure at moderate and higher levels increased the odds of child behaviour problems with the dose, pattern and timing of exposure affecting the type of behaviour problems expressed. Larger studies with more power are needed to confirm these findings.


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61. THE EFFECTIVENESS OF A COMMUNITY-BASED INTERVENTION FOR PARENTS WITH FASD

Denys K, Rasmussen C, Henneveld D.
Department of Pediatrics, University of Alberta, 266, Glenrose Rehabilitation Hospital, 10230-111 Ave, Edmonton, AB, T5G 0B7, Canada
kennedydenys@gmail.com.
ABSTRACT
The purpose of this study was to evaluate the effectiveness of the Step by Step program in which mentors work with parents affected by Fetal Alcohol Spectrum Disorder (FASD) on a one-to-one basis. Mentors help clients identify and work towards meeting their needs and achieving their goals.
Data from 24 closed client files was collected and analyzed and as predicted, the program was effective in helping clients reduce their needs and achieve their goals. The client's reason for leaving the program as well as whether or not they had a formal FASD diagnosis had an impact on their success in the program.
Data collected on additional mental health issues, experience of abuse and addictions helped to characterize the sample of clients and correlations were found between client's experience of abuse and their past and/or present addictions issues. Limitations of this study as well as future implications were also discussed.

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62. COLLABORATIVE INITIATIVE ON FETAL ALCOHOL SPECTRUM DISORDERS: METHODOLOGY OF CLINICAL PROJECTS

ABSTRACT
The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) was created in 2003 to further understanding of fetal alcohol spectrum disorders. Clinical and basic science projects collect data across multiple sites using standardized methodology. This article describes the methodology being used by the clinical projects that pertain to assessment of children and adolescents. Domains being addressed are dysmorphology, neurobehavior, 3-D facial imaging, and brain imaging.

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63. A 14-YEAR RETROSPECTIVE MATERNAL REPORT OF ALCOHOL CONSUMPTION IN PREGNANCY PREDICTS PREGNANCY AND TEEN OUTCOMES
Hannigan JH, Chiodo LM, Sokol RJ, James Janisse, Ager JW, Greenwald MK, Delaney-Black V. Merrill Palmer Skillman Institute, Wayne State University, Detroit, MI 48202, USA; Department of Obstetrics & Gynecology, Wayne State University School of Medicine, Detroit, MI 48201, USA; Department of Psychology, Wayne State University, Detroit, MI 48202, USA; C.S. Mott Center
ABSTRACT
Detecting patterns of maternal drinking that place fetuses at risk for fetal alcohol spectrum disorders (FASDs) is critical to diagnosis, treatment, and prevention but is challenging because information on antenatal drinking collected during pregnancy is often insufficient or lacking. Although retrospective assessments have been considered less favored by many researchers due to presumed poor reliability, this perception may be inaccurate because of reduced maternal denial and/or distortion. The present study hypothesized that fetal alcohol exposure, as assessed retrospectively during child adolescence, would be related significantly to prior measures of maternal drinking and would predict alcohol-related behavioral problems in teens better than antenatal measures of maternal alcohol consumption. Drinking was assessed during pregnancy, and retrospectively about the same pregnancy, at a 14-year follow-up in 288 African-American women using well-validated semistructured interviews. Regression analysis examined the predictive validity of both drinking assessments on pregnancy outcomes and on teacher-reported teen behavior outcomes. Retrospective maternal self-reported drinking assessed 14 years postpartum was significantly higher than antenatal reports of consumption. Retrospective report identified 10.8 times more women as risk drinkers (>= one drink per day) than the antenatal report. Antenatal and retrospective reports were moderately correlated and both were correlated with the Michigan Alcoholism Screening Test. Self-reported alcohol consumption during pregnancy based on retrospective report identified significantly more teens exposed prenatally to at-risk alcohol levels than antenatal, in-pregnancy reports. Retrospective report predicted more teen behavior problems (e.g., attention problems and externalizing behaviors) than the antenatal report. Antenatal report predicted younger gestational age at birth and retrospective report predicted smaller birth size; neither predicted teen IQ. These results suggest that if only antenatal, in-pregnancy maternal report is used, then a substantial proportion of children exposed prenatally to risk levels of alcohol might be misclassified. The validity of retrospective assessment of prior drinking during pregnancy as a more effective indicator of prenatal exposure was established by predicting more behavioral problems in teens than antenatal report. Retrospective report can provide valid information about drinking during a prior pregnancy and may facilitate diagnosis and subsequent interventions by educators, social service personnel, and health-care providers, thereby reducing the life-long impact of FASDs.


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64. IMPLEMENTATION OF A SHARED DATA REPOSITORY AND COMMON DATA DICTIONARY FOR FETAL ALCOHOL SPECTRUM DISORDERS RESEARCH

ABSTRACT
Many previous attempts by fetal alcohol spectrum disorders researchers to compare data across multiple prospective and retrospective human studies have failed because of both structural
differences in the collected data and difficulty in coming to agreement on the precise meaning of
the terminology used to describe the collected data. Although some groups of researchers have
an established track record of successfully integrating data, attempts to integrate data more
broadly among different groups of researchers have generally faltered. Lack of tools to help
researchers share and integrate data has also hampered data analysis. This situation has
delayed improving diagnosis, intervention, and treatment before and after birth. We worked with
various researchers and research programs in the Collaborative Initiative on Fetal Alcohol
Spectrum Disorders (CI-FASD) to develop a set of common data dictionaries to describe the
data to be collected, including definitions of terms and specification of allowable values. The
resulting data dictionaries were the basis for creating a central data repository (CI-FASD Central
Repository) and software tools to input and query data. Data entry restrictions ensure that only
data that conform to the data dictionaries reach the CI-FASD Central Repository. The result is an
effective system for centralized and unified management of the data collected and analyzed by
the initiative, including a secure, long-term data repository. CI-FASD researchers are able to
integrate and analyze data of different types, using multiple methods, and collected from multiple
populations, and data are retained for future reuse in a secure, robust repository.

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65. A NEURODEVELOPMENTAL FRAMEWORK FOR THE DEVELOPMENT OF
INTERVENTIONS FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS
Kodituwakku PW.
Center for Development and Disability, University of New Mexico School of Medicine,
Albuquerque, NM 87107, USA.

ABSTRACT
Despite considerable data published on cognitive and behavioral disabilities in children with fetal
alcohol spectrum disorders (FASD), relatively little information is available on behavioral or
pharmacological interventions for alcohol-affected children. The main goals of this article,
therefore, are to summarize published intervention studies of FASD and to present a
neurodevelopmental framework, based on recent findings from a number of disciplines, for
designing new therapies for alcohol-affected children. This framework assumes a
neuroconstructionist view, which posits that reciprocal interactions between neural activity and
the brain's hardware lead to the progressive formation of intra & interregional neural connections.
In this view, behavioral interventions can be conceptualized as a series of guided experiences
that are designed to produce neural activation. Based on evidence from cognitive neuroscience,
it is hypothesized that specific interventions targeting executive attention and self-regulation may
produce greater generalizable results than those aimed at domain-specific skills in children with
FASD. In view of reciprocal interactions between environmental effects and neural structures, the
proposed framework suggests that the maximum effects of interventions can eventually be
achieved by optimally combining behavioral methods and cognition-enhancing drugs.

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66. ZEBRAFISH FETAL ALCOHOL SYNDROME MODEL: EFFECTS OF ETHANOL ARE RESCUED BY RETINOIC ACID SUPPLEMENT
Marrs JA, Clendenon SG, Ratcliffe DR, Fielding SM, Liu Q, Bosron WF. Department of Biology, Indiana University - Purdue University Indianapolis, Indianapolis, IN 46202, USA; Department of Medicine, Indiana University Medical Center, Indianapolis, IN 46202, USA.

ABSTRACT
This study was designed to develop a zebrafish experimental model to examine defects in retinoic acid (RA) signaling caused by embryonic ethanol exposure. RA deficiency may be a causative factor leading to a spectrum of birth defects classified as fetal alcohol spectrum disorder (FASD). Experimental support for this hypothesis using Xenopus showed that effects of treatment with ethanol could be partially rescued by adding retinoids during ethanol treatment. Previous studies show that treating zebrafish embryos during gastrulation and somitogenesis stages with a pathophysiological concentration of ethanol (100mM) produces effects that are characteristic features of FASD. We found that treating zebrafish embryos with RA at a low concentration (10(-9)M) and 100mM ethanol during gastrulation and somitogenesis stages significantly rescued a spectrum of defects produced by treating embryos with 100mM ethanol alone. The rescued phenotype that we observed was quantitatively more similar to embryos treated with 10(-9)M RA alone (RA toxicity) than to untreated or 100mM ethanol-treated embryos. RA rescued defects caused by 100mM ethanol treatment during gastrulation and somitogenesis stages that include early gastrulation cell movements (anterior-posterior axis), craniofacial cartilage formation, and ear development. Morphological evidence also suggests that other characteristic features of FASD (e.g., neural axis patterning) are rescued by RA supplement.


67. HEAVY IN UTERO ETHANOL EXPOSURE IS ASSOCIATED WITH THE USE OF OTHER DRUGS OF ABUSE IN A HIGH-RISK POPULATION
Shor S, Nulman I, Kulaga V, Koren G. Motherisk Program, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; Department of Pharmacology, University of Toronto, Toronto, Ontario M5S 1A1, Canada.

ABSTRACT
Many ethanol dependent women also use other drugs of abuse that may affect pregnancy outcome and long-term child neurodevelopment. This study investigated the association between drugs of abuse and concurrent use of ethanol in pregnancy. A study cohort of neonates with FAEE levels above 2nmol per gram meconium, indicative of heavy in utero ethanol exposure, was identified (n=114). Meconium and hair analyses for the presence of other drugs of abuse were obtained for some of these neonates and the rates of drug exposure were compared with the rates in a cohort of neonates who were tested negative (FAEE below 2nmol per gram
meconium) for ethanol exposure (n=622). Odds ratios (ORs) for various drugs were calculated with ethanol exposure. A 15.5% positive rate for intrauterine ethanol exposure was detected. A high rate of in utero drug exposure was detected in neonates with and without in utero ethanol exposure, 60.5% versus 62.7% respectively. Neonates with heavy in utero ethanol exposure were almost twice as likely to be exposed to narcotic opiates (OR=1.90; 95% confidence interval [CI]: 1.13-3.20) and 3.3 times as likely to be exposed to amphetamine (OR=3.30; 95% CI 1.06-10.27) when compared to neonates with no ethanol exposure. Exposure to cannabinoids predicted less likely exposure to ethanol (OR=0.61; 95% CI: 0.38-0.98) and no significant difference was noted in the exposure to cocaine (OR=1.24, 95% CI: 0.81-1.91). Neonates suspected of heavy in utero ethanol exposure should be tested for other drugs of abuse and vice versa. Early detection of drug exposures can facilitate early intervention to both the neonate and the mother, thus decreasing the risk of long-term neurodevelopmental outcomes for the child, including secondary disabilities associated with fetal alcohol spectrum disorder.

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**Conclusion:** This result suggests that contrary to PDE1, PDE4 inhibition does not play a role in the restoration of OD plasticity in the ferret model of FASD.

Read Full Article,  
http://www3.interscience.wiley.com/journal/123216957/abstract

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70. ETHANOL-INDUCED OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN RAT PLACENTA: RELEVANCE TO PREGNANCY LOSS

Fusun Gundogan, Gwen Elwood, Princess Mark, Adrian Feijoo, Lisa Longato, Ming Tong, and Suzanne M. de la Monte

From the Department of Pathology (FG), Women and Infants Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island; Rhode Island Hospital (SMD), Warren Alpert Medical School of Brown University, Providence, Rhode Island; Department of Medicine (GE, PM, AF, LL, MT, SM), Liver Research Center, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island.

ABSTRACT

Background: Ethanol consumption during pregnancy increases the risk of early pregnancy loss and causes intrauterine growth restriction. We previously showed that chronic gestational exposure to ethanol impairs placentation, and that this effect is associated with inhibition of insulin and insulin growth factor signaling. Since ethanol also causes oxidative stress and DNA damage, we extended our investigations to assess the role of these pathological processes on placentation and placental gene expression.

Methods: Pregnant Long Evans rats were pair-fed liquid diets containing 0% or 24% ethanol by caloric content. Placentas harvested on gestation day 16 were used to examine DNA damage, lipid peroxidation, apoptosis, mitochondrial gene/protein and hormonal gene expression in relation to ethanol exposure.

Results: Gestational exposure to ethanol increased fetal resorption, and trophoblast apoptosis/necrosis, oxidative stress, DNA damage, and lipid peroxidation. These adverse effects of ethanol were associated with increased expression of pro-apoptotic (Bax and Bak) and reduced levels of the anti-apoptotic Bcl-2 protein. In addition, increased trophoblast apoptosis proneness was associated with p53-independent activation of p21, reduced mitochondrial gene and protein expression, and dysregulated expression of prolactin (PRL) family hormones that are required for implantation and pregnancy-related adaptations.

Conclusions: Chronic gestational exposure to ethanol increases fetal demise due to impaired survival and mitochondrial function, increased oxidative stress, DNA damage and lipid peroxidation, and dysregulated expression of prolactin family hormones in placental trophoblasts.


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71. DIFFERENTIAL EFFECTS OF CHRONIC ETHANOL EXPOSURE ON CYTOCHROME P450 2E1 AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN THE MATERNAL-FETAL UNIT OF THE GUINEA PIG

Hewitt AJ, Walker KR, Kobus SM, Poklewska-Koziell M, Reynolds JN, Brien JF. Department of Pharmacology and Toxicology, Queen's University, Kingston, ON, Canada.
ABSTRACT

Background: Ethanol neurobehavioural teratogenicity is a leading cause of developmental mental deficiency, in which the hippocampus is a target site of injury. The multi-faceted mechanism of ethanol teratogenicity is not completely understood. This study tested the hypothesis that chronic ethanol exposure (CEE), via chronic maternal ethanol administration, increases cytochrome P450 2E1 (CYP2E1) expression and alters hypothalamic-pituitary-adrenal (HPA) axis activity in the maternal-fetal unit during the third-trimester-equivalent of gestation.

Methods: Pregnant Dunkin-Hartley-strain guinea pigs received daily oral administration of ethanol (4 g ethanol/kg maternal body weight) or isocaloric-sucrose/pair-feeding (control) throughout gestation (term, about gestational day (GD) 68). On GD 45, 55 and 65, pregnant animals were euthanized 2h after the last daily dose. Maternal and fetal body weights and fetal hippocampal brain weight were determined. Maternal and fetal samples were collected for the determination of liver CYP2E1 enzymatic activity and plasma free cortisol and ACTH concentrations.

Results: CEE, with maternal blood ethanol concentration of 108-124 mg/dl at 2h after the last dose, decreased fetal hippocampal weight only at GD 65 and had no effect on fetal body weight compared with control. CYP2E1 activity increased with gestational age in the fetal liver microsomal and mitochondrial fractions. CEE increased CYP2E1 activity in the microsomal and mitochondrial fractions of maternal liver at the three gestational ages and in both hepatic subcellular fractions of the GD 65 fetus compared with control. There was a gestational-age-dependent increase in maternal and fetal plasma free cortisol concentrations, but no effect of CEE compared with control. Maternal and fetal plasma ACTH concentrations were unaffected by CEE compared with control, and were virtually unchanged during the third-trimester-equivalent that was studied.

Conclusion: These data demonstrate that, in the pregnant guinea pig, this CEE regimen increases liver CYP2E1 activity, without affecting HPA axis function, in the maternal-fetal unit during near-term gestation. The CEE-induced increase in liver CYP2E1 activity and potential oxidative stress in the maternal-fetal unit may play a role in the pathogenesis of ethanol teratogenicity.


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72. FETAL ALCOHOL SPECTRUM DISORDER (FASD)
Mahendra Kumar Banakar1,4, Nirvana Swamy Kudlur2 and Sanju George3
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(2) Department of Psychiatry, Worcester Community Psychiatric Hospital, Worcester, UK
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ABSTRACT
Fetal alcohol syndrome (FAS) is the leading cause of mental retardation worldwide but is also the
foremost preventable cause of neurobehavioral and developmental abnormalities. It is equally important to know spectrum of disorders due to maternal alcoholism during pregnancy such as Fetal alcohol spectrum disorder (FASD) in order to identify and treat affected child and family effectively. This article aims to create awareness among practising clinicians most of whom are only aware of phenotypical variant of FASD which is FAS. In this article we discuss those aspects of FASD relevant to the clinician such as: terminological ambiguity, assessment, diagnosis and prevention.

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http://www.springerlink.com/content/011vvhg58h122418/

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Wiley InterScience -American Journal of Medical Genetics Volume 152A Issue 1, Pages 32-41. Published Online 11 Dec 2009

73. MORPHOMETRIC ANALYSIS AND CLASSIFICATION OF THE FACIAL PHENOTYPE ASSOCIATED WITH FETAL ALCOHOL SYNDROME IN 5- AND 12-YEAR-OLD CHILDREN
Tinashe E.M. Mutsvangwa 1, Ernesta M. Meintjes 1, Dennis L. Viljoen 2, Tania S. Douglas 1
1 MRC/UCT Medical Imaging Research Unit, Department of Human Biology, University of Cape Town, Cape Town, South Africa
2 Foundation for Alcohol-Related Research, Cape Town, South Africa
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ABSTRACT
Landmark-based morphometric analysis holds promise for quantitative assessment of craniofacial dysmorphology. We describe an application of facial shape analysis to characterize the facial anomalies associated with fetal alcohol syndrome (FAS) in a mixed ancestry population. Generalized Procrustes analysis, regression and discriminant function analysis were applied to stereo-photogrammetrically derived 3D coordinates of landmarks taken from 34 subjects (n = 17 FAS and n = 17 normal controls).

Four shape analyses were carried out, namely a comparison of the FAS and control facial shapes at age 5, and one at age 12; a comparison of the FAS facial shapes at ages 5 and 12; and a comparison of control facial shapes at ages 5 and 12. The first two analyses showed that the FAS face is characterized by small palpebral fissures, a thin upper lip, and midfacial hypoplasia. Classification of subjects as having FAS using leave-one-out cross-validation showed that the 5-year-old group could be classified with 95.46% accuracy and the 12-year-olds with 80.13% accuracy. The third and fourth analyses revealed that the differences in facial shape between FAS individuals in different age groups were more pronounced than for control individuals, supporting the notion that FAS facial anomalies diminish with age. Geometric morphometric analysis of stereo-photogrammetrically derived 3D facial landmarks allows visualization of the facial anomalies associated with FAS, as well as classification of facial shapes.

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http://www3.interscience.wiley.com/journal/123210943/abstract

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A SYSTEMATIC REVIEW OF CONTINUOUS PERFORMANCE TASK RESEARCH IN CHILDREN PRENATALLY EXPOSED TO ALCOHOL
Dolan GP, Stone DH, Briggs AH.
Department of Public Health and Health Policy, Faculty of Medicine, University of Glasgow, UK. Gayle.Dolan@northtyneside-pct.nhs.uk

ABSTRACT
Aims: The aim of this study was to review systematically, research investigating an association between the continuous performance task (CPT) in children and exposure to alcohol in utero, in order to identify any evidence of a specific deficit in performance.

Methods: Seven electronic databases and three websites were searched. Papers were selected in accordance with specific inclusion criteria and scored in terms of the methodological quality using the Newcastle-Ottawa score. Marked methodological heterogeneity limited the validity of any statistical meta-analysis and a descriptive synthesis was performed instead.

Results: A total of 14 papers were identified for inclusion. There was no consistent evidence of any association between prenatal alcohol exposure and correct responses, reaction time, commission or omission errors during CPT testing. Apparent trends in the reported results, however, suggest that a potential effect might have been missed.

Conclusions: Identifying a specific profile of CPT performance may assist in the detection and management of attention deficits amongst children with prenatal alcohol exposure. Future research with more consistent measures of exposure and outcome is, however, required before any valid generalizations about CPT performance can be made.


[POSSIBLE REGENERATIVE MEDICINE TO TREAT ALCOHOL-INDUCED BRAIN DAMAGE] [ARTICLE IN JAPANESE]
Hashimoto E, Yoshinaga T, Ishii T, Saito S, Ugai W, Saito T.

ABSTRACT
Alcohol exposure causes various kinds of neuronal damage, resulting from increased cell death or decreased cell proliferation in several brain regions. Recent neuroimaging studies demonstrated brain atrophy in alcoholics, and these morphological changes are considered as the result of neural network impairment.

We have previously evaluated that alcohol suppressed neuronal differentiation at concentrations that did not affect the survival of neural stem cells (NSCs), indicating that alcohol-induced alteration of neurogenesis can also contribute to neuronal loss and then CNS dysfunctions. As the nervous system, unlike many other tissues, has a limited capacity for self-repair, there is great interest in the possibility of repairing the CNS by transplanting NSCs. We transplanted
NSCs to the fetal alcohol effects (FAE) model for the purpose of repairing the impaired neural network and investigating the possibility of regenerative therapy for alcohol-induced brain damage. The intravenously administrated NSCs were detected in brain by visualizing a fluorescent marker. The number of the transplanted NSCs in brains of FAE model rats was greater than in the control rat brains in wide areas of brain by measuring RI labeling, suggesting effective migration of the transplanted NSCs in the impairment neural network in FAE model rats. Furthermore, NSC transplantation improved the abnormal behavior of the model rats. These results suggest that the intravenous NSC transplantation might be a possible approach to recover the alcohol-induced damage of neuronal network and CNS dysfunction. The new strategy to promote proper NSC function in brain by the combined therapy of NSC transplantation and psychotropic drugs which have neuroprotective and/or neurogenetic potential may have a great impact on the improvement of alcohol related psychiatric disease especially cognitive and emotional problems.

Link to the Article,


76. INCLUDING A SCREENING AND BRIEF ALCOHOL INTERVENTION PROGRAM IN THE CARE OF THE OBSTETRIC PATIENT
Keough VA, Jennrich JA.
Marcella Niehoff School of Nursing, Loyola University, 2160 S. First Ave, Maguire 2853, Chicago, IL 60641, USA. vkeough@luc.edu

ABSTRACT
Alcohol is the drug most commonly abused by pregnant women and the leading cause of preventable birth defects across the United States. Screening, Brief Intervention, and Referral for Treatment is a program developed by the Emergency Nurses Association that has demonstrated success in treating patients who have alcohol use disorders. This interventional program can be useful to perinatal nurses caring for pregnant women with alcohol use disorders in a variety of settings.

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77. THE RELATIONSHIP BETWEEN OBSTETRICAL OUTCOMES AND ALCOHOL USE IN THE YEAR PRIOR TO PREGNANCY
Flynn HA, Berman D, Marcus SM.
Department of Psychiatry, University of Michigan, Ann Arbor, Michigan 48108, USA.

ABSTRACT
Objectives: The purpose of this study was to examine problems related to alcohol use as
reported covering the year prior to pregnancy in a general prenatal care seeking sample. The relationship of alcohol use to a number of pregnancy and birth complications (premature rupture of membrane, birthweight, weeks gestation and APGAR) was examined.

**Methods:** A total of 940 prenatal care-seeking women completed the TWEAK, a brief measure of alcohol use problems during the previous year. Measures were completed by women at an average of 25 weeks gestation (SD = 9.7) in the waiting areas of university-affiliated obstetrics clinics in the US. Pregnancy and birth complications were gathered via medical record search and completed on all cases.

**Results:** Controlling for cigarette use and key demographic variables, only pre-pregnancy elevated TWEAK (> or =2) was significantly and consistently related to each obstetrical outcome in multivariate analyses in the total sample. Analyses showed that pre-pregnancy TWEAK was related to PROM and lower birthweight among the sample of women (n = 800) who reported no actual alcohol use during pregnancy.

**Conclusions:** Results suggest that a brief screening for alcohol use problems may detect women either in early pregnancy or pre-conceptually, that may be at risk for potentially harmful pregnancy and birth outcomes, including women who deny prenatal alcohol use.


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**78. IMPACT OF ETHANOL ON THE DEVELOPING GABAERGIC SYSTEM**

Isayama RN, Leite PE, Lima JP, Uziel D, Yamasaki EN.
Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

**ABSTRACT**

Alcohol intake during pregnancy has a tremendous impact on the developing brain. Embryonic and early postnatal alcohol exposures have been investigated experimentally to elucidate the fetal alcohol spectrum disorders' (FASD) milieu, and new data have emerged to support a devastating effect on the GABAergic system in the adult and developing nervous system. GABA is a predominantly inhibitory neurotransmitter that during development excites neurons and orchestrates several developmental processes such as proliferation, migration, differentiation, and synaptogenesis.

This review summarizes and brings new data on neurodevelopmental aspects of the GABAergic system with FASD in experimental telencephalic models.


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79. DURING PREGNANCY, RECREATIONAL DRUG-USING WOMEN STOP TAKING ECSTASY (3,4-METHYLENEDIOXY-N-METHYLAMPHETAMINE) AND REDUCE ALCOHOL CONSUMPTION, BUT CONTINUE TO SMOKE TOBACCO AND CANNABIS: INITIAL FINDINGS FROM THE DEVELOPMENT AND INFANCY STUDY
Institute for Research in Child Development, Department of Psychology, University of East London, Romford Road.

ABSTRACT
While recreational drug use in UK women is prevalent, to date there is little prospective data on patterns of drug use in recreational drug-using women immediately before and during pregnancy. A total of 121 participants from a wide range of backgrounds were recruited to take part in the longitudinal Development and Infancy Study (DAISY) study of prenatal drug use and outcomes. Eighty-six of the women were interviewed prospectively while pregnant and/or soon after their infant was born. Participants reported on use immediately before and during pregnancy and on use over their lifetime. Levels of lifetime drug use of the women recruited were high, with women reporting having used at least four different illegal drugs over their lifetime. Most users of cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA) and other stimulants stopped using these by the second trimester and levels of use were low. However, in pregnancy, 64% of the sample continued to use alcohol, 46% tobacco and 48% cannabis. While the level of alcohol use reduced substantially, average tobacco and cannabis levels tended to be sustained at pre-pregnancy levels even into the third trimester (50 cigarettes and/or 11 joints per week). In sum, while the use of 'party drugs' and alcohol seems to reduce, levels of tobacco and cannabis use are likely to be sustained throughout pregnancy. The data provide polydrug profiles that can form the basis for the development of more realistic animal models.

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80. ONTOGENY OF THE ENHANCED FETAL-ETHANOL-INDUCED BEHAVIORAL AND NEUROPHYSIOLOGIC OLFACTORY RESPONSE TO ETHANOL ODOR
Amber M. Eade, Paul R. Sheehe, and Steven L. Younghentob
From the Department of Neuroscience and Physiology (AME, PRS, SLY), State University of New York, Upstate Medical University, Syracuse, New York; and (AME, PRS, SLY) State University of New York, Developmental Exposure Alcohol Research Center, Syracuse & Binghamton, New York.

ABSTRACT
Background: Studies report a fundamental relationship between chemosensory function and the responsiveness to ethanol, its component orosensory qualities, and its odor as a consequence of fetal ethanol exposure. Regarding odor, fetal exposed rats display enhanced olfactory neural and behavioral responses to ethanol odor at postnatal (P) day 15. Although these consequences are
absent in adults (P90), the behavioral effect has been shown to persist into adolescence (P37). Given the developmental timing of these observations, we explored the decay in the response to ethanol odor by examining ages between P37 and young adulthood. Moreover, we sought to determine whether the P15 neurophysiologic effect persists, at least, to P40.

**Methods:** Behavioral and olfactory epithelial (OE) responses of fetal ethanol exposed and control rats were tested at P40, P50, P60, or P70. Whole-body plethysmography was used to quantify each animal's innate behavioral response to ethanol odor. We then mapped the odorant-induced activity across the OE in response to different odorants, including ethanol, using optical recording methods.

**Results:** Relative to controls, ethanol exposed animals showed an enhanced behavioral response to ethanol odor that, while significant at each age, decreased in magnitude. These results, in conjunction with previous findings, permitted the development of an ontologic odor response model of fetal exposure. The fitted model exemplifies that odor-mediated effects exist at birth, peak in adolescence and then decline, becoming absent by P90. There was no evidence of an effect on the odor response of the OE at any age tested.

**Conclusions:** Fetal exposure yields an enhanced behavioral response to ethanol odor that peaks in adolescence and wanes through young adulthood. This occurs absent an enhanced response of the OE. This latter finding suggests that by P40 the OE returns to an ethanol "neutral" status and that central mechanisms, such as ethanol-induced alterations in olfactory bulb circuitry, underlie the enhanced behavioral response. Our study provides a more comprehensive understanding of the ontogeny of fetal-ethanol-induced olfactory functional plasticity and the behavioral response to ethanol odor.


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81. HIPPOCAMPAL N-METHYL-D-ASPARTATE RECEPTOR SUBUNIT EXPRESSION PROFILES IN A MOUSE MODEL OF PRENATAL ALCOHOL EXPOSURE
Samudio-Ruiz SL, Allan AM, Sheema S, Caldwell KK

**ABSTRACT**

**Background:** Although several reports have been published showing prenatal ethanol exposure is associated with alterations in N-methyl-d-aspartate (NMDA) receptor subunit levels and, in a few cases, subcellular distribution, results of these studies are conflicting.

**Methods:** We used semi-quantitative immunoblotting techniques to analyze NMDA receptor NR1, NR2A, and NR2B subunit levels in the adult mouse hippocampal formation isolated from offspring of dams who consumed moderate amounts of ethanol throughout pregnancy. We employed subcellular fractionation and immunoprecipitation techniques to isolate synaptosomal membrane- and postsynaptic density protein-95 (PSD-95)-associated pools of receptor subunits.

**Results:** We found that, compared to control animals, fetal alcohol-exposed (FAE) adult mice had: (i) increased synaptosomal membrane NR1 levels with no change in association of this subunit with PSD-95 and no difference in total NR1 expression in tissue homogenates; (ii)
decreased NR2A subunit levels in hippocampal homogenates, but no alterations in synaptosomal membrane NR2A levels and no change in NR2A-PSD-95 association; and (iii) no change in tissue homogenate or synaptosomal membrane NR2B levels but a reduction in PSD-95-associated NR2B subunits. No alterations were found in mRNA levels of NMDA receptor subunits suggesting that prenatal alcohol-associated differences in subunit protein levels are the result of differences in post-transcriptional regulation of subunit localization.

Conclusions: Our results demonstrate that prenatal alcohol exposure induces selective changes in NMDA receptor subunit levels in specific subcellular locations in the adult mouse hippocampal formation. Of particular interest is the finding of decreased PSD-95-associated NR2B levels, suggesting that synaptic NR2B-containing NMDA receptor concentrations are reduced in FAE animals. This result is consistent with various biochemical, physiological, and behavioral findings that have been linked with prenatal alcohol exposure.

Link to the Article,
http://www.unboundmedicine.com/medline/ebm/record/19951292/abstract/Hippocampal_N_Methyl_d_Aspartate_Receptor_Subunit_Expression_Profiles_in_a_Mouse_Model_of_Prenatal_Alcohol_Exposure

82. PRENATAL ALCOHOL EXPOSURE: IMPLICATIONS FOR CARDIOVASCULAR FUNCTION IN THE FETUS AND BEYOND
Helena C Parkington, Harold A Coleman, E Marelyn Wintour and Marianne Tare
Department of Physiology, Monash University, Melbourne, Victoria, Australia

ABSTRACT
1. The effects of heavy maternal alcohol consumption during pregnancy on cognitive and behavioural performance and craniofacial malformations in the offspring have been studied extensively. In contrast, the impact of maternal alcohol intake on the cardiovascular system of the offspring and the effects of more modest consumption have received very scant consideration.
2. Adverse conditions in the pre- and neonatal periods can have a profound legacy on offspring health, including the risk of cardiovascular disease. Prenatal alcohol exposure can modulate vascular reactivity, including endothelial and smooth muscle function.
3. Other effects of prenatal alcohol exposure are emerging, including impairment of nephrogenesis and kidney function and increased arterial stiffness. The impact of even modest prenatal alcohol exposure on cardiovascular health in the offspring remains to be determined.
4. It is envisaged that the culmination of reduced renal and vascular capacity will render the offspring more vulnerable to cardiovascular disease with ageing and exposure to additional insults and lifestyle factors.

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http://www3.interscience.wiley.com/journal/123189693/abstract

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83. MATERNAL ALCOHOL USE BEFORE AND DURING PREGNANCY AMONG WOMEN IN TARANAKI, NEW ZEALAND
Ho R, Jacquemard R.
Department of Medicine, Middlemore Hospital, Hospital Road, Otahuhu, Auckland 1062, New Zealand. reena.ho@waitematadhb.govt.nz

ABSTRACT
Aims: The study researched alcohol consumption and drinking patterns before and during pregnancy.

Method: This was a 1 month self report survey of postnatal women from 21 May-22 June 2006. A multiple choice questionnaire was handed out to them on the first or second postnatal day.

Results: There were a total of 117 deliveries. The questionnaire was completed by 100 of the 104 women who received it. Before pregnancy, 80% of women reported drinking alcohol; 66% binge drinking. Twenty-eight percent continued consuming alcohol throughout pregnancy. The majority did reduce or stop their alcohol consumption, 7% however did not. Ten percent were drinking more than 2 units per typical day and more than 7 units per week during pregnancy. Four percent was drinking a lot more than this. Nine percent of the total cohort reported binge drinking during pregnancy.

Conclusion: Just over a quarter of women drink alcohol throughout pregnancy. A significant minority of women drink relatively heavily (more than 4 units per occasion and multiple times per week) during pregnancy. Many women do reduce their alcohol use because of the pregnancy, but often only after they become aware of it. In New Zealand there is a real risk of fetal alcohol spectrum disorders.


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84. ESTIMATING THE NEUROCOGNITIVE EFFECTS OF AN EARLY INTERVENTION PROGRAM FOR CHILDREN WITH PRENATAL ALCOHOL EXPOSURE
Parvaneh Yazdani, Mary Motz, Gideon Koren

ABSTRACT
Background: Animal studies suggest that early intervention in pups exposed heavily to ethanol in utero can mitigate their neurocognitive damage. No human studies on this promising mechanism exists.

Methods: Breaking the Cycle is an early intervention program for drug-and alcohol addicted mothers and their young children. We compared BSID-III scores between infants heavily exposed to ethanol and a group exposed only to drugs of abuse, mainly cocaine. Both groups benefited from all aspects of our early intervention program.
Results: The two groups did not differ in any aspect of the BSID-III. These data are in contradistinction to the damage seen in heavily ethanol-exposed infants not benefiting from early intervention.

Conclusions: This pilot suggests that early intervention may mitigate some of the well described damages caused by heavy in utero alcohol exposure.

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85. WHAT WOMEN IN FRANCE SAY ABOUT ALCOHOL ABSTINENCE DURING PREGNANCY
Stéphanie Toutain
Université Paris Descartes, Sciences Socials, Paris, France

ABSTRACT
Introduction and Aims: In spite of the implemented policies warning of the dangers of alcohol consumption for pregnant women, many women still continue drinking during pregnancy. This article focuses on the question of the representations of alcohol consumption during pregnancy in France.

Design and Methods: A qualitative approach based on discussions with 42 pregnant women in three Internet chat groups in 2007 was used for our study.

Results: The recommendation for total abstinence is often misunderstood by women, as are the consequences of drinking for the unborn babies. Besides, these Internet users do not seem to know much about the consequences of alcohol consumption for unborn babies. Finally, their sources of information are varied (written, oral, television, Internet, professionals of health, family networks and friends); however, their mothers remain the most credible source for them.

Discussion and Conclusion: Alcohol consumption during pregnancy already constitutes a real taboo for the heath care professionals in France. It is extremely urgent and imperative that they recommend total abstinence during pregnancy, in order to avoid any irreversible consequences for the unborn babies.


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TIMING OF MODERATE LEVEL PRENATAL ALCOHOL EXPOSURE INFLUENCES GENE EXPRESSION OF SENSORY PROCESSING BEHAVIOR IN RHESUS MONKEYS
Schneider ML, Moore CF, Larson JA, Barr CS, Dejesus OT, Roberts AD.
Department of Kinesiology, University of Wisconsin-Madison Madison, WI, USA.

ABSTRACT
Sensory processing disorder, characterized by over- or under-responsivity to non-noxious environmental stimuli, is a common but poorly understood disorder. We examined the role of prenatal alcohol exposure, serotonin transporter gene polymorphic region variation (rh5-HTTLPR), and striatal dopamine (DA) function on behavioral measures of sensory responsivity to repeated non-noxious sensory stimuli in macaque monkeys. Results indicated that early gestation alcohol exposure induced behavioral under-responsivity to environmental stimuli in monkeys carrying the short (s) rh5-HTTLPR allele compared to both early-exposed monkeys homozygous for the long (l) allele and monkeys from middle-to-late exposed pregnancies and controls, regardless of genotype. Moreover, prenatal timing of alcohol exposure altered the relationship between sensory scores and DA D(2)R availability. In early-exposed monkeys, a positive relationship was shown between sensory scores and DA D(2)R availability, with low or blunted DA function associated with under-responsive sensory function. The opposite pattern was found for the middle-to-late gestation alcohol-exposed group. These findings raise questions about how the timing of prenatal perturbation and genotype contributes to effects on neural processing and possibly alters neural connections.

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87. PHYSICAL AND NEURODEVELOPMENTAL EVALUATION OF CHILDREN ADOPTED FROM EASTERN EUROPE
Monique Robert, Ana Carceller, Valerie Domken, Felix Ramos, Otilia Dobrescu, Marie-Noelle Simard, Julie Gosselin

ABSTRACT
Background: Children adopted from Eastern Europe are at risk of prenatal alcohol exposure, consequently at risk of Fetal Alcohol Spectrum Disorders (FASD). To our knowledge, a systematic complete assessment of these disabilities among adoptees from Eastern Europe has not yet been reported.

Objective: To assess physical and neurodevelopmental status to identify FASD in children adopted from Eastern Europe.

Method: Cross sectional study at International Adoption Clinic of a paediatric academic hospital. This evaluation was realized according to the 4-Digit Diagnostic Code (4-DDC).

Results: Twenty-nine children were evaluated. Five years after adoption, 7% (N=2) still presented growth delay and 24% (N=7) microcephaly. Facial evaluation demonstrated moderate
Fetal Alcohol Syndrome (FAS) features in 7% (N=2) of children. Amiel-Tison Neurological Assessment was non optimal in 46% (N=13/28) of children. Visual-motor perception skills were mainly normal, but 14% (N=4) showed distal somatopraxic problems. Cognition, executive functioning, abstract reasoning and memory were normal. Full scale IQ was 105.5 ± 13.3; verbal IQ < performance IQ (p<0.005), work memory < short memory (p<0.0001), receptive <expressive language (p<0.0001). Attention-deficit hyperactive disorder was presented in 31% (N=9). Concerning adaptive behaviour, social skills and social communication, 29% (N=8) performed <-2 SD and 33% (N=5/15) needed school assistance. According to 4-DDC, 7% (N=2) of children were normal, 21% (N=6) of children were known exposed to alcohol, one of these was classified as Partial FAS and five others presented neurological damage, or neurobehavioral disorders with or without sentinel physical findings. Three percent (N=1) were classified FAS although alcohol exposure was unknown. Sixty-nine percent (N=20) of children presented physical findings alone or neurological anomalies with or without physical findings.

Conclusion: In our cohort, the 4-DDC was useful. Systematic and multidisciplinary neurodevelopmental assessment is needed in these adopted children, for an early intervention to prevent secondary disabilities and therefore optimize children’s outcome.

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http://www.cjcp.ca/pubmed.php?articleId=224

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88. MAGNETIC RESONANCE MICROSCOPY DEFINES ETHANOL-INDUCED BRAIN ABNORMALITIES IN PRENATAL MICE: EFFECTS OF ACUTE INSULT ON GESTATIONAL DAY 7
From the Bowles Center for Alcohol Studies (EAG, SOM, AAK, SEP, JJA, DBD, KKS), Neurodevelopmental Disorders Research Center (MAS), University of North Carolina, Chapel Hill, North Carolina; and Center for In Vivo Microscopy (BWJ, GAJ), Duke University, Durham, North Carolina.

ABSTRACT
Background: This magnetic resonance microscopy (MRM)-based report is the second in a series designed to illustrate the spectrum of craniofacial and central nervous system (CNS) dysmorphia resulting from single- and multiple-day maternal ethanol treatment. The study described in this report examined the consequences of ethanol exposure on gestational day (GD) 7 in mice, a time in development when gastrulation and neural plate development begins; corresponding to the mid- to late third week postfertilization in humans. Acute GD 7 ethanol exposure in mice has previously been shown to result in CNS defects consistent with holoprosencephaly (HPE) and craniofacial anomalies typical of those in Fetal Alcohol Syndrome (FAS). MRM has facilitated further definition of the range of GD 7 ethanol-induced defects.

Methods: C57Bl/6J female mice were intraperitoneally (i.p.) administered vehicle or 2 injections
of 2.9 g/kg ethanol on day 7 of pregnancy. Stage-matched control and ethanol-exposed GD 17 fetuses selected for imaging were immersion fixed in a Bouins/Prohance solution. MRM was conducted at either 7.0 Tesla (T) or 9.4 T. Resulting 29 μm isotropic spatial resolution scans were segmented and reconstructed to provide 3D images. Linear and volumetric brain measures, as well as morphological features, were compared for control and ethanol-exposed fetuses. Following MRM, selected specimens were processed for routine histology and light microscopic examination.

Results: Gestational day 7 ethanol exposure resulted in a spectrum of median facial and forebrain deficiencies, as expected. This range of abnormalities falls within the HPE spectrum; a spectrum for which facial dysmorphology is consistent with and typically is predictive of that of the forebrain. In addition, other defects including median facial cleft, cleft palate, micrognathia, pituitary agenesis, and third ventricular dilatation were identified. MRM analyses also revealed cerebral cortical dysplasia/heterotopias resulting from this acute, early insult and facilitated a subsequent focused histological investigation of these defects.

Conclusions: Individual MRM scans and 3D reconstructions of fetal mouse brains have facilitated demonstration of a broad range of GD 7 ethanol-induced morphological abnormality. These results, including the discovery of cerebral cortical heterotopias, elucidate the teratogenic potential of ethanol insult during the third week of human prenatal development.

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Wiley InterScience - International Journal of Nursing Terminologies and Classifications, Volume 24 Issue 4, Pages 181-188. Published Online 22 Oct 2009

89. PROBLEMS EXPRESSED BY CAREGIVERS OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER

Linda M. Caley, PhD, RN 1 , Theresa Winkelman, MS, SNP, RN 1 , and Kathleen Mariano, DNS, RN, CPNP 2

1. Linda M. Caley, PhD, RN, and Theresa Winkelman, MS, SNP, RN, are Assistant Professor and Clinical Assistant Professor, respectively, at the University at Buffalo, School of Nursing, State University of New York, Buffalo, New York;
2. Kathleen Mariano, DNS, RN, CPNP, is Department Chair at D'Youville College, School of Nursing, Buffalo, New York.

ABSTRACT

Purpose: The purpose of this study was to determine if use of a standardized classification system could help identify potential nursing sensitive problems for caregivers of children with fetal alcohol spectrum disorder (FASD).

Method: This study is a secondary analysis of data obtained from transcripts of public testimonies. Content analysis was conducted using a standardized classification system. The sample consisted of 376 statements from electronic transcripts of first person testimonies given by 48 caregivers of children with FASD in four states.

Findings: Forty-eight caregivers expressed a total of 53 signs and symptoms. The majority was
in the problem areas: communication with community resources, caretaking/parenting, mental health, and income.

**Conclusions and Implications for nursing practice:** Using a nursing classification system, investigators were able to identify nursing sensitive problems expressed by caregivers of children with FASD. The information from this study can be used in future studies to confirm or revise the signs/symptoms identified in this study.

Read Full Article,  
http://www3.interscience.wiley.com/journal/122659899/abstract


90. **FETAL ALCOHOL SPECTRUM DISORDER IN ISRAEL**
Child Development and Rehabilitation Institute, Schneider Children's Medical Center of Israel, Petah Tikva, Israel. Senekimi@zahav.net.il

**ABSTRACT**

**Background:** Fetal alcohol spectrum disorder is a range of disabilities caused by gestational exposure to alcohol. FASD is the leading cause of preventable mental retardation and developmental disability in the United States, with an incidence of 1-10 per 1000 live births. FASD in Israel has yet to be examined systematically. **OBJECTIVES:** To evaluate professionals' experience, awareness and knowledge of FASD in Israel and their awareness of maternal consumption of alcohol, and to collect epidemiological data on the syndrome in Israel.

**Methods:** A short questionnaire was sent to all 43 program directors of genetic institutes (n = 14) and child developmental centers in Israel (n = 29). Four questions related to their experience and knowledge of FASD. The epidemiological survey included data from all 17 hospitals in Israel and from the two main health management organizations within the public health care system.

**Results:** The response rate was 98% (n = 42). A total of 38.1% of respondents reported having diagnosed at least one case of FASD and fewer than 10% of respondents stated that the knowledge regarding FASD among physicians in Israel was adequate. Developmental pediatricians were more likely to have diagnosed at least one case as compared to geneticists. During the period 1998-2007 the diagnosis of FASD appeared in the records of only 4 patients from the total number of 17 hospitals in Israel. During the same period only six patients were diagnosed at the HMO within the public health care system.

**Conclusions:** Despite the accumulated knowledge on FASD in many countries and the increase in alcohol consumption in Israel, professionals' awareness of its potential damage is limited. Educational programs to increase physician awareness should accompany publicity campaigns warning the public of the dangers associated with alcohol consumption during pregnancy.

Read Full Article,  

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91. ALCOHOL EXPOSURE ALTERS DNA METHYLATION PROFILES IN MOUSE EMBRYOS AT EARLY NEURULATION
Division of Biostatistics, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA.

ABSTRACT
Alcohol exposure during development can cause variable neurofacial deficit and growth retardation known as fetal alcohol spectrum disorders (FASD). The mechanism underlying FASD is not fully understood. However, alcohol, which is known to affect methyl donor metabolism, may induce aberrant epigenetic changes contributing to FASD. Using a tightly controlled whole-embryo culture, we investigated the effect of alcohol exposure (88mM) at early embryonic neurulation on genome-wide DNA methylation and gene expression in the C57BL/6 mouse. The DNA methylation landscape around promoter CpG islands at early mouse development was analyzed using MeDIP (methylated DNA immunoprecipitation) coupled with microarray (MeDIP-chip). At early neurulation, genes associated with high CpG promoters (HCP) had a lower ratio of methylation but a greater ratio of expression. Alcohol-induced alterations in DNA methylation were observed, particularly in genes on chromosomes 7, 10, and X; remarkably, a >10 fold increase in the number of genes with increased methylation on chromosomes 10 and X was observed in alcohol-exposed embryos with a neural tube defect phenotype compared to embryos without a neural tube defect. Significant changes in methylation were seen in imprinted genes, genes known to play roles in cell cycle, growth, apoptosis, cancer, and in a large number of genes associated with olfaction. Altered methylation was associated with significant (p<0.01) changes in expression for 84 genes. Sequenom EpiTYPER DNA methylation analysis was used for validation of the MeDIP-chip data. Increased methylation of genes known to play a role in metabolism (Cyp4f13) and decreased methylation of genes associated with development (Nlgn3, Elavl2, Sox21 and Sim1), imprinting (Igf2r) and chromatin (Hist1h3d) was confirmed. In a mouse model for FASD, we show for the first time that alcohol exposure during early neurulation can induce aberrant changes in DNA methylation patterns with associated changes in gene expression, which together may contribute to the observed abnormal fetal development.

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Wiley InterScience - Synapse. Volume 64 Issue 2, Pages 127 - 135.
Published Online: 21-Sep-2009

92. POSTNATAL BINGE-LIKE ALCOHOL EXPOSURE DECREASES DENDRITIC COMPLEXITY WHILE INCREASING THE DENSITY OF MATURE SPINES IN MPFC LAYER II/III PYRAMIDAL NEURONS
Gillian F. Hamilton, Lee T. Whitcher, Anna Y. Klintsova
Psychology Department, University of Delaware, Newark, Delaware 19716

ABSTRACT
Prenatal exposure to alcohol in humans can result in a wide range of deficits collectively referred to as fetal alcohol spectrum disorders. Of these deficits, cognitive impairments are among the
most debilitating and long-lasting. Specifically, cognitive impairments in executive functioning suggest damage to the prefrontal cortex (PFC). Several external stimuli, such as morphine, chronic stress, and maternal stress have been found to alter the dendritic structure of cells within the PFC. In this study, three groups of rat pups were used: intubated with alcohol (5.25 g/kg/day; AE), sham intubated (SI), or suckle controls (SC) on PD 4-9. On PD 26-30 rats were anesthetized, perfused with saline and brains were processed for Golgi-Cox staining. Basilar dendritic complexity, spine density, and spine phenotypes were evaluated for Layer II/III neurons in the medial PFC. Results indicate that AE rats have an altered basilar dendritic complexity due to a significant decrease in both length and number of intersections in proximity to the neuronal soma. Furthermore, spine density patterns of basilar dendrites remain unchanged while the density of mature vs. immature spines significantly changes. These effects were not seen in the apical dendrites, indicating alcohol's influence on different neuronal parts in a single cell. In addition, these results suggest that the innervations of the soma and basilar dendrites by thalamic projections may play a role. Thus, our data demonstrates that postnatal exposure to alcohol produces changes in the neuronal organization of rat adolescent PFC that may affect the performance on prefrontal-dependant behavioral tasks.


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Wiley InterScience - Alcoholism: Clinical and Experimental Research - Volume 33 Issue 12, Pages 2172 - 2179. Published Online: 17 Sep 2009

93. EFFECTS OF ETHANOL ON MOUSE EMBRYONIC STEM CELLS
Alla Arzumanyan, Helen Anni, Raphael Rubin, and Emanuel Rubin
From the Department of Pathology, Anatomy and Cell Biology, Jefferson Medical College, Philadelphia, Pennsylvania.

ABSTRACT
Background: Fetal alcohol syndrome (FAS) reflects a constellation of congenital abnormalities caused by excess maternal consumption of alcohol. It is likely that interference with embryonic development plays a role in the pathogenesis of the disorder. Ethanol-induced apoptosis has been suggested as a causal factor in the genesis of FAS. Mouse embryonic stem (mES) cells are pluripotent cells that differentiate in vitro to cell aggregates termed embryoid bodies (EBs), wherein differentiation capacity and gene expression profile are similar to those of the early embryo.

Methods: To investigate the effects of ethanol during differentiation, mES cells were cultured on a gelatin surface in the presence of leukemia inhibitory factor which maintains adherent undifferentiated cells or in suspension to promote formation of EBs. All cells were treated (1–6 days) with 80 mM ethanol. The pluripotency and differentiation of mES cells were evaluated by western blotting of stage-specific embryonic antigen (SSEA-1), transcription factors Oct-3/4, Sox-2, and Nanog, using alkaline phosphatase staining. Apoptosis (early to late stages) was assessed by fluorescence-activated cell sorting using TdT-mediated biotin–dUTP nick-end labelling assay and fluorescein isothiocyanate-Annexin V/propidium iodide staining.

Results: Ethanol increased apoptosis during in vitro differentiation of mES cells to EBs, whereas undifferentiated cells were not affected. Ethanol exposure also interfered with pluripotency marker patterns causing an upregulation of SSEA-1 under self-renewal conditions. In EBs,
ethanol delayed the downregulation of SSEA-1 and affected the regulation of transcription factors during differentiation.

**Conclusion:** Our findings suggest that ethanol may contribute to the pathogenesis of FAS by triggering apoptotic pathways during differentiation of embryonic stem cells and deregulating early stages of embryogenesis.

*Read Full Article,*
http://www3.interscience.wiley.com/journal/122600962/abstract

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**MAGNETIC RESONANCE SPECTROSCOPY OUTCOMES FROM A COMPREHENSIVE MAGNETIC RESONANCE STUDY OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**


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**ABSTRACT**

Magnetic resonance (MR) technology offers noninvasive methods for in vivo assessment of neuroabnormalities. A comprehensive neuropsychological/behavioral, MR imaging (MRI), MR spectroscopy (MRS) and functional MRI (fMRI) assessment was administered to children with fetal alcohol spectrum disorders (FASD) to determine whether global and/or focal abnormalities could be identified and to distinguish diagnostic subclassifications across the spectrum. The four study groups included:-

(1) FAS/partial FAS; (2) static encephalopathy/alcohol exposed (SE/AE); (3) neurobehavioral disorder/alcohol exposed (ND/AE) as diagnosed with the FASD 4-Digit Code; and (4) healthy peers with no prenatal alcohol exposure. Results are presented in four separate reports: MRS (reported here) and neuropsychological/behavioral, MRI and fMRI outcomes (reported separately). MRS was used to compare neurometabolite concentrations [choline (Cho), n-acetyl-aspartate (NAA) and creatine (Cre)] in a white matter region and a hippocampal region between the four study groups. Choline concentration in the frontal/parietal white matter region, lateral to the midsection of the corpus callosum, was significantly lower in FAS/PFAS relative to all other study groups. Choline decreased significantly with decreasing frontal white matter volume and corpus callosum length. These outcomes suggest low choline concentrations may reflect white matter deficits among FAS/PFAS. Choline also decreased significantly with increasing severity of the 4-Digit FAS facial phenotype, increasing impairment in psychological performance and increasing alcohol exposure. NAA and Cre concentrations did not vary significantly. This study provides further evidence of the vulnerability of the cholinergic system in FASD.

*Read Full Article,*

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94. MAGNETIC RESONANCE SPECTROSCOPY OUTCOMES FROM A COMPREHENSIVE MAGNETIC RESONANCE STUDY OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS

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95. NEUROPSYCHOLOGICAL AND BEHAVIORAL OUTCOMES FROM A COMPREHENSIVE MAGNETIC RESONANCE STUDY OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS
Susan J Astley, Heather Carmichael Olson, Kimberly Kerns, Allison Brooks, Elizabeth H Aylward, Truman E Coggins, Julian Davies, Susan Dorn, Beth Gendler, Tracy Jirikowic, Paul Kraegel, Kenneth Maravilla, Todd Richards

ABSTRACT

Background: Clinical and research advancements in the field of fetal alcohol spectrum disorders (FASD) require accurate and valid identification of FASD clinical subgroups.

Objectives: A comprehensive neuropsychological battery, coupled with magnetic resonance imaging, (MRI), MR spectroscopy (MRS), and functional MRI (fMRI) were administered to children with fetal alcohol spectrum disorders (FASD) to determine if global and/or focal abnormalities could be identified across the spectrum, and distinguish diagnostic subclassifications within the spectrum. The neuropsychological outcomes of the comprehensive neuroimaging study are presented here.

Methods: The study groups included: 1) FAS/Partial FAS; 2) Static Encephalopathy/Alcohol Exposed (SE/AE); 3) Neurobehavioral Disorder/Alcohol Exposed (ND/AE) as diagnosed by an interdisciplinary team using the FASD 4-Digit Code; and 4) healthy peers with no prenatal alcohol. A standardized neuropsychological battery was administered to each child and their primary caregiver by a psychologist.

Results: Use of the 4-Digit Code produced three clinically and statistically distinct FASD clinical subgroups. The three subgroups (ND/AE, SE/AE and FAS/PFAS) reflected a linear continuum of increasing neuropsychological impairment and physical abnormality, representing the full continuum of FASD. Behavioral and psychiatric disorders were comparably prevalent across the three FASD groups, and significantly more prevalent than among the Controls. All three FASD subgroups had comparably high levels of prenatal alcohol exposure.

Conclusions: Although ND/AE, SE/AE, and FAS/PFAS are distinct FASD subgroups, these groups are not distinguishable solely by their neuropsychological profiles. While all children within a group shared the same magnitude of neuropsychological impairment, the patterns of impairment showed considerable individual variability. MRI, MRS and fMRI further distinguished these FASD subgroups.

Read Full Article,
http://www.cjcp.ca/pubmed.php?articleId=191

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96. BRIEF REPORT: LIE-TELLING IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER
Carmen Rasmussen, PhD\textsuperscript{1}, Victoria Talwar, PhD\textsuperscript{2}, Carly Loomes\textsuperscript{3} and Gail Andrew, MDCM, FRCP\textsuperscript{C4}
\textsuperscript{1} Department of Pediatrics, University of Alberta
\textsuperscript{2} Department of Educational and Counselling Psychology, McGill University
\textsuperscript{3} Department of Pediatrics, University of Alberta
\textsuperscript{4} Department of Pediatrics, University of Alberta & Glenrose Rehabilitation Hospital

ABSTRACT
Objectives: The lie-telling abilities of children with fetal alcohol spectrum disorder (FASD) (aged 4–8 years) were tested using a temptation resistance paradigm.

Methods: Children were told not to peek at a forbidden toy while left alone in a room. Later children were asked if they peeked at the toy as well as follow-up questions to see if they could conceal their peeking behavior and maintain their lie in subsequent verbal statements.

Results: Approximately 78% of the children peeked at the toy. However, 94% of the FASD children lied about peeking, a rate that is much higher than the non-FASD control group (72%). As age increased, FASD children were better at concealing their lies and maintaining semantic leakage control than non-FASD children.

Conclusions: This is the first study to specifically test lying in children with FASD and has implications for remediation and understanding secondary disabilities in these children, which will lead to further research in this area.

Link to the Article,
http://jpepsy.oxfordjournals.org/cgi/content/abstract/33/2/220

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A. NEW TRANS-CANADA INITIATIVE TO STUDY CHILD BRAIN DEVELOPMENT IS LAUNCHED

NeuroDevNet, the first trans-Canadian network dedicated to studying the spectrum of disorders that affect brain development and devising treatments and interventions to enable children to live more fulfilling lives was established in December 2009. Hosted by the University of British Columbia, the network received start up funds of (CDN) $19.5M over five years from the Networks of Centres of Excellence of Canada (NCE).

NCE is a joint program of the Natural Sciences and Engineering Research Council of Canada, the Social Sciences and the Humanities Research Council of Canada, the Canadian Institutes of Health Research and Industry Canada. The Government of Canada created the NCE Secretariat after recognizing that multi-sectoral and multi-disciplinary collaborations are critical for meeting the economic, social and environmental challenges of the 21st century. The NCE program fosters partnerships between researchers and industry to support on-going programs and products that address today’s concerns and needs.

“This is hugely exciting because we can do worlds of good to help children overcome developmental disorders,” says NeuroDevNet’s scientific director Dr. Dan Goldowitz, “I look forward to all that we will accomplish together through this network, ultimately to benefit children and their families through earlier diagnosis and innovative treatments.” NeuroDevNet is comprised of researchers, whose expertise ranges from child development to brain imaging, genetics and developmental biology with representation spanning all of Canada. This group will assess what happens during normal development, and then focus on three causes of neurological deficits to determine what goes wrong.

Fetal alcohol spectrum disorders (FASD) has been selected as one of the first developmental disorders that will be investigated as it relates to abnormal brain development and what can be done to repair damaged brains. This group is led by Dr. James Reynolds (Queen’s University, Kingston, Ontario), Dr. Sterling Clarren (University of British Columbia, Vancouver, BC) and Dr. Joanne Weinberg (University of British Columbia, Vancouver, BC), who have identified six key research foci: genetic susceptibility, cortical thickness, brain volume, brain connectivity, eye tracking, and cognition and behaviour. These areas will be investigated using model organism and clinical studies.

In the model organism studies, both mouse and rat models have been developed. Dr. Dan Goldowitz (Senior Scientist at the Centre for Molecular Medicine and Therapeutics at the Child and Family Research Institute) and Dr. Joanne Weinberg (University of British Columbia, Vancouver, BC) are the lead researchers in mouse and rat models of FASD, respectively, and their work will comprise the organism studies of this FASD project. Interestingly, some mice strains appear sensitive to alcohol teratogenicity, whereas others are resistant. By cross-breeding these strains, it will be possible to identify candidate genes that may convey to the offspring either genetic susceptibility or resistance to alcohol teratogenicity. These loci can be further studied and translated to the clinical situation, with the long-term goal of developing a genetic screening tool that can be used to identify at-risk individuals. The rat studies will further explore the area of genetic and epigenetic markers that are indicative of altered gene expression...
as a consequence of prenatal alcohol exposure, and how these alterations in gene expression correlate to cognitive and behavioural deficits and structural brain injury in offspring.

The clinical studies encompass a wide array of projects that include genetic and epigenetic analyses, saccadic eye movement and imaging studies. Dr. Sterling Clarren will lead the recruitment of children from existing FASD diagnostic clinics across Canada. Subjects between the ages of 5 and 18 years with confirmed gestational alcohol exposure will be enrolled in the study and undergo a comprehensive neuropsychological assessment. Controls will also be recruited from the same regions. Candidate gene analysis and genetic association testing will be conducted by Dr. Marie-Pierre Dube's (Director of StatGen at the Universite de Montreal, Quebec) laboratory in an effort to identify genetic determinants that are predictive of the severity of brain damage. Dr. Michael Kobor’s (Scientist at the Centre for Molecular Medicine and Therapeutics at the Child and Family Research Institute, Vancouver, BC) laboratory will study how early life experiences, such as alcohol exposure, can affect the way genes are expressed, an emerging field called epigenetics. Eye movement control will be measured using mobile eye tracking equipment and led by Drs. James Reynolds and James Brien (Queen’s University, Kingston, Ontario). Data from previous projects have suggested that eye movement control may be a powerful screening tool for identifying individuals with brain damage. Finally, Dr. Christian Beaulieu’s (University of Alberta, Edmonton) laboratory will lead all imaging studies that will be conducted in children with FASD. The volume of specific brain structures, cortical thickness, and connectivity between major brain structures will be investigated. By integrating the information obtained in all of these studies, NeuroDevNet will be able to determine the relationship between structural alterations in the brain, subsequent cognitive and behavioural deficits, and genetic and epigenetic traits in children with FASD.

In addition to supporting research in brain development, NeuroDevNet is committed to cultivating the next generation of researchers in paediatric brain development, and to translating new knowledge into improved diagnosis, treatments and interventions from healthcare delivery to public policy. All of these objectives comprise the ultimate goal, namely, to insure healthier brains in the youngest members of Canadian society.

For more information, visit NeuroDevNet's website: http://www.neurodevnet.ca

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Times Colonist. Published Online 17th April 2010
By Mary Agnes Welch, Winnipeg Free Press

B. IDENTIFYING YOUNG CRIMINALS WITH FETAL-ALCOHOL SYNDROME WORTH THE COST, JUDGE SAYS

VANCOUVER — More than 300 young criminals are waiting to get diagnosed and treated for alcohol-related birth defects through a crime-fighting program in Manitoba courts.

In the last five years, the FASD Youth Justice Program has diagnosed about 72 kids with fetal alcohol spectrum disorder. But judges, lawyers, probation officers and other court officials have referred about five times that many kids to the program, which screens repeat offenders, sends them to doctors for an official diagnosis and helps tailor a sentence that might help a young person with a brain injury stay out of trouble.
It’s a unique program that helps the courts deal with kids whose brains are simply not hardwired to learn from traditional punishments like jail and probation, justice officials told a national FASD conference here this week.

“We’re very good at the sausage-factory justice, the Kentucky Fried justice, the millions and millions served,” said Manitoba provincial court Judge Mary Kate Harvie. “But if you take the time to do it properly, it’s worth the investment.”

The problem is that the youth justice program can only refer two kids a month to doctors at the FASD clinic at Winnipeg’s Health Sciences Centre to get an official diagnosis that counts as evidence in court. If resources were available, justice staff say they could send five times that many kids with suspected FASD to the clinic per month.

The youth justice program, now five years old, has flown largely under the radar in Manitoba despite constant public outcry about chronic car thieves and young offenders.

Everyone from defence lawyers to judges to probation officers can refer a youth to the program, where a team of co-ordinators do an initial screen and do some detective work, checking out old case files and even tracking down biological mothers to ask if they drank during pregnancy.

Program co-ordinator Dan Neault said, when he started his job, he had to go out for a cigarette before getting up the nerve to call mothers and pose such a tough question. But he found mothers remarkably willing to admit they’d been drinking, partly because they were so desperate to get help for their out-of-control teen.

“They were never picked up in the school system, they were never picked up in the child welfare system, they weren’t picked up anywhere,” said Neault.

More than 90 per cent of the kids diagnosed with FASD have IQs in the low to “mentally deficient” range, raising questions about how effective punitive jail-time is in deterring crime when young people might not have the mental capacity to understand the nature of what they’ve done.

Once kids get a diagnosis, that sparks a shift in sentencing and followup. Probation officers can tailor how they communicate all the arcane rules of probation, staff at group homes and the youth centre can offer more proactive supervision and the youth can get access to services and programs meant especially for people with FASD.

Link to the Article,

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C. FASD: NUMBERS CRUNCH ON DISEASE'S COST - AFFECTED KIDS NEED FUNDING TRIPLE THAT OF GENERAL POPULATION: STUDY

Regina woman displays message at recent awareness day. Vancouver conference is hearing about FASD’s economic toll.

VANCOUVER -- Children with fetal alcohol spectrum disorder require three times as much funding for health care and education as kids from the general population, a new Manitoba report shows.

The study, released Thursday at the Fourth National Biennial Conference on Adolescents and Adults with Fetal Alcohol Spectrum Disorder in Vancouver, is the first of its kind in Canada. It looked at hospitalization rates, doctor visits, prescription-drug use, education costs and child care costs of kids with FASD both in and outside the child welfare system, and kids without an FASD diagnosis but whose parents have alcohol-abuse problems, and compared those results to the general population of kids in Manitoba.

Findings show kids with FASD or children whose parents have alcohol-abuse problems are far more likely to see a doctor, end up in the hospital and be prescribed medications than kids from the general population, and that the costs associated with those things are far higher for kids with FASD.

It also found nearly half of all children in care with FASD need special education support in school.

Study co-author Don Fuchs, a social work professor at the University of Manitoba, said this study, along with an earlier report showing the high costs of FASD to the child welfare system, are ample proof of the need to prevent more kids from being born with this fully preventable but incurable disease.

"Our model clearly shows because FASD is preventable, it would make sense to move more money into prevention," Fuchs said while presenting the findings at the conference Thursday. Shelagh Marchenski, a research associate in the faculty of social work at the U of M, said the findings show not only do children with FASD use health-care services more often, it costs more per visit when they do. For example, of 1,360 kids who either had FASD or had parents with alcohol problems, the total cost in 2006 of doctor visits, hospital visits and prescription drugs was $1.4 million. That compares to just under $2 million for 4,964 kids studied in the general population. "What that means is 22 per cent of the children incurred 41 per cent of the costs," said Marchenski.

One of the prime drivers of those costs are mental illnesses, which account for a far greater number of doctor visits and hospitalizations for FASD kids than for the general population. In 2006, 31 per cent of kids with FASD in care and 23 per cent of kids with FASD but not in care, saw a doctor for a mental illness compared to 4.6 per cent of kids from the general population. As well, 14.3 per cent of the hospitalizations of kids with FASD were the result of a mental illness, compared to 2.9 per cent for the general population.
Kids with FASD are also far more likely to require psychiatric drugs. More than one in three kids with FASD were prescribed an antipsychotic medication in 2006, compared to fewer than one in 10 kids from the general population.

The education system is also heavily affected by FASD, with half of all kids in care with FASD needing additional supports in school, compared to just 2.9 per cent of the general population of kids.

**FASD Facts**
What is FASD? FASD stands for fetal alcohol spectrum disorder, an umbrella term used to describe a number of physical and neurological conditions affecting people whose mothers drank while pregnant. They include physical, mental, behavioural and learning disabilities. The conditions are incurable, though people with FASD can fare well with specific services and supports. FASD is, however, preventable.

Average total health-care total cost per child:  
Kids in care with FASD: $1,403  
General population: $403

Education, average total cost per child:  
Kids in care with FASD: $7,343  
General population: $2,177

Average number of doctor visits per year, average cost per visit:  
Kids in care with FASD: 4.4, $364  
General population: 3.0, $208

Percentage of kids who saw a doctor for a mental illness:  
Kids in care with FASD: 30.9%  
General population: 4.6 per cent

Percentage of kids who spent time in the hospital, average cost per hospital visit:  
Kids in care with FASD: 9.0 per cent, $5,804  
General population: 4.7%, $3,497

Percentage of kids who were hospitalized with a mental illness:  
Kids in care with FASD: 14.3%  
General population: 2.9%

Average number of prescriptions issued to kids:  
Kids in care with FASD: 12.1  
General population: 2.4

-- As Conservative estimates say about one in 100 people have FASD and Canada's population is about 33 million, about 330,000 Canadians likely have FASD.

Source: The Economic Impact of Children in Care with FASD and Parental Alcohol Issues, 2009; Dr. Sterling Clarren, FASD researcher.

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D. MOTOR-SKILL ACTIVITIES HOLD PROMISE OF REWIRING CHILDREN'S DAMAGED BRAINS

The six-year-old boy plays the game Operation, skillfully wielding a pair of tweezers in a school gym that doubles as a research lab. His brain has been damaged by the alcohol his mother drank when he was in the womb, but he's adept at extracting tiny plastic bones.

“When it gets too easy we will have him switch to his left hand,” says Chris Bertram, a scientist at the University of the Fraser Valley in Abbotsford, B.C., who is investigating whether children with a fetal alcohol spectrum disorder, or FASD, can rewire their brains by improving their strongest motor skills. Advances in understanding neuroplasticity, or how experience can change the brain, have led to therapies that have helped people who have suffered strokes or traumatic brain injuries learn to speak again or move paralyzed limbs. Now, a growing number of scientists hope the revolution can help children whose brains were damaged by alcohol before they were born.

They are testing different approaches – including computer games and other specialized training – in hopes of helping kids with FASD strengthen connections in their brains and boost their cognitive skills.

Dr. Bertram and his colleagues have assessed all eight kids with FASD who are hard at play at various stations in the gymnasium. All are good at something, perhaps the fine motor skills needed to pluck a rib out of a cartoonish chest or the co-ordination needed for the interactive videogame Dance Dance Revolution.

But they have a wide variety of cognitive and emotional problems that include trouble paying attention, remembering what they have learned, anticipating the consequences of their actions and controlling their impulses. Hyperactivity is common; they can be challenging to manage at
home and at school. Dr. Bertram's hypothesis is that the eight-week program will do more than just improve their rope climbing and free-throw shooting.

The idea is that improving one area of brain function, in this case motor skills, will also boost their ability to pay attention and to regulate their impulses. He is still analyzing the data from the 35 kids who have been through the program, but the preliminary results have been encouraging, he says.

“We call it transfer of learning, or transfer of performance,” Dr. Bertram says.

Alcohol damages many parts of the developing brain, says Christian Beaulieu, a brain imaging expert at the University of Alberta. It can affect areas and structures critical for memory, learning and abstract thinking. He and his colleagues have shown it also damages white matter, the connections that allow parts of the brain to communicate and work together.

But recent experiments with laboratory animals offer hope. At the University of Victoria, Brian Christie has been able to reverse the brain damage caused by fetal alcohol exposure in rats by getting them to exercise.

No one expects it will be so easy in humans.

“The rat brain doesn't have the same complexities,” says Dr. Christie, a member of B.C's Brain Research Centre.

Dr. Bertram says that many of the current therapies or interventions being used with children with FASD focus on their deficits – for example, anger management therapy for a child who is acting out in school or extra time devoted to reading or math for a child struggling in those subjects.

“Traditional intervention programs have these kids doing things their brains are not adept at doing, and their success rates are not great. We flipped things around and said, 'Why don't we build intervention programs based on things they are good at.'”

He and his colleagues build an individual program for each child based on three areas of strength, making it increasingly challenging over the eight weeks. The kids also get to pick a fourth activity they like. The researchers carefully monitor their progress when they come twice a week after school for two hours. He is also monitoring levels of cortisol, a stress hormone, to see if it drops after the eight weeks.

There is growing scientific evidence that children with FASD have a heightened response to stress that can make it difficult for them to cope with situations at home or in the classroom.

At the University of British Columbia, Joanne Weinberg is investigating this phenomenon in laboratory animals and, in particular, how areas of the brain that are important in the stress response system overlap to a large extent with areas of the brain involved in depression, addictions and other mental-health problems, also common among people with FASD.

One day, the work could lead to new drugs that target the stress response system.

Other researchers are studying drugs that improve cognitive function in laboratory animals. In the lab, these drugs help animals remember how to negotiate a maze.
These kinds of drugs will probably become part of future treatments for alcohol-affected children, says Piyadasa Kodituwakku, an expert in FASD at the University of New Mexico.

But he cautions not to expect too much. A reasonable goal, he says, is to reduce or eliminate some of the problems that can come with FASD, including dropping out, drug and alcohol abuse, troubles with the law or mental illness.

Sterling Clarren, a UBC researcher who is CEO of the Canada Northwest FASD Research Network, says an ambitious project, recently funded by the federal government, should yield important new information about the brains of people with FASD.

NeuroDevNet, a new national centre of excellence, will get $19.5-million over five years and will focus on FASD and two other disorders. Researchers will combine brain imaging and genetic studies to explore what goes wrong in brain development, and perhaps, how it can be fixed.

Few people understand the challenges of FASD better than Jan Lutke. She and her husband, who died two years ago, adopted 15 children with the diagnosis. They are now adults – the oldest is 46 – and seven still live with her in Surrey, B.C., because they can't cope on their own.

The range of difficulties is astronomical, she says, and no two people have the same constellation of symptoms. One of her daughters enjoys reading Shakespeare but can't tell time or make change from a dollar. Some people with FASD don't feel pain. Others are hypersensitive to it. But they do have many common problems, including difficulties with abstract thinking and memory.

One daughter had been setting the table for a long time, but one night she couldn't remember what to do with the knives. As adults, they need programs tailored to their handicap, she says, and support so they don't end up on the streets or in jail.

She says she doesn't delude herself that there will be a quick fix or miracle therapy for people with FASD. But she can't help hoping that the work, now in its early stages, will lead to progress.

"I would like to think that if the best minds could put themselves together with a lot of money, and real energy to do it, I believe we can find things that work."

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The impetus of the program will be to improve transition into adulthood. The new program will focus on teaching important life skills, such as how to cope with new situations and minimize disruptive behaviors that could lead to loss of employment or trouble with the law.

According to Leigh Tenkku, Ph.D., assistant professor of family and community medicine at Saint Louis University, while the effects of FASD are lifelong, currently there are very few support systems in place to help these individuals and their families as they get older.

“The brains of individuals with FASD are not fully developed, which affects their ability to handle emotions, problem solve and pick up on social cues,” Tenkku said.

“As they get older, these problems affect their ability to maintain a job, their relationships and their parenting abilities.”

The new program, called Partners for Success, combines personal mentors and therapeutic home visits to provide one-on-one support similar to the popular Parents as Teachers model, only intensified. The goal of the program is to give individuals with FASD the tools and support necessary to successfully navigate the challenges of adulthood.

“This is a totally new approach to mentoring older children and adults with FASD, but it’s built on well-established research in the field. This program is very promising and we’re hopeful that it will revolutionize the way we support these individuals,” Tenkku said.

Currently in the U.S., there are no social service programs geared to the specific needs of youth and young adults with FASD. Instead, social agencies offer a hodgepodge of programs that address the broader needs of those with developmental disabilities.

In a time of budget cuts and tightening financial belts, Tenkku says one of the most important aspects of the program is that it is financially feasible and easy for other agencies to implement.

“We want our program to be practical and easily replicated by other agencies that provide FASD services. We’re creating the tool, but they have to be able to use it. That’s how we’ll help the greatest number of people,” Tenkku said.

“The overall cost of the program is relatively low. The Partner for Success program is an investment in the future of these individuals. Doing nothing would certainly cost us more in the long run.”

About Fetal Alcohol Spectrum Disorder

Drinking during pregnancy can lead to serious physical abnormalities, neurological and behavioral problems, all characteristics of fetal alcohol spectrum disorders. FASD is the greatest cause of children born with developmental disabilities each year in America even though it is 100 percent preventable.

Fetal alcohol syndrome is the most severe form of FASD. Babies born with fetal alcohol syndrome, which is estimated to affect one to two babies born per 1,000, are often born preterm, have low birth weight and long-term growth problems.

During the first year of the Partners for Success study, researchers at Saint Louis University will collaborate with several community partners, including the Family Support Network, to design the program.
At the same time, they will recruit 100 youth and young adults with FASD to participate in the study.

The program will be implemented during the second year. Half of the study participants will be enrolled in the new program, while the other half will continue to receive standard support services.

Participants enrolled in the program will receive biweekly home visits from a licensed clinical social worker. They also will be assigned a mentor who will meet with them weekly to socialize, model appropriate behavior in the community, and help the individuals integrate the techniques taught during home visits, in their daily lives.

During the final year of the study, researchers will follow up with participants to measure the success of the program.

“Of course ultimately we’d like to prevent FASD from occurring. But the sad reality is that 1 percent of children and young adults in our society suffer with the lifelong effects of drinking during pregnancy. It’s imperative that we find better ways to support these individuals,” Tenkku said.

F. CAN PRENATAL SCREENING FOR FETAL ALCOHOL SPECTRUM DISORDER BE JUSTIFIED? A COMMENTARY

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ABSTRACT
Fetal alcohol spectrum disorder (FASD) is the leading cause of non-genetic mental retardation in the USA, possibly exceeding even Down syndrome, which is currently approaching 1 in 500 live births. Alcohol consumption during pregnancy results in brain, craniofacial and heart defects, neurotoxicity, and immune dysfunction. The preferred action taken to prevent alcohol consumption during pregnancy is abstinence. However, the detection, diagnosis, and treatment of FASD remain a major public health need in this country and throughout the world. The biochemical molecules involved in the developmental abnormalities encompass a vast array of signal transduction and synaptic pathways which involve neurotransmitters and neurotrophic peptides. Recent advances in medicine-based therapies for FASD have been reported, and include the use of small molecule agonists, antagonists, and competitive inhibitors. Since biomarkers for FASD have previously been identified in clinical research reports, multicenter screening feasibility studies now seem warranted and could be initiated following adequate funding, protocols, procedures, and institutional review board approvals.


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PROFILE OF THE FIRST 1,400 PATIENTS RECEIVING DIAGNOSTIC EVALUATIONS FOR FETAL ALCOHOL SPECTRUM DISORDER AT THE WASHINGTON STATE FETAL ALCOHOL SYNDROME DIAGNOSTIC & PREVENTION NETWORK

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ABSTRACT

Background
An interdisciplinary approach to fetal alcohol spectrum disorder (FASD) diagnosis using rigorously defined diagnostic guidelines has been adopted as best practice. Diagnostic clinics are being established worldwide. If these clinics are to successfully compete for limited health care dollars, it is essential to document their value.

Objective
The primary objectives were to document the value of the largest and longest standing interdisciplinary FASD diagnostic program; the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FAS DPN). Now in its 17th year of operation, the WA FAS DPN is a statewide network of diagnostic clinics all using the 4-Digit Diagnostic Code and contributing to a centralized electronic database.

Methods
The clinical database was used to generate comprehensive profiles of all patients evaluated for FASD from 1993-2005. These profiles were used to answer a multitude of clinical, research, and public health questions including: What is the demand for FASD diagnostic services, who is referred to the clinics, and what are their FASD diagnostic outcomes? Can FAS/D prevalence estimates from this clinical population be used to estimate FAS/D prevalence estimates in the general population? Do FASD diagnostic outcomes vary by race, age or alcohol exposure? Does the presence of other adverse exposures/events lead to more severe outcomes? Does this approach to diagnosis meet the needs of families?

Results
Demand for diagnosis remains very high. Of 1,400 patients (newborn to adult) with confirmed prenatal alcohol exposure, 11% were diagnosed with FAS/PFAS, 28% with static encephalopathy, 52% with neurobehavioral disorder, and 9% with no evidence of CNS abnormality. FASD outcomes varied significantly by age, race, gender, alcohol exposure, and presence of other risk factors. Families reported high satisfaction with the diagnostic process, and receipt of information/services they were unable to obtain elsewhere.

Conclusions
This report documents the immense contribution of a statewide FASD diagnostic program, and underscores the extraordinary value of a comprehensive FASD clinical dataset.

Key Words: Fetal Alcohol Spectrum Disorders (FASD), FASD 4-Digit Diagnostic Code

The Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FAS DPN) is a network of statewide, fetal alcohol spectrum disorder (FASD) diagnostic clinics linked by the core clinical/research/training clinic located at the Center on Human Development and Disability at the University of Washington (UW) in Seattle.
Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

Washington. The FAS DPN began as a single CDC-sponsored clinic at the University of Washington in 1993 in response to a national request for proposals for FASD prevention. The philosophy behind the UW proposal was...If you build a clinical diagnostic program that meets the needs of the families raising children with FASD, they would seek out the services of the clinic. In so doing, each time you identified (diagnosed) a child with FAS/D, you had an opportunity to identify and potentially intervene with a woman at high risk for bearing subsequent children with FAS/D (the child’s birth mother). The results of that FASD primary prevention effort are presented in Astley et al.\textsuperscript{1,2} When the UW FAS DPN clinic first opened in 1993, it was the first to introduce an interdisciplinary approach to FASD diagnosis.\textsuperscript{3} The interdisciplinary team included a medical doctor, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, and a family advocate. A gestalt\textsuperscript{4} approach to FASD diagnosis was initially used, reflecting the most current guidelines available at the time. This gestalt approach was replaced in 1995 by a more rigorous, case-defined FASD diagnostic system (the FASD 4-Digit Diagnostic Code\textsuperscript{5-8}) developed by the UW FAS DPN. The 4-Digit Code was formally released to the public in 1997, with updates in 1999 and 2004. During the first two years of operation, the single UW FASDPN clinic was overwhelmed by demand for FASD diagnostic services, far exceeding its capacity. In 1995, the Washington Chapter of the National March of Dimes provided funding to establish two satellite FASD clinics in two large cities just north (Everett) and south (Federal Way) of Seattle. In 1995, the state legislature through Senate Bill SB5688 mandated further expansion of the program to six satellite clinics (located in Everett, Federal Way, Tacoma, Yakima, Pullman, and Spokane) linked by the core UW clinic in Seattle, establishing the WA FAS DPN.\textsuperscript{9} The WA FAS DPN is now in its 17\textsuperscript{th} year of funding support from the state.

The mission of the WA FAS DPN is FASD prevention through FASD screening, diagnosis, intervention, research, and training. To this end, the WA FAS DPN has created a myriad of diagnostic tools, training programs, and screening programs (FASD 4-Digit Diagnostic Code and Lip-Philtrum Guides\textsuperscript{5-8} (1997,1999,2004), FASD 4-Digit Diagnostic Code Online Training Course\textsuperscript{15} (2004)), all of which are available to clinical professionals free or at cost to maximize access. Over the decades, this interdisciplinary approach to FASD diagnosis using the FASD 4-Digit Code has been adopted worldwide.

The core mission of the FAS DPN has always been the advancement of the field through translational research (the rapid translation of clinical research into practice). The foundation of translational research is data management. From the FAS DPN’s first day of operation in 1993, all data from the diagnostic clinics have been methodically collected and entered into an electronic clinical/research database with patient consent and Human Subjects Review Board approval. Over the years, this dataset has grown to over 8,000 cases, each with up to 2,000 fields of information, providing a comprehensive documentation of statewide demand for FASD evaluations and extensive detail on the antecedents and outcomes of these evaluations. This dataset supported the development of the diagnostic tools, screening programs, and training programs listed above, and serves as one of the largest research registries of individuals with FASD (n = 2,000) for enrollment into research studies that directly benefit individuals with FASD and their families.\textsuperscript{16-25}

Over the years, the clinical field of FASD has come to adopt, as best practice, an interdisciplinary approach to FASD diagnosis using more rigorous, case-defined diagnostic guidelines.\textsuperscript{6,7,26,27} Interdisciplinary FASD diagnostic clinics are being established worldwide. If these clinics are to successfully compete for limited health care dollars, it is essential to document their value. To demonstrate the extraordinary and unique value of a statewide interdisciplinary FASD diagnostic clinical program (and the essential role of data collection), the outcomes of the first 13 years of operation of the WA FAS DPN are presented below. The primary objectives of this study were to:

1. Construct a comprehensive profile (based on factors A-K below) of all 1,400 Washington State residents who obtained an FASD diagnostic evaluation at one of seven
Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

WA FAS DPN clinics between 1993 and 2005.
2. Divide the clinical population into four FASD diagnostic subgroups (ranging from no adverse outcomes to severe adverse outcomes), construct a comprehensive profile of each subgroup (based on factors A-K below), and identify risk and protective factors that differentiate the four groups.

Factors
A. Sociodemographics
B. Birth mother and birth father characteristics
C. Growth
D. FAS facial features
E. CNS structural, neurological, and functional outcomes
F. Patient’s behavioral profile: Summary of Caregiver Interview and Child Behavior Check List
G. Prenatal alcohol exposure
H. Other prenatal and postnatal risk factors
I. Prevalence of other syndromes
J. Prevalence of mental health disorders
K. Patient satisfaction with the FASD diagnostic process and access to intervention services.

Primary objectives 1 and 2 allow a multitude of clinical, research, and public health questions to be addressed. For example, if a statewide FASD diagnostic program is built, what is the demand for services, who is referred to the clinics, and what are their FASD diagnostic outcomes? Are there individuals with prenatal alcohol exposure who present with no evidence of adverse outcome? Can FAS/D prevalence estimates from the clinical population be used to estimate FAS/D prevalence estimates in the general population? Do FASD diagnostic outcomes vary by race, age, or level of prenatal alcohol exposure? What is the prevalence of mental health disorders and other syndromes in this patient population? Does the presence of other adverse exposures/events (e.g., prenatal exposure to illicit drugs, poor prenatal care, multiple home placements, physical/sexual abuse) lead to more severe dysfunction? Growth deficiency has always been a hallmark of FAS/D. How prevalent is growth deficiency in this patient population? The FASD literature suggests that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children? Is this true? Should a diagnosis of FAS be rendered in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the presence of CNS dysfunction (intelligence, executive function, memory, language)? Does the presence of the full FAS facial phenotype increase the correlation between microcephaly and brain dysfunction? Who are the birth mothers and birth fathers of these children? What proportion of these patients are still in the care of their birth parents? How satisfied are patients with the services provided by the clinics? Are they provided information/services they were unable to obtain elsewhere? These questions and many more are answered in this report.

METHODS

The Washington State FAS DPN electronic clinical/research database was utilized to construct a comprehensive profile of all 1,400 Washington State residents (birth through adult) who received an interdisciplinary FASD diagnostic evaluation using the FASD 4-Digit Diagnostic Code at one of the seven WA FAS DPN clinics in the first 13 years (1993-2005) of operation. The protocol was approved by the University of Washington Human Subjects Review Board.

Interdisciplinary FASD Diagnostic Model.
All WA FAS DPN clinics use the same interdisciplinary approach to FASD diagnosis using the FASD 4-Digit Diagnostic Code.6,7 Interdisciplinary Model. The WA FAS DPN interdisciplinary teams include a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker and a family advocate. The patient population served by the WA FAS DPN has expressed strong preference for an evaluation that can be completed in one visit. Thus, a diagnostic evaluation is conducted in one 4-hour session. In preparation for the evaluation, the patient’s birth, medical, school, psychological, and social service records are collected by the clinic coordinator and pre-reviewed by the lead psychologist. On the day of the evaluation, the lead psychologist presents the patient’s case history, including the outcomes of
any prior medical/psychological assessments, to the team in a 30-minute case conference. While the case-conference is being conducted, the patient’s growth is measured and facial photograph is taken for computerized analysis.10 After the case-conference, the pediatrician and lead psychologist conduct an interview with the caregiver(s) while the child is assessed over a 2-hour period by the second psychologist, speech-language pathologist, and occupational therapist. The child receives a brief physical examination by the pediatrician at the end of their 2-hour assessment. The caregiver interview and child assessment sessions focus on gathering information that is needed for diagnosis and not already present in the child’s records. The battery of assessments administered to each patient (both historically and on the day of the diagnostic evaluation) vary by patient age and area of developmental concern. The team reconvenes for 1 hour to derive the FASD 4-Digit Code and generate an intervention plan. The diagnosis and intervention plan are shared with the family in the final 30 minutes of the evaluation. A single comprehensive medical summary documenting the diagnostic outcome, all data used to derive the diagnostic outcome, and intervention recommendations are submitted to the patient’s medical record.

**The FASD 4-Digit Code.** The 4-Digit Code was developed by the UW FAS DPN in 1997 with the most recent 3rd edition published in 2004.5-8,23 Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1. Growth deficiency, 2. FAS facial phenotype, 3. CNS structural/functional abnormalities, and 4. Prenatal alcohol exposure (Figure 1). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong “classic” presence of the FASD feature. Each Likert rank is specifically case defined. There are 256 possible 4-Digit Diagnostic Codes, ranging from 1111 to 4444. Each 4-Digit Diagnostic Code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall broadly under the designation of FASD (A. FAS/Alcohol Exposed, B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E-F. Static Encephalopathy/Alcohol Exposed, and G-H. Neurobehavioral Disorder/Alcohol Exposed).

**FIG. 1A** FASD 4-Digit Diagnostic Code grid. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage/dysfunction, and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on 4-point, case-defined, Likert scales. The 4-Digit Code (3444) inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS. B) FASD 4-Digit Code FAS facial phenotype (view image). The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the norm; (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), an (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the full Rank 4 FAS facial phenotype for Caucasian, Native American, African American, and Asian American children are shown.
Patient Referral Criteria and Diagnostic Capacity
The only criteria required for a patient to be seen in a WA FAS DPN clinic is a confirmed prenatal alcohol exposure history, at any level. The presence of the full FAS facial phenotype (4-Digit Face Rank 4) can be used in lieu of a confirmed alcohol history, since the Rank 4 facial phenotype, as defined by the 4-Digit Code is so specific to prenatal alcohol exposure.11,12,14 The UW FAS DPN clinic provides evaluations to patients of all ages (newborn to adult). The other statewide FAS DPN clinics focus their services on pediatric populations. The diagnostic capacity of the WA FAS DPN has fluctuated over the years. Current funding levels support 130 evaluations per year: 80 at the UW FAS DPN and 50 at the four statewide FAS DPN clinics.

WA FAS DPN Electronic Clinical/Research Database
All data collected by the WA FAS DPN clinics since 1993 has been entered into an electronic clinical/research database with patient consent and Human Subjects Review Board approval. The majority of the data entered into the database come from two standardized data collection forms: 1) the New Patient Information Form, and 2) the FASD Diagnostic Form. These forms are provided in the Diagnostic Guide for FASD6 and are posted on the FAS DPN website (www.fasdpn.org). The New Patient Information Form is completed by all families requesting an FASD diagnostic evaluation in a WA FAS DPN clinic. The form provides the clinic with key information regarding the patient’s sociodemographics, growth, and development, lifetime prenatal and postnatal adverse exposures and events, including prenatal alcohol exposure, and social, educational, medical, psychological, psychiatric, and family history. The FASD Diagnostic Form is designed to capture all information required to derive and support the FASD 4-Digit Diagnostic Code (growth, facial features, CNS structural, neurological, functional measures, prenatal alcohol exposure, all other adverse prenatal and postnatal exposures, events, and conditions including all other physical anomalies and/or syndromes). The FASD Diagnostic Form is completed by the interdisciplinary team at the time of the FASD diagnostic evaluation. Data entered into the FASD Diagnostic Form include all data collected at the time of the FASD diagnostic evaluation as well as all information collected from previous records in preparation for the diagnostic evaluation (birth, medical, school, psychological, psychiatric, social service, placement, and legal records). All data collection forms are reviewed and prepared for data entry into an ACCESS28 electronic database by SJA. Data is exported from ACCESS to SPSS29 for statistical analysis. All 4-Digit Codes were upgraded to the most current 2004 version of the FASD 4-Digit Code.6

Study Population.
The following inclusion/exclusion criteria were applied to the WA FAS DPN database to establish the study population for this report.

Inclusion Criteria:
1. Received an FASD diagnostic evaluation at one of the seven WA FAS DPN clinics between 1993 and 2005.
2. Was a resident of Washington State at the time of their FASD diagnostic evaluation.
3. Had confirmed prenatal alcohol exposure, at any level. May have an unknown prenatal alcohol exposure history only if their FASD 4-Digit Code diagnostic outcome was full FAS (the Rank 4 FAS facial phenotype is so specific to prenatal alcohol exposure, it can be used in lieu of a prenatal alcohol exposure.11,12,14,23)
4. Male or female, all ages, all races/ethnicities.

Exclusion Criteria:
1. None.

A total of 1,400 patients met the inclusion/exclusion criteria for this study. Patients evaluated in the WA FAS DPN after 2005 were not included in this study because their data are still in various phases of data entry, monitoring, and cleaning.

Study Groups
The study population was divided into four FASD diagnostic subgroups defined below. A recently completed FASD magnetic resonance study, conducted on a subset of this clinical population, confirmed these first three groups reflect three clinically meaningful and statistically distinct...
Using the FASD terminology introduced by the Institute of Medicine, the SE/AE group most closely reflects ‘severe Alcohol-Related Neurodevelopmental Disorder (ARND)’ and the ND/AE group most closely reflects ‘mild ARND’. The 4th group (Normal CNS/AE) by definition does not fall fully under the umbrella of FASD. This group represents individuals who have a confirmed prenatal alcohol exposure, but present with no evidence of adverse CNS outcomes. Some, but not all, present with growth deficiency and/or FAS facial features. The very existence of this group confirms that not all individual exposed to prenatal alcohol present with evidence of adverse outcomes. Inclusion of this group in this study presents an opportunity to identify potential ‘protective’ factors against prenatal alcohol exposure. The diagnostic features specific to each group were as follows:

1. **Patients in Group 1** had a 4-Digit diagnosis of FAS or Partial FAS (FAS/PFAS) (e.g., 4-Digit Diagnostic Categories A,B,C: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 2-4) (Figure 1). Alcohol Rank 2 (unknown exposure) could only be present if the patient had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure. In summary, patients in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.

2. **Patients in Group 2** had a 4-Digit diagnosis of Static Encephalopathy / Alcohol Exposed (SE/AE) (e.g., 4-Digit Diagnostic Categories E,F: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4). In summary, patients in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.

3. **Patients in Group 3** had a 4-Digit diagnosis of Neurobehavioral Disorder / Alcohol Exposed (ND/AE) (e.g. 4-Digit Diagnostic Categories G, H: with Growth Ranks 1-4, Face Ranks 1-2, CNS Rank 2, Alcohol Ranks 3-4). In summary, patients in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but in comparison to Groups 1 and 2 had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.

4. **Patients in Group 4** had a 4-Digit diagnosis of Sentinel Physical Findings/Alcohol Exposed or No Physical Findings or CNS Abnormalities Detected / Alcohol Exposed (Normal CNS/AE) (e.g., 4-Digit Diagnostic Categories I and J: with Growth Ranks 1-4, Face Ranks 1-4, CNS Rank 1, and Alcohol Ranks 3-4. In summary, patients in Group 4 had prenatal alcohol exposure, no CNS abnormalities, and may or may not have had growth deficiency and/or FAS facial features.

**Data Analysis**

**Objective 1**: Descriptive statistics (means, SDs, proportions) were used to summarize the sociodemographic and clinical profiles of the clinical population as a whole, and each of the four diagnostic subgroups (1. FAS/PFAS; 2. SE/AE; 3. ND/AE; and 4. Normal CNS/AE). Proportions are expressed as valid column percents in all tables unless otherwise specified.

**Objective 2**: Empirical analyses were conducted to identify risk and protective factors that differentiated the four diagnostic subgroups. Chi-square tests (or Fishers Exact where appropriate) were used to compare proportions between 2 or more subgroups. T-tests were used to compare means between two groups. ANOVA was used to compare means between 3 or more groups. When ANOVA was employed, the overall f-statistic was statistically significant, the Duncan post hoc range test was used to identify which group means differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Means are ordered from highest to lowest, and extreme differences are tested first. The Duncan test sets a protection level for the error rate for the collection of tests. The Duncan test identifies homogeneous subsets of means that are not different from one another. For example, if the outcome of a Duncan test is presented as 1,23,4, this means the mean for groups 2 and 3 were comparable to one another, but significantly higher and lower than the means for groups 1 and 4 respectively. Two-tailed p-values of 0.05 were used throughout the analyses. Due to multiple comparisons, resulting p-values should be interpreted accordingly.
general point of reference (since sample size varied with each analysis), this study had 80% power or greater to detect the following effect sizes (at a two-tailed alpha level of 0.05) when a study group had 65 or more subjects: 1) A difference in means one-half the standard deviation of the mean difference; 2) A 24-point or greater difference in proportions between two groups.

RESULTS

Demand for FASD Diagnostic Services and Ability to Meet the Demand

Although the WA FAS DPN provides FASD diagnostic evaluations to patients from all over the U.S., the vast majority (95%) reside in WA State. Demand for FASD diagnostic services has always exceeded the FAS DPN’s capacity, but expansion from the single clinic to a statewide network of clinics doubled its capacity and increased access to FASD diagnostic services. The WA FAS DPN’s current capacity is 130 diagnostic evaluations per year. A total of 6,586 families from WA State requested an FASD diagnostic evaluation between 1993 and 2005; on average 506 per year. Patients request an appointment by sending their name and address to the clinic via voicemail or email. All patients requesting an appointment are sent an information packet that includes a description of the clinical services and a New Patient Information Form (NPIF). Patients are requested to complete the NPIF and submit it to the clinic for review. The NPIF documents why a diagnostic evaluation is being requested, what the developmental concerns are, if any, and whether the patient has a confirmed prenatal alcohol exposure. Of the 6,586 requests, 3,004 (47%) completed and submitted the NPIF. In a survey conducted in the mid 1990’s, the primary reason stated for not submitting the NPIF was lack of a confirmed prenatal alcohol exposure. Oftentimes, families are requesting evaluations because they are concerned about their child’s development, have confirmation of maternal illicit drug use during pregnancy and therefore suspect prenatal alcohol exposure. Exclusion of the 2,462 patients with unknown alcohol exposure produced the sample of 1,400 patients summarized in this report.

FASD Diagnostic Outcomes (Table 1)

Of the 1,400 residents of WA state evaluated in the WA FAS DPN in the first 13 years of operation, 4% were diagnosed with FAS, 7% had PFAS, 28% had Static Encephalopathy (without the FAS facial phenotype), 52% had Neurobehavioral Disorder, 2% presented with growth deficiency and/or FAS facial features, but no evidence of CNS abnormalities, and 7% presented with no growth deficiency, no FAS facial features, and no evidence of CNS structural, neurological, or functional abnormalities, despite their prenatal alcohol exposure. The core clinic at the University of Washington provided diagnostic evaluations for 930 (66%) of the 1,400 patients. The remaining 470 were evaluated at one of the six other FAS DPN statewide clinics. The distribution of FASD diagnoses rendered by the core UW FAS DPN clinic was comparable to the distribution of FASD diagnoses rendered by the six other statewide FAS DPN clinics.

Sociodemographic Profile (Table 2)

Although patients of all races and ethnicities were evaluated in the FAS DPN clinics, the racial distribution of the clinical population was significantly different from the racial distribution of the state ($\chi^2 = 100$, $p < 0.000$). The WA State 2000 census reported the following distribution of single races: White 82%, American Indian/Native
Alaskan 2%, Black 3%, Asian 6%). By comparison, Caucasians (48.9%) and Asians (0%) were under-represented in the clinical population and Black (6.6%) and American Indian/Native Alaskan (8.2%) groups were over-represented. Males were significantly more prevalent (58%) than females (42%) (chi^2 18, p< 0.000). The vast majority of the population (90%) was under 16 years of age with a mean age of 9.9 years (6.2 SD) and an age range of 7 days old to 50.8 years old. Only 22% percent of the patients were accompanied to clinic by their birth mother. The vast majority (70.5%) were not residing with their birth mother or birth father at the time of their diagnostic evaluation.

**Contrasts between FASD Diagnostic Subgroups**

Factors A-K below are compared and contrasted between the four clinical subgroups (1. FAS/PFAS, 2. SE/AE, 3. ND/AE, and 4. Normal CNS/AE).

**Factors**

A. Sociodemographics (Table 2)
B. Birth mother and birth father characteristics (Table 3)
C. Growth (Table 4)
D. FAS facial features (Table 4)
E. CNS structural, neurological, and functional outcomes (Tables 5 and 6)
F. Patient’s behavioral profile: Summary of Caregiver Interview and Child Behavior Check List (Tables 7 and 8, Figures 2 and 3)
G. Prenatal alcohol exposure (Table 9)
H. Other prenatal and postnatal risk factors (Table 10)
I. Prevalence of other syndromes (Table 10)
J. Prevalence of mental health disorders (Table 11)
K. Patient satisfaction with the FASD diagnostic process and access to intervention services. (Table 12)

Use of the FASD 4-Digit Code by seven statewide, interdisciplinary teams, over a period of 13 years, produced three clinically and statistically distinct FASD clinical subgroups. The three subgroups (ND/AE, SE/AE and FAS/PFAS) reflected a linear continuum of increasing neuropsychological impairment and physical abnormality, representing the full continuum of FASD.

**DISCUSSION**

An infinite array of clinical, research, and public health questions can be addressed using the WA FAS DPN clinical dataset. The answers to a selection of questions are presented and discussed below to document the immense value and contribution of a statewide FASD diagnostic program, and underscore the extraordinary value of a comprehensive FASD clinical dataset.

1. **Does the prevalence and distribution of the FASD diagnostic outcomes observed in this statewide clinical population reflect the prevalence and distribution one would expect to observe in the statewide general population?**

No. The prevalence of FASD will be higher in this clinical population than in the general population for two reasons: 1) all individuals in this clinical population have a prenatal alcohol exposure, and 2) individuals experiencing difficulties are more likely to be referred to a clinic than those not experiencing difficulties. How much higher will the prevalence be? Below are some FASD prevalence estimates from other population samples (and their corresponding alcohol-exposure estimates) to compare to our clinical sample. The prevalence of FAS in our statewide clinical population was 4.2%. One hundred percent had a confirmed prenatal alcohol exposure. The prevalence of FAS in the King County subset of our statewide clinical population (were Seattle and the University of Washington are located) was 4.7%. Again, 100% had a confirmed prenatal alcohol exposure. In comparison, the prevalence of FAS in a foster care population residing in King County (as documented by a 10-year, active case-ascertainment FAS screening program) was 1.5%. Fifteen percent of this foster care population had a documented prenatal alcohol exposure in their foster records. Forty-eight percent had a confirmed prenatal alcohol exposure. Thus the true prevalence of prenatal alcohol exposure in this foster population was likely somewhere between 15% and 48%. The FAS prevalence estimates from these clinical and high-risk foster populations are 15 to 47 times greater than the FAS prevalence estimate often cited for the general U.S. population (0.1 – 0.3%).

National surveys of the general population
estimate 12% of women report drinking during pregnancy. If one plots the prevalence of FAS to the prevalence of alcohol exposure across these three populations (clinical, foster care, and general), an interesting trend appears (Figure 4).

FIG. 4 Prevalence of FAS and prevalence of maternal alcohol use during pregnancy in three populations: ♦General U.S. population (FAS = 0.2%, alcohol use = 12.2%). ●King County WA foster care population (FAS = 1%, alcohol use = 15% to 48%). ■King County WA FAS Diagnostic & Prevention Network (FAS DPN) clinical population (FAS = 4.7%, alcohol use = 100%). Best fit linear trend line: $y = 18.989x + 12.352$; R-squared = 0.89. FAS: fetal alcohol syndrome.

Another related question that is often raised is: How much more prevalent is “ARND” than FAS? The prevalence of SE/AE and ND/AE combined (what other diagnostic systems refer to as ARND) was 7.2-fold greater than the prevalence of FAS/PFAS in our clinical population. Does this mean there are 7 times more individuals with ARND than FAS in the general population? The true ratio is likely higher for the following reason. Since individuals with severe outcomes are more likely to be referred to a clinic than individuals with less severe outcomes, diagnostic subgroups with the most severe outcomes will likely be disproportionately over-represented in a clinical population. Thus, if FAS is more severe than SE/AE, the prevalence of SE/AE to FAS would likely be higher in the general population than was observed in this clinical population. The published literature suggests ARND is as least three times more prevalent than FAS. Unfortunately, the published literature does not specifically case-define ARND or FAS, so it is difficult to know which of our clinical subgroups to compare them to. The ratio of ARND to FAS, generated from our clinical population, ranges from a low of 2.6-fold (if ARND is defined as SE/AE+ND/AE and FAS is defined as FAS+PFAS) to a high of 18.9-fold (if ARND is defined as SE/AE + ND/AE and FAS is defined as FAS). No matter how one chooses to define ARND and FAS, our clinical data strongly suggest “ARND” is at least 3-fold greater than FAS, but likely much higher. In summary, prevalence estimates derived from clinical populations will exceed those of the general population, but clinical estimates can play an important role in formulating estimates for the general population. An FASD diagnostic clinic is a form of passive population-based FASD screening. The individuals referred are the subset of the general population who were identified by community professionals as at-risk and in need of diagnostic and intervention services.
2. Did the prevalence estimates for FAS/PFAS, SE/AE, and ND/AE vary by race? Yes (Table 13). And these variations were correlated with racial variations in drinking patterns during pregnancy. The prevalence of FAS/PFAS was significantly higher among Caucasians (12.7%) and Blacks (18.5%) than among American/Alaskan Natives (5.2%) (Caucasian versus Native: Chi=5.4, p=0.02; Black versus Native: Chi=9.1, p=0.003). Caucasians and Blacks also reportedly drank significantly more days per week during pregnancy (on average 4.6 and 5.7, respectively) than American/Alaskan Natives (on average 3.6). Interestingly, the only measure of prenatal alcohol exposure that significantly differentiated FAS/PFAS from all other FASD diagnoses, across the entire study population of 1,400, was a higher mean number of days per week of drinking during pregnancy. This same finding was observed in the recently completed FASD magnetic resonance study. Since the window of vulnerability for producing the FAS facial features appears to be very short in duration (a few hours in the mouse, a few days in the nonhuman primate), perhaps the more days per week of drinking, the more likely drinking will occur during this narrow window of vulnerability. In contrast to FAS/PFAS, the prevalence of SE/AE “severe ARND without the FAS facial features” was significantly higher in American/Alaskan Natives (41.7%) than in Caucasians (26.6%) or Blacks (20.7%). American/Alaskan Natives reportedly drank a significantly higher number of drinks per drinking occasion during pregnancy than Caucasian or Blacks. Perhaps binge drinking places a fetus at greater risk for CNS structural/functional abnormalities, whereas more frequent drinking increases the odds of also having the FAS facial features.

3. Did the prevalence estimates for FAS/PFAS, SE/AE, and ND/AE vary by age? The prevalence of FAS/PFAS did not vary significantly by age at diagnosis: 0-3.9 yrs (15%), 4-5.9 yrs (9%), 6-10.9 yrs (11%), 11-15.9 yrs (9%), 16+ yrs (10%); Chi=6.3 (p=0.18). An infant was as likely to receive a diagnosis of FAS/PFAS as an adult. As a point of reference, the prevalence of FAS/PFAS across the entire study sample of 1,400 was 11%. The prevalence of ND/AE varied from 45.3% to 58.4% across the age categories, but these variations were not statistically significant. Again, for reference, the prevalence of ND/AE across all 1,400 subjects was 51.6%. The prevalence of SE/AE did vary significantly by age. Children under the age of 6 years were significantly less likely to receive a diagnosis of SE/AE than older individuals. This may be explained, in part, by the fact that a key clinical feature of SE/AE is significant dysfunction across three or more domains of cognitive/behavioral function. A child typically is not old enough to engage in an assessment of higher level functioning (executive function, memory, language, etc) until they are 7 to 8 years of age. But an individual does not have to have significant dysfunction to meet the CNS criteria for SE/AE. They could meet the criteria with microcephaly. In fact, the CNS criteria for FAS/PFAS and SE/AE are identical (presence of a CNS structural/neurological abnormality and/or significant dysfunction across 3 or more domains of brain function). So why are individuals with SE/AE significantly older (mean = 10.1 years) than individuals with FAS/PFAS (mean = 8.9 years) if the CNS criteria to achieve these two diagnoses are identical? Remember, the only feature that distinguishes FAS/PFAS from SE/AE is the FAS facial phenotype. As it turns out, those with the FAS facial phenotype are significantly more likely to have microcephaly (the prevalence of microcephaly among FAS/PFAS was 45%) than those with comparable brain dysfunction, but no FAS facial phenotype (the prevalence of microcephaly among SE/AE was 25%). This same finding was observed in the recently completed FASD MRI study. More specifically, individuals with FAS/PFAS had significantly and disproportionately smaller frontal lobes than individuals with SE/AE. Since head circumference can be accurately assessed in children less than 8 years of age, but a comprehensive assessment of brain dysfunction cannot, the higher prevalence of microcephaly among FAS/PFAS was 45%) than those with comparable brain dysfunction, but no FAS facial phenotype (the prevalence of microcephaly among SE/AE was 25%). This same finding was observed in the recently completed FASD MRI study. More specifically, individuals with FAS/PFAS had significantly and disproportionately smaller frontal lobes than individuals with SE/AE. Since head circumference can be accurately assessed in children less than 8 years of age, but a comprehensive assessment of brain dysfunction cannot, the higher prevalence of microcephaly among FAS/PFAS was 45%) than those with comparable brain dysfunction, but no FAS facial phenotype (the prevalence of microcephaly among SE/AE was 25%). This same finding was observed in the recently completed FASD MRI study.

4. Is it clinically cogent to render a diagnosis of FAS in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the
presence of brain dysfunction (intelligence, executive function, memory, language, etc)? Is the presence of microcephaly in an infant with the FAS facial phenotype predictive of brain dysfunction that will not be revealed until an infant is old enough to participate in higher level functional assessments? The answers to both questions are yes. Among the 154 patients with FAS/PFAS, 69 (44.8%) had microcephaly (Table 5). Of the 69 with microcephaly, 36 (52%) had no evidence of brain dysfunction (Rank 1), 14 (20%) had moderate (Rank 2) brain dysfunction, and 19 (28%) had severe (Rank 3) brain dysfunction. Did the 52% with no evidence of brain dysfunction, truly have normal function, or were they too young to accurately/comprehensively assess function? The data would suggest they were too young to assess. The subset with no evidence of brain dysfunction (Rank 1) had a mean age of 4.7 (6.0 SD) years. The subset with Rank 2 moderate dysfunction had a mean age of 7.5 (5.9 SD) years. And the subset with Rank 3 severe dysfunction had a mean age of 10.3 (5.9 SD) years. The older the patient, the more likely they revealed evidence of moderate to severe dysfunction (ANOVA F=5.8 (df 2), p=.005). This data suggests rendering a diagnosis of FAS/PFAS in a newborn/infant that presents with microcephaly, but is too young to assess/confirm brain dysfunction, is clinically sound. The combined presence of the FAS facial phenotype, microcephaly, and prenatal alcohol exposure serves as a strong risk factor for (predictor of) brain dysfunction. The correlations between increasing magnitude of expression of the 4-Digit FAS facial phenotype and 1) increasing CNS dysfunction, and 2) decreasing head circumference are quite high (Figures 5A,B). Early diagnosis affords early intervention. Postponing a FAS/PFAS diagnosis in children with microcephaly, who were not old enough to participate in higher-level functional assessments to confirm brain dysfunction, could lead to missed opportunities for early intervention.

**FIG. 5A** The mean Performance Intelligence Quotient (PIQ) standard score (WISC III) decreased significantly as the FAS facial phenotype increased in magnitude from 4-Digit Face Rank 1 to 4 (ANOVA: F 2.7(3df), p=.046).

**FIG. 5B** The mean occipital frontal head circumference (OFC) in centimeters (cm) decreased significantly as the FAS facial phenotype increased in magnitude from 4-Digit Face Rank 1 to 4 (ANOVA: F 26 (3df), p < .001).
5. Do the CNS functional profiles of the FAS/PFAS, SE/AE and ND/AE groups differ when generated by a single, age-appropriate, comprehensive neuropsychological battery administered to all patients, as compared to when generated by variable neuropsychological batteries that may focus more on deficits than strengths (as is often the case in clinical settings)? The CNS functional profiles of the FAS/PFAS, SE/AE, and ND/AE groups presented in Table 6 were generated from two primary sources of data: 1) past school/psychological assessments, and 2) current assessments conducted at the time of the FASD diagnostic evaluation. These school and clinic-based assessment protocols are more likely to target areas of deficit (rather than areas of strength) because the primary goals of these assessments are to determine if an individual qualifies for school-based services or meets established FASD diagnostic criteria. As a result, no two patients in the FASD PN clinical dataset necessarily received the same test battery, and their test batteries likely focused more on their deficits than their strengths. This could lead to group profiles that underestimate the mean performance levels of each group as a whole. If every patient received the same age-appropriate test battery, and the battery assessed all areas of function, not just the areas with perceived deficits, how different might the profiles be? The recently completed FASD magnetic resonance research study provided an opportunity to answer this question.24 Sixty-five children across the full continuum of FASD were randomly selected for enrollment into the magnetic resonance study from among these 1,400 WA FASD PN patients. As a standard of research protocol, a single, comprehensive neuropsychological battery was administered to all 65 children. The CNS functional profiles generated by the single, comprehensive research battery were near identical to the functional profiles generated by the more variable, less comprehensive clinical batteries (Table 6). For example, the mean FSIQ standard scores for the FAS/PFAS, SE/AE, and ND/AE groups in the magnetic resonance study were 77.5, 79.3, and 99.2 respectively. The mean Rey Complex Figure Test Copy Raw Scores for the FAS/PFAS, SE/AE, and ND/AE groups in the magnetic resonance study were 17.4, 20.5, and 25.6 respectively. These outcomes suggest the CNS profiles presented in Table 6 were not markedly influenced by the variable clinical batteries used to generate them.

6. Do FASD diagnostic outcomes vary by level of prenatal alcohol exposure? Yes (Table 9). Individuals with FAS/PFAS had a significantly higher mean number of days per week (5.6) of prenatal alcohol exposure than individuals with a comparable level of CNS dysfunction, but no facial features (SE/AE) (4.3 days/week) , or individuals with less severe CNS dysfunction and no facial features (ND/AE) (4.4 days/week). This same finding was observed in the FASD magnetic resonance study.24

7. Is the presence of other adverse exposures/events (e.g., prenatal exposure to illicit drugs, poor prenatal care, multiple home placements, physical/sexual abuse) associated with more severe developmental outcomes? Yes (Table 10). Prenatal alcohol exposure was rarely, if ever, the sole risk factor present among patients evaluated at the WA FASD PN. One third of the population had no documented prenatal care. Ninety-three percent had other adverse prenatal exposures (e.g., tobacco, illicit drugs). Seventy percent were no longer in the care of their birth parents and had on average three out-of-home placements. At least 34% were physically abused and 24% sexually abused. Seventy-five percent had one or more mental health disorders documented in their medical record. The prevalence of adverse exposures and events was for the most part, comparably high across the three FASD groups (e.g., tobacco, illicit drug use, neglect, out-of-home placements). Occasionally the prevalence increased incrementally with increasing severity of FASD diagnostic outcome from NE/AE to SD/AE to FAS/PFAS (e.g., no prenatal care). Most striking, however, were the contrasts observed between the three FASD groups and Group 4 (the group with no evidence of CNS abnormality). Physical and sexual abuse was 2- to 5-fold more prevalent in the FASD groups than in Group 4. Children in the FASD
groups were twice as likely to be in adoptive care and significantly less likely to receive prenatal care than children in Group 4. Prenatal exposure to alcohol and other illicit drugs was comparably high across all four groups.

8. What proportion of individuals with prenatal alcohol exposure present with no evidence of CNS structural, neurological, or functional abnormalities? Were they exposed to less alcohol? Of the 1,400 subjects with prenatal alcohol exposure, 130 (9.3%) presented with no evidence of CNS abnormality (Table 1). Ninety-six of the 130 subjects in Group 4 presented with no growth or FAS facial features either. Although one might expect to see a lower reported alcohol exposure among this group, their reported level of exposure was comparable to that of the SE/AE and ND/AE groups. Three features that did distinguish this unaffected group from the other groups were their gender, age, and postnatal adverse experiences. The unaffected group was significantly more likely to be female (57.7%) than the other FASD clinical subgroup (FAS/PFAS 48.1%; ND/AE 41.6%; SE/AE 35.3%). And the unaffected group was significantly younger (46.2% were under 4 years of age) compared to 25.3% among the FAS/PFAS, 10.7% among the SE/AE, and 16.2% among the ND/AE. It is likely that some of the subjects in the unaffected group were classified as functionally within the normal range because they were too young to assess and rule-out higher level functional deficits. The only way an infant could meet the CNS functional criteria for SE/AE is with significantly delayed mental and motor development (e.g., Mental and Motor Developmental Index standard scores of 50 on the Bayley Scales of Infant Development43). But young age does not explain why the 130 patients in Group 4 did not meet the CNS functional criteria for ND/AE. A third factor that markedly differentiated the unaffected group from the three affected groups was adverse postnatal experiences. As reported above, the unaffected group was significantly less likely to experience high-risk (Rank 4) postnatal adverse events like physical or sexual abuse.

9. How often are other syndromes present in this patient population? Eighteen (1.3%) of the 1,400 subjects were diagnosed with other syndromes (Table 10). Only one of the seven clinics had a dysmorphologist on their interdisciplinary team. When the prevalence estimate was restricted to the 664 patients seen at the UW FAS DPN between 1993 and 1999 when a dysmorphologist served as the pediatrician on the team, 13 (1.9%) were identified with other syndromes. When syndromes other than FAS were suspected by the other pediatricians on the teams (the pediatricians who were not dysmorphologists or geneticists), the patients were referred to a geneticist. Of the 736 patients seen by the other pediatricians 5 (0.7%) were documented to have another syndrome and an additional 8 (1.1%) were suspected to have another syndrome and were referred to a geneticist. Thus, the pediatricians documented or suspected the same proportion of patients with other syndromes (1.8%) as was diagnosed when a dysmorphologist was on the team (1.9%). It is worth noting that one child diagnosed with FAS in the WA FAS DPN also had Down syndrome. Alcohol is a teratogen to all developing fetuses, including those with genetic disorders. The child presented with growth deficiency below the 2nd percentile on a growth chart for children with Down syndrome. The child presented with the facial features of Down syndrome and FAS. The facial features of Down syndrome are distinct from the facial features of FAS. The two phenotypes were readily apparent and easily distinguished. The child presented with microcephaly (3 SDs below the mean for boys with normal development, 1 SD below the mean for children with Down syndrome). The child presented with BayleyMotor and Mental Index scores below 50; a level of developmental delay that can be observed in both Down syndrome and FAS. The birth mother was reported to have consumed alcohol daily throughout pregnancy.

10. The FASD literature suggests that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children. Is there evidence of this in this dataset? No. The proportion of subjects who presented with the full FAS facial phenotype (Rank 4) by age group was as follows: birth to 3.9 yrs (36/258, 14%), 4 to 16.9 years (78/1001, 7.7%), and 17 to 53 years (12/141, 9.5%). The age group with the highest prevalence of the FAS facial phenotype was infants under one year of age (23%) (Figure 6).
11. Growth deficiency has always been a hallmark of FAS/D. How prevalent is growth deficiency in this patient population? Only 34.1% of the 1,400 subjects presented with height and/or weight below the 10th percentile (Growth Ranks 2, 3 or 4). Only 7.9% presented with height and weight below the 3rd percentile (Growth Rank 4). Of the patients with FAS/PFAS, 35.7% presented with no growth deficiency (Growth Rank 1: height and weight above the 10th percentile) and thus received a diagnosis of PFAS.

12. Who are the birth fathers of these children? The names of 76% of the birth fathers were known, compared to 95% of the birth mothers. The more severe the FASD diagnostic outcome, the less likely the birth father’s name was documented in the child’s records. Only 7.6% of them accompanied their child to the FASD diagnostic evaluation. The fathers were on average 29 years old at the birth of their child with FASD and 38 years old at the time the child was being diagnosed with FASD (Table 3). Thirty-nine percent did not finish high school, 45% completed high school, and 16% attended college. They were in general, older and more highly educated than the birth mothers. Approximately half of them reportedly had learning disabilities.

13. What proportion of patients were no longer in the care of their birth parents at the time of their FASD diagnostic evaluation? Seventy percent of the patients were no longer in the care of either birth parent at the time of their FASD diagnostic evaluation (Table 1). The average number of home placements across the 1,400 patients was 2.9 ± 3.1. Nineteen percent had four or more home placements.

14. Does a caregiver’s impression of their child’s behavior differ between FAS/PFAS, SE/AE, and ND/AE? Yes and No. Among the 1,270 caregivers who completed the Child Behavior Checklist34 (for children 6 to 18 years of age), the prevalence and magnitude of behavior problems was comparably high across all FASD subgroups. Attention problems were reported most often (Table 7, Figure 2). When the results of the 2-hour, structured interview with the caregiver(s) (conducted by the medical doctor and psychologist on the day of the FASD diagnostic evaluation) were tabulated (Table 8, Figure 3), the
prevalence and magnitude of behavioral concerns often increased significantly and incrementally as one advanced from the ND/AE to SE/AE to FAS/PFAS group. It is important to note that these parent impressions of their child’s behavior were recorded before the parent or the clinicians knew the FASD diagnostic outcome of the child.

FIG. 2 Child Behavior Check List$^{34}$ (CBCL/ 6-18) Syndrome Scales (see Table 7) among the 516 patients administered a CBCL when they were between 6 and 18 years of age. All abbreviations are defined in Table 7.
FIG. 3 Proportion of patients classified by the pediatrician as ‘significantly delayed/impaired’ in behaviors addressed in a 2-hour, structured caregiver interview administered jointly by the pediatrician and psychologist during the FASD diagnostic evaluation. This is a graphical presentation of the data presented in Table 8 to illustrate the cumulative increase in impairment as one advances across the study groups. Each color in a bar reflects the behaviors listed in Table 8 under each Domain. Abbreviations are defined in Table 8. The number printed in each colored section is the proportion of patients with significant impairment for that behavior. For example, the bar for the FAS/PFAS group in the Planning Domain reflects the following: blue square (24% present with significant impairment for “Needs considerable help organizing daily tasks”); red square (31.3% present with significant impairment for “Cannot organize time”); green square: (31.5% present with significant impairment for “Does not understand concept of time”); and purple square (26.5% present with significant impairment for “Difficulty carrying out multistep tasks”).

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15. **What is the prevalence of other mental health disorders in this patient population?**

Among the 1,064 patients, five or more years of age at the time of their FASD diagnostic evaluation, 82% had one or more mental health disorders documented in their medical records (Table 11). The most prevalent was ADD/ADHD (53.9%). Despite this high overall prevalence, the prevalence estimates for each disorder (based on review of medical records available to the FASD clinics) may substantially under-estimate the true prevalence of each disorder. Many of these disorders fail to be formally diagnosed and recorded in the medical record. When a representative subset of these children (n=65) were administered the Computerized Diagnostic Interview Schedule for Children during their enrollment in the FASD magnetic resonance study, the prevalence estimates for many disorders were substantially higher. For example, Oppositional Defiant Disorder was reported in 6.8% of this clinical population, but was diagnosed in 52% of the subset that participated in the magnetic resonance study. Obsessive compulsive disorder was reported in 0.7% of this clinical population, but was diagnosed in 9.2% of the subset that participated in the magnetic resonance study.

16. **Were patients satisfied with the interdisciplinary FASD diagnostic evaluation process? Were they provided information they were unable to obtain elsewhere? Was the 4-Digit Code approach to diagnosis easy to understand? Was their ability to access and benefit from recommended intervention services influenced by what diagnosis their child received under the umbrella of FASD? Would they recommend the clinic to other families with similar needs?** A 10-question patient satisfaction survey has been sent to all patients evaluated at the UW FAS DPN clinic since 1993. The survey may be completed anonymously and comes with a stamped-addressed return envelope to maximize participation in the survey. Patients universally expressed high satisfaction for the FASD diagnostic services provided by the University of Washington (Table 12). Ninety-nine percent would recommend the Clinic to other families with similar needs. Ninety-one percent said they received information they were unable to obtain elsewhere, despite the fact the clinic is located in a large metropolitan area (Seattle) with many genetic, neurodevelopmental, and psychological evaluation services available. Eighty-six percent found the explanation of the diagnosis using the 4-Digit Code easy to understand. And perhaps most informative; family’s whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family’s whose child received a diagnosis of FAS/PFAS. This is in contrast to the oft stated belief that a family will not qualify for services if the diagnosis is not FAS/PFAS or at least given a name that implies alcohol is the causal agent (e.g., ARND). Overall, 82.1% of families reported being somewhat to very successful in finding the recommended intervention services and 83.7% reported these services met some to all of their needs.

**Strengths and Limitations**

The outcomes presented in this report reflect a very large, 13-year, statewide, clinical population of patients (newborn to adult) who all received an identical, interdisciplinary approach to FASD diagnostic evaluation using the FASD 4-Digit Code. By virtue of this, the outcomes presented in this report are highly representative of the study’s intended target population (a statewide clinical population of individuals with prenatal alcohol exposure seeking an FASD diagnostic evaluation). The outcomes presented in this report should not be construed to represent the population of all individuals exposed to prenatal alcohol exposure. Even though the only requirement to obtain an FASD diagnostic evaluation in the WA FAS DPN is a confirmed prenatal alcohol exposure, alcohol-exposed individuals with developmental concerns are more likely to be referred to the clinic than alcohol-exposed individuals with no developmental concerns. Other features inherent to this clinical dataset should also be taken into consideration when interpreting the reported outcomes. 1) Data in the FAS DPN clinical dataset are obtained from a variety of sources (medical/educational/social service record review,
caregiver interview, and direct clinical evaluation). The accuracy of the data will vary by source. 2) No two patients have an identical dataset. The amount and type of data available on each patient varies by their age and the existence and availability of previous medical/educational assessments. 3) Prior medical and educational assessments may focus more on areas of concern than areas of strength. As a result, inclusion of these data sources could generate group profiles that over represent deficits. Overall, clinical datasets are an invaluable, ubiquitous resource that, when interpreted in the proper context can greatly inform and advance a field.

CONCLUSION

In summary, the existence of the WA FAS DPN diagnostic program and electronic database over the past 17 years confirms it is possible to establish and maintain a comprehensive statewide FASD diagnostic program and dataset. As demonstrated in this report, a broad array of clinical, research, and public health questions can be addressed with a FASD clinical dataset. The outcomes presented in this report reflect the experience of WA State. With the worldwide replication of this interdisciplinary approach to FASD diagnosis using the 4-Digit Code, the opportunity now exists, for the first time ever, to construct and validly compare clinical profiles across very diverse, geographically dispersed populations. This report serves as a formal appeal to FASD clinical programs worldwide to do just that. The benefits to individuals with FASD and their families would be immense.

Acknowledgements

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TABLE 1  FASD 4-Digit Diagnostic Categories within each of the four FASD diagnostic study subgroups.

<table>
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<th>Characteristic</th>
<th>1. FAS/PFAS</th>
<th>2. SE/AE</th>
<th>3. ND/AE</th>
<th>4. Normal CNS/AE</th>
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<td>24.1</td>
<td>95</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>F. Static Encephalopathy / Alcohol Exposed</td>
<td></td>
<td></td>
<td>299</td>
<td>75.9</td>
<td>299</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>G. Sentinel Physical Findings / Neurobehavioral Disorder / Alcohol Exposed</td>
<td></td>
<td></td>
<td>160</td>
<td>22.2</td>
<td>160</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>H. Neurobehavioral Disorder / Alcohol Exposed</td>
<td></td>
<td></td>
<td>562</td>
<td>77.8</td>
<td>562</td>
<td>40.1</td>
<td></td>
</tr>
<tr>
<td>I. Sentinel Physical Findings / Alcohol Exposed</td>
<td></td>
<td></td>
<td>34</td>
<td>26.2</td>
<td>34</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>J. No Sentinel physical findings or CNS abnormalities detected / Alcohol Exposed</td>
<td></td>
<td>96</td>
<td>73.8</td>
<td>96</td>
<td>6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic outcomes across FAS DPN clinics: N (valid row %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.2 (.36)</td>
<td></td>
</tr>
<tr>
<td>University of Washington Core Clinic in Seattle</td>
<td>107</td>
<td>11.5</td>
<td>248</td>
<td>26.7</td>
<td>487</td>
<td>52.4</td>
<td>88</td>
</tr>
<tr>
<td>Six other statewide FAS DPN clinics</td>
<td>47</td>
<td>10.0</td>
<td>146</td>
<td>31.1</td>
<td>235</td>
<td>50.0</td>
<td>42</td>
</tr>
</tbody>
</table>

**TABLE 2  Sociodemographic profiles across the four study groups.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistics</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 154</td>
<td>N = 394</td>
<td>N = 722</td>
<td>N = 130</td>
</tr>
<tr>
<td>Gender: N (valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>80</td>
<td>51.9</td>
<td>255</td>
</tr>
<tr>
<td>Race (one race): N (valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87</td>
<td>56.5</td>
<td>182</td>
</tr>
<tr>
<td>Black</td>
<td>17</td>
<td>11.1</td>
<td>19</td>
</tr>
<tr>
<td>American Indian/Native Alaskan</td>
<td>6</td>
<td>3.9</td>
<td>48</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All others (including mixed race)</td>
<td>44</td>
<td>28.6</td>
<td>145</td>
</tr>
<tr>
<td>Age at diagnosis (yr): N (row-column valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 3.9</td>
<td>39</td>
<td>15.1-25.3</td>
<td>42</td>
</tr>
<tr>
<td>4 – 5.9</td>
<td>22</td>
<td>9.4-14.3</td>
<td>52</td>
</tr>
<tr>
<td>6 – 10.9</td>
<td>53</td>
<td>11.0-34.4</td>
<td>157</td>
</tr>
<tr>
<td>11 – 15.9</td>
<td>26</td>
<td>9.1-16.9</td>
<td>93</td>
</tr>
<tr>
<td>16+</td>
<td>14</td>
<td>9.9-9.1</td>
<td>50</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.9</td>
<td>8.3-10.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>0.3</td>
<td>0.5-0.5</td>
<td>50.8</td>
</tr>
<tr>
<td>Patient’s caregiver at diagnosis: N (valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth mother</td>
<td>26</td>
<td>17.3</td>
<td>79</td>
</tr>
<tr>
<td>Birth Father</td>
<td>10</td>
<td>6.7</td>
<td>34</td>
</tr>
<tr>
<td>Other biological family member</td>
<td>25</td>
<td>16.7</td>
<td>39</td>
</tr>
<tr>
<td>Adoptive parent</td>
<td>39</td>
<td>26.0</td>
<td>81</td>
</tr>
<tr>
<td>Foster parent</td>
<td>35</td>
<td>23.3</td>
<td>80</td>
</tr>
<tr>
<td>Social or caseworker</td>
<td>5</td>
<td>3.4</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>6.7</td>
<td>40</td>
</tr>
<tr>
<td>Annual income &lt; $35,000: N (valid%)</td>
<td>37</td>
<td>59.7</td>
<td>98</td>
</tr>
</tbody>
</table>

Abbreviations: Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/ AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/ AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/ AE: Static encephalopathy/alcohol exposed. **Notations:** A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Birth parent versus not birth parent.
### TABLE 3  Birth mother and birth father characteristics across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1. 59 FAS/ 95 PFAS</th>
<th>2. SE/AE</th>
<th>3. ND/AE</th>
<th>4. Normal CNS/AE</th>
<th>Total</th>
<th>ANOVA</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 154</td>
<td>N = 394</td>
<td>N = 722</td>
<td>N = 130</td>
<td>N = 1400</td>
<td>F (p)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Duncan&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MOTHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s name known</td>
<td>143</td>
<td>93.3</td>
<td>370</td>
<td>93.9</td>
<td>683</td>
<td>94.6</td>
<td>129</td>
</tr>
<tr>
<td>Mother attended FASD evaluation: N (valid%)</td>
<td>26</td>
<td>17.3</td>
<td>79</td>
<td>21.4</td>
<td>152</td>
<td>21.9</td>
<td>36</td>
</tr>
<tr>
<td>Mother’s age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At child’s birth: N mean (SD)</td>
<td>119</td>
<td>28.3 (6.6)</td>
<td>318</td>
<td>25.5 (6.1)</td>
<td>594</td>
<td>25.6 (6.3)</td>
<td>116</td>
</tr>
<tr>
<td>Min-Max</td>
<td>16.0</td>
<td>43.0</td>
<td>15.0</td>
<td>41.0</td>
<td>14.0</td>
<td>43.0</td>
<td>14.2</td>
</tr>
<tr>
<td>At FASD diagnosis: N mean (SD)</td>
<td>119</td>
<td>37.1 (10.6)</td>
<td>318</td>
<td>35.4 (8.5)</td>
<td>594</td>
<td>34.5 (8.2)</td>
<td>116</td>
</tr>
<tr>
<td>Min-Max</td>
<td>22.1</td>
<td>81.5</td>
<td>19.3</td>
<td>77.6</td>
<td>17.5</td>
<td>75.3</td>
<td>16.0</td>
</tr>
<tr>
<td>Maternal highest education level: N (valid%)</td>
<td>1.8(61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not finish high school</td>
<td>56</td>
<td>53.3</td>
<td>166</td>
<td>57.6</td>
<td>272</td>
<td>52.8</td>
<td>59</td>
</tr>
<tr>
<td>Finished high school</td>
<td>37</td>
<td>35.2</td>
<td>91</td>
<td>31.6</td>
<td>171</td>
<td>33.2</td>
<td>26</td>
</tr>
<tr>
<td>College</td>
<td>12</td>
<td>11.5</td>
<td>31</td>
<td>10.8</td>
<td>72</td>
<td>14.0</td>
<td>22</td>
</tr>
<tr>
<td>Maternal learning disabilities: N (valid%)</td>
<td>57</td>
<td>56.4</td>
<td>168</td>
<td>60.6</td>
<td>291</td>
<td>59.5</td>
<td>47</td>
</tr>
<tr>
<td>Mother deceased: N (valid%)</td>
<td>9</td>
<td>12.3</td>
<td>17</td>
<td>8.8</td>
<td>34</td>
<td>9.6</td>
<td>2</td>
</tr>
<tr>
<td>Parity of index child: N mean (SD)</td>
<td>122</td>
<td>3.0 (1.8)</td>
<td>317</td>
<td>2.7 (1.8)</td>
<td>600</td>
<td>2.7 (1.7)</td>
<td>117</td>
</tr>
<tr>
<td>Min-Max</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Gravity of index child: N mean (SD)</td>
<td>83</td>
<td>3.5 (2.2)</td>
<td>174</td>
<td>3.1 (2.2)</td>
<td>322</td>
<td>3.2 (2.0)</td>
<td>52</td>
</tr>
<tr>
<td>Min-Max</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>FATHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s name known</td>
<td>105</td>
<td>68.2</td>
<td>299</td>
<td>75.9</td>
<td>555</td>
<td>76.9</td>
<td>107</td>
</tr>
<tr>
<td>Father attended FASD evaluation: N (valid%)</td>
<td>10</td>
<td>6.7</td>
<td>34</td>
<td>9.2</td>
<td>47</td>
<td>6.8</td>
<td>11</td>
</tr>
<tr>
<td>Father’s age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At child’s birth: N mean (SD)</td>
<td>62</td>
<td>31.5 (8.4)</td>
<td>189</td>
<td>29.4 (7.3)</td>
<td>369</td>
<td>28.7 (7.3)</td>
<td>70</td>
</tr>
<tr>
<td>Min-Max</td>
<td>17</td>
<td>66</td>
<td>15</td>
<td>61</td>
<td>15</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>At FASD diagnosis: N mean (SD)</td>
<td>62</td>
<td>40.6 (13.2)</td>
<td>189</td>
<td>39.6 (9.2)</td>
<td>369</td>
<td>38.1 (9.8)</td>
<td>70</td>
</tr>
<tr>
<td>Min-Max</td>
<td>19</td>
<td>87</td>
<td>23</td>
<td>81</td>
<td>20</td>
<td>87</td>
<td>15</td>
</tr>
<tr>
<td>Paternal highest education level: N (valid%)</td>
<td>21</td>
<td>33.9</td>
<td>79</td>
<td>40.9</td>
<td>129</td>
<td>38.4</td>
<td>22</td>
</tr>
<tr>
<td>Did not finish high school</td>
<td>32</td>
<td>51.6</td>
<td>85</td>
<td>45.7</td>
<td>153</td>
<td>45.5</td>
<td>22</td>
</tr>
<tr>
<td>Finished high school</td>
<td>9</td>
<td>14.5</td>
<td>25</td>
<td>13.4</td>
<td>54</td>
<td>16.1</td>
<td>16</td>
</tr>
<tr>
<td>College</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal learning disabilities: N (valid%)</td>
<td>22</td>
<td>43.1</td>
<td>97</td>
<td>53.9</td>
<td>165</td>
<td>54.3</td>
<td>24</td>
</tr>
</tbody>
</table>

**Abbreviations:** Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Did versus did not finish high school.
### TABLE 4  
Growth and FAS facial outcomes across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASD Diagnostic Subgroups Statistics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANOVA</td>
<td>Overall</td>
<td>Post Hoc</td>
</tr>
<tr>
<td>N</td>
<td>154</td>
<td>394</td>
</tr>
<tr>
<td>F (p)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth Rank in 4-Digit Code: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1</td>
<td>55</td>
<td>35.7</td>
</tr>
<tr>
<td>Rank 2</td>
<td>13</td>
<td>13.6</td>
</tr>
<tr>
<td>Rank 3</td>
<td>35</td>
<td>13.6</td>
</tr>
<tr>
<td>Rank 4</td>
<td>43</td>
<td>27.9</td>
</tr>
<tr>
<td>Gestational age (wks): N mean (SD)</td>
<td>116</td>
<td>36.8 (3.2)</td>
</tr>
<tr>
<td>Birth weight percentile: N mean (SD)</td>
<td>124</td>
<td>33.2 (28.9)</td>
</tr>
<tr>
<td>Birth length percentile: N mean (SD)</td>
<td>103</td>
<td>36.5 (34.7)</td>
</tr>
<tr>
<td>Wgt percentile at diagnosis: N mean (SD)</td>
<td>143</td>
<td>33.6 (32.4)</td>
</tr>
<tr>
<td>Hgt percentile at diagnosis: N mean (SD)</td>
<td>143</td>
<td>25.1 (26.9)</td>
</tr>
<tr>
<td>Face Rank in 4-Digit Code: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rank 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rank 3</td>
<td>69</td>
<td>44.8</td>
</tr>
<tr>
<td>Rank 4</td>
<td>85</td>
<td>55.2</td>
</tr>
<tr>
<td>Mean PFL zscore: mean (SD)</td>
<td>-3.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean PFL &lt; -2 SD: N (valid%)</td>
<td>144</td>
<td>93.5</td>
</tr>
<tr>
<td>Innercanthal distance zscore: mean (SD)</td>
<td>-0.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Innercanthal distance &gt; 2SD: N (valid%)</td>
<td>4</td>
<td>5.3</td>
</tr>
<tr>
<td>Philtrum Smoothness Rank: N (valid%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (very deep)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 (somewhat deep)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (normal)</td>
<td>30</td>
<td>20.0</td>
</tr>
<tr>
<td>4 (almost smooth)</td>
<td>76</td>
<td>50.7</td>
</tr>
<tr>
<td>5 (completely smooth)</td>
<td>44</td>
<td>29.3</td>
</tr>
<tr>
<td>Upper Lip Thinness Rank: N (valid%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (very thick)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 (moderately thick)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (normal)</td>
<td>30</td>
<td>19.4</td>
</tr>
<tr>
<td>4 (moderately thin)</td>
<td>77</td>
<td>50.0</td>
</tr>
<tr>
<td>5 (very thin)</td>
<td>43</td>
<td>29.1</td>
</tr>
</tbody>
</table>

**Abbreviations:** Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. Hgt: height. P: p-value. PFAS: partial FAS. PFL: palateal fissure length. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Wgt: weight. Wks: weeks. Notes: A: Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B: The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C: All 55 Rank 1 growths are PFAS. D: All 69 Rank 3 faces are PFAS; E: 25 too young to rule out CNS Rank 3 (<8yrs). F: All 7 are too young to rule out CNS Rank 3 (<8yrs). G: All 30 Rank 3 philtrums are PFAS. H: All 30 Rank 3 lips are PFAS.
### TABLE 5 CNS structural / neurological outcomes (4-Digit CNS Rank 4) across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 154</td>
<td>N = 394</td>
<td>N = 722</td>
</tr>
<tr>
<td>CNS Rank in 4-Digit Code: N (valid%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rank 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rank 3</td>
<td>65</td>
<td>42.2</td>
</tr>
<tr>
<td>Rank 4</td>
<td>89</td>
<td>57.8</td>
</tr>
<tr>
<td>CNS functional Rank independent of Rank 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (valid%)</td>
<td>Age yrs mean(SD)</td>
<td>N (valid%)</td>
</tr>
<tr>
<td>Rank 1 (no dysfunction)</td>
<td>40 (26)</td>
<td>4.4 (5.8)</td>
</tr>
<tr>
<td>Rank 2 (mild dysfunction)</td>
<td>19 (12.3)</td>
<td>7.1 (5.1)</td>
</tr>
<tr>
<td>Rank 3 (severe dysfunction)</td>
<td>95 (61.7)</td>
<td>11.2 (8.8)</td>
</tr>
</tbody>
</table>

### ANOVA

<table>
<thead>
<tr>
<th>Duncan comparing mean age between CNS Ranks 1, 2, 3: F(p)</th>
<th>Rank 1, 2, 3</th>
<th>Rank 1, 2, 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 11.3(.00)</td>
<td>F 2.9(.06)</td>
<td></td>
</tr>
</tbody>
</table>

### Chi-square

<table>
<thead>
<tr>
<th>Rank 1, 2, 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1740(00)</td>
</tr>
</tbody>
</table>

### Microcephaly: N (valid%) 69 44.8 99 25.3 0 0 0 0 168 12.1 | |
| OFC percentile: N, mean (SD) | 152 24.0(28.0) | 391 39.6(31.4) | 715 52.0(23.8) | 126 53.5(24.4) | 1384 45.7(28.3) | 57(00) 1,2,34 |

### Abnormal MRI among those imaged: N (valid%) 7 26.9 18 30.5 0 0 0 0 25 18.1 |

### Seizure disorder: N (valid%) 10 6.5 32 8.1 0 0 0 0 42 3.0 |

### Why CNS Rank 4: N (valid%) Of the 89 with Rank 4 | Of the 150 with Rank 4 |
| 1. Microcephaly only | 66 | 82.5 |
| 2. Abnormal MRI only | 2 | 0.3 |
| 3. Seizure disorder only | 7 | 0.9 |
| 4. Microcephaly & abnormal MRI | 3 | 0.4 |
| 5. Microcephaly & seizures | 0 | 0 |
| 6. Abnormal MRI & seizures | 2 | 0.3 |
| 7. All 3 | 0 | 0 |

### Vision problems: N (valid%) 42 37.5 108 33.2 155 25.2 20 18.5 325 28.0 |

### Chronic hearing loss: N (valid%) | |
| 23 | 21.3 |

Abbreviations: Chi2: chi-square test across the four study groups, unless otherwise noted. CNS: central nervous system. F: F statistic. FAS: fetal alcohol syndrome. Microcephaly: OFC <= -2SD. MRI: magnetic resonance image. OFC: Occipital frontal circumference. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Yrs: years. Notes: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Of those with Rank 4 CNS, are those with Rank 1 too young to rule-out Rank 3? D. Only 5 (12%) of the 40 with Rank 1 function are >7yrs old. E. Only 4 (21%) of the 19 with Rank 2 function are >7 yrs old. F. 28 (42%) of the 66 with Rank 1 function are >7 yrs old. G) 27 (52%) of the 52 with Rank 2 function were > 7 yrs old. H) Group 1 versus Group 2.

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TABLE 6  CNS Functional outcomes (4-Digit CNS Ranks 1-3) across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>ANOVA</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 154</td>
<td>N = 394</td>
<td>N = 722</td>
</tr>
<tr>
<td>CNS functional Rank: N (valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1 (no dysfunction)</td>
<td>40</td>
<td>26.0</td>
<td>66</td>
</tr>
<tr>
<td>Rank 2 (mild dysfunction)</td>
<td>19</td>
<td>12.3</td>
<td>52</td>
</tr>
<tr>
<td>Rank 3 (severe dysfunction)</td>
<td>95</td>
<td>61.7</td>
<td>276</td>
</tr>
<tr>
<td>Domain with Significant Dysfunction: N (valid%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development</td>
<td>38</td>
<td>51.4</td>
<td>66</td>
</tr>
<tr>
<td>MC/ADHD</td>
<td>49</td>
<td>43.4</td>
<td>149</td>
</tr>
<tr>
<td>Intelligence (WISC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ Std: N mean (SD)</td>
<td>13</td>
<td>78.8 (13.5)</td>
<td>274</td>
</tr>
<tr>
<td>PIQ Std</td>
<td>88</td>
<td>77.4 (14.0)</td>
<td>229</td>
</tr>
<tr>
<td>VIQ Std: N mean (SD)</td>
<td>26</td>
<td>20.0</td>
<td>72</td>
</tr>
<tr>
<td>PIQ Std &lt;= 70: N (valid%)</td>
<td>144 (00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIQ Std &lt;= 70: N (valid%)</td>
<td>144 (00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceptual Organization Std: N (valid%)</td>
<td>12</td>
<td>79.5 (14.5)</td>
<td>36</td>
</tr>
<tr>
<td>Similarities Sc Score: N mean (SD)</td>
<td>46</td>
<td>7.3 (3.2)</td>
<td>137</td>
</tr>
<tr>
<td>Vocabulary Sc: N mean (SD)</td>
<td>46</td>
<td>6.0 (3.4)</td>
<td>143</td>
</tr>
<tr>
<td>Compensation Sc: N mean (SD)</td>
<td>44</td>
<td>6.5 (3.1)</td>
<td>132</td>
</tr>
<tr>
<td>Digit Span Sc: N mean (SD)</td>
<td>35</td>
<td>6.3 (3.9)</td>
<td>23</td>
</tr>
<tr>
<td>Picture Completion Sc: N mean (SD)</td>
<td>46</td>
<td>6.9 (3.3)</td>
<td>139</td>
</tr>
<tr>
<td>Block Design Sc: N mean (SD)</td>
<td>47</td>
<td>6.3 (3.2)</td>
<td>119</td>
</tr>
<tr>
<td>Object Assembly Sc: N mean (SD)</td>
<td>44</td>
<td>7.5 (3.3)</td>
<td>125</td>
</tr>
<tr>
<td>Coding Sc: N mean (SD)</td>
<td>35</td>
<td>5.8 (3.2)</td>
<td>113</td>
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<tr>
<td>Mazes Sc: N mean (SD)</td>
<td>6</td>
<td>3.8 (1.9)</td>
<td>25</td>
</tr>
<tr>
<td>Visual-Motor/Sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSP Total = Definite Difference: N (valid%)</td>
<td>59</td>
<td>77.3 (11.4)</td>
<td>76</td>
</tr>
<tr>
<td>NSP Total = Difference: N (valid%)</td>
<td>29</td>
<td>37.2 (16.9)</td>
<td>82</td>
</tr>
<tr>
<td>Executive Function/ Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTF Copy R: mean (SD)</td>
<td>13</td>
<td>15.2 (6.9)</td>
<td>40</td>
</tr>
<tr>
<td>RCTF 3min recall T: mean (SD)</td>
<td>13</td>
<td>25.2 (6.5)</td>
<td>35</td>
</tr>
<tr>
<td>RCTF 30min recall T: mean (SD)</td>
<td>4</td>
<td>31.6 (5.0)</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD: attention deficit hyperactivity disorder. Chi: chi-square statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. FSIQ: full scale IQ. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. PIQ: Performance IQ. QNST: Quick Neurological Screening Test. RCFT: Rey Complex Figure Test. T: raw score. Sc: scaled score. SD: standard deviation. SE/EA: Static encephalopathy/alcohol exposed. SSP: Short Sensory Profile. Std. standard score. T: t score. VIQ: Verbal IQ. VMI: Beery Buktenica Developmental Test of Visual Motor Integration. WISC: Wechsler Intelligence Scale for Children. Notes: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Only groups 1, 2 and 3 are compared.
TABLE 7  Child Behavior Check List (CBCL/ 6-18) outcomes (see Figure 2) among the 516 patients administered a CBCL when they were between 6 and 18 years of age.

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N = 154</td>
<td>N = 394</td>
<td>N = 722</td>
<td>N = 130</td>
<td></td>
<td>Overall Post Hoc</td>
</tr>
<tr>
<td></td>
<td>N Mean (SD)</td>
<td>N Mean (SD)</td>
<td>N Mean (SD)</td>
<td>N Mean (SD)</td>
<td>F (p)</td>
<td>Duncan $^A$</td>
</tr>
<tr>
<td>Problems: T-score $^C$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>51 63.4(10.1)</td>
<td>154 64.5(10.9)</td>
<td>270 66.6(10.9)</td>
<td>25 60.8(14.1)</td>
<td>500 64.8(11.0)</td>
<td>1.9 (.14)  --</td>
</tr>
<tr>
<td>Externalizing</td>
<td>51 69.1(9.9)</td>
<td>154 69.6(10.9)</td>
<td>270 70.8(10.3)</td>
<td>25 60.3(13.2)</td>
<td>500 69.8(10.8)</td>
<td>7.6 (.000) 123.4</td>
</tr>
<tr>
<td>Total</td>
<td>51 71.4(8.9)</td>
<td>154 71.3(9.3)</td>
<td>270 72.1(9.0)</td>
<td>25 61.9(12.7)</td>
<td>500 71.3(9.5)</td>
<td>9.1 (.000) 123.4</td>
</tr>
<tr>
<td>Syndrome Scales: T-score $^D$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious/Depressed</td>
<td>51 63.0(11.3)</td>
<td>153 64.0(9.9)</td>
<td>269 64.9(10.9)</td>
<td>25 62.6(12.1)</td>
<td>498 64.3(10.7)</td>
<td>0.8 (.53)  --</td>
</tr>
<tr>
<td>Withdrawn/Depressed</td>
<td>50 62.4(8.6)</td>
<td>153 64.6(11.2)</td>
<td>269 65.0(11.1)</td>
<td>25 63.1(12.4)</td>
<td>497 64.5(10.9)</td>
<td>0.9 (.42)  --</td>
</tr>
<tr>
<td>Somatic Complaints</td>
<td>51 60.0(9.3)</td>
<td>153 60.6(10.8)</td>
<td>269 61.8(10.0)</td>
<td>25 57.9(7.0)</td>
<td>498 61.0(10.1)</td>
<td>1.6 (.19)  --</td>
</tr>
<tr>
<td>Social Problems</td>
<td>50 72.0(12.0)</td>
<td>153 69.7(10.2)</td>
<td>269 68.5(10.2)</td>
<td>25 59.1(10.3)</td>
<td>497 68.8(10.7)</td>
<td>9.3 (.00) 123.4</td>
</tr>
<tr>
<td>Thought Problems</td>
<td>50 70.7(10.7)</td>
<td>153 69.1(10.6)</td>
<td>270 68.4(10.2)</td>
<td>25 61.6(8.8)</td>
<td>498 68.5(10.4)</td>
<td>4.6 (.003) 123.4</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>51 75.5(11.9)</td>
<td>153 75.7(11.0)</td>
<td>270 74.3(11.4)</td>
<td>25 64.2(13.1)</td>
<td>497 74.4(11.6)</td>
<td>7.6 (.000) 123.4</td>
</tr>
<tr>
<td>Rule-Breaking Behavior</td>
<td>51 67.9(8.9)</td>
<td>153 67.5(10.2)</td>
<td>269 69.7(10.0)</td>
<td>25 61.5(11.4)</td>
<td>498 68.4(10.2)</td>
<td>6.0 (.001) 123.4</td>
</tr>
<tr>
<td>Aggressive Behavior</td>
<td>50 70.2(13.1)</td>
<td>153 71.7(12.1)</td>
<td>269 72.0(12.2)</td>
<td>25 61.6(12.5)</td>
<td>497 71.2(12.4)</td>
<td>5.7 (.001) 123.4</td>
</tr>
<tr>
<td>Competence Scales: T-score $^E$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities</td>
<td>44 41.5(8.9)</td>
<td>135 42.8(8.8)</td>
<td>220 44.3(7.7)</td>
<td>18 46.1(7.2)</td>
<td>417 43.8(8.2)</td>
<td>2.5 (.05) 123,234</td>
</tr>
<tr>
<td>Social</td>
<td>44 36.0(9.2)</td>
<td>130 34.5(9.1)</td>
<td>211 36.4(9.8)</td>
<td>18 40.3(11.9)</td>
<td>403 35.9(9.7)</td>
<td>2.3 (.07) 123,34</td>
</tr>
<tr>
<td>School</td>
<td>37 28.3(6.4)</td>
<td>111 29.6(6.0)</td>
<td>181 31.9(6.2)</td>
<td>13 38.9(9.0)</td>
<td>342 31.0(6.6)</td>
<td>12.7 (.00) 12,23,4</td>
</tr>
<tr>
<td>Total</td>
<td>37 31.8 (10.0)</td>
<td>109 32.4 (8.2)</td>
<td>172 35.1 (7.6)</td>
<td>13 40.3 (9.4)</td>
<td>331 34.0 (8.4)</td>
<td>5.9 (.003) 123,4</td>
</tr>
</tbody>
</table>

Abbreviations: F: f-statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Borderline clinical range (T score 60-63). Clinical range (T score > 63). D. Borderline clinical range (T score 65-69). Clinical range (T score > 69). E. (Activities, Social, School): Borderline clinical range (T score 31-35). Clinical range (T score <31); (Total): Borderline clinical range (T score 37-40). Clinical range (T score <37).
### TABLE 8  Proportion of patients classified by the pediatrician as ‘significantly delayed/impaired’ across a spectrum of behaviors at the conclusion of a 2-hour, structured caregiver interview administered jointly by the pediatrician and psychologist during the FASD diagnostic evaluation (see Figure 3).

<table>
<thead>
<tr>
<th>Patient Behaviors addressed in Caregiver Interview</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 59 FAS/95 PFAS</td>
<td>2. SE/AE</td>
</tr>
<tr>
<td></td>
<td>N = 154</td>
<td>N = 394</td>
</tr>
<tr>
<td><strong>Planning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs considerable help organizing daily tasks</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>Cannot organize time</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Does not understand concept of time</td>
<td>17</td>
<td>31.5</td>
</tr>
<tr>
<td>Difficulty carrying out multistep tasks</td>
<td>27</td>
<td>26.5</td>
</tr>
<tr>
<td><strong>Behavioral Regulation/Sensory Motor Integration:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor management of anger/tantrums</td>
<td>24</td>
<td>18.8</td>
</tr>
<tr>
<td>Mood swings</td>
<td>19</td>
<td>16.7</td>
</tr>
<tr>
<td>Impulsive</td>
<td>28</td>
<td>24.8</td>
</tr>
<tr>
<td>Compulsive</td>
<td>7</td>
<td>8.6</td>
</tr>
<tr>
<td>Perseverative</td>
<td>18</td>
<td>18.8</td>
</tr>
<tr>
<td>Inattentive</td>
<td>20</td>
<td>24.3</td>
</tr>
<tr>
<td>Inappropriate activity level</td>
<td>27</td>
<td>24.5</td>
</tr>
<tr>
<td>Lying/stealing</td>
<td>16</td>
<td>14.4</td>
</tr>
<tr>
<td>Unusual high/low reactivity to sound/touch/light</td>
<td>27</td>
<td>27.6</td>
</tr>
<tr>
<td><strong>Abstract Thinking/Judgment:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor judgment</td>
<td>28</td>
<td>31.1</td>
</tr>
<tr>
<td>Cannot be left alone</td>
<td>19</td>
<td>26.4</td>
</tr>
<tr>
<td>Concrete, unable to think abstractly</td>
<td>17</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>Memory/Learning/Information Processing:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor memory, inconsistent retrieval of learned information</td>
<td>33</td>
<td>28.0</td>
</tr>
<tr>
<td>Slow to learn new skills</td>
<td>21</td>
<td>17.2</td>
</tr>
<tr>
<td>Does not seem to learn from past experiences</td>
<td>21</td>
<td>22.6</td>
</tr>
<tr>
<td>Problems recognizing consequences of actions</td>
<td>21</td>
<td>21.9</td>
</tr>
<tr>
<td>Problems with information processing speed/accuracy</td>
<td>21</td>
<td>19.6</td>
</tr>
<tr>
<td><strong>Spatial Memory:</strong></td>
<td></td>
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<tr>
<td>Gets lost easily, Difficulty navigating from A to B</td>
<td>10</td>
<td>16.1</td>
</tr>
<tr>
<td><strong>Social Skills and Adaptive Behavior:</strong></td>
<td></td>
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</tr>
<tr>
<td>Behaves at a level notably younger than chronological age</td>
<td>32</td>
<td>27.8</td>
</tr>
<tr>
<td>Poor social/adaptive skills</td>
<td>30</td>
<td>25.2</td>
</tr>
<tr>
<td><strong>Motor/Oral Motor Control:</strong></td>
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<td></td>
</tr>
<tr>
<td>Poor/delayed motor skills</td>
<td>20</td>
<td>16.5</td>
</tr>
<tr>
<td>Poor balance</td>
<td>20</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Abbreviations: Chi: chi-square test statistic across Groups 1, 2 and 3. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed. Notations: Not all patients are old enough to demonstrate each of the behaviors listed above. Thus the valid % reflects the proportion of patients with significant impairment among those old enough to demonstrate the behavior.
### TABLE 9 Alcohol exposure history across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1. 59 FAS/95 PFAS</th>
<th>2. SE/AE</th>
<th>3. ND/AE</th>
<th>4. Normal CNS/AE</th>
<th>Total</th>
<th>ANOVA</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prenatal Alcohol Rank: N (valid%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1: Confirmed Absent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rank 2: Unk.</td>
<td>7</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>Rank 3: Confirmed; amount moderate or unk.</td>
<td>60</td>
<td>39.0</td>
<td>164</td>
<td>41.6</td>
<td>356</td>
<td>47.9</td>
<td>56</td>
</tr>
<tr>
<td>Rank 4: Confirmed; amount high</td>
<td>154</td>
<td>56.5</td>
<td>230</td>
<td>58.4</td>
<td>376</td>
<td>52.1</td>
<td>74</td>
</tr>
<tr>
<td>Before Pregnancy: N, mean (SD)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ave # drinks per drinking occasion</td>
<td>50</td>
<td>8.2(7.0)</td>
<td>162</td>
<td>9.8(0.1)</td>
<td>308</td>
<td>9.3(10.1)</td>
<td>67</td>
</tr>
<tr>
<td>Max # drinks per drinking occasion</td>
<td>52</td>
<td>12.0(9.4)</td>
<td>156</td>
<td>16.0(15.8)</td>
<td>264</td>
<td>14.8(14.7)</td>
<td>64</td>
</tr>
<tr>
<td>Ave # drinking days per week</td>
<td>72</td>
<td>5.5(2.0)</td>
<td>206</td>
<td>4.4(2.2)</td>
<td>373</td>
<td>4.7(2.2)</td>
<td>82</td>
</tr>
<tr>
<td>Type of alcohol consumed: N (valid%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beer</td>
<td>63</td>
<td>40.9</td>
<td>140</td>
<td>35.5</td>
<td>273</td>
<td>37.8</td>
<td>55</td>
</tr>
<tr>
<td>wine</td>
<td>20</td>
<td>13.0</td>
<td>58</td>
<td>14.7</td>
<td>100</td>
<td>13.9</td>
<td>19</td>
</tr>
<tr>
<td>liquor</td>
<td>45</td>
<td>29.2</td>
<td>122</td>
<td>31.0</td>
<td>197</td>
<td>27.3</td>
<td>32</td>
</tr>
<tr>
<td>During Pregnancy: N, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ave # drinks per drinking occasion</td>
<td>54</td>
<td>8.0(4.7)</td>
<td>176</td>
<td>8.2(8.4)</td>
<td>331</td>
<td>8.6(10.2)</td>
<td>69</td>
</tr>
<tr>
<td>Max # drinks per drinking occasion</td>
<td>56</td>
<td>12.5(10.0)</td>
<td>169</td>
<td>12.9(11.0)</td>
<td>275</td>
<td>13.3(13.9)</td>
<td>65</td>
</tr>
<tr>
<td>Ave # drinking days per week</td>
<td>81</td>
<td>5.6(2.1)</td>
<td>227</td>
<td>4.3(2.4)</td>
<td>409</td>
<td>4.4(2.3)</td>
<td>86</td>
</tr>
<tr>
<td>Type of alcohol consumed: N (valid%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beer</td>
<td>64</td>
<td>41.6</td>
<td>153</td>
<td>38.8</td>
<td>280</td>
<td>38.8</td>
<td>60</td>
</tr>
<tr>
<td>wine</td>
<td>22</td>
<td>14.3</td>
<td>58</td>
<td>14.7</td>
<td>102</td>
<td>14.1</td>
<td>18</td>
</tr>
<tr>
<td>liquor</td>
<td>42</td>
<td>27.3</td>
<td>114</td>
<td>28.9</td>
<td>197</td>
<td>27.3</td>
<td>31</td>
</tr>
<tr>
<td>Trimester of Alcohol Use: N (valid%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st only</td>
<td>17</td>
<td>13.8</td>
<td>55</td>
<td>17.2</td>
<td>71</td>
<td>12.4</td>
<td>11</td>
</tr>
<tr>
<td>2nd and 3rd only</td>
<td>17</td>
<td>13.8</td>
<td>38</td>
<td>11.9</td>
<td>61</td>
<td>10.6</td>
<td>19</td>
</tr>
<tr>
<td>All 3</td>
<td>88</td>
<td>71.5</td>
<td>214</td>
<td>66.9</td>
<td>418</td>
<td>72.9</td>
<td>74</td>
</tr>
<tr>
<td>Had an alcohol use problem: N (valid%)</td>
<td>127</td>
<td>93.4</td>
<td>315</td>
<td>86.5</td>
<td>622</td>
<td>93.1</td>
<td>113</td>
</tr>
<tr>
<td>Diagnosed with alcoholism: N (valid%)</td>
<td>90</td>
<td>82.6</td>
<td>241</td>
<td>76.3</td>
<td>545</td>
<td>79.8</td>
<td>102</td>
</tr>
<tr>
<td>Received alcohol treatment: N (valid%)</td>
<td>86</td>
<td>78.9</td>
<td>214</td>
<td>70.4</td>
<td>412</td>
<td>72.8</td>
<td>95</td>
</tr>
<tr>
<td>Source of alcohol information: N (valid%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth mother report</td>
<td>51</td>
<td>35.9</td>
<td>170</td>
<td>43.8</td>
<td>300</td>
<td>42.5</td>
<td>58</td>
</tr>
<tr>
<td>Person who directly observed birth mother</td>
<td>55</td>
<td>38.7</td>
<td>133</td>
<td>34.3</td>
<td>248</td>
<td>35.0</td>
<td>44</td>
</tr>
<tr>
<td>Other Source (med/legal/social reports)</td>
<td>36</td>
<td>25.4</td>
<td>85</td>
<td>21.9</td>
<td>160</td>
<td>22.6</td>
<td>27</td>
</tr>
</tbody>
</table>

**Abbreviations:** Chi: chi-square test statistic across Groups 1, 2 and 3, unless otherwise noted. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed. Unk: unknown. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. All 7 unknown alcohol exposures have a full FAS diagnosis. D. When FAS/PFAS are split, 35 (81.4%) of the FAS group were exposed all 3 trimesters, compared to 53 (66.3%) of the PFAS group. E. All 3 trimesters versus less than 3 trimesters.
### TABLE 10  Other prenatal and postnatal adverse exposures and events across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1. 59 FAS/95 PFAS</th>
<th>2. SE/SE</th>
<th>3. ND/ND</th>
<th>4. Normal CNS/SE</th>
<th>Total</th>
<th>F (p)</th>
<th>Post Hoc Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal Rank from 4-Digit Code: N (valid%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 1: No risk</td>
<td>2</td>
<td>1.3</td>
<td>6</td>
<td>3.6</td>
<td>4</td>
<td>0.6</td>
<td>12</td>
</tr>
<tr>
<td>Rank 2: Unknown Risk</td>
<td>27</td>
<td>17.9</td>
<td>55</td>
<td>14.2</td>
<td>89</td>
<td>12.4</td>
<td>19</td>
</tr>
<tr>
<td>Rank 3: Some Risk</td>
<td>102</td>
<td>67.5</td>
<td>283</td>
<td>73.3</td>
<td>574</td>
<td>79.9</td>
<td>101</td>
</tr>
<tr>
<td>Rank 4: High Risk</td>
<td>20</td>
<td>13.2</td>
<td>42</td>
<td>10.9</td>
<td>51</td>
<td>7.1</td>
<td>10</td>
</tr>
<tr>
<td>No prenatal care: N (valid%)</td>
<td>32</td>
<td>42.7</td>
<td>59</td>
<td>30.7</td>
<td>106</td>
<td>30.0</td>
<td>18</td>
</tr>
<tr>
<td>Maternal learning disabilities: N (valid%)</td>
<td>28</td>
<td>37.3</td>
<td>62</td>
<td>41.2</td>
<td>126</td>
<td>34.0</td>
<td>23</td>
</tr>
<tr>
<td>Paternal learning disabilities: N (valid%)</td>
<td>57</td>
<td>56.4</td>
<td>168</td>
<td>60.6</td>
<td>201</td>
<td>59.5</td>
<td>47</td>
</tr>
<tr>
<td>Other syndromes</td>
<td>22</td>
<td>43.1</td>
<td>97</td>
<td>53.9</td>
<td>165</td>
<td>54.3</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>1394</td>
<td>722</td>
<td>130</td>
<td>1400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Chi-square test statistic across the 4 study groups unless otherwise noted. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/ND: Neurodevelopmental disorder/alcohol exposed. Normal CNS/SE: No central nervous system abnormalities/alcohol exposed. SE/SE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Fisher Exact Test: FASD groups versus Group 4. D. High risk versus all other risk groups.
**TABLE 11** Mental health disorders reported in the medical records of the 1,064 patients 5 or more years of age at the time of the FASD diagnostic evaluation across the four study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Health Disorders: N (valid%)</td>
<td>N = 154</td>
<td>N = 394</td>
</tr>
<tr>
<td>One or more disorders</td>
<td>73</td>
<td>71.6</td>
</tr>
<tr>
<td>ADD/ADHD</td>
<td>53</td>
<td>59.6</td>
</tr>
<tr>
<td>Adjustment Disorder</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Antipersonality Disorder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Reactive Attachment Disorder</td>
<td>6</td>
<td>3.9</td>
</tr>
<tr>
<td>Bipolar/Manic Depression</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
<td>4.5</td>
</tr>
<tr>
<td>Dysthymic Disorder</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>8</td>
<td>5.2</td>
</tr>
<tr>
<td>Post Traumatic Stress Disorder</td>
<td>10</td>
<td>6.5</td>
</tr>
<tr>
<td>Suicidal</td>
<td>2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

TABLE 12  Patient Satisfaction Survey outcomes from the University of Washington FAS DPN Clinic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FASD Diagnostic Subgroups</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 43 FAS/ 64 PFAS</td>
<td>2. SE/ AE</td>
</tr>
<tr>
<td></td>
<td>N = 107</td>
<td>N = 248</td>
</tr>
<tr>
<td>Question on Patient Satisfaction Survey: N (valid%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Did we provide you with information you needed and were unable to get elsewhere?</td>
<td>30 96.8 73 93.6 122 88.4 19 90.5 244 91.0</td>
<td>3.9 (.28)</td>
</tr>
<tr>
<td>2. Was the explanation of the patient’s diagnosis easy to understand?</td>
<td>36 90.0 71 81.6 133 85.8 22 91.7 262 85.6</td>
<td>2.5 (.48)</td>
</tr>
<tr>
<td>3. When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?</td>
<td>15 46.9 33 55.0 55 44.0 9 52.9 112 47.9</td>
<td>3.7 (.30)</td>
</tr>
<tr>
<td>Very successful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat successful</td>
<td>11 34.4 18 30.0 48 38.4</td>
<td>3 17.6 80 34.2</td>
</tr>
<tr>
<td>4. If you were able to find the people and services we recommended to you, were they able to meet your needs?</td>
<td>7 36.8 20 44.4 34 34.3 10 66.7 71 39.9</td>
<td>6.8 (.08)</td>
</tr>
<tr>
<td>Yes, met all my needs</td>
<td>10 52.6 16 42.2 46 46.5 3 20.0 78 43.8</td>
<td></td>
</tr>
<tr>
<td>No, they met none of my needs</td>
<td>1 5.3 3 6.7 6 6.1 0 0 10 5.6</td>
<td></td>
</tr>
<tr>
<td>I was not able to find the people/services</td>
<td>1 5.3 3 6.7 13 13.1 2 13.3 19 10.7</td>
<td></td>
</tr>
<tr>
<td>5. Would you recommend the FAS Clinic to other families with similar needs?</td>
<td>32 100 75 98.7 143 98.6 21 100 271 98.9</td>
<td>0.7 (.87)</td>
</tr>
<tr>
<td>Duration of wait to get a diagnostic appointment, (yrs): mean SD</td>
<td>.53 .65 .59 .68 .56 .57 .49 .38 .56 .60</td>
<td>1.1 (.37)</td>
</tr>
</tbody>
</table>

TABLE 13  Selected contrasts between races.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Race (recorded as one race)</th>
<th>1. Caucasian</th>
<th>2. Black</th>
<th>3. American Indian or Alaskan Native</th>
<th>4. Other (including mixed race)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 684</td>
<td>N = 92</td>
<td>N = 115</td>
<td>N = 509</td>
<td>N = 1400</td>
<td>F (p)</td>
</tr>
<tr>
<td>FASD Diagnostic Group: N (valid%)</td>
<td>1. FAS/PFAS</td>
<td>87</td>
<td>12.7</td>
<td>17</td>
<td>18.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2. SE/AE</td>
<td>182</td>
<td>26.6</td>
<td>19 20.7</td>
<td>48 41.7</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>3. ND/AE</td>
<td>357</td>
<td>52.2</td>
<td>45 48.9</td>
<td>57 49.6</td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>4. Normal CNS/AE</td>
<td>58</td>
<td>8.5</td>
<td>11 12.0</td>
<td>5 7.0</td>
<td>0</td>
</tr>
<tr>
<td>Growth Rank: N (valid%)</td>
<td>1</td>
<td>436</td>
<td>63.7</td>
<td>60 65.2</td>
<td>87 75.7</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>95</td>
<td>13.9</td>
<td>15 16.3</td>
<td>10 8.7</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>88</td>
<td>12.9</td>
<td>12 13.0</td>
<td>10 8.7</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>65</td>
<td>9.8</td>
<td>5 5.4</td>
<td>8 7.0</td>
<td>33</td>
</tr>
<tr>
<td>Face Rank: N (valid%)</td>
<td>1</td>
<td>155</td>
<td>22.7</td>
<td>21 22.8</td>
<td>24 20.9</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>372</td>
<td>54.4</td>
<td>46 50.0</td>
<td>79 68.7</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>77</td>
<td>11.3</td>
<td>17 18.5</td>
<td>10 8.7</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>80</td>
<td>11.7</td>
<td>8 8.7</td>
<td>2 1.7</td>
<td>36</td>
</tr>
<tr>
<td>CNS Functional Rank: N (valid%)</td>
<td>1</td>
<td>106</td>
<td>15.5</td>
<td>20 21.7</td>
<td>12 10.4</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>397</td>
<td>58.0</td>
<td>49 53.3</td>
<td>59 51.3</td>
<td>288</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>181</td>
<td>26.5</td>
<td>23 25.0</td>
<td>44 38.3</td>
<td>123</td>
</tr>
<tr>
<td>Alcohol Rank: N (valid%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>40.6</td>
<td>39 42.4</td>
<td>39 33.9</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>401</td>
<td>58.6</td>
<td>53 57.6</td>
<td>76 66.1</td>
<td>237</td>
</tr>
<tr>
<td>Alcohol Use Before Pregnancy: N, mean (SD)</td>
<td>Ave # drinks per drinking occasion</td>
<td>302</td>
<td>7.6(6.2)</td>
<td>45 8.5(6.9)</td>
<td>48 16.8(15.2)</td>
<td>192 10.8(13.1)</td>
</tr>
<tr>
<td></td>
<td>Max # drinks per drinking occasion</td>
<td>266</td>
<td>13.3(13.9)</td>
<td>43 12.7(9.1)</td>
<td>44 22.5(17.5)</td>
<td>183 16.0(17.4)</td>
</tr>
<tr>
<td></td>
<td>Ave # drinking days per week</td>
<td>383</td>
<td>4.7(2.2)</td>
<td>53 5.3(2.2)</td>
<td>55 4.1(2.3)</td>
<td>242 4.6(2.2)</td>
</tr>
<tr>
<td>Alcohol Use During Pregnancy: N, mean (SD)</td>
<td>Ave # drinks per drinking occasion</td>
<td>325</td>
<td>7.3(7.2)</td>
<td>45 8.2(6.2)</td>
<td>49 12.9(10.8)</td>
<td>211 9.4(13.4)</td>
</tr>
<tr>
<td></td>
<td>Max # drinks per drinking occasion</td>
<td>282</td>
<td>11.6(11.7)</td>
<td>41 13.4(8.2)</td>
<td>45 19.3(14.4)</td>
<td>197 12.9(13.0)</td>
</tr>
<tr>
<td></td>
<td>Ave # drinking days per week</td>
<td>415</td>
<td>4.6(3.3)</td>
<td>57 5.7(1.9)</td>
<td>57 3.8(2.3)</td>
<td>274 4.4(2.3)</td>
</tr>
<tr>
<td>Drank only in 1st trimester: N (valid%)</td>
<td>67</td>
<td>12.1</td>
<td>6.7</td>
<td>20 20.2</td>
<td>61 15.3</td>
<td>154 13.6</td>
</tr>
<tr>
<td>Drank all 3 trimesters: N (valid%)</td>
<td>395</td>
<td>71.2</td>
<td>59 76.1</td>
<td>65 65.7</td>
<td>275 69.1</td>
<td>794 70.3</td>
</tr>
<tr>
<td>Had an alcohol use problem: N (valid%)</td>
<td>569</td>
<td>90.5</td>
<td>66 82.5</td>
<td>107 94.7</td>
<td>435 92.8</td>
<td>1177 91.2</td>
</tr>
<tr>
<td>Diagnosed with alcoholism: N (valid%)</td>
<td>431</td>
<td>78.6</td>
<td>41 62.1</td>
<td>95 90.5</td>
<td>320 81.6</td>
<td>887 79.8</td>
</tr>
<tr>
<td>Received alcohol treatment: N (valid%)</td>
<td>383</td>
<td>70.8</td>
<td>43 63.2</td>
<td>79 78.2</td>
<td>302 78.2</td>
<td>807 73.6</td>
</tr>
<tr>
<td>Other adverse exposures in pregnancy: N (valid %)</td>
<td>486</td>
<td>92.6</td>
<td>77 96.3</td>
<td>65 87.8</td>
<td>345 94.8</td>
<td>975 93.3</td>
</tr>
<tr>
<td>Child's age at diagnosis (yrs): N mean (SD)</td>
<td>684</td>
<td>9.3(6.9)</td>
<td>92 8.9(4.4)</td>
<td>115 9.5(5.8)</td>
<td>509 8.6(5.8)</td>
<td>1400 9.0(6.2)</td>
</tr>
<tr>
<td>Mom's age(yr) at child's diagnosis: N mean (SD)</td>
<td>579</td>
<td>35.7(9.5)</td>
<td>73 35.1(6.1)</td>
<td>86 35.9(8.0)</td>
<td>412 33.4(7.9)</td>
<td>1147 34.8(7.8)</td>
</tr>
<tr>
<td>Mom's age(yr) at child's birth: N mean (SD)</td>
<td>576</td>
<td>26.4(6.5)</td>
<td>73 26.7(5.3)</td>
<td>86 26.5(6.1)</td>
<td>412 24.9(6.1)</td>
<td>1147 25.9(6.3)</td>
</tr>
<tr>
<td>Parity of index child: N mean (SD)</td>
<td>570</td>
<td>2.5(1.5)</td>
<td>77 3.2 (1.8)</td>
<td>99 3.3 (2.1)</td>
<td>410 2.8 (1.8)</td>
<td>1156 2.7 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Chi: chi-square test statistic across the 4 racial groups. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05.

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Brain Microstructure Is Related to Math Ability in Children With Fetal Alcohol Spectrum Disorder

Catherine Lebel, Carmen Rasmussen, Katy Wyper, Gail Andrew, and Christian Beaulieu

**Background:** Children with fetal alcohol spectrum disorder (FASD) often demonstrate a variety of cognitive deficits, but mathematical ability seems to be particularly affected by prenatal alcohol exposure. Parietal brain regions have been implicated in both functional and structural studies of mathematical ability in healthy individuals, but little is known about the brain structure underlying mathematical deficits in children with FASD. The goal of this study was to use diffusion tensor imaging (DTI) to investigate the relationship between mathematical skill and brain white matter structure in children with FASD.

**Methods:** Twenty-one children aged 5 to 13 years diagnosed with FASD underwent DTI on a 1.5-T MRI scanner and cognitive assessments including the Woodcock-Johnson Quantitative Concepts test. Voxel-based analysis was conducted by normalizing subject images to a template and correlating fractional anisotropy (FA) values across the brain white matter with age-standardized math scores.

**Results:** Voxel-based analysis revealed 4 clusters with significant correlations between FA and math scores: 2 positively-correlated clusters in the left parietal region, 1 positively-correlated cluster in the left cerebellum, and 1 negatively-correlated cluster in the bilateral brainstem. Diffusion tractography identified the specific white matter tracts passing through these clusters, namely the left superior longitudinal fasciculus, left corticospinal tract and body of the corpus callosum, middle cerebellar peduncle, and bilateral projection fibers including the anterior and posterior limbs of the internal capsule.

**Conclusions:** These results identify 4 key regions related to mathematical ability and provide a link between brain microstructure and cognitive skills in children with FASD. Given previous findings in typically developing children and those with other abnormal conditions, our results highlight the consistent importance of the left parietal area for mathematical tasks across various populations, and also demonstrate other regions that may be specific to mathematical processing in children with FASD.

**Key Words:** Mathematics, Arithmetic, Fetal Alcohol Spectrum Disorder, Diffusion Tensor Imaging, White Matter.

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Diffusion tensor imaging (DTI) is a powerful technique (Basser et al., 1994) that is excellent for studying white matter microstructure. DTI yields a quantitative diffusion parameter, fractional anisotropy (FA), that is related to axonal packing and myelination (Beaulieu, 2002). DTI has been used to study brain abnormalities in children with FASD (Fryer et al., 2009; Lebel et al., 2008; Li et al., 2009; Sowell et al., 2008a; Wozniak et al., 2006, 2009), but only 2 studies reported correlations between cognitive tests and brain structure. Sowell and colleagues (2008a) observed a relationship between white matter integrity in the splenium of the corpus callosum and scores on a visuomotor integration task. Wozniak and colleagues (2009) observed a significant positive correlation between working memory and FA in the genu of the corpus callosum, and negative correlations between splenium MD and both perceptual organization and working memory. Another study reported correlations between FA and both intelligence and processing speed across a group of healthy controls and FASD youth, but these correlations were not significant in the FASD group alone (Ma et al., 2005), although their small sample size (n = 9) limits the power to detect correlations within the FASD group alone.

Two previous DTI studies correlated FA with mathematical abilities in children, 1 in a typically developing cohort (van Eimeren et al., 2008) and 1 in a rare genetic disorder, velocardiofacial syndrome (Barnea-Goraly et al., 2005). Both studies reported left parietal correlations; the former also implicated the left inferior temporal area. However, correlations between brain structure and mathematical abilities have never been reported in FASD. Given the severity of mathematical deficits in FASD, there is likely to be a relationship between these difficulties and the underlying brain structure. The purpose of this study was to use DTI to examine the relationship between mathematical ability and white matter anisotropy in 21 children with FASD.

MATERIALS AND METHODS

Subjects

Subjects were 21 children aged 5 to 13 years (mean ± SD: 9.2 ± 2.2 years, 12 males/9 females, 16 right-handed/5 left-handed) diagnosed with a condition falling under the umbrella term FASD, recruited through a hospital FASD clinic. Child assent and parent/guardian consent were obtained from all participants in the study. These subjects were a subset of the 24 children (the other 3 did not have math scores) examined in our previous study focusing on group comparisons of DTI parameters between children with FASD and a healthy cohort (Lebel et al., 2008). All children had confirmed prenatal alcohol exposure which was validated by a social worker (prior to entry into the clinic) based on extensive review of birth records, Child and Youth Services documentation, and/or parental interview. All participants had a medical diagnosis of an alcohol-related disorder falling under the umbrella term FASD, made by a multidisciplinary team using the Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code (Astley, 2004). The 4-Digit Diagnostic Code ranks diagnostic information in the areas of growth deficiency, facial phenotype, brain dysfunction, and alcohol use. The magnitude of expression of each diagnostic feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the fetal alcohol syndrome (FAS) feature and 4 reflecting a strong “classic” presence of the FAS feature. To meet the criteria for FASD, all children must have a brain code of 2 or higher as well as confirmed alcohol exposure, as indicated by Alcohol Use scores of 3 (some risk) or 4 (high risk).

Table 1 presents subject characteristics for each participant. Two subjects were diagnosed with FAS, 1 with partial FAS, 10 had neurobehavioral disorder-alcohol exposed, 4 had static encephalopathy-alcohol exposed, 3 had sentinel physical findings/static encephalopathy-alcohol exposed, and 1 had sentinel physical findings/neurobehavioral disorder-alcohol exposed. Specific information about quantity and timing of alcohol use during pregnancy was not available for most subjects; however, all children had confirmed significant alcohol exposure, as shown in Table 1. Exposure to other drugs in utero was reported for 13 subjects; substances included tobacco, marijuana, and cocaine. Although this is a potential concern, the 13 subjects with other exposures were spread across the range of math scores; the children with the top 5 math scores and 5 of the 6 children with the lowest math scores all had exposure to other drugs. Gestational age of the 17 children for whom this information was available ranged from 36 to 41 weeks; 3 children were born preterm at 36 to 37 weeks. Birth weight and head circumference were within the normal range for most children: 8 children had birth weights below the 25th percentile and 4 were below the 10th percentile, but all head circumferences were above the 25th percentile, according to growth charts (Astley, 2004). Of the 17 children with recorded Apgar scores, 1 minute scores ranged from 4 to 9, with 12

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Dominant hand</th>
<th>Sex</th>
<th>4-Digit codea</th>
<th>Diagnosis</th>
<th>Math score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.3</td>
<td>R</td>
<td>M</td>
<td>1124</td>
<td>NBD-AE</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>11.8</td>
<td>R</td>
<td>M</td>
<td>4433</td>
<td>FAS</td>
<td>62</td>
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<tr>
<td>3</td>
<td>8.4</td>
<td>R</td>
<td>F</td>
<td>1223</td>
<td>NBD-AE</td>
<td>70</td>
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<tr>
<td>4</td>
<td>8.2</td>
<td>R</td>
<td>F</td>
<td>1124</td>
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<tr>
<td>5</td>
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<td>M</td>
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<td>NBD-AE</td>
<td>73</td>
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<tr>
<td>6</td>
<td>6.7</td>
<td>R</td>
<td>M</td>
<td>1123</td>
<td>NBD-AE</td>
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<tr>
<td>7</td>
<td>11.0</td>
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<td>F</td>
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<td>SP/SE-AE</td>
<td>79</td>
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<tr>
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<td>R</td>
<td>M</td>
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<tr>
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<td>Partial FAS</td>
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<td>14</td>
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<tr>
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<td>9.7</td>
<td>R</td>
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<td>SP/SE-AE</td>
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<td>16</td>
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<td>F</td>
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<td>SP/SE-AE</td>
<td>101</td>
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<tr>
<td>17</td>
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<td>F</td>
<td>2–23b</td>
<td>NBD-AE</td>
<td>103</td>
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<tr>
<td>18</td>
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<td>M</td>
<td>1323</td>
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<td>105</td>
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<tr>
<td>19</td>
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<td>1223</td>
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<td>20</td>
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<td>M</td>
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<td>NBD-AE</td>
<td>113</td>
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<tr>
<td>21</td>
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<td>F</td>
<td>1123</td>
<td>NBD-AE</td>
<td>115</td>
</tr>
</tbody>
</table>

NBD-AE, neurobehavioral disorder—alcohol exposed; FAS, fetal alcohol syndrome; SE-AE, static encephalopathy—alcohol exposed; SP/SE-AE, sentinel physical findings/static encephalopathy—alcohol exposed; SP/NBD-AE, sentinel physical findings/neurobehavioral disorder—alcohol exposed.

aThe first digit represents growth deficiency, the second facial phenotype, third brain dysfunction, and the fourth indicates prenatal alcohol exposure. A score of 1 indicates complete absence of the classic fetal alcohol syndrome feature, while a 4 indicates its strong presence.

bThis subject was not assessed a facial score due to cleft palate.

cCode not available due to inaccessible file.
children within the normal range of 7 to 10. At 5 minutes, all children were within the normal range.

**Cognitive Assessment**

A battery of cognitive assessments was performed on each child including the Woodcock Johnson III (WJ-III) Tests of Achievement-Quantitative Concepts subtest to assess mathematical ability (listed in Table 1 per subject). For the full battery and mean scores for other cognitive tests, please refer to our previous study (Lebel et al., 2008). The Quantitative Concepts subtest involves knowledge of math concepts, symbols, and vocabulary. Initial items involve counting, as well as identifying numbers, shapes, sequences, and identification of math operations and signs. Later items involve figuring out number patterns and identifying missing numbers in a series. Test scores were normalized based on participant age, and standardized Quantitative Concepts scores were compared to the typical mean score of 100 using a 1 sample t-test with a significance level of 0.05.

**Image Acquisition**

All data were acquired on the same 1.5 T Siemens Sonata MRI scanner using identical methods. Total acquisition time was approximately 25 minutes and included DTI, and anatomical T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging. DTI was acquired using a dual spin-echo, single shot echo-planar imaging sequence with the following parameters: 40 3 mm thick axial-oblique slices with no inter-slice gap, repetition time (TR) = 6400 ms, echo time (TE) = 88 ms, 6 non-collinear diffusion sensitizing gradient directions with \( b = 1000 \text{s/mm}^2 \), 8 averages, field-of-view 220 x 220 mm\(^2\), matrix of 128 x 128 zero-filled to 256 x 256, 75% phase partial Fourier, acquisition time 6:06 minutes. In the non-diffusion-weighted (\( b = 0 \text{s/mm}^2 \)) images, signal-to-noise ratio (SNR) was quite high with a range of 67 to 88 (mean = 79) and thus yielded excellent quality FA maps (Fig. 1). High resolution (1 x 1 x 1 mm\(^3\)) T1-weighted images were acquired using MPRAGE with TE = 4.38 ms, TR = 1870 ms, TI = 1100 ms, and a scan time of 4:29 minutes. Head motion was minimized using ear pads, but not all children were able to complete the entire 25-minute protocol. Therefore, T1-weighted images were obtained in 18 of the 21 children, while conventional T2-weighted and FLAIR scans were obtained for 17 children, and were used to ensure that there were no frank lesions.

**Voxel-Based Image Analysis**

Non-diffusion weighted images (\( b = 0 \text{s/mm}^2 \)) were normalized to the ICBM EPI template using non-affine transformations in statistical parametric mapping software (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK). The same transformation parameters were then used to normalize each individual’s FA map to Montreal Neurological Institute (MNI) space, and normalized FA maps were smoothed using a 4-mm kernel. Voxel-based correlation of FA with age-standardized math scores was performed in SPM5. Because FA values increase with age, age was controlled in the analysis by including it in the regression model in SPM5. To minimize inter-subject registration errors and to avoid inclusion of voxels associated with cortical gray matter or cerebrospinal fluid in any 1 individual, only voxels with FA \( \geq 0.2 \) (i.e. white matter) in all 21 subjects were included for further analysis. Due to the FA thresholding, many voxels are excluded from analysis and a simple false discovery rate correction across the brain is not appropriate. Monte Carlo simulations were conducted in AlphaSim (B. Ward, http://afni.nimh.nih.gov/afni/doc/ manual/AlphaSim) to determine the probability that clusters of various sizes would randomly occur. These simulations showed that a p-value threshold of 0.05 per voxel and a cluster size threshold of 81 contiguous voxels produced an overall alpha value of 0.048.

Therefore, these thresholds were used with an F-test to determine clusters with significant correlations between FA values and math scores. Clusters were overlaid on each individual subject’s FA map and visualized in a movie loop to ensure adequate registration and that each cluster was within the same structure(s) in each individual.

A separate analysis was conducted on the 16 right-handed subjects using the exact same methods. Monte Carlo simulations for this data showed that a p-value threshold of 0.05 and a cluster threshold of 101 voxels gave an overall alpha value of 0.05.

**Diffusivities**

To give an indication of the primary cause of any correlations between FA and math scores, the parallel and perpendicular diffusivities (\( l_p \) and \( l_s \)) were measured. Significant clusters from normalized space were warped back to native space for each individual using the inverse of the original template transformation parameters. FA, parallel, and perpendicular diffusivities were averaged across each cluster for each individual and correlated with standardized math scores, controlling for age.

**Tractography**

Diffusion tensor imaging tractography was used to evaluate which white matter tracts passed through the significant FA-math ability clusters. Inverse transformation parameters were calculated from the original non-diffusion weighted image transformations to the EPI template. These parameters were used to transform significant math ability-FA clusters from MNI space to native space for each individual. Once in native space, each cluster was used separately as a seeding region for tractography. FA thresholds were set to 0.25 to initiate and continue tracking, while the angle threshold was set to 60\(^\circ\). Deterministic streamline tractography was performed in Matlab using code from ExploreDTI (A. Leman, Utrecht, the Netherlands). All tracts produced by each seeding region were retained (i.e., no target or exclusion regions were used).

Fig. 1. Significantly correlated clusters of fractional anisotropy versus math ability in 21 fetal alcohol spectrum disorder (FASD) children. The locations of the 4 significantly correlated clusters are shown in yellow (positive correlations) and cyan (negative correlation). On the left, each cluster is shown with a backdrop of a coronal and a sagittal slice (T1-weighted images). On the right, one slice through each cluster is shown, with the significantly correlated voxels in that slice overlaid onto an individual FA map. The location of each axial slice is shown as a red line through the coronal and sagittal slices. MNI coordinates of each slice are given. All images shown are normalized images from a 10-year-old girl with FASD who scored 75 on the WJ Quantitative Concepts test.
RESULTS

Quantitative Concepts Scores

The children with FASD in this study scored significantly below average (average normalized score in healthy children is 100 ± 15) on the Woodcock-Johnson III (WJ-III) Tests of Achievement—Quantitative Concepts subtest of mathematical ability (mean ± standard deviation = 87 ± 17, \( p = 0.002 \)). See Table 1 for individual scores.

Correlations of FA With Math Scores

Voxel-based analysis revealed 4 clusters with significant correlations between FA and standardized Quantitative Concepts scores, after controlling for age (see Table 2, Fig. 1). Of these 4 clusters, 3 in the left hemisphere showed positive correlations between FA and math scores and one spanning both hemispheres was negatively correlated. The largest positively correlated cluster contained 186 voxels and was located in the left anterior cerebellum. The 2 other positively correlated clusters were located in the left parietal lobe, one in the lower parietal area (83 voxels), and the other more superiorly (114 voxels); both parietal clusters were close to the left IPS. The negatively correlated cluster was located in the brainstem bilaterally (110 voxels). Mean FA values in each cluster (averaged over all voxels in the cluster per individual) ranged from 0.31 to 0.51 for the cerebellar cluster, 0.38 to 0.54 for the brainstem, 0.29 to 0.56 for the lower parietal cluster, and 0.33 to 0.48 for the upper parietal cluster. The location of the most correlated voxel in each cluster is shown in Fig. 2, along with plots of FA versus math score (both corrected for age) for that voxel. Correlations between math scores and FA were very high for these voxels, with \( R \) values of 0.74, 0.69, 0.64, and −0.69 (\( p < 0.001 \)).

Right-Handed Subjects Only

Excluding the 5 left-handed subjects, a repeat of the voxel-based analysis on right-handed subjects only (\( n = 16 \)) revealed 5 significantly correlated clusters. Three clusters were in the same regions as the significant clusters from the analysis on all 21 subjects: a positively correlated left cerebellum cluster (290 voxels), a positively correlated lower left parietal cluster (124 voxels), and a positively correlated upper left parietal cluster (142 voxels). Two additional clusters were observed: a negatively correlated left occipital cluster (154 voxels) and a positively correlated left splenium cluster (322 voxels).

Diffusivities

Average FA values, as measured across the entire cluster in native space for each individual, were strongly and significantly correlated with standardized math scores (after age correction), as expected. Correlations of FA, parallel diffusivity \((\lambda_p)\), and perpendicular diffusivity \((\lambda_n)\) with math scores (both age-corrected) are shown in Fig. 3. Note that these correlations are slightly different than the ones shown in Fig. 2, as FA is not taken only from the most significantly correlated voxel (as it was for Fig. 2), but has been averaged across the entire cluster. For the lower and upper left parietal clusters, parallel diffusivity \((\lambda_p)\) was also correlated with math scores \((p = 0.001, <0.001; R = 0.68, 0.75, \text{respectively})\). Perpendicular diffusivity \((\lambda_n)\) in the parietal clusters was not significantly correlated with math scores. In contrast, perpendicular diffusivity was the primary cause of FA-math score correlations in the cerebellum and brainstem clusters \((p = 0.005, 0.002; R = −0.58, 0.64, \text{respectively})\), while parallel diffusivity in these regions was not significantly correlated with math scores.

White Matter Tracts Passing Through Clusters

Diffusion tractography was used to determine which white matter tracts were contained within each of the 4 significant clusters (see Fig. 4). The cerebellar cluster produced tracts from the middle cerebellar peduncle, a white matter tract connecting the cerebellum and the pontine nuclei. Although the entire cerebellar cluster was located in the left hemisphere, middle cerebellar peduncle tracts cross the midline so fiber tracking yielded streamlines in both hemispheres. Using the lower left parietal cluster as a seeding region gave tracts belonging to the left superior longitudinal fasciculus, a frontal–parietal–temporal connection. The upper left parietal cluster revealed tracts belonging to both the body of the corpus callosum and the left corticospinal tracts. The negatively correlated cluster in the brainstem produced projection fibers bilaterally, including the anterior and posterior limbs of the internal capsule, as well as some cerebellar tracts. Tractography results were consistent from subject to subject, with each cluster

<table>
<thead>
<tr>
<th>Cluster size (no. voxels)</th>
<th>Anatomical location</th>
<th>MNI coordinates of most correlated voxel</th>
<th>Correlation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>186</td>
<td>Left cerebellum</td>
<td>−12, −34, −42</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>83</td>
<td>Left parietal lobe</td>
<td>−36, −16, 26</td>
<td>0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>114</td>
<td>Upper left parietal lobe</td>
<td>−22, −28, 50</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>110</td>
<td>Brainstem (bilateral)</td>
<td>−6, −24, −20</td>
<td>−0.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Correlation \( R \) value and significance shown is from correlation of FA with math scores, controlling for age, in the most correlated voxel of each cluster.
DISCUSSION

Diffusion tensor imaging has demonstrated correlations between mathematics scores and FA in white matter of the left parietal lobe, left cerebellum, and bilateral brainstem in children with FASD for the first time. Brain structure in the left parietal region seems to be consistently involved in mathematics across both healthy and abnormal populations, as it has been previously implicated in both healthy individuals (van Eimeren et al., 2008) and those with a rare genetic disorder (Barnea-Goraly et al., 2005). The observed positive correlations in the cerebellar region and the negative correlations in the brainstem are new findings that may or may not be specific to children with FASD.

Parietal gray matter bilaterally has been consistently implicated in mathematical abilities by both functional (Ansari and Dhital, 2006; Chochon et al., 1999; Dehaene et al., 1999; Eger et al., 2003; Kucian et al., 2006; Molko et al., 2003; Price et al., 2007) and structural (Isaacs et al., 2001; Molko et al., 2003; Rotzer et al., 2008) imaging studies. The entire parietal area is important for mathematical processing, but the horizontal segment of the IPS, in particular, seems to be specific to the number domain. The horizontal IPS, on both the left and right sides, is activated by the great majority of functional imaging studies of mathematics and number processing, and shows increased activation with more quantitative tasks (Dehaene et al., 2003). It is also the left horizontal IPS region that has been implicated in lesion studies showing that strokes here are associated with subsequent acalculia (Ashkenazi et al., 2008; Takayama et al., 1994). While the underlying white matter has not been as extensively examined,

Fig. 2. Correlations between math scores and fractional anisotropy. Math scores were highly correlated with fractional anisotropy (FA) in 4 clusters: 2 in the left parietal lobe (A, B), 1 in the left cerebellum (C), and 1 in the bilateral brainstem (D). The most correlated voxel for each cluster is shown with a plot of FA versus standardized math score (Woodcock Johnson Quantitative Concepts), after controlling for age (residuals of age correlations are shown). For all 4 correlations, p < 0.001.
2 DTI studies, 1 in healthy children and 1 in children with the genetic-based velocardiofacial syndrome, showed correlations between left parietal white matter anisotropy and math ability (Barnea-Goraly et al., 2005; van Eimeren et al., 2008). Here, we show that left parietal white matter microstructure directly underlying the horizontal IPS is related to mathematical skills in children with FASD. Figure 5 demonstrates the proximity of the 2 left parietal clusters with significant FA-math correlations.

Fig. 3. Parallel and perpendicular diffusivities. Correlations of fractional anisotropy (FA) and parallel and perpendicular diffusivities with math scores (both corrected for age) are shown for all voxels averaged over each of the 4 significant clusters. For the cerebellum and brainstem clusters, changes of perpendicular diffusivity were the primary cause of the FA-math correlations, while for the 2 left parietal clusters, it was parallel diffusivity driving the FA-math score correlations.
correlations to the left horizontal IPS. Both clusters are adjacent to the horizontal IPS, and the tracts passing through them surround the sulcus. Clearly, there is consistent involvement of the intraparietal region, both gray matter and white matter, in mathematical processing tasks. This study provides further evidence that this area is crucial to mathematical tasks across both typically developing and abnormal populations, given the previously observed DTI correlations in healthy children and those with a genetic condition. Interestingly, however, we (and the other 2 DTI math studies) find that only the left white matter is correlated with mathematical ability, in contrast to the bilateral activation of the IPS region shown by the majority of functional imaging studies.

We identified using tractography which specific white matter connections are contained in these parietal clusters, namely the superior longitudinal fasciculus, corticospinal tracts, and body of the corpus callosum (see Figs. 4 and 5). The superior longitudinal fasciculus, the tract containing the lower left parietal cluster observed in this study, is a frontal–parietal–temporal connection known to be involved in language and intelligence tasks (Marslen-Wilson and Tyler, 2007). FA in the superior longitudinal fasciculus has been correlated with IQ (Schmithorst et al., 2005), language (Ashtari et al., 2007), and processing speed (Turken et al., 2008); here we show that a portion of it is also correlated with math ability in children with FASD. The second, upper parietal cluster contained left corticospinal tracts and part of the body of the corpus callosum. This region has been previously implicated in DTI studies of reading ability in children (Beaulieu et al., 2005; Deutsch et al., 2005; Niogi and McCandliss, 2006) and adults (Klingberg et al., 2000), suggesting that it is an important region for a variety of cognitive tasks. Structurally, the parietal brain regions are known to be abnormal in children with FASD, having thicker cortices (Sowell et al., 2008b), smaller volumes (Archibald et al., 2001), and abnormal diffusion parameters (Fryer et al., 2009; Lebel et al., 2008) compared to typically developing children, and previous studies have speculated that abnormal parietal function in children with FASD may lead to their mathematical deficits (Riikonen et al., 1999).

A third positively correlated cluster was observed in the left anterior region of the cerebellum, suggesting that this area is also related to math ability in FASD. The fiber tracts that contain this cluster belong to the middle cerebellar peduncle, the largest of the cerebellar peduncles, and connect the cerebellum with the pontine nuclei. The cerebellum is one of the regions most affected by prenatal alcohol exposure (Archibald et al., 2001; Jones and Smith, 1973; Spadoni et al., 2007), particularly the anterior portion (Sowell et al., 1996). Although the cerebellum is traditionally thought to regulate motor coordination and balance, recent studies have suggested it also plays a role in higher cognition. Cerebellar volume correlates positively with intelligence measures in healthy young adults (Andreasen et al., 1993) and preterm adolescents (Parker et al., 2008), cerebellar abnormalities are associated with a variety of intellectual deficits (Steinlin, 2008), and the cerebellum is often activated during cognitive tasks (Baillieux et al., 2008). The cerebellum plays an important role in learning processes, and it is hypothesized that the earlier abnormalities are present, the more severe the deficits.

**Fig. 4.** White matter tracts passing through significant fractional anisotropy (FA)-math score clusters. Each of the 4 clusters with significant correlations between FA and Quantitative Concepts math scores was used as a seeding region for tractography. All tracts produced from each cluster in a 9-year-old boy with fetal alcohol spectrum disorder and a math score of 100 are shown above in native space. Three positive clusters (top) were observed: an upper left parietal cluster (tracts in blue) that produced corticospinal tracts and part of the corpus callosum; a lower parietal cluster (tracts in green) that contained the superior longitudinal fasciculus; and a cerebellar cluster (tracts in orange) whose tracts are part of the middle cerebellar peduncle. The negative cluster (bottom) produced projection fibers (tracts in purple).

**Fig. 5.** Parietal fractional anisotropy (FA)-math clusters in relation to the left intraparietal sulcus. The 2 left parietal clusters (yellow) that showed significant correlations between FA and mathematics scores are in very close proximity to the left intraparietal sulcus shown in red. The tracts passing through each cluster are also shown: the left corticospinal tracts and part of the corpus callosum pass through the upper parietal cluster (tracts in blue), while the superior longitudinal fasciculus (tracts in green) passes through the lower parietal cluster. All structures shown are in native space in a 9-year-old boy with fetal alcohol spectrum disorder (math score = 100).
with math ability in either of the previous DTI math studies (Steinlin, 2008). This region was not observed to correlate with the 3 positively correlated clusters, which were all found in the left hemisphere. Tracts from this cluster were primarily projection fibers, including both the anterior and posterior limbs of the internal capsule (see Fig. 4). Although the observed negative correlations may seem counter intuitive, negative relationships have been observed previously between cognitive scores and brain structure, in healthy children (Dougherty et al., 2007), dyslexic adults (Frye et al., 2008), and adults with Williams Syndrome, a neurodevelopmental disorder (Hoeft et al., 2007). Negative correlations may also be related to changes in crossing fiber areas. The standard tensor model attributes artificially low FA values to areas in which 2 or more fiber bundles intersect. Therefore, degradation of one of the fiber bundles in the crossing area would actually lead to higher FA values in that region, and it is possible that negative correlations between FA and math scores may actually still represent lower white matter integrity in that region of children who are poorer at math.

One negatively correlated cluster was observed in the brainstem, located on both sides of the midline. This is in contrast to the 3 positively correlated clusters, which were all found in the left hemisphere. Tracts from this cluster were primarily projection fibers, including both the anterior and posterior limbs of the internal capsule (see Fig. 4). Although the observed negative correlations may seem counter intuitive, negative relationships have been observed previously between cognitive scores and brain structure, in healthy children (Dougherty et al., 2007), dyslexic adults (Frye et al., 2008), and adults with Williams Syndrome, a neurodevelopmental disorder (Hoeft et al., 2007). Negative correlations may also be related to changes in crossing fiber areas. The standard tensor model attributes artificially low FA values to areas in which 2 or more fiber bundles intersect. Therefore, degradation of one of the fiber bundles in the crossing area would actually lead to higher FA values in that region, and it is possible that negative correlations between FA and math scores may actually still represent lower white matter integrity in that region of children who are poorer at math.

Analysis of the parallel and perpendicular diffusivities gives insight into the cause of the FA-math score correlations observed (see Fig. 3). For the 2 left parietal clusters, parallel diffusivity was significantly positively correlated with math scores, after correcting for age, but perpendicular diffusivity was not. Parallel diffusivity is often associated with axonal integrity, and axonal damage has been linked to decreases of parallel diffusivity (Song et al., 2003). In the cerebellar and brainstem clusters, the FA-math score correlations were driven by the perpendicular diffusivity, while the parallel diffusivity-math score correlations were not significant. Perpendicular diffusivity in the cerebellar cluster was negatively correlated with math scores, while it was positively correlated in the brainstem cluster. Perpendicular diffusivity is generally associated with myelination and axonal packing, and studies have shown that demyelination and remyelination lead to increases and decreases of perpendicular diffusivity, respectively (Song et al., 2002, 2005).

Although both functional and structural brain laterality exist for language tasks, laterization and handedness in mathematics have been less well studied. Although our left-handed subjects were spread across the range of math scores, grouping both left- and right-handed subjects together for analysis is a potential concern. To address this concern, a separate analysis was conducted in exactly the same way on the 16 right-handed subjects only. This analysis revealed 5 significantly correlated clusters, 3 of which corresponded to the left cerebellar and 2 left parietal clusters observed within the whole group. These results should increase confidence in those 3 particular clusters, as those results were consistent whether or not left handers were included. The discrepancies between the results with right handers only versus the entire group, specifically the absence of the brainstem cluster in the right handers only, and the appearance of 2 other clusters in the left occipital area and left splenium in the right-hander analysis may be due to handedness and lateralization differences, or may simply be caused by a slightly different subject group. Due to the small number \( n = 5 \) of left handers, a left hander only analysis was not feasible. Nonetheless, there were strong similarities between the right hander only results and the entire group, suggesting robust correlations between FA and math scores in the parietal and cerebellar regions.

Although gender differences have not been examined by most brain imaging studies of mathematical abilities (Ansari and Dhital, 2006; Barnea-Goraly et al., 2005; Dehaene et al., 1999; Eger et al., 2003; van Eimeren et al., 2008), they are a potential concern. With our relatively small sample size, it was not feasible to further subdivide our group into males \( (n = 12) \) and females \( (n = 9) \) for separate analyses. Males and females are plotted separately in Fig. 3, and it appears as though they both follow the same relationships between diffusion parameters and math scores. Furthermore, including gender as an additional covariate for correlations between math scores and diffusion parameters averaged across each cluster produced exactly the same results as not including gender, suggesting that gender differences are minimal. Future studies with larger sample sizes will be better able to investigate gender (and handedness) differences and may help determine the consistency of the clusters and their dependence on these variables.

Alcohol exposure during fetal development affects secondary calcium signaling pathways (Kumada et al., 2007), alters glutamate NMDA receptor function (Hughes et al., 1998), increases apoptotic neurodegeneration (Ikonomidou et al., 2001), and impairs neuronal proliferation and migration (Miller, 1986). These disruptions to the developing nervous system can result in abnormal cerebral and axonal growth (Ma et al., 2003; Mennerick and Zorumski, 2000; Olney, 2004), leading to brain malformations caused by neuronal and glial migration errors (Clarens et al., 1978; Jones and Smith, 1973; Peiffer et al., 1979). Clearly, the many cognitive deficits observed in FASD (Jacobson and Jacobson, 2002; Mukherjee et al., 2006) are related to the widespread structural brain abnormalities (Fryer et al., 2009; Lebel et al., 2008; Li et al., 2009; Sowell et al., 2008a; Wozniak et al., 2006, 2009), and here DTI measures of tissue microstructure have yielded 4 select white matter regions related to math ability.

Future studies combining DTI with other techniques such as functional MRI or shape and thickness measurements of various brain structures in children with FASD would be useful for linking mathematical abilities with functional, cortical, and underlying white matter abnormalities. Ultimately, a better understanding of the brain structures related to cognitive skills such as mathematics may lead to
earlier diagnoses and more effective treatment of such difficulties, not only in children with FASD, but also in the wider population.

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REFERENCES


Magnetic Resonance Microscopy Defines Ethanol-Induced Brain Abnormalities in Prenatal Mice: Effects of Acute Insult on Gestational Day 7


Background: This magnetic resonance microscopy (MRM)-based report is the second in a series designed to illustrate the spectrum of craniofacial and central nervous system (CNS) dysmorphia resulting from single- and multiple-day maternal ethanol treatment. The study described in this report examined the consequences of ethanol exposure on gestational day (GD) 7 in mice, a time in development when gastrulation and neural plate development begins; corresponding to the mid- to late third week postfertilization in humans. Acute GD 7 ethanol exposure in mice has previously been shown to result in CNS defects consistent with holoprosencephaly (HPE) and craniofacial anomalies typical of those in Fetal Alcohol Syndrome (FAS). MRM has facilitated further definition of the range of GD 7 ethanol-induced defects.

Methods: C57BL/6J female mice were intraperitoneally (i.p.) administered vehicle or 2 injections of 2.9 g/kg ethanol on day 7 of pregnancy. Stage-matched control and ethanol-exposed GD 17 fetuses selected for imaging were immersed in a Bouins/Prohance solution. MRM was conducted at either 7.0 Tesla (T) or 9.4 T. Resulting 29 µm isotropic spatial resolution scans were segmented and reconstructed to provide 3D images. Linear and volumetric brain measures, as well as morphological features, were compared for control and ethanol-exposed fetuses. Following MRM, selected specimens were processed for routine histology and light microscopic examination.

Results: Gestational day 7 ethanol exposure resulted in a spectrum of median facial and forebrain deficiencies, as expected. This range of abnormalities falls within the HPE spectrum; a spectrum for which facial dysmorphology is consistent with and typically is predictive of that of the forebrain. In addition, other defects including median facial cleft, cleft palate, micrognathia, pituitary agenesis, and third ventricular dilatation were identified. MRM analyses also revealed cerebral cortical dysplasia/heterotopias resulting from this acute, early insult and facilitated a subsequent focused histological investigation of these defects.

Conclusions: Individual MRM scans and 3D reconstructions of fetal mouse brains have facilitated demonstration of a broad range of GD 7 ethanol-induced morphological abnormality. These results, including the discovery of cerebral cortical heterotopias, elucidate the teratogenic potential of ethanol insult during the third week of human prenatal development.

Key Words: Magnetic Resonance Microscopy, Fetal Alcohol Spectrum Disorder, Holoprosencephaly, Cortical Dysplasia, Leptomeningeal Heterotopia.
holoprosencephaly (HPE) and that in fish, there is a very narrow (3 hour) window of sensitivity during the beginning of gastrulation that is associated with this endpoint. Using a mouse model to examine ethanol teratogenesis, Sulik and Johnston (1982) also illustrated HPE resulting from acute ethanol insult during early gastrulation stages; i.e., during GD 7 in mice.

The HPE spectrum includes phenotypes ranging from the most severe, alobar form, which is characterized by a single forebrain holosphere in which there is broad communication of the lateral ventricles with each other and the third ventricle, accompanied by agenesis of the corpus callosum and olfactory bulbs; to semilobar, an intermediate form characterized by cerebral hemispheres that are most deficient rostrally and are only entirely separate through approximately their caudal half; to at least a severe, lobar, form in which there is a distinct interhemispheric fissure that may or may not be interrupted anteriorly and in which the corpus callosum may be absent, hypoplastic, or normal and the olfactory bulbs may or may not be present (DeMyer and Zeman, 1963). Accompanying holoprosencephalic brains are varying degrees of ocular and midfacial dysmorphism (DeMyer et al., 1964; reviewed by Muenke and Cohen, 2000; Sulik and Johnston, 1982). Examining this spectrum of defects in humans, DeMyer and colleagues (1964) noted that frequently (although not always) the face “predicts” the brain; i.e., that the severity of craniofacial and brain dysmorphology are often directly correlated.

HPE is not rare. This spectrum of abnormalities is now recognized as the most commonly occurring type of birth defect, being present in as many as 1/250 human conceptuses (Matsunaga and Shiota, 1977). However, most of those affected are lost prenatally, resulting in only a 1/10,000 live birth incidence (Croen et al., 1996; reviewed in Leoncini et al., 2008; Rasmussen et al., 1996).

Study of the genesis of ethanol-induced facial and brain defects in mice (Sulik and Johnston, 1982; Sulik et al., 1981; Webster et al., 1983) led to the hypothesis that those individuals who present with the characteristic facies of full blown FAS will have brain dysmorphology falling within the HPE spectrum (Sulik and Johnston, 1982). Indeed, histological analyses of fetal mice that had FAS-like facies and had been acutely exposed to ethanol on their 7th GD have illustrated the presence of forebrain deficiencies including hypoplasia or aplasia of the corpus callosum and septal nuclei (Schambra et al., 1990; Sulik et al., 1984). Importantly, in a nonhuman primate model, ethanol exposure early in pregnancy, specifically on GD 19 and 20, corresponding to the early gastrulation stage, also yielded HPE (Astley et al., 1999; Siebert et al., 1991). Features of HPE have been reported in human FAS. Indeed, in the first autopsy case report, Jones and Smith (1975) described corpus callosum agenesis. Other autopsies revealed olfactory bulb deficiencies and pituitary abnormalities (Majewski, 1981; Peiffer et al., 1979; Shiota et al., 2007).

The advent of clinical MRI has made structural analyses of the brains in live patients with FASD possible. Initial MRI studies illustrated deficiencies in the cerebellar vermis, basal ganglia and corpus callosum in individuals with FAS (Archibald et al., 2001; Mattson et al., 1996; Riley et al., 1995). More recently, the corpus callosum has been the focus of detailed FASD imaging studies. Variability in its shape, size, and microstructure among individuals exposed to alcohol prenatally has been described (Bookstein et al., 2002; Fryer et al., 2009; Lebel et al., 2008; Ma et al., 2005; Sowell et al., 2001; Spadoni et al., 2007; Wozniak et al., 2006). While its protracted development is expected to make the corpus callosum vulnerable to teratogenic insult during many prenatal stages, when found in combination with the typical facies of FAS, it is most likely that the dysmorphology is, indeed, the result of ethanol exposure during gastrulation.

Employing a mouse FASD model, the current investigation is directed toward further defining and documenting the types and range of brain and facial defects that prenatal ethanol exposure can cause and, thus, to informing improved pre- and postnatal FASD clinical recognition and diagnosis. The acute GD7 ethanol exposure time used for this study corresponds to the mid- to late third week postfertilization in humans and is the earliest of a number of times during embryogenesis from which MR-based data is currently being collected and compared. As most human pregnancies remain unrecognized at this early stage, for education-based FASD prevention efforts clear illustration of the vulnerability of the brain to ethanol-mediated damage at this time is particularly important.

METHODS

Animal Maintenance

C57Bl/6j mice, purchased from The Jackson Laboratory (Bar Harbor, ME), were housed in a temperature and humidity-controlled AAALAC-approved environment. They were maintained on an ad libitum diet of standard laboratory chow and water. For mating, 2 females were placed with 1 male for 2 hours early in the light portion of a 12/12 hours light/dark cycle. The beginning of the breeding period in which a copulation plug was detected was defined as GD 0, 0 hours.

Maternal Treatment Paradigm

On day 7 of pregnancy, mice in the experimental group were administered 2 i.p. doses of 25% (v/v) ethanol in lactated Ringer’s solution at a dosage of 2.9 g/kg maternal body weight. The injections were given 4 hours apart, with the first administered at GD 7, 0 hours. Control animals were injected with an equivalent volume of lactated Ringer’s solution according to the above treatment paradigm. To determine the peak blood ethanol concentration (BEC), a separate group of mice were administered ethanol, utilizing the previously described paradigm (Webster et al., 1983). Thirty minutes after the second injection, 35 μl of tail blood were obtained from each dam and analyzed using an Analox Alcohol Analyser (Model AM1; Analox Instruments USA Inc., Lunenburg, MA). All animal treatment protocols were approved by the University of North Carolina at Chapel Hill, Institutional Animal Care and Use Committee (IACUC).

Fetal Specimen Selection and Preparation

At the beginning of their 17th day of pregnancy, dams were anesthetized via CO2 inhalation, followed by cervical dislocation. Following laparotomy, the uteri were removed and the fetuses were
immediately dissected free of decidua in ice-cold phosphate buffered-saline (PBS). The GD 17 fetuses were examined for the presence of gross abnormalities. For the control group, 7 fetuses (from 4 litters) were selected for MRM scanning based on normal morphology and developmental stage-matching with the ethanol-exposed fetuses. Staging was based on degree of limb, skin, and hair follicle development (Theiler, 1989). For the ethanol group, 19 fetuses (from 8 litters) were selected for MRM scanning. As for the Parnell and colleagues (2009a) MRM study, selection of the ethanol-exposed fetuses was based on the presence of grossly observable dysmorphology; an approach that is not unlike selection of children with known physical features of FAS for subsequent central nervous system (CNS) analyses. For this investigation, all of the ethanol-exposed fetuses selected had ocular defects and among these, some had apparently normal facies, while others had obvious facial dysmorphia. To account for the entire spectrum of effect, fetuses with apparently normal, subtly affected and severely affected facies were included. Following photography to document ocular and facial abnormalities, the fetuses were immersion fixed for 9 hours in a 20:1 solution of Bouin’s fixative (Sigma-Aldrich, St Louis, MO) containing Prohance® (Bracco Diagnostics Inc., Princeton, NJ) (Petiet et al., 2007). The specimens were then immersed in a storage solution of 200:1 PBS:Prohance in which they were held until imaged.

**Magnetic Resonance Microscopy**

Magnetic resonance microscopy images were acquired at either 7.0 Tesla (T) or 9.4 T using a GE EXCITE console modified for MRM. To provide full resolution at the Nyquist frequency, a 3D rf refocused spin echo sequence (7.0 T: TR = 100 ms, TE = 6.2 ms; 9.4T: TR = 75 ms, TE = 5.2 ms) with asymmetric partial Fourier sampling was used (Johnson et al., 2007). For all MRM scans acquired, the matrix size was $1024 \times 512 \times 512$ and the FOV was $30 \times 15 \times 15 \text{mm}^3$, which yielded an isotropic spatial resolution of 29 μm. The total scan time was approximately 4 hours for each specimen. During scanning, specimens were immersed in fomblin, a perfluorocarbon used to limit dehydration and reduce susceptibility artifacts.

**Linear Measurements**

To ensure accurate orientation, each MRM scan was aligned in the horizontal, coronal and sagittal plane using ImageJ (Version 1.38x, NIH; http://rsb.info.nih.gov/ij/). This program was also used to obtain linear measurements. For each fetus, the following were determined: crown rump length (CRL), mid-sagittal brain length, frontothalamic distance (FTD) (excluding olfactory bulbs), bulbothalamic distance (BTD) (including olfactory bulbs), brain width (biparietal distance), third ventricle width, and transverse cerebellar distance (Fig. 1.4). All measurements were taken at the level of the anterior commissure, except the transverse cerebellar distance which was measured at its widest level and are reported in Table 1.

**Volume Measurements**

Total body (including the head) and brain volume, as well as regional brain volumes for each fetus were computed using ITK-Snap, a software program originally developed at the University of North Carolina, Chapel Hill (Yushkevich et al., 2006; http://www.itksnap.org). Total body volume was ascertained using the automatic segmentation feature of this program. Total brain volume was determined by adding the volumes of 17 brain regions that were each

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**Fig. 1.** Magnetic resonance microscopy scans of GD 17 mouse fetuses allow for linear measurements, regional segmentation, and 3D reconstruction. Illustrated in (A) is a horizontal scan with lines depicting sites of linear measurement as follows: brain width (biparietal distance), line 1; bulbothalamic distance, line 2; mid-sagittal brain length, line 3; frontothalamic distance, line 4; third ventricle width, line 5. [Cerebellar width (transverse cerebellar distance, not included) was measured at its greatest dimension.] Manual segmentation, as depicted by the color-coded regions in (B) allowed for subsequent 3D reconstruction (C) and analyses of selected brain regions. In (C), the upper right quadrant of the brain has been removed to allow for visualization of the interior structures. Color codes for the segmented brain regions shown are at the bottom of the figure. Other regions that were also examined for each of the animals in this study, but are not shown in this illustration, are the pituitary and the ocular globe and lens of each eye (modified from Figs. 1 and 2, Parnell et al., 2009a).
Table 1. Linear Brain Measurements (mm) are Represented as the Mean ± Standard Error of the Mean

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>non-HPE</th>
<th>HPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-sagittal brain length</td>
<td>7.46 ± 0.08</td>
<td>7.21 ± 0.09</td>
<td>6.75 ± 0.18</td>
</tr>
<tr>
<td>Brain width</td>
<td>4.70 ± 0.09</td>
<td>4.44 ± 0.04</td>
<td>4.07 ± 0.19</td>
</tr>
<tr>
<td>Bulbothalamic distance</td>
<td>3.79 ± 0.06</td>
<td>3.78 ± 0.06</td>
<td>3.27 ± 0.15</td>
</tr>
<tr>
<td>Frontothalamic distance</td>
<td>3.45 ± 0.05</td>
<td>3.32 ± 0.04</td>
<td>3.17 ± 0.10</td>
</tr>
<tr>
<td>Third ventricle width</td>
<td>0.22 ± 0.02</td>
<td>0.23 ± 0.01</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Transverse cerebellar distance</td>
<td>3.46 ± 0.05</td>
<td>3.34 ± 0.04</td>
<td>3.37 ± 0.14</td>
</tr>
</tbody>
</table>

HPE, holoprosencephaly.

Range of measurements in each region and group are indicated in parentheses. For controls, n = 7; non-HPE, n = 14; HPE, n = 4.

*Significant difference from controls.

*Significant difference from the non-HPE group.

manually segmented, allowing subsequent 3D reconstruction of each region (Fig. 1C). The manually segmented regions were the right and left cortex, right and left olfactory bulb, right and left striatum, right and left hippocampus, septal region, diencephalon, mesencephalon, pons/medulla, cerebellum, putitary gland, lateral ventricles, third ventricle, mesencephalic (cerebral aqueduct), and fourth ventricle. In addition, for the eyes, each globe and lens was segmented. Segmentation entailed tracing each MRM slice (Fig. 1B) via a computer mouse or a pen tablet. Tracings were performed by only 1 individual for each selected region, for every fetus examined. Intra-rater reliability was assessed following a blind repeated segmentation of each of the selected structures in 1 control and 1 non-HPE ethanol-exposed fetus. Regional boundaries were determined based on existing fetal mouse atlases (Kaufman, 1992; Schambra, 2008; Schambra et al., 1992). Coronal, sagittal, and horizontal planes of section were used to ensure anatomical accuracy. In addition to volumetric analyses, 3D reconstructions allowed visual assessment of shape changes in ethanol-exposed versus control brains.

Routine Histology

Following imaging, each fetus was held in a 70% ethanol solution to clear the residual Bouin’s fixative and to prepare the specimens for subsequent routine histological analyses. The latter was performed on selected specimens to confirm and extend MRM findings. Prior to processing, the fixed fetuses were photographed to further document facial dysmorphology. Fetal heads were removed and processed routinely for paraffin embedding using a tissue processor. Sections were cut at 10 μm, mounted on glass slides, stained with aqueous hematoxylin and cosin (H & E), cover-slipped and viewed with a light microscope.

Statistical Analyses

Group comparisons were made between stage-matched control fetuses (control) (n = 7), ethanol-exposed fetuses with 2 distinctly separate cerebral hemispheres (non-HPE) (n = 14), and ethanol-exposed fetuses with features of semilobar or alobar HPE (HPE) (n = 5). Group differences among regional brain volumes, ocular measurements, and linear measurements were assessed using multivariate analyses of variance (MANOVAs). Crown-rump length, whole brain volume, and whole body volume (including head) were analyzed using one-way ANOVAs. When applicable, posthoc analyses were performed using Student–Newman–Keuls (SNK). An alpha value of 0.05 was maintained for all analyses.

To assess the reliability of manual segmentation of regional brain and ocular volumes, intra-rater reliability was analyzed using coefficients of variation (CV). The average CV was 3.8% (range: 0.5 to 11.8%), thus, demonstrating high reliability for manual brain segmentation.

RESULTS

General Features of the Study Population

With a research goal of accomplishing detailed MRM-based analyses of a broad spectrum of structural brain abnormalities resulting from acute GD 7 ethanol exposure, this work employed a previously published ethanol exposure paradigm known to yield sufficient numbers of viable fetuses having a range of effect. Consistent with previous reports, the ethanol treatment yielded peak maternal BECs (30 minutes after the second dose) averaging 440 mg/dl (range: 400 to 466).

The 19 ethanol-exposed GD 17 fetuses that underwent detailed MRM analyses were selected based, in part, on the presence of defects involving one or both eyes, and in part, based on facial morphology. The eye defects ranged from apparently slight microphthalmia, to iridal coloboma, to apparent anophthalmia. The facial appearance in the ethanol-exposed fetuses ranged from apparently normal to severely dysmorphic. The facial characteristics, along with MRM-based brain findings, provided for distinction and comparison between subgroups of ethanol-exposed fetuses, as described below.

HPE

Illustrated in Fig. 2 are light micrographs of the faces and the respective brain and ventricle reconstructions of a control GD 17 fetus and of 5 ethanol-exposed fetuses that presented with varying degrees of facial dysmorphia. The facial abnormalities are consistent with those in the HPE spectrum. In the affected animals, notable features of the upper midface include a long upper lip and closely spaced nostrils. Additionally, the lower jaw is slightly to severely reduced in size (micrognathic), appearing narrow from a frontal view.

Frontal views of the reconstructed brains of the affected fetuses (Fig. 2H–L) clearly show a spectrum of rostral union of the cerebral hemispheres along with olfactory bulb reduction to agensis. These rostro-medial telencephalic deficiencies are consistent with HPE and grade in severity from semilobar (H) to lobar (L). From a dorsal view (Fig. 2M–R), the
Fig. 2. Shown are the face and reconstructed brain of a control GD 17 fetal mouse along with the faces and brains of ethanol-exposed fetuses having semilobar and alobar holoprosencephaly (HPE). As compared to the control face (A), those fetuses with HPE (B–F) have varying degrees of midfacial abnormality; each presenting with a long (from nose to mouth) upper lip, a small nose with closely set nostrils, and micrognathia (narrow, pointed chin), the latter of which is severe in the specimens shown in (B) and (F). Segmented magnetic resonance microscopy scans of control (G, M, S) and ethanol-exposed fetuses (H–L, N–R, T–X) were reconstructed to yield whole brain (frontal view, G–L; dorsal view, M–R) and ventricular system (S–X) images. Notable forebrain abnormalities include varying degrees of olfactory bulb deficiency and rostral union of the cerebral hemispheres, accompanied by dysmorphic lateral ventricles. From a dorsal view, the mid- and hindbrain and their ventricles appear relatively normal in all of the affected fetuses. Color codes for the segmented brain regions are shown at the bottom of the figure.

Varying degrees of forebrain reduction/dysmorphology are readily appreciated in the ethanol-exposed fetuses as compared to the control. Also apparent in 2 of the affected fetuses are asymmetries involving the olfactory bulbs. The animal shown in Fig. 2H and 2N is more severely affected on its right, while that in I and O is more severely affected on its left. As expected, and notable in regional reconstructions and in individual MRM scans as shown in Fig. 3, are reductions in the septal region with union of the striatum across the midline. Also illustrated in Figs. 2 and 3 are the overall size reduction in the brains and the remarkably normal morphology of the brain segments caudal to the forebrain of the ethanol exposed versus the control fetuses.

Overall, the morphology of the ventricles reflects the median forebrain deficiency in the holoprosencephalic fetuses. Most notably, rather than being continuous with the third ventricle via the narrow passages at the foramina of Monro, the lateral ventricles are broadly united with each other in the rostral midline. Accompanying the very dysmorphic lateral ventricles are third ventricles that appear relatively normal. From a dorsal view, while the ventricular space of the mesencephalon and the fourth ventricle appear normally shaped, the aqueductal isthmus was found to be abnormally narrow in the 2 fetuses whose faces are shown in Fig. 2E and 2F. The isthmus appears normal in the 3 less severely affected fetuses in this group.

Of interest, MRM scans of all of the ethanol-exposed specimens shown in Fig. 2 revealed an aberrant tissue mass located between the base of the rostral forebrain and the nasal septum (Fig. 4B). In some, the mass was continuous with the forebrain and in others it was not. Typically, a single mass was found to occupy a median position. However, in the animal shown in Fig. 4C, there were 2 similar, more laterally positioned masses. Subsequent routine histological coronal sections illustrate that the tissue is continuous, through the cribiform plate, with the nasal epithelium (Fig. 4C and 4D;
from the fetus shown in Fig. 2D). The control counterpart is represented by olfactory nerves that extend from the nasal epithelium to the olfactory bulbs.

Cerebral Cortical Dysplasia/Heterotopia

Magnetic resonance microscopy and subsequent routine histology revealed cerebral cortical dysplasia/heterotopias in ethanol-exposed fetuses whose brains were not overtly holoprosencephalic (i.e., they did not present with semilobar or alobar HPE) (Fig. 5). These cortical defects were observed in animals having facies that were apparently normal, presented with a long upper lip and severe micrognathia, foreshortened, or cleft in the midline (Fig. 5B–E, respectively). In all of these animals, the cerebral hemispheres were completely separate and slightly widely spaced as evidenced by the ability to

Fig. 3. Horizontal magnetic resonance microscopy (MRM) scans at 2 different levels through a control (A, D) and 2 affected fetuses (B, E) with semilobar HPE and C, F with alobar HPE; shown in Fig. 2B and 2F, respectively) illustrate rostro-median tissue loss. The septal region (long arrow), which is apparent in the rostral midline of the control, is absent in the affected fetuses. In the more mildly affected fetus (B, E), the striatal tissue (short arrow) can be defined and, in the absence of the septal region, is united across the midline. In the more severely affected fetus (C, F), MRM does not allow clear identification of the striatal boundaries. Notable in both affected fetuses is the vastly enlarged and rostro-mediadorslateral ventricles (\( \triangledown \)).

Fig. 4. Magnetic resonance microscopy (MRM) and routine histology illustrate olfactory nerve abnormality in a holoprosencephalic fetus. As compared to an MRM image of a normal coronal scan (A; arrow indicates olfactory bulb) that from an ethanol-exposed fetus (B; fetus also shown in Fig. 2D), reveals absence of the olfactory bulbs and the presence of an aberrant intracranial median mass that is located dorsal to the nasal septum (boxed area). Subsequent examination of histological sections through this region revealed that the tissue is continuous, through the cribriform plate, with the nasal epithelium (arrow in D). Bar in C = 0.5 mm, in D = 0.2 mm.
visualize deep brain structures (septal region and diencephalon) from a frontal view. Additionally, both olfactory bulbs, though in some cases small and widely spaced, were present. Initially observed in the reconstructed brain images (Fig. 5G and 5J) of the fetuses shown in Fig. 5B and 5E, the cortical defects present as focal protrusions on the otherwise smooth cerebral surfaces. Histological sections of these 2 fetuses (Fig. 5L, 5Q, 5O, and 5T), along with sections from the other ethanol-exposed fetuses pictured in Fig. 5M, 5R, 5N, and 5S reveal relatively large and numerous, to minute and isolated irregularities in the cerebral cortex. Typically, the dysplastic/heterotopic cortical tissue was adherent to the associated leptomeninges. In the fetus with the median facial cleft (Fig. 5E) the dysplastic cortex is localized to the medial aspect of both cerebral hemispheres, with cortical layers I through IV being involved. Subsequent to the MRM-based discovery of ethanol-induced cerebral cortical dysplasia/heterotopia, careful examination of histological sections of the brains of the fetuses with semilobar and alobar HPE revealed a small heterotopia in the frontal cortex of the most severely affected animal; the fetus shown in Fig. 2F. No heterotopias were found in any of the control animals or any of the other ethanol-exposed fetuses.

**Other Dysmorphologies**

A profile view (Fig. 6B) of the fetus that is also shown in Fig. 5D illustrates that in addition to being anophthalmic, its snout is abnormally short. MRM revealed that the nasal cavities of this fetus are very small; the turbinates are absent; and along its entire length, the nasal septum is short in the dorsoventral direction (Fig. 6D). Additionally, 3D reconstruction of the ventricular spaces illustrated dysmorphology involving the third ventricle presenting as excessive width and extension ventrally beyond the normal boundaries (Fig. 6F). Both a frontal (Fig. 5J) and a ventral view (Fig. 6H), of the reconstructed brain of this fetus show that the olfactory bulbs are small and widely spaced. Remarkable is the complete absence
of the pituitary gland. Subsequent to MRM, examination of H & E stained coronal histological sections of this animal revealed that the corpus callosum, while identifiable in control fetuses, was not apparent (Fig. 6J). With the concurrent small olfactory bulbs and pituitary absence/deficiency, the dysmorphology of this brain appears to be consistent with lobar HPE.

Severe micrognathia was noted in 3 of the ethanol-exposed fetuses; those pictured in Fig. 2B and 2F and in Fig. 5C. MRM scans revealed severe micro/aglossia in all of these animals and clefting of the secondary palate in the Figs. 2B and 5C fetuses. These features in the latter specimen are shown in Fig. 7, as is the reconstructed mesencephalic and fourth ventricle. Marked narrowing of the aqueductal isthmus is apparent in this fetus and is also present in 2 others (fetuses in 2E and 2F; described above).

Linear and Volume Assessments

Due to the marked morphological differences in the brains of ethanol-exposed animals that presented with overt HPE versus the remainder that had 2 entirely separate cerebral hemispheres (non-HPE), measurements made for these 2 groups of ethanol-exposed fetuses were separately compared to controls and to each other. In spite of developmental stage-matching, there were significant differences in CRL \( F(2.22) = 5.44, p < 0.05 \), total body volume \( F(2.23) = 4.065, p < 0.05 \), and total brain volume \( F(2.23) = 4.51, p < 0.05 \) between the 3 groups examined. Posthoc tests revealed that HPE subjects were significantly smaller than controls in terms of CRL (\~{}9% reduction) but neither group differed from non-HPE ethanol-exposed subjects (control: 17.27 \( \pm \) 0.23 mm [mean \( \pm \) SEM], non-HPE: 16.38 \( \pm \) 0.23 mm; HPE: 15.74 \( \pm \) 0.31 mm). In addition, the HPE group also had a significantly smaller total brain volume (\~{}20% reduction) compared to controls but non-HPE ethanol-exposed animals did not differ from either HPE subjects or controls (control: 52.86 \( \pm \) 2.58 mm\(^3\), non-HPE: 47.75 \( \pm \) 1.52 mm\(^3\), HPE: 42.38 \( \pm \) 2.50 mm\(^3\)). Finally, whole body volume measures for the non-HPE and HPE ethanol-exposed fetuses were decreased by 15 and 16%, respectively, compared to controls, but SNK posthoc tests only approached significance \( p = 0.06 \) (control: 679.15 \( \pm \) 25.95 mm\(^3\), non-HPE: 537.09 \( \pm \) 22.17 mm\(^3\), HPE: 576.81 \( \pm \) 45.93 mm\(^3\)).
Linear brain measurements are shown in Table 1. A MANOVA indicated significant group differences in linear brain measurements \( F(14,34) = 4.197, p < 0.05 \) with significant between group effects for brain length, BTD, FTD, brain width, and third ventricle width (all \( p < 0.05 \)). Posthoc tests indicated that the HPE group had significantly smaller brain length, BTD, and third ventricle widths compared to non-HPE subjects and controls \( (p < 0.05) \). FTD in HPE subjects differed only compared to controls \( (p < 0.05) \). Brain widths were significantly smaller in HPE subjects compared to the non-HPE subjects and both ethanol-exposed groups had smaller brain widths compared to controls \( (p < 0.05) \). There were no differences between groups in transverse cerebellar distance \( (p > 0.05) \).

In spite of the overall decrease in brain volume in the HPE subjects, analyses of the regional volume measurements indicated that the overall brain volume reductions is largely the result of insult to the rostral brain structures with a remarkable sparing of more caudal regions. As expected, MANOVAs illustrated significant group differences in regional brain volumes \( F(34,16) = 3.68, p < 0.05 \) and ocular volumes \( F(8,42) = 5.65, p < 0.05 \) between HPE, non-HPE, and control groups (Fig. 8). Significant between group effects were seen for the following brain measurements: left and right cortex, left and right olfactory bulbs, left and right striatum, septal region, diencephalon, lateral, and third ventricles (all \( p < 0.05) \). Consistent with visual inspection of the 3D reconstruction data, posthoc tests illustrated that HPE subjects had significantly smaller cortices, olfactory bulbs, striata, and septal regions (which were nonexistent in all HPE subjects) compared to controls and non-HPE ethanol-exposed subjects \( (p < 0.05) \). In addition, lateral ventricles were significantly larger in HPE subjects than non-HPE and controls while the third ventricle was significantly larger in the non-HPE ethanol-exposed group compared to HPE and control groups \( (p < 0.05) \). Reductions in volumes of both the left and right globe and lens of the eyes were apparent in both ethanol-exposed groups (HPE and non-HPE) compared to controls \( (p < 0.05) \). Remarkably, despite significant dysmorphology accompanied with volumetric reductions in ethanol-exposed animals, no group differences were evident in the hippocampus, pituitary, or hindbrain regions (mesencephalon, pons/medulla, cerebellum, mesencephalic, and fourth ventricle) \( (p > 0.05) \) illustrating the regional specificity of defects following exposure at this time.

In Fig. 8, volumetric data is expressed to illustrate the broad range of insult. Specifically, mean control values from 7 fetuses are indicated by a black dot and the bars indicate the 95% confidence interval for the control mean. Individual data points for each ethanol-exposed subject are plotted for each region in order to convey the range of volumetric data ascertained. Values for the 5 ethanol-exposed animals with overt HPE are expressed as X’s; and for all of the other ethanol-exposed animals (non-HPE, \( n = 14 \)) a grey circle is employed.

**DISCUSSION**

This report describes MRM-based discovery and documentation of structural abnormalities resulting from early gastrulation stage ethanol insult in mice. In addition to providing a 3D perspective of ethanol-induced HPE, with its range of median forebrain deficiencies, other CNS and craniofacial abnormalities were also identified. As discussed below, these findings extend our understanding of the spectrum of ethanol-induced birth defects and of the critical periods for their induction.

It is clear that, as with other teratogens, both dosage and timing (developmental stage) dictate the consequences of prenatal ethanol exposure. Regarding the former, with the objective of identifying even the most severe of ethanol’s dysmorphogenic effects, a previously reported maternal ethanol dose high enough to yield abnormalities without substantially increasing resorption rates was selected. This dosage was somewhat higher (yielding peak maternal BECs of approx. 380 vs. 440 ± mg/dl) than utilized for an MRM-based GD 8 ethanol exposure study by Parnell and colleagues (2009a) (the first publication in a series of which this is a part). On GD 8, exposure to the higher ethanol dose typically yields severe heart defects and substantial embryo lethality. As shown in previous studies that employed the same treatment paradigm as for the current investigation, peaking within 30 minutes of the last dose, the maternal BEC remains above 100 mg/dl for a total of approximately 9 hours and reaches 0 within a few
more hours (Kotch et al., 1992; Webster et al., 1983). Thus, exposure to ethanol totals less than 12 hours, including a period for which the concentration is expected to be less than teratogenic. An i.p. route of maternal ethanol administration was employed for both the GD 8 and the GD 7 studies. As compared to maternal dietary ethanol intake, i.p. administration provides interlitter outcomes that are more consistent. It is recognized that with the i.p. treatment, embryos may experience a higher peak ethanol concentration than occurs in the maternal blood (Clarke et al., 1985). However, it is notable that abnormalities consistent with those described herein also occur following a dietary exposure paradigm that yields maternal BECs comparable to those in the current study (Webster et al., 1983).

Regarding timing, it is clear that ethanol is teratogenic at virtually every postimplantation stage. Remarkable is that ethanol exposure occurring within a relatively narrow window in 2 hour time-mated inbred animals can yield not only a range of defects within a single spectrum, but also defects that appear to be virtual opposites. This is exemplified by the occurrence of median forebrain and facial deficiencies typical of semilobar and alobar HPE (a narrow snout and forebrain) in some fetuses and median split face accompanied by widely spaced cerebral hemispheres and olfactory bulbs in others; all following acute insult on GD 7. Undoubtedly, the fact that in C57Bl/6J mice there is significant intra-litter variation, representing as much as 12 hours difference in developmental staging among littermates, plays an important role in this variability (Parnell et al., 2009b). HPE has been the most commonly reported dysmorphology following GD 7 ethanol exposure in mice (Higashiyama et al., 2007; Myers et al., 2008; Schambra et al., 1990; Sulik and Johnston, 1982; Sulik et al., 1984; Webster et al., 1983), and was also observed in the current study population. GD 8 has previously been identified as the time in mouse development when median facial clefts and excessive brain width are induced by ethanol.

**Fig. 8.** Ethanol induces volume changes in selected regions of GD 17 fetal mouse brains following acute GD 7 exposure. Data is expressed to illustrate the broad range of insult. Mean values from 7 control fetuses are indicated by a black dot, with a bar indicating the 95% confidence interval of the control mean. Values for the 5 ethanol-exposed animals with overt HPE are expressed as mean values; and for all of the other ethanol-exposed animals (n = 14) a grey circle is employed. Please note differing scales on the right and left, as needed to facilitate representation of the data.
(Kotch and Sulik, 1992; Parnell et al., 2009a; Webster et al., 1983), while HPE is not a typical result of GD 8 ethanol treatment. Thus, it appears that among the dysmorphic fetuses described herein, those without HPE were more developmentally advanced at the time of ethanol insult than those with HPE. While insult on each individual day of mouse development is expected to yield a specific pattern of dysmorphology, it is also expected that, due to inter- and intra-litter variability in developmental stages, there will be some overlap.

With respect to HPE, via individual scans and 3D reconstructions, MRM has made it possible to readily show the range and severity of median forebrain deficiency that occurs in the absence of overt hindbrain dysmorphology. In those cases with semilobar and alobar forms of HPE, the severity of brain effect is consistent with that of the upper midface as evidenced, to a large extent, by the proximity of the nostrils. In all of the mouse fetuses whose nostrils are too closely positioned the median portion of the upper lip is too long (from nose to oral cavity). Notable was one fetus in which an effect on nostril positioning was subtle (if present), and that still had an unmistakably long upper lip. In this fetus, the cerebrum had a complete interhemispheric fissure. It is expected that this phenotype is consistent with lobar HPE. Ongoing studies employing diffusion tensor imaging and 3D facial analyses based on MRM reconstructions (Hammond et al., 2005) are designed to enable identification of subtle changes in facial morphology and to better define the brain fiber tracts in fetuses such as this.

The genesis of the HPE-related facial dysmorphology has previously been described as resulting from ethanol-induced loss of medial nasal prominence tissue (i.e., the progenitor of both the nasal tip and the intermaxillary segment, the latter of which becomes the philtrum of the lip and the primary palate) and subsequent overconvergence of the maxillary prominences, yielding the excessively long upper lip (Sulik and Johnston, 1983). DeMyer (1975) recognized hypoplasia of the intermaxillary segment as being pathognomonic of brain malformation; the greater the deficiency of intermaxillary tissue, the greater the likelihood of a malformed brain. In the HPE spectrum, the human face presents with an absent or indistinct philtrum accompanied by a thin (vermilion) upper lip border; a phenotype that undoubtedly results from medial nasal prominence deficiency. These facial features are also characteristic of FAS.

In addition to ethanol exposure, other environmental agents (e.g., retinoic acid, cyclospamine, cholesterol biosynthesis inhibitors) and mutations in a number of different genes including sonic hedgehog (SHH), ZIC2, SIX3, and TGIF2 can cause HPE and the associated facial abnormalities (Cohen, 2006; Monuki, 2007; reviewed by Muenke and Cohen, 2000). Of particular note is interference with sonic hedgehog signaling (Shh-s) as a basis for these defects. Shh-s is a primary event in neural plate induction. Studies by Ahlgren and colleagues (2002) in chicken and fish embryos (Loucks and Ahlgren, 2009) and also by Li and colleagues (2007) in the latter species, have illustrated that ethanol interferes with this signaling. Strongly supporting this as a key mechanism underlying ethanol-induced defects is that enhancing Shh-s can diminish the teratogenesis (Loucks and Ahlgren, 2009). The prevalence of alcohol (ethanol) use and abuse and the multiple genes involved in the genesis of HPE contribute to the likelihood that via gene-environment interactions ethanol significantly factors into the high (1/250) incidence of HPE among human conceptuses (Matsunaga and Shiota, 1977).

Along with the forebrain and upper midfacial defects that characterize HPE, other defects that are associated with this spectrum were noted in this study. Micrognathia commonly occurs both in human HPE and in FASD (Ades and Sillence, 1992; Blaas et al., 2002; Cohen, 1989; Jones and Smith, 1975; Lemoine et al., 1968; Majewski, 1981; Pauli et al., 1981, 1983), and was clearly evident in a third of the 19 ethanol-exposed mouse fetuses. 3D facial analyses are expected to also identify more subtle mandibular deficiencies resulting from ethanol exposure on GD 7. Severe micrognathia was accompanied by narrowing of the cerebral aqueduct in some specimens. The latter abnormality is commonly and causally associated with hydrocephalus, a condition that co-occurs with human HPE (Barr and Cohen, 1999; Dickinson et al., 2006) and that was previously noted to result from GD 7 ethanol treatment in mice (Sulik and Johnston, 1983). Micro/aglossia and cleft palate, as seen in this study, also co-occur with HPE (Cohen, 1989; Pauli et al., 1981, 1983; Porteous et al., 1993). In part, due to the relatively long period of genesis of the secondary palate, clefting of this structure (a recognized feature of FASD) is expected to also result from ethanol insult at later developmental stages. Of these ("other") defects, for the fetuses in this study, certainly aqueductal stenosis, and probably cleft palate would not have been readily recognized without MRM.

Also with MRM, tissue that appears to correspond to misplaced olfactory nerves was found in the overly holoprosencephalic animals. Normally, the olfactory nerves should project from the nasal epithelium, through the cribiform plate, to synapse in the olfactory bulbs. In the absence of olfactory bulbs, these nerves still extend upward, but lacking a target, form an intracranial mass that remains unattached to the brain. Recent analyses of holoprosencephalic mouse fetuses whose defects resulted from Shh-inhibition via in utero exposure to a potent cyclospamine analog revealed comparable olfactory nerve masses (R.J.L. Lipinski, personal communication).

Two of the ethanol-exposed fetuses in this study have small, widely spaced olfactory bulbs. Of these, one is anophthalmic and has an enlarged third ventricle (indicating hypothalamic deficiency), no pituitary, apparent absence of the corpus callosum, and markedly small/stenotic nasal cavities. The other has a median facial cleft. The collection of defects in these mice is consistent with the following recognized human syndromes/associations: (i) median cleft face syndrome; a condition for which agenesis of the corpus callosum and anomalies of the pituitary gland have been reported (DeMyer, 1967),
(ii) septo-optic dysplasia; a syndrome characterized by absence of the septum pellucidum, pituitary hormone deficiency, and optic nerve hypoplasia; features of which a clinical report by Coulter and colleagues (1993) attributed to prenatal ethanol exposure, and (iii) CHARGE association which includes nasal cavity narrowing, growth and mental retardation, along with a variety of structural brain abnormalities including absence/hypoplasia of the olfactory bulbs and tracts, dysgenesis/hypoplasia of the frontal lobes and optic nerves, and agenesis of the corpus callosum and septum pellucidum. CHARGE association was highlighted in the Parnell and colleagues (2009a) report as resulting from GD 8 ethanol exposure in mice. Indeed, although each has its own key features, there is significant overlap between HPE and these 3 clinical conditions (Bonomberg et al., 1987; Fitz, 1994; Lin et al., 1990; Polizzi et al., 2005; de Toni et al., 1985). This is also true for the dysmorphology resulting from GD 7 versus GD 8 ethanol exposure in mice.

The MRM-based discovery of cerebral cortical dysplasia/ heterotopias resulting from acute GD 7 ethanol exposure is novel and is expected to be of significant clinical importance. Nearly 35 years ago the first autopsy report by Jones and Smith (1975) of a newborn with FAS described a large heterotopia encompassing the left cerebral hemisphere. Under this mass of tissue, the cortex was thin and disorganized and the lateral ventricles were enlarged. In more recent studies of rodent FASD models, one of which was conducted utilizing cultured GD17 fetal rat cortical slices (Mooney et al., 2004) and one which employed maternal dietary ethanol exposure on days 10 through 21 in the rat (Komatsu et al., 2001; Sakata-Haga et al., 2004), cortical heterotopias have also been found. The cerebral defects noted in the current study ranged from extremely small and isolated, to involving the medial aspect of both cerebral hemispheres. In most cases, the morphology is consistent with leptomeningeal heterotopia, though a more accurate descriptor for the most extensive defects is probably cortical dysplasia. Cortical heterotopias are generally considered as resulting from neuronal migration errors (Verrootti et al., 2009). It is remarkable that they can result from an acute teratogenic insult occurring as early as the time of neural plate induction.

The presence of cortical heterotopias is highly correlated with seizure activity. Indeed, Verrootti and colleagues (2009) state that “neuronal migration disorders are considered to be one of the most significant causes of neurological and developmental disabilities and epileptic seizures in childhood.” Among individuals with FAS the prevalence of epilepsy is higher than in the general population (1%), with estimates varying from 3 to 21% (Dorris, 1989; Ioffe and Chernick, 1990; Jones et al., 1973; Majewski, 1981; Marcus, 1987; Murray-Lyon, 1985; O’Malley and Barr, 1998; Olegard et al., 1979; Streissguth et al., 1978). Work directed toward identifying pathologic changes that may underlie alcohol-induced seizure threshold reduction has shown an association with hippocampal abnormalities induced during the human third trimester equivalent (Bonthius et al., 2001a,b). These studies employed a rat FASD model in which both behavioral and electrographic seizure thresholds were examined. Similar testing of postnatal animals following acute ethanol exposure during early gastrulation is needed.

Linear and volume measurements made in this study from MRM scans and 3D reconstructions are consistent with the visually assessed dysmophlogy. Notable in the ethanol-exposed animals are reduced frontothalamic and brain width measures and lateral ventricular enlargement; features that can be readily assessed in human fetal ultrasounds. Work by Kifir and colleagues (2009), showing that both second and third trimester ultrasound can detect frontothalamic reductions in the fetuses of moderate to heavy alcohol users, is consistent with the mouse data (Sulik et al., 2009). Together, the human and experimental studies illustrate the diagnostic potential of early (prenatal) forebrain measures.

In conclusion, this work contributes significantly to defining the CNS dysmophlogy that results from ethanol insult at times corresponding to the middle through the end of the third week of human development. Individual MRM scans and 3D reconstructions of fetal mouse brains have facilitated this effort, allowing documentation and discovery of ethanol-induced CNS defects and appreciation of their relationship to co-occurring facial abnormalities. These results promise to aid in clinical recognition, diagnosis, and prevention of FASD.

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ETHANOL-INDUCED BRAIN DEFECTS IN PRENATAL MICE