December 2012 Issue 8

The International Medical e-Network devoted to

Fetal Alcohol Spectrum Disorders

NOFAS-UK
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INTRODUCTION

The world of FASD research is always producing new innovative diverse studies. This year is no exception. FASD has stirred up the media several times. In June the media went into overdrive when studies published in Denmark were interpreted by the press as providing evidence that children exposed to prenatal alcohol were not showing deficits. The media translated this to suggest that there was no evidence of fetal alcohol harm to children up to the age of 5.

In fact, the authors of the studies actually stated that their studies were not conclusive and would need further follow-up. This was omitted by the media. It is known that fetal alcohol effects may not become apparent until the child is 7 years old. You will find abstracts of the Danish studies in Issue 7 of the FETAL ALCOHOL FORUM.

Once again the media have challenged the power of prenatal alcohol in November when the National Perinatal Epidemiology Unit in Oxford presented evidence that the IQ of 8 year old children was lower due to their mother's alcohol consumption during pregnancy, even though it was low level consumption. You will also find this study in this issue. The lead author of the study, Consultant Ron Gray has written an original article in the first section.

The growing interest in genes and environmental factors are also discussed in the article by Dr. Nina Kaminen-Aholain, Finland.

Turning to FASD education, we are privileged to have an article written for us from leading UK FASD Educator, Prof Barry Carpenter.

Prevention and intervention are discussed in a fascinating report from Tatiana Balachova PhD, Barbara Bonner PhD and Glaina Isurina PhD about the Russian government’s unique plans for FASD prevention and Shao-yu Chen writes about molecular targets for prevention in the US.

I expect you will find this new research exciting and promising for the future. We are on the horizon of a new age for FASD education and prevention.

The table on the next page shows the FASD Studies done worldwide during the past 6 months.

Susan Fleisher

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FASD studies worldwide during the past 6 months

<table>
<thead>
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</thead>
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</table>

We always appreciate your comments and valuable feedback at info@nofas-uk.org. You can download issues of the FETFAL ALCOHOL FORUM from our website: www.nofas-uk.org, or if you would like to be added to the FETAL ALCOHOL FORUM mailing list, please click here.

Susan Fleisher
Publisher

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# TABLE OF CONTENTS

*In the interest of brevity, Fetal Alcohol Spectrum Disorder has been abbreviated to FASD

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="#">ORIGINAL ARTICLES BY FASD EXPERTS</a></td>
</tr>
<tr>
<td><a href="#">RESEARCH ABSTRACTS</a></td>
</tr>
<tr>
<td><a href="#">ARTICLE ABSTRACTS</a></td>
</tr>
<tr>
<td><a href="#">NEWS AND PRESS</a></td>
</tr>
<tr>
<td><a href="#">FULL STUDIES</a></td>
</tr>
</tbody>
</table>
I. HOW HARMFUL COULD MODERATE DRINKING DURING PREGNANCY BE TO THE FETUS?  
Dr. Ron Gray

II. IN SEARCH OF CURRICULUM: EVOLVING LEARNING PATHWAYS FOR STUDENTS WITH FASD  
Professor Barry Carpenter

III. TOWARD ENHANCED TEACHER PREPARATION FOR MEETING THE NEEDS OF STUDENTS WITH FASD  
Jacqueline Pei and Cheryl Poth

IV. UNRAVELING THE MOLECULAR MECHANISMS OF FETAL ALCOHOL SPECTRUM DISORDERS: NOVEL INSIGHTS AND EMERGING MOLECULAR TARGETS FOR PREVENTION  
Shao-yu Chen

V. A BRIEF OVERVIEW OF STUDIES SUPPORTING THE RECOMMENDATION THAT EVEN LIGHT DRINKING SHOULD BE AVOIDED DURING PREGNANCY  
Fernando Valenzuela

VI. PREVENTING FASD IN RUSSIA  
Tatiana Balachova, Barbara Bonner and Galina Isurina

VII. EPIGENETIC APPROACH TO UNDERSTAND THE ETIOLOGY OF FASD  
Nina Kaminen-Ahola Nina
RESEARCH ABSTRACTS

1. **EFFECTS OF NEONATAL ALCOHOL DOSE AND EXPOSURE WINDOW ON LONG DELAY AND TRACE EYEBLINK CONDITIONING IN JUVENILE RATS**
   Nathen J. Murawski, Sarah A. Jablonski, Kevin L. Brown, Mark E. Stanton
   Publication – ScienceDirect
   1st January 2013

2. **DIFFERENT PATTERNS OF REGIONAL PURKINJE CELL LOSS IN THE CEREBELLAR VERMIS AS A FUNCTION OF THE TIMING OF PRENATAL ETHANOL EXPOSURE IN AN OVINE MODEL**
   Sawant OB, Lunde ER, Washburn SE, Chen WJ, Goodlett CR, Cudd TA.
   Publication – PubMed
   26th November 2012

3. **AUTHORS’ RESPONSE TO: DIFFERENT PERSPECTIVES ON THE METHODOLOGY OF STUDYING THE POTENTIAL EFFECTS OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY PREGNANCY ON THE NEUROPSYCHOLOGICAL DEVELOPMENT OF YOUNG CHILDREN**
   U Schiøler Kesmodel, E Lykke Mortensen, on behalf of the Lifestyle During Pregnancy Study Group
   Publication – Wiley Online Library - BJOG: An International Journal of Obstetrics & Gynaecology
   19th November 2012

4. **ANOTHER PERSPECTIVE ON ‘THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID PREGNANCY ON THE CHILD’S INTELLIGENCE, ATTENTION, AND EXECUTIVE FUNCTION’**
   S Astley, T Grant.
   Publication – Wiley Online Library - BJOG: An International Journal of Obstetrics & Gynaecology
   19th November 2012

5. **LOW AND MODERATE ALCOHOL CONSUMPTION DURING PREGNANCY: EFFECTS ON SOCIAL BEHAVIOUR AND PROPENSITY TO DEVELOP SUBSTANCE ABUSE IN LATER LIFE**
   MO Parker, CH Brennan.
   Publication – Wiley Online Library - BJOG: An International Journal of Obstetrics & Gynaecology
   19th November 2012

6. **THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID-PREGNANCY**
   O Garcia-Algar1,2, D Black2, C Guerri2,3, S Pichini
   Publication – Wiley Online Library - BJOG: An International Journal of Obstetrics & Gynaecology
   19th November 2012

7. **DANISH STUDIES SUGGESTING LOW AND MODERATE PRENATAL ALCOHOL EXPOSURE HAS NO ADVERSE EFFECTS ON CHILDREN AGED 5 YEARS DID NOT USE APPROPRIATE OR EFFECTIVE MEASURES OF EXECUTIVE FUNCTIONING**
   G Powell
   Publication – Wiley Online Library - BJOG: An International Journal of Obstetrics & Gynaecology
   19th November 2012
8. **ONTOGENY OF CONTEXTUAL FEAR MEMORY FORMATION, SPECIFICITY, AND PERSISTENCE IN MICE**
Akers KG, Arruda-Carvalho M, Josselyn SA, Frankland PW.
Publication – PubMed
16<sup>th</sup> November 2012

Krans EE, Davis MM, Schwarz EB.
Publication – PubMed
15<sup>th</sup> November 2012

10. **AFFECTIVE DECISION-MAKING ON THE IOWA GAMBLING TASK IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDERS**
Kully-Martens K, Treit S, Pei J, Rasmussen C.
Publication – PubMed
15<sup>th</sup> November 2012

11. **FETAL ALCOHOL EXPOSURE AND IQ AT AGE 8: EVIDENCE FROM A POPULATION-BASED BIRTH-COHORT STUDY**
Publication – PubMed
14<sup>th</sup> November 2012

12. **STEM CELL THERAPY: SOCIAL RECOGNITION RECOVERY IN A FASD MODEL**
Shirasaka T, Hashimoto E, Ukai W, Yoshinaga T, Ishii T, Tateno M, Saito T.
Publication – PubMed
13<sup>th</sup> November 2012

13. **EXPERT EVIDENCE BY MENTAL HEALTH PROFESSIONALS: THE COMMUNICATION CHALLENGE POSED BY EVIDENCE ABOUT AUTISM SPECTRUM DISORDER, BRAIN INJURIES, AND HUNTINGTON’S DISEASE**
Freckelton I.
Publication – PubMed
11<sup>th</sup> November 2012

14. **WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN CHILDREN WITH PRENATAL METHAMPHETAMINE/POLYDRUG EXPOSURE**
Colby JB, Smith L, O’Connor MJ, Bookheimer SY, Van Horn JD, Sowell ER.
Publication – PubMed
10<sup>th</sup> November 2012

15. **THREE-DIMENSIONAL SURFACE DEFORMATION-BASED SHAPE ANALYSIS OF HIPPOCAMPUS AND CAUDATE NUCLEUS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**
Publication – PubMed
5<sup>th</sup> November 2012

16. **FATTY ACID ETHYL ESTERS (FAEES) AS MARKERS FOR ALCOHOL IN MECONIUM: METHOD VALIDATION AND IMPLEMENTATION OF A SCREENING PROGRAM FOR PRENATAL DRUG EXPOSURE**
Hastedt M, Krumbiegel F, Gapert R, Tsokos M, Hartwig S.
Publication – PubMed
5<sup>th</sup> November 2012
17. **DOES ANTENATAL TOBACCO OR ALCOHOL EXPOSURE INFLUENCE A CHILD’S CEREBRAL PALSY? A POPULATION-BASED STUDY**
Kyriakopoulos P, Oskoui M, Dagenais L, Shevell M.
Publication – PubMed
November 2012

18. **THE TREATMENT OF ALCOHOL AND OPIOID DEPENDENCE IN PREGNANT WOMEN**
Heberlein A, Leggio L, Stichtenoth D, Hillemacher T.
Publication – PubMed
November 2012

19. **THE DETECTION AND QUANTIFICATION OF ETHYL GLUCURONIDE IN PLACENTAL TISSUE AND PLACENTAL PERFUSATE BY HEADSPACE SOLID-PHASE MICROEXTRACTION COUPLED WITH GAS CHROMATOGRAPHY-MASS SPECTROMETRY**
Matlow JN, Aleksa K, Lubetsky A, Koren G.
Publication – PubMed
31st October 2012

20. **A LONGITUDINAL STUDY OF THE LONG-TERM CONSEQUENCES OF DRINKING DURING PREGNANCY: HEAVY IN UTERO ALCOHOL EXPOSURE DISRUPTS THE NORMAL PROCESSES OF BRAIN DEVELOPMENT**
Publication – PubMed
31st October 2012

21. **THE EFFECT OF ETHYL ALCOHOL ON THE FUNCTION OF SPATIAL MEMORY IN RATS**
Publication – PubMed
31st October 2012

22. **CONSENSUS DIAGNOSTIC CRITERIA FOR FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA: A MODIFIED DELPHI STUDY**
Publication – PubMed
25th October 2012

23. **COCAETHYLENE AS A BIOMARKER TO PREDICT HEAVY ALCOHOL EXPOSURE AMONG COCAINE USERS**
Publication – PubMed
24th October 2012

24. **EFFECT OF PREDICTIVE CUING ON RESPONSE INHIBITION IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE**
Publication – PubMed
24th October 2012

25. **CHOLECALCIFEROL ATTENUATES PERSEVERATIVE BEHAVIOR ASSOCIATED WITH DEVELOPMENTAL ALCOHOL EXPOSURE IN RATS IN A DOSE-DEPENDENT MANNER**
Idrus NM, Happer JP, Thomas JD.
Publication – PubMed
23rd October 2012
26. **ADEQUACY OF MATERNAL IRON STATUS PROTECTS AGAINST BEHAVIORAL, NEUROANATOMICAL, AND GROWTH DEFICITS IN FETAL ALCOHOL SPECTRUM DISORDERS**
Rufer ES, Tran TD, Attridge MM, Andrzejewski ME, Flentke GR, Smith SM.
Publication – PubMed
19th October 2012

27. **A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF SPATIAL WORKING MEMORY IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE: CONTRIBUTION OF FAMILIAL HISTORY OF ALCOHOL USE DISORDER**
Norman AL, O'Brien JW, Spadoni AD, Tapert SF, Jones KL, Riley EP, Mattson SN
Publication – Unbound Medline
16th October 2012

28. **ETHICAL CONSIDERATIONS WHEN COMMUNICATING A DIAGNOSIS OF A FETAL ALCOHOL SPECTRUM DISORDER TO A CHILD**
Michelle Todorow, Karrela Paris, Ellen Fantus
Publication – Journal of Population Therapeutics and Clinical Pharmacology
October 2012

29. **CDON MUTATION AND FETAL ETHANOL EXPOSURE SYNERGIZE TO PRODUCE MIDLINE SIGNALING DEFECTS AND HOLOPROSENCEPHALY SPECTRUM DISORDERS IN MICE**
Hong M, Krauss RS.
Publication – PubMed
11th October 2012

30. **L1 CELL ADHESION MOLECULE SIGNALING IS INHIBITED BY ETHANOL IN VIVO**
Littner Y, Tang N, He M, Bearer CF
Publication – Unbound Medline
10th October 2012

31. **NEUROPROTECTIVE PEPTIDES INFLUENCE CYTOKINE AND CHEMOKINE ALTERATIONS IN A MODEL OF FETAL ALCOHOL SYNDROME**
Robin Roberson, Thea Kuddo, Ines Benassou, Daniel Abebe, Catherine Y. Spong
Publication – American Journal of Obstetrics and Gynecology
8th October 2012

32. **GESTATIONAL NALTREXONE AMELIORATES FETAL ETHANOL EXPOSURES ENHANCING EFFECT ON THE POSTNATAL BEHAVIORAL AND NEURAL RESPONSE TO ETHANOL**
Youngentob SL, Kent PF, Youngentob LM.
Publication – PubMed
8th October 2012

33. **AUTISM CHARACTERISTICS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**
Stevens SA, Nash K, Koren G, Rovet J.
Publication – PubMed
3rd October 2012

34. **ETHANOL DISRUPTS AXON OUTGROWTH STIMULATED BY NETRIN-1, GDNF, AND L1 BY BLOCKING THEIR CONVERGENT ACTIVATION OF SRC FAMILY KINASE SIGNALING**
Chen S, Charness ME.
Publication – PubMed
28th September 2012
35. **FETAL ALCOHOL-RELATED GROWTH RESTRICTION FROM BIRTH THROUGH YOUNG ADULTHOOD AND MODERATING EFFECTS OF MATERNAL PREPREGNANCY WEIGHT**

Publication – Wiley Online Library - Alcoholism: Clinical and Experimental Research
26th September 2012

36. **BRIEF INTERVENTION TO REDUCE RISKY DRINKING IN PREGNANCY: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL**

Publication – PubMed
24th September 2012

37. **ALCOHOL-RELATED DEVELOPMENTAL ORIGIN OF ADULT HEALTH - POPULATION STUDIES IN POLAND AMONG MOTHERS AND NEWBORNS (2010-2012)**

Wojtyła A, Kapka-Skrzypczak L, Diatczyk J, Fronczak A, Paprzycki P.
Publication – PubMed
20th September 2012

38. **INTERACTIONS AMONG ALCOHOL DEPENDENCE, PERINATAL COMMON MENTAL DISORDERS AND VIOLENCE IN COUPLES IN RURAL VIETNAM: A CROSS-SECTIONAL STUDY USING STRUCTURAL EQUATION MODELLING**

Tran TD, Tran T, Wynter K, Fisher J.
Publication – PubMed
19th September 2012

39. **FETAL BRAIN FUNCTION IN RESPONSE TO MATERNAL ALCOHOL CONSUMPTION: EARLY EVIDENCE OF DAMAGE**

Peter G. Hepper, James C. Dornan, Catherine Lynch
Publication – Wiley Online Library – Alcoholism: Clinical and Experimental Research
14th September 2012

40. **THE BRAIN IN THE BELLY: WHAT AND HOW OF FETAL NEUROIMAGING?**

Nadine J. Girard MD, Kathia Chaumoître MD, PhD
Publication - Wiley Online Library - Journal of Magnetic Resonance Imaging
14th September 2012

41. **THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON PSYCHOPATHOLOGY AND BEHAVIOR**

Publication – PubMed
13th September 2012

42. **FURTHER DEVELOPMENT OF A NEUROBEHAVIORAL PROFILE OF FETAL ALCOHOL SPECTRUM DISORDERS**

Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Adnams CM, Jones KL, Riley EP.
Publication – PubMed
13th September 2012
43. DETERMINANTS OF PREGNANT WOMEN’S COMPLIANCE WITH ALCOHOL GUIDELINES: A PROSPECTIVE COHORT STUDY
Publication – PubMed
13th September 2012

44. BLOOD ALCOHOL LEVELS FOR AMERICAN INDIAN MOTHERS AND NEWBORNS
Kvine VL, Randall B, Simanton EG, Brenneman G, Welty TK.
Publication – PubMed
10th September 2012

45. INDUCTION OF BRAIN CYP2E1 BY CHRONIC ETHANOL TREATMENT AND RELATED OXIDATIVE STRESS IN HIPPOCAMPUS, CEREBELLUM, AND BRAINSTEM
Publication – PubMed
6th September 2012

46. ALCOHOL-INDUCED ALTERATIONS IN MATERNAL UTERINE ENDOTHELIAL PROTEOME: A QUANTITATIVE ITRAQ MASS SPECTROMETRIC APPROACH
Ramadoss J, Magness RR.
Publication – PubMed
5th September 2012

47. ALCOHOL AND PREGNANCY: DO ABSTINENCE POLICIES HAVE UNINTENDED CONSEQUENCES?
O’Leary CM.
Publication – PubMed
4th September 2012

48. DEVELOPMENT OF MULTI-ROUTE PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS FOR ETHANOL IN THE ADULT, PREGNANT, AND NEONATAL RAT
Publication – PubMed
September 2012

49. A REVIEW OF EVIDENCE-BASED APPROACHES FOR REDUCTION OF ALCOHOL CONSUMPTION IN NATIVE WOMEN WHO ARE PREGNANT OR OF REPRODUCTIVE AGE
Montag A, Clapp JD, Calac D, Gorman J, Chambers C.
Publication – PubMed
September 2012

50. HIGH-THROUGHPUT CLASSIFICATION OF CLINICAL POPULATIONS FROM NATURAL VIEWING EYE MOVEMENTS
Tseng PH, Cameron IG, Pari G, Reynolds JN, Munoz DP, Itti L.
Publication – PubMed
25th August 2012

51. HIGH PREVALENCE OF VITAMIN D DEFICIENCY IN PREGNANT WOMEN: A NATIONAL CROSS-SECTIONAL SURVEY
Vandevijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R.
Publication – PubMed
24th August 2012
52. **THE IMPACT OF ALCOHOL USE DURING PREGNANCY ON MATERNAL RESPONSES AFTER BIRTH**
Pearson RM, Heron J, Melotti R, Joinson C, Evans J.
Publication – PubMed
23rd August 2012

53. **ETHANOL-INDUCED FACE-BRAIN DYSMORPHOLOGY PATTERNS ARE CORRELATIVE AND EXPOSURE-STAGE DEPENDENT**
Publication – PubMed
22nd August 2012

54. **ALCOHOL, TOBACCO AND DRUG USE AS REASONS FOR ABORTION**
Roberts SC, Avalos LA, Sinkford D, Foster DG.
Publication – PubMed
22nd August 2012

55. **SEVERE GASTROESOPHAGEAL REFLUX DISEASE ASSOCIATED WITH FOETAL ALCOHOL SYNDROME**
Sujay NK, Jones M, Whittle E, Murphy H, Auth MK.
Publication – PubMed
21st August 2012

56. **HIGHER FUNCTIONING CHILDREN WITH PRENATAL ALCOHOL EXPOSURE: IS THERE A SPECIFIC NEUROCOGNITIVE PROFILE?**
Quattlebaum JL, O'Connor MJ.
Publication – PubMed
21st August 2012

57. **PRENATAL ETHANOL EXPOSURE ALTERS SYNAPTIC PLASTICITY IN THE DORSOLATERAL STRIATUM OF RAT OFFSPRING VIA CHANGING THE REACTIVITY OF DOPAMINE RECEPTOR**
Zhou R, Wang S, Zhu X.
Publication – PubMed
16th August 2012

58. **EFFECTS OF HEAVY PRENATAL ALCOHOL EXPOSURE AND IRON DEFICIENCY ANEMIA ON CHILD GROWTH AND BODY COMPOSITION THROUGH AGE 9 YEARS**
R. Colin Carter, Joseph L. Jacobson, Christopher D. Molteno, Hongyu Jiang, Ernesta M. Meintjes, Sandra W. Jacobson, Christopher Duggan
Publication – Wiley Online Library - Alcoholism: Clinical and Experimental Research
15th August 2012

59. **ALCOHOL INTAKE IN PREGNANCY INCREASES THE CHILD’S RISK OF ATOPIC DERMATITIS. THE COPSAC PROSPECTIVE BIRTH COHORT STUDY OF A HIGH RISK POPULATION**
Carson CG, Halkjaer LB, Jensen SM, Bisgaard H.
Publication – PubMed
15th August 2012

60. **SLEEP PROBLEMS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**
Chen ML, Olson HC, Picciano JF, Starr JR, Owens J.
Publication – PubMed
15th August 2012

www.nofas-uk.org 12
61. **MATERNAL ALCOHOL USE DURING PREGNANCY, BIRTH WEIGHT AND EARLY BEHAVIORAL OUTCOMES**
Chen JH.
Publication – PubMed
14th August 2012

62. **HEALTH CARE BURDEN AND COST ASSOCIATED WITH FETAL ALCOHOL SYNDROME: BASED ON OFFICIAL CANADIAN DATA**
Popova S, Lange S, Burd L, Rehm J.
Publication – PubMed
10th August 2012

63. **ALCOHOL-INDUCED PREMATURE PERMEABILITY IN MOUSE PLACENTA-YOLK SAC BARRIERS IN VIVO**
Publication – PubMed
9th August 2012

64. **ADVANCED GESTATIONAL AGE INCREASES SERUM CARBOHYDRATE-DEFICIENT TRANSFERRIN LEVELS IN ABSTINENT PREGNANT WOMEN**
Bakhireva LN, Cano S, Rayburn WF, Savich RD, Leeman L, Anton RF, Savage DD.
Publication – PubMed
8th August 2012

65. **A REVIEW OF EXECUTIVE FUNCTION DEFICITS AND PHARMACOLOGICAL MANAGEMENT IN CHILDREN AND ADOLESCENTS**
Hosenbocus S, Chahal R.
Publication – PubMed
August 2012

66. **INTERGENERATIONAL INFLUENCES ON EARLY ALCOHOL USE: INDEPENDENCE FROM THE PROBLEM BEHAVIOR PATHWAY**
Kerr DC, Capaldi DM, Pears KC, Owen LD.
Publication – PubMed
August 2012

67. **CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE EXPERIENCE REDUCED CONTROL OF ISOTONIC FORCE**
Tanya T. Nguyen, Susan S. Levy, Edward P. Riley, Jennifer D. Thomas, Roger W. Simmons
Publication – Wiley Online Library - Alcoholism: Clinical and Experimental Research
26th July 2012

68. **OMEGA-3 SUPPLEMENTATION CAN RESTORE GLUTATHIONE LEVELS AND PREVENT OXIDATIVE DAMAGE CAUSED BY PRENATAL ETHANOL EXPOSURE**
Patten AR, Brocardo PS, Christie BR.
Publication – PubMed
25th July 2012

69. **ETHANOL-INDUCED DISRUPTION OF GOLGI APPARATUS MORPHOLOGY, PRIMARY NEURITE NUMBER AND CELLULAR ORIENTATION IN DEVELOPING CORTICAL NEURONS**
Powrozek TA, Olson EC.
Publication – PubMed
25th July 2012

www.nofas-uk.org 13
70. **ACUTE AND CHRONIC EXPOSURE OF CHICK EMBRYO TO ETHANOL ALTERS BRAIN NEUROSTEROID LEVELS**
Taherianfard M, Davazdahemamy M, Shojaeifard M, Sharifi M.
Publication – PubMed
24th July 2012

71. **BIOCHEMICAL AND GENETIC ANALYSES OF CHILDHOOD ATTENTION DEFICIT/HYPERACTIVITY DISORDER**
Emrah Caylak
Publication – Wiley Online Library - American Journal of Medical Genetics Part B: Neuropsychiatric Genetics
23rd July 2012

72. **MICROGLIA PLAY A ROLE IN ETHANOL-INDUCED OXIDATIVE STRESS AND APOPTOSIS IN DEVELOPING HYPOTHALAMIC NEURONS**
Boyadjieva NI, Sarkar DK.
Publication – PubMed
23rd July 2012

73. **A PROSPECTIVE COHORT STUDY OF THE PREVALENCE OF GROWTH, FACIAL, AND CENTRAL NERVOUS SYSTEM ABNORMALITIES IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE**
Publication – PubMed
23rd July 2012

74. **EXPLANATION OF SOCIAL INEQUALITIES IN HYPERACTIVITY/INATTENTION IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE**
Pfrender M, Liebig S, Feldmann R.
Publication – PubMed
20th July 2012

75. **PRENATAL ALCOHOL EXPOSURE, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AND SLAGGHIS COGNITIVE TEMPO**
Publication – PubMed
20th July 2012

76. **ALCOHOL USE AND BINGE DRINKING AMONG WOMEN OF CHILDBEARING AGE--UNITED STATES, 2006-2010**
Centers for Disease Control and Prevention (CDC).
Publication – PubMed
20th July 2012

77. **NORTHERN BRITISH COLUMBIAN ABORIGINAL MOTHERS: RAISING ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDER**
Johnston S, Boyle JS.
Publication – PubMed
16th July 2012

78. **DIAGNOSING FETAL ALCOHOL SYNDROME: NEW INSIGHTS FROM NEWER GENETIC TECHNOLOGIES**
Publication – PubMed
14th July 2012

www.nofas-uk.org
79. ATTENUATION OF OXIDATIVE STRESS, NEUROINFLAMMATION, AND APOPTOSIS BY CURCUMIN PREVENTS COGNITIVE DEFICITS IN RATS POSTNATALLY EXPOSED TO ETHANOL
Tiwari V, Chopra K.
Publication – PubMed
13th July 2012

80. ALCOHOL BIOMARKERS
Ingall GB.
Publication – PubMed
13th July 2012

81. PRENATAL ETHANOL EXPOSURE IMPAIRS PASSIVE AVOIDANCE ACQUISITION AND ENHANCES UNCONDITIONED FREEZING IN RAT OFFSPRING
Ohta K, Sakata-Haga H, Fukui Y.
Publication – PubMed
7th July 2012

82. INHIBITION OF HISTONE ACETYLATION BY CURCUMIN REDUCES ALCOHOL-INDUCED EXPRESSION OF HEART DEVELOPMENT-RELATED TRANSCRIPTION FACTORS IN CARDIAC PROGENITOR CELLS
Publication – PubMed
7th July 2012

83. USE OF THE DIAGNOSTIC CLASSIFICATION OF MENTAL HEALTH AND DEVELOPMENTAL DISORDERS OF INFANCY AND EARLY CHILDHOOD: REVISED EDITION (DC:0–3R) WITH CANADIAN INFANTS AND YOUNG CHILDREN PRENATALLY EXPOSED TO SUBSTANCES
Mary Motz, Stacey D. Espinet, Jessica Jeihyun Jeong, Patricia Zimmerman, Julie Chamberlin, Debra J. Pepler
Publication – Wiley Online Library - Infant Mental Health Journal
6th July 2012

84. PARADOXICAL EFFECTS OF ALCOHOL AND THIAMINE DEFICIENCY ON THE EYE OPENING IN RAT PUPS
Bâ A.
Publication – PubMed
5th July 2012

85. PROGRAMMED CELL DEATH 4 (PDCD4): A NOVEL PLAYER IN ETHANOL-MEDIATED SUPPRESSION OF PROTEIN TRANSLATION IN PRIMARY CORTICAL NEURONS AND DEVELOPING CEREBRAL CORTEX
Madhusudhanan Narasimhan1,2, Marylatha Rathinam1, Amanjot Riar1, Dhyanesh Patel1, Srinivas Mummidi3,4, Hsin-Shen Yang5, Nancy H. Colburn6, George I. Henderson1,2, Lenin Mahimainathan
Publication – Wiley Online Library - Alcoholism: Clinical and Experimental Research
3rd July 2012

86. LONG-TERM ALTERATIONS OF STRIATAL PARVALBUMIN INTERNEURONS IN A RAT MODEL OF EARLY EXPOSURE TO ALCOHOL
De Giorgio A, Comparini SE, Intra FS, Granato A.
Publication – PubMed
3rd July 2012

www.nofas-uk.org 15
87. **ABORIGINAL WOMEN, ALCOHOL AND THE ROAD TO FETAL ALCOHOL SPECTRUM DISORDER**
Lorian G Hayes
Publication – MJA- The Medical Journal of Australia
2nd July 2012

88. **ALCOHOL USE PATTERN IN PREGNANT WOMEN CARED FOR IN A PUBLIC UNIVERSITY HOSPITAL AND ASSOCIATED RISK FACTORS**
Souza LH, Santos MC, Oliveira LC.
Publication – PubMed
July 2012

89. **ALCOHOL USE AND CIGARETTE SMOKING DURING PREGNANCY AMONG AMERICAN INDIANS/ALASKA NATIVES**
Watt TT
Publication – PubMed
July 2012

90. **ANOTHER STEP FORWARD IN RELATING FACIAL AND BRAIN DYSMORPHOLOGIES ASSOCIATED WITH PRENATAL ALCOHOL EXPOSURE**
Fryer SL.
Publication – PubMed
July 2012

91. **EFFECTS OF EXPOSURE TO MODERATE LEVELS OF ETHANOL DURING PRENATAL BRAIN DEVELOPMENT ON DENDRITIC LENGTH, BRANCHING, AND SPINE DENSITY IN THE NUCLEUS ACCUMBENS AND DORSAL STRIATUM OF ADULT RATS**
Rice JP, Suggs LE, Lusk AV, Parker MO, Candelaria-Cook FT, Akers KG, Savage DD, Hamilton DA.
Publication – PubMed
27th June 2012

92. **PRENATAL ETHANOL EXPOSURE STIMULATES NEUROGENESIS IN HYPOTHALAMIC AND LIMBIC PEPTIDE SYSTEMS: POSSIBLE MECHANISM FOR OFFSPRING ETHANOL OVERCONSUMPTION**
Chang GQ, Karatayev O, Liang SC, Barson JR, Leibowitz SF.
Publication – PubMed
26th June 2012

93. **OVEREXPRESSION OF SERUM RESPONSE FACTOR IN ASTROCYTES IMPROVES NEURONAL PLASTICITY IN A MODEL OF EARLY ALCOHOL EXPOSURE**
Paul AP, Medina AE.
Publication – PubMed
26th June 2012

94. **RECORDING A HISTORY OF ALCOHOL USE IN PREGNANCY: AN AUDIT OF KNOWLEDGE, ATTITUDES AND PRACTICE AT A CHILD DEVELOPMENT SERVICE**
Mutch R, Wray J, Bower C.
Publication – PubMed
23rd June 2012

95. **VASCULAR EFFECTS OF MATERNAL ALCOHOL CONSUMPTION**
Ramadoss J, Magness RR.
Publication – PubMed
22nd June 2012
96. **AUSTRALIA'S DOUBLE STANDARD ON THAILAND'S ALCOHOL WARNING LABELS**
   O'Brien P.
   Publication – PubMed
   20th June 2012

97. **THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID PREGNANCY ON THE CHILD’S INTELLIGENCE, ATTENTION, AND EXECUTIVE FUNCTION**
   Kesmodel US, Bertrand J, Støvring H, Skarpness B, Denny CH, Mortensen EL; Lifestyle During Pregnancy Study Group.
   Publication – PubMed
   20th June 2012

98. **SAFETY CONCERNS REGARDING BINGE DRINKING IN PREGNANCY: A REVIEW**
   Elizabeth Ann Conover, Kenneth Lyons Jones
   Publication – Wiley Online Library - Birth Defects Research Part A: Clinical and Molecular Teratology
   18th June 2012

99. **PROTECTIVE EFFECT OF EXOGENOUS NUCLEOTIDES ON THE DEVELOPMENTAL TOXICITY OF ALCOHOL**
   Dong WH, Zhao J, Zhang JX, Xu LL, Xu YJ.
   Publication – PubMed
   18th June 2012

100. **PATHWAYS TO ALCOHOL-INDUCED BRAIN IMPAIRMENT IN YOUNG PEOPLE: A REVIEW**
    Publication – PubMed
    17th June 2012

101. **ROLE OF NON-CODING RNAs IN THE NEUROADAPTATION TO ALCOHOLISM AND FETAL ALCOHOL EXPOSURE**
    Reilly M.
    Publication – PubMed
    15th June 2012

102. **ETHANOL EXPOSURE ALTERS PROTEIN EXPRESSION IN A MOUSE MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS**
    Publication – PubMed
    14th June 2012

103. **EFFECTS OF THIRD TRIMESTER-EQUIVALENT ETHANOL EXPOSURE ON CL(-) CO-TRANSPORTER EXPRESSION, NETWORK ACTIVITY, AND GABAERGIC TRANSMISSION IN THE CA3 HIPPOCAMPAL REGION OF NEONATAL RATS**
    Everett JC, Licón-Muñoz Y, Valenzuela CF.
    Publication – PubMed
    14th June 2012

104. **HEALTH PROFESSIONALS' PERCEPTIONS ABOUT THE ADOPTION OF EXISTING GUIDELINES FOR THE DIAGNOSIS OF FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA**
    Publication – PubMed
    14th June 2012
105. **PRENATAL ETHANOL EXPOSURE LEADS TO GREATER ETHANOL-INDUCED APPETITIVE REINFORCEMENT**
Pautassi RM, Nizhnikov ME, Spear NE, Molina JC.
Publication – PubMed
12th June 2012

106. **REDUCED SLEEP AND IMPAIRED SLEEP INITIATION IN ADULT MALE RATS EXPOSED TO ALCOHOL DURING EARLY POSTNATAL PERIOD**
Volgin DV, Kubin L.
Publication – PubMed
12th June 2012

107. **SUPPLEMENTAL CHOLINE DURING THE PERIWEANING PERIOD PROTECTS AGAINST TRACE CONDITIONING IMPAIRMENTS ATTRIBUTABLE TO POST-TRAINING ETHANOL EXPOSURE IN ADOLESCENT RATS**
Hunt PS.
Publication – PubMed
11th June 2012

108. **ALCOHOL DELAYS THE EMERGENCE OF THE FETAL ELICITED STARTLE RESPONSE, BUT ONLY TRANSIENTLY**
Hepper PG, Dornan JC, Lynch C, Maguire JF.
Publication – PubMed
9th June 2012

109. **IMPACT OF CHRONIC ETHANOL INTAKE OF RAT MOTHERS ON THE SEIZURE SUSCEPTIBILITY OF THEIR IMMATURE MALE OFFSPRING**
Riljak V, Maresova D, Jandova K, Bortelova J, Pokorny J.
Publication – PubMed
June 2012

110. **MALE GERMLINE TRANSMITS FETAL ALCOHOL ADVERSE EFFECT ON HYPOTHALAMIC PROOPiomelanocortin GENE ACROSS GENERATIONS**
Govorko D, Bekdash RA, Zhang C, Sarkar DK.
Publication – PubMed
22nd May 2012

111. **COMPARISON OF SPATIAL WORKING MEMORY IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE AND THOSE DIAGNOSED WITH ADHD; A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY**
Publication – PubMed
18th May 2012

112. **EFFECTS OF ALCOHOL, LITHIUM, AND HOMOCYSTEINE ON NONMUSCLE MYOSIN-II IN THE MOUSE PLACENTA AND HUMAN TROPHOBLASTS**
Han M, Neves AL, Serrano M, Brinez P, Huita JC, Acharya G, Linask KK.
Publication – PubMed
14th May 2012

113. **MOTION PERCEPTION IN CHILDREN WITH FOETAL ALCOHOL SYNDROME**
Kristina Gummel, Jan Ygge, Mariagrazia Benassi, Roberto Bolzan
Publication – Wiley Online Library - Acta Paediatrica
5th May 2012
114. MATERNAL SMOKING AND ALCOHOL CONSUMPTION DURING PREGNANCY AS RISK FACTORS FOR SUDDEN INFANT DEATH
McDonnell-Naughton M, McGarvey C, O'Regan M, Matthews T.
Publication – PubMed
April 2012

115. ELEVATION OF GM2 GANGLIOSIDE DURING ETHANOL-INDUCED APOPTOTIC NEURODEGENERATION IN THE DEVELOPING MOUSE BRAIN
Mitsuo Saito, Goutam Chakraborty, Relish Shah, Rui-Fen Mao, Asok Kumar, Dun-Sheng Yang, Kostantin Dobrenis, Mariko Saito
Publication – Wiley Online Library - Journal of Neurochemistry
20th March 2012

116. PREGNANT WOMEN AND ALCOHOL USE IN THE BOSOMTWE DISTRICT OF THE ASHANTI REGION-Ghana
Adusi-Poku Y, Edusei AK, Bonney AA, Tagbor H, Nakua E, Otupiri E.
Publication – PubMed
March 2012

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Cole GJ, Zhang C, Ojiaku P, Bell V, Devkota S, Mukhopadhyay S.
Publication – PubMed
2012

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Svanidze IK, Museridze DP, Didimova EV, Sanikidze TV, Gegenava LG, Gvinadze NN.
Publication – PubMed
2012

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Probyn ME, Zanini S, Ward LC, Bertram JF, Moritz KM.
Publication – PubMed
2012

120. PREGNANT WOMEN AND MOTHERS USING ALCOHOL, TOBACCO AND ILLEGAL DRUGS
Nechanská B, Mravčík V, Sopko B, Velebil P.
Publication – PubMed
2012
1. **SECOND EUROPEAN CONFERENCE ON FASD**  
   European FASD Alliance  
   Publication – Journal of Population Therapeutics and Clinical Pharmacology  
   21st-24th October 2012

2. **THE POWER OF NETWORKING – HIGHLIGHTS OF THE WORK OF CANADA’S NETWORK ACTION TEAM ON FASD PREVENTION FROM A WOMEN’S HEALTH DETERMINANTS PERSPECTIVE**  
   Poole, N  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

3. **NOW YOU SEE ME, NOW YOU DON’T – SERVICE DELIVERY TO FASD OFFENDERS IN SASKATCHEWAN COMMUNITY CORRECTIONS**  
   Gerger, B  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

4. **EVERYDAY MEMORY IMPAIRMENTS IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDER**  
   Agnihotri , Sheard E, Keightley M, & Rovet J  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

5. **CORTICAL MORPHOLOGY IN CHILDREN WITH ALCOHOL-RELATED NEURODEVELOPMENTAL DISORDER**  
   Rajaprakash M, Chakravarty MM, Lerch JP, & Rovet J  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

6. **SERVICE UTILIZATION PATTERNS AMONG CHILDREN AND ADOLESCENTS WITH PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDER**  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

7. **EXAMINING THE VALIDITY OF THE ASANTE FASD SCREENING AND REFERRAL TOOL FOR YOUTH PROBATION OFFICERS IN JUSTICE INVOLVED YOUTH**  
   McLachlan K, & Roesch R  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012

8. **IMPROVING OUTCOMES FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER IN CARE**  
   McHenry SA, Cheng J, Popham J, & Muhajarine N  
   Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts  
   11th September 2012
9. **UNDERSTANDING THE EFFICACY OF TREATMENT OF SLEEP DISORDERS AMONG CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER (FASD) AND PRENATAL ALCOHOL EXPOSURE (PAE)**
McHenry SA, & Muhajarine N
Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts
11th September 2012

10. **COLLABORATIVELY DEVELOPING CAPACITY FOR SCREENING FOR FASD AND LITERACY IN EDUCATIONAL CONTEXTS IN SASKATCHEWAN**
Mitten, R
Publication - 13th Annual Fetal Alcohol Canadian Expertise (FACE) Poster Competition Abstracts
11th September 2012

[Back to Table of Contents]
A. **FETAL ALCOHOL EXPOSURE AFFECTS BRAIN STRUCTURE IN CHILDREN**
   Publication – EurekAlert
   25th November 2012

B. **COLLEGE LAUNCHES FETAL ALCOHOL PROGRAM**
   Article by Brian Kelly, Sault Star
   Publication – Sault Star
   17th November 2012-11-27

C. **TWO CHICAGO STUDENTS DEVELOP NOVEL TREATMENT METHOD FOR FETAL ALCOHOL SYNDROME**
   Publication – News-Medical.net
   19th October 2012

Back to Table of Contents
1) **FETAL ALCOHOL EXPOSURE AND IQ AT AGE 8: EVIDENCE FROM A POPULATION-BASED BIRTH-COHORT STUDY**
   Publication – PubMed
   14th November 2012

2) **PRENATAL ETHANOL EXPOSURE ALTERS SYNAPTIC PLASTICITY IN THE DORSOLATERAL STRIATUM OF RAT OFFSPRING VIA CHANGING THE REACTIVITY OF DOPAMINE RECEPTOR**
   Zhou R, Wang S, Zhu X.
   Publication – PubMed
   16th August 2012

[Back to Table of Contents]
I. HOW HARMFUL COULD MODERATE DRINKING DURING PREGNANCY BE TO THE FETUS?

Dr. Ron Gray
Consultant Clinical Epidemiologist
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Following work we completed in 2006 at NPEU, which identified a number of gaps in the evidence on the effects of moderate alcohol consumption during pregnancy, I was fortunate to work with colleagues at the Universities of Bristol, Nottingham, Leicester and Queensland on a study using a new technique which gets round some of the problems with existing studies in this area. We wanted to see what impact drinking between one and six units weekly would have on children’s IQ measured at age eight. You may think, well why not just compare the IQs of children of non-drinkers with those of moderate drinkers, but therein lies the problem. It’s not a fair comparison. Generally moderate drinkers are more affluent, better educated, older and less likely to smoke. So a naïve comparison might well show the children of moderate drinkers to be more intelligent – indeed some studies have shown just that. We call this spurious effect confounding. There are some statistical techniques we can use to reduce confounding, but it is notoriously difficult to completely remove this influence. The technique of Mendelian Randomisation pioneered by epidemiologists at Bristol helps get round this problem by using genetic variation to give information on the impact of various environmental risk factors, for example the effect of alcohol on the fetus. But the great thing is that this technique is not susceptible to confounding.

The end result of the study: there is a link between certain genetic variants concerned with alcohol metabolism and IQ — but only in the children of moderate drinkers and not in abstainers.

You can download the paper for free if you are interested in pursuing it further at the link below. Like all results, it is important to replicate this one and we are currently working on another study to do this. We clearly need to intensify research efforts into the effects of moderate and light drinking in pregnancy. We have a number of other studies in progress but there are still a lot of uncertainties. In the meantime, what should we say to women to help them make choices? We would say, best avoid it, why take the chance?

Ron Gray, National Perinatal Epidemiology Unit, University of Oxford, UK.


http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0049407

Back to Table of Contents
II. IN SEARCH OF CURRICULUM: EVOLVING LEARNING PATHWAYS FOR STUDENTS WITH FASD

Barry Carpenter
Professor of Special Education

In 2007 a set of referral papers arrived for a placement at the school I was then Principal of. The school was predominantly for children with Autistic Spectrum Disorder. The student referred has an intriguing diagnosis which read "The causal base of A's Autistic Spectrum Disorder is maternal abuse of alcohol e.g. Fetal Alcohol Spectrum Disorder (FASD)."

"A" was duly admitted to the school. Almost immediately staff were commenting that he was "different" in his responses to our typical ASD students: he was far more sociable and interactive, his language skills richer and more focussed than the majority of other students in the school. As we observed "A" (who was 12 years old) it was obvious that he had some significant intellectual impairment, which he clearly masked with his gregarious behaviour, and (seeming) linguistic skills.

His teacher reported that he was always enthusiastic to participate in classroom activities, but his retention and overlearning were poor. "Here today - gone tomorrow", was how she described his learning. I saw this first hand myself on a visit to "A's" classroom. His teacher suggested to him that he show me his latest achievement, which was to write his full name. He did this with great pride.

The next day I showed a visitor around the school, and when in "A's" classroom asked him to write his name, as he had the day before. He smiled and began the task with enthusiasm. He picked up the pen, and it hovered over the paper. And it hovered .......... After what seemed like an eternity he looked up at me. The smile had gone: his eyes were two pits of bewilderment. Try as he might he could not recall those two words that were his name. I made light of the situation, but felt his disappointment deeply.

Later that day I googled FASD, seeking some guidelines on how to teach such children. There was no British material. There were Canadian guidelines with helpful suggestions, but in the U.K. we have a distinctive National Curriculum, and everything we do for every child has to be mapped into that framework. Not being able to help and guide my teachers troubled me greatly, and spurred me on to seek resolution.

In 2008 I was elected as a Research Fellow to the University of Oxford, and could nominate the area of research. The choice was obvious - FASD - but not what is it? Rather how do you teach children with FASD? How do they learn? How can high-quality education potentially transform their life chances?

The research focussed on twenty teachers currently working with children with FASD. My quest was to discover from them, through interview, observation and narrative accounts, what they identified as the learning challenges of children with FASD, and what approaches, interventions, strategies they had found most successful. These were collated and described in the context of a small scale study I called "Pedagogically Bereft!" - for that is what we, as a teaching profession, were when it came to this group of children. (This study was eventually published in the British Journal of Special Education, 38, (1), 37 - 48.)

Following this initial, exploratory educational research I discussed with the Training and Development Agency for Schools (TDA) the possibility of funding a small scale research project to further identify a pedagogy suitable for children and young people with FASD.

A grant was awarded, enabling me to set up a small research team with myself as Director,
Carolyn Blackburn as Principal Researcher and Jo Egerton as Research Advisor. Carolyn was the full-time field worker, with Jo and I 'in advisory.' The project was hosted by NOFAS-UK, with Susan Fleisher acting as a Project Consultant. Carolyn had previously undertaken a piece of research looking at children with FASD in the Early Years, "Building Bridges to Understanding". (www.worcestershire.gov.uk/eyes)

The NOFAS-UK research was a nine site trial, across three primary, three secondary and three special schools in England. Findings were reported through articles (Blackburn, Carpenter and Egerton, "Support for Learning", 25, (3), 139 - 145), and eventually by a landmark report, "Facing the Challenge and Shaping the Future of Primary and Secondary Aged Students with Fetal Alcohol Spectrum Disorders", (online at www.nofas-uk.org).

Late in 2008 I was appointed by the Secretary of State for Education to act as Director for the National Research Project on Children with Complex Learning Difficulties and Disabilities. Within the national cohort of children established for this project were children with FASD, who certainly met the criteria for presenting with complex learning needs. One of the outputs from this project were briefing sheets that covered a whole new generation of learning disabilities and difficulties in children. There are three briefing sheets on FASD, giving different levels of information, and tiered to match the professional learning needs of teacher and education support staff. The briefing sheets can be found on http://complexld.ssatrust.org.uk

Also on the website can be found "new generation pedagogy"; new ways of teaching children with complex learning difficulties and disabilities including those with FASD. The pedagogy is built on the key tenet of "Engagement"; the goal and purpose in every classroom is to engage the child as an effective, participative learner. The Engagement Profile and Scale are becoming widely used across U.K. schools, as a subject-free medium for assessing, planning and monitoring student engagement in learning. (An article, "The rules of engagement" can be accessed on www.barrycarpentereducation.com)

By now this journey of inquiry, seeking to discover how to teach children with FASD, had taken me to mid 2011. Another opportunity then presented itself, to act as National Director for the development of Teacher Training modules in the area of Complex Learning Difficulties and Disabilities. Whilst this was not exclusively about FASD, the opportunity to embed information about FASD, to look at the learning pattern and pathways of those children, and to suggest effective strategies for teaching was a real possibility. These materials include interviews with children with FASD, their families and their teachers, and are now available online.

At around the same time, mid 2011, I was approached by the Publishers Routledge, to consider writing a book on the education of children with FASD. So much of the journey in the previous four years had involved the excellent input and support of my colleagues Carolyn Blackburn and Jo Egerton, that I could not envisage the book without their contribution.

There was a dearth of literature about how to teach children with FASD, particularly in the UK. This had to be our focus for the book, which indeed it was. "Educating Children and Young People with Fetal Alcohol Spectrum Disorders" was published by Routledge in 2012. It is the first British text on the education of children with FASD. It's "official" launch took place on 16th May 2012 in Adelaide, Australia, where Sue Meirs of NOFASRD, Australia, described it as "groundbreaking". Later this year it will have a European launch at the FASD Conference in Barcelona.

It is a source of great professional satisfaction that from a blank sheet of paper in 2007, from those days of watching the sadness in "A's" eyes, we have moved to a position of a range of UK relevant, web-based information.

Even more so, that with the combined expertise of Carolyn, Jo and myself, we have produced a text, our legacy to the teaching profession, but also our testimony to the power of education to transform lives and to enhance the lives of children with FASD. Too many children with FASD are...
denied quality education because people do not know how to teach them. This can no longer be the excuse. Education is key to quality of life for children and young people with FASD.

Barry Carpenter
Professor of Special Education

Educating Children and Young People with Fetal Alcohol Spectrum Disorders. Carolyn Blackburn, Barry Carpenter, Jo Egerton
London: Routledge

Further information about the book, and a forthcoming text on "Interdisciplinary Approaches to Fetal Alcohol Spectrum Disorders", can be found on www.barrycarpentereducation.com

Back to Table of Contents

III. TOWARD ENHANCED TEACHER PREPARATION FOR MEETING THE NEEDS OF STUDENTS WITH FASD

Jacqueline Pei and Cheryl Poth

Jacqueline Pei
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Cheryl Poth
Assistant Professor; Centre for Research in Applied Measurement and Evaluation, Educational Psychology

THE PROJECT

This project builds on our research team’s previous work (e.g., Job et al, 2011; Job et al., 2012) responding to the need for greater communication among teachers with respect to effective school-driven interventions targeted to meet the unique needs of students affected by Fetal Alcohol Spectrum Disorder (FASD). Researchers have catalogued a long list of deficits that result from the prenatal exposure to alcohol and the related diagnosis of an FASD (Bertrand, 2009). What has become clear is that FASD is associated with lifelong challenges across a diverse continuum including cognitive and academic difficulties, and behavioural problems (Howell et al., 2006; Olson et al., 1997) and that knowledge of how to best support students in the classroom is limited. A pressing priority for researchers is to identify best-practices that support the cognitive and behavioural needs of students with FASD (Dybdahl & Ryan, 2009). Current practices integrating students with FASD into mainstream classes has led to increased feelings of frustration and discouragement for those involved in supporting them. Blackburn and colleagues (2010) suggest that all teachers would benefit from an increased understanding of the learning needs and possible strategies that support the personalization of learning for this population.

Thus, the purpose of this project was to address the reported isolation of these teachers by providing an opportunity for participating in the development and piloting of a collaborative professional development process and tools to enhance their professional learning networks and relationships among the teaching team and with University researchers. This collaborative process was aimed at generating opportunities to discuss challenges, share strategies and create tools that encourage the teaching team to reflect, communicate, and act in ways that would best help students with FASD experience more positive school environments. In this way the following model was implemented:
THE PROCESS

Four sessions were held with teachers and Educational Assistants (EA’s) from an urban high school, over the course of four months. In the first session the project was introduced and participation invited. In the second session participants were provided with two hours of “teaching” about FASD and the brain. This teaching focused on processes that contribute to difficulties in the classroom, rather than specific deficits. As such, participants were encouraged to connect what they were hearing about the brain processes with what they see in the classroom and identify potential places where misinterpretation of behaviour may occur. Participants were asked to note behavioural incidents transpiring with a student(s) with FASD before the second session, including what action they took, consequences of their action, and why they thought that consequence occurred. During the next session three participants shared their experiences – successes and challenges – with other participants. The result was a conversation that provided evidence regarding enhanced understanding, reflective practice, and shifts in how they made decisions regarding actions. A similar activity was requested for preparing for the third and fourth sessions as well as ways in which they could incorporate reflection and collaboration (communication) into their regular activities.

THE RESEARCH

The case study approach (Merriam, 2002) was to generate an in-depth understanding of the process the group was engaged and comprised of five data sources; a) field notes from researchers, b) meeting summaries from 5 University-based team planning, c) meeting summaries from 6 school teams and a University-based team planning & debriefs, d) audio-recordings of four sessions with participants, and e) a post-collaborative training survey. The latter was designed using a five point Likert scale and open-ended questions to assess the effectiveness of the sessions related to appropriateness of logistics, quality of facilitators, usefulness of content and overall impact of the experience. The participants included four teachers and three educational assistants (EA), the two-member support team (WRaP success coach and the special needs coordinator), and the three member University-based team (Poth, Pei, and Hayes). All teachers, EAs, and special needs coordinator were employees of the Edmonton Public School District at an urban senior high school with over 1,000 students and an estimated 26 students diagnosed (or suspected) with an FASD. As part of an Alberta-wide initiative, success coaches are agents of the Wellness, Resilience and Partnership (WRaP) Project are imbedded in nine school districts and focus on supporting student engagement, academic success, and their emotional, physical, and...
social well-being (CanFASD, 2012). The qualitative data was analyzed using standard methods of inductive analysis and constant comparison (McMillan & Schumacher, 2005) whereas the quantitative survey data was analyzed using SPSS and descriptive statistics were generated.

CONCLUSIONS

Two types of findings have emerged from this study: immediate project outcomes and anticipated longer-term project outcomes. Immediate project outcomes included developing and implementing an innovative approach to professional learning characterized by responding to emerging needs. This contrasts traditional models of professional learning where the goals are pre-determined and the experience facilitated by experts. Working together, researchers and educators had an opportunity to discuss and brainstorm, provide feedback about what is helpful and relevant to classroom-practice, and generate tools (see Appendix A) to support their work with students with FASD. The educators felt these tools were useful to use as they evaluated their practice and considered new ways of understanding the true root of the behavior they were seeing – in order to conceptualize best responses. All participants reported agreement that the approach was useful for increasing their knowledge of FASD, and FASD-related classroom strategies, as well as increased their understanding of their colleague’s challenges. Furthermore, all participants indicated an interest in remaining involved in the group and motivated to learn further about FASD. Anticipated longer-term outcomes include enhanced individual teacher ability to meet the needs of students with FASD and expanded professional learning networks by contributing to an online collaboration of learning strategies at http://www.fasdcommunity.ca. Links to the Canada Research Network (http://www.canfasd.ca/aboutus/overview.aspx) and the knowfasd.ca website have also been emphasized as ways to continue to develop and share resources.

References


IV. UNRAVELING THE MOLECULAR MECHANISMS OF FETAL ALCOHOL SPECTRUM DISORDERS: NOVEL INSIGHTS AND EMERGING MOLECULAR TARGETS FOR PREVENTION

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About twenty years ago, I received an offer for a postdoctoral position from Dr. Kathleen Sulik, an international renowned Fetal Alcohol Spectrum Disorders (FASD) researcher at the University of North Carolina at Chapel Hill. Accompanying the offer letter was a funded NIH grant application which proposed to elucidate the role of oxidative stress in ethanol-induced teratogenesis as well as a number of papers published by Dr. Sulik’s laboratory. This was the first time I had ever seen mouse embryo images and heard the term Fetal Alcohol Syndrome. I accepted the offer and joined Dr. Sulik’s laboratory in 1993 because of my strong interest in oxidative stress. By that time, I never thought that I would spend my entire career doing research on FASD and that I would get so many rewards from my twenty year journey in to FASD research.

The first project I was involved in after I joined Dr. Sulik’s laboratory was to demonstrate the involvement of oxidative stress in ethanol-induced birth defects using the whole embryo culture system. Whole embryo culture is technically challenging not only for a new postdoctoral fellow who has never seen a mouse embryo before but also for the most experienced embryologist as it requires considerable finesse. I still remember how excited I was when I first saw the heartbeat in the embryos I cultured. The effort is worth it. Using this system, our study showed that ethanol exposure resulted in the generation of superoxide anion in embryos and that exogenously added
superoxide dismutase (SOD) diminished superoxide generation, reduced cell death and neural tube defects in ethanol-exposed cultured embryos (1). Then we extended this study into a primary cultured neural crest cells (NCCs), an alcohol-sensitive cell population. Confocal imaging has made it possible to show that in cultured living NCCs, ethanol exposure resulted in the generation of reactive oxygen species (ROS) and cell death (2). In addition, we have shown that these cells were sensitive to oxidative damage resulting from iron overload and that this damage was exacerbated by co-administration of ethanol. Both ethanol and iron-induced NCC death were prevented by the addition of the iron chelators desferoxamine and phenanthroline, as well as antioxidants, N-acetylcysteine (NAC) and SOD (3, 4). These results indicate that antioxidants can protect mouse embryos from ethanol-induced apoptosis and malformation in vitro.

Then the next question we asked was whether antioxidant could also reduce ethanol-induced malformation in vivo. Using developing limb as an in vivo model system, we have demonstrated that concurrent maternal treatment with EUK-134, an agent that has both superoxide dismutase and catalase-like activity, and ethanol substantially reduced apoptosis in the apical ectodermal ridge in the developing limb. Additionally, the incidence of limb malformations noted in near term fetuses was reduced by approximately 50%. These results not only support the premise of a causal link between excessive ethanol-induced cell death and subsequent malformations, but also show that oxidative stress is a major player in ethanol-induced malformations. This work was published in FASEB Journal in 2004 (5). These findings demonstrate the capacity of a potentially therapeutic antioxidant compound to significantly diminish major malformations caused by in vivo prenatal alcohol exposure. Then we took this work a step further by investigating the incidence and severity of birth defects in mice whose mothers self-administer ethanol and the potential of antioxidants added to the maternal diet to diminish alcohol’s damage. We found that concurrent exposure of the pregnant mice to ethanol and antioxidant, NAC resulted in a lower incidence and severity of ocular abnormalities. The group co-treated with ethanol and 600 mg/kg/day NAC had a significantly decreased incidence of ocular defects in both the left and right eyes compared with mice that received ethanol alone (6).

These results and the studies from others have suggested a major contribution of ROS to ethanol-induced apoptosis and teratogenesis. However, the signaling mechanisms underlying ethanol-induced oxidative stress in embryos are not clear. More recently, my studies have been focused on the ROS signaling. One of these studies was to determine the major source of ROS in ethanol-exposed mouse embryos. Using an in vivo FASD model, we found that ethanol treatment resulted in a significant increase in mRNA expression of NOX catalytic subunit Duox-1 and regulatory subunits, p22phox, p67phox, NOXA1 and NOXO1 in early mouse embryos. In addition, a significant increase in NOX enzyme activity was found in the ethanol-exposed embryos. Co-treatment with the NOX inhibitor, diphenyleneiodonium (DPI), significantly prevented ethanol-induced increases in NOX enzyme activity, ROS generation and oxidative DNA damage, reduced caspase-3 activation and diminished apoptosis in ethanol-exposed embryos (7). These results support the hypothesis that NOX is a critical source of ROS in ethanol-exposed embryos and that it plays an important role in ethanol-induced oxidative stress and pathogenesis.

Although studies have demonstrated that exogenous antioxidants can diminish ethanol-induced apoptosis and malformation, the prevention is not complete. This points to the limitations associated with the use of exogenous antioxidants. Therefore, a strategy for protecting against ethanol’s teratogenesis through induction of endogenous antioxidants is more promising. In 2008, I received an RO1 grant from NIH to study the role of Nrf2 in induction of endogenous antioxidants in ethanol-exposed mouse embryos. We have demonstrated for the first time the critical role of Nrf2 in ethanol-induced apoptosis and malformation.

Nrf2 is a transcription factor that regulates the induction of genes encoding antioxidant proteins through antioxidant response element (ARE) and plays a key role in cellular defense against oxidative stress (8). In our studies, maternal ethanol treatment was found to increase both Nrf2 protein levels and Nrf2-ARE binding in mouse embryos. It also resulted in a moderate increase in the mRNA expression of Nrf2 downstream target antioxidant genes and proteins. Pretreatment with the Nrf2 inducer, 3H-1,2 dithiole-3-thione (D3T), significantly increased Nrf2 protein levels and

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Nrf2-ARE binding, and strongly induced the mRNA expression of Nrf2 downstream target antioxidant genes. It also increased the expression of antioxidant proteins and the activities of the antioxidant enzymes. Additionally, D3T pretreatment resulted in a significant decrease in ethanol-induced ROS generation and apoptosis in mouse embryos (9). These results demonstrate that Nrf2 signaling is involved in the induction of antioxidant response in ethanol-exposed embryos. In addition, the potency of D3T in inducing antioxidants as well as in diminishing ethanol-induced apoptosis suggests that further exploration of the antiteratogenic effect of this compound and other Nrf2 inducers will be fruitful.

While the studies of intact embryos have contributed significantly to our base of knowledge regarding Nrf2 activation in ethanol-exposed mouse embryos, for a more complete understanding of the role of Nrf2 in ethanol-induced teratogenesis, studies focused on vulnerable cell populations are needed. To this end, we have used cultured NCCs to test whether ethanol can activate Nrf2 signaling in NCCs and whether the Nrf2 inducer, tBHQ, can provide protection against ethanol-induced oxidative stress and apoptosis in NCCs. We found that Nrf2 dependent antioxidant response can be induced in NCCs and that tBHQ-mediated antioxidant response can prevent ethanol-induced oxidative stress and NCC apoptosis. The potency of tBHQ in preventing ethanol-induced oxidative stress and apoptosis in NCCs, along with the fact that tBHQ is a metabolite of a widely used food antioxidant makes tBHQ a promising therapeutic agent for FASD (10).

In addition to D3T and tBHQ, sulforaphane (SFN) is another Nrf2 inducer with therapeutic potential for FASD. SFN is a chemical that is abundant in broccoli sprouts. We have recently discovered that treatment of NCCs with SFN along with ethanol significantly decreased ethanol-induced oxidative stress and apoptosis. Knockdown of Nrf2 signaling by siRNA in NCCs significantly diminished SFN-mediated antioxidant response and abolished the protective effects of SFN on ethanol-induced oxidative stress and apoptosis, indicating that the protective effects of this compound are Nrf2-dependent (11). These results support the potential of dietary consumption of SFN or SFN-rich broccoli sprouts to attenuate ethanol-induced oxidative tissue damage and confer in vivo protection against FASD.

In addition to oxidative stress, alcohol may also damage embryos by interfering with the L1 cell adhesion molecule (L1). In collaboration with Dr. Michael Charness and co-workers at Harvard University, we have shown that low concentrations of 1-octanol, an antagonist of ethanol-induced inhibition of L1-mediated cell adhesion, can diminish the apoptotic cell death and ameliorate the adverse developmental effects of ethanol in a whole embryo culture system. These findings suggest that ethanol’s disruption of L1-mediated cell adhesion contributes to its teratogenic actions. This work has been published in the FASEB Journal in 2001 (12). In addition to 1-octanol, other agents that can antagonize ethanol inhibition of L1 adhesion have also been studied. Of particular interest are the peptides NAP and SAL, which are small fragments of the glial-derived activity dependent neuroprotective protein and activity dependent neurotrophic factor, respectively. As published by us and our collaborators at Harvard University in the Proceedings of the National Academy of Sciences, NAP protects against alcohol-induced embryo toxicity and growth retardation in mice. NAP’s antagonism of ethanol inhibition of L1 appears to be central to its antiteratogenic effect (13). Additionally, we have shown that D-NAP effectively reduced ethanol-induced growth retardation in mouse whole embryo culture (14) and that both NAP and SAL can prevent ethanol-induced neural tube defects (15). In addition to preventing ethanol’s teratogenesis in vitro, using an oral-intake FASD model, we found that maternal dietary administration of D-SAL also reduced the incidence and the severity of ocular defects in ethanol-exposed fetuses (16). These findings highlight the potential importance of ethanol’s effect on L1-mediated cell adhesion in the pathophysiology of FASD and suggest that development of pharmacological agents that prevent alcohol-induced inhibition of L1 cell adhesion may serve as therapeutic agents to reduce the severity of FASD.

I was recruited to the University of Illinois College of Medicine in 2009 to establish a new laboratory for FASD research. Since I moved to Illinois, in addition to continuing studies on Nrf2 signaling, my research work has been focusing on identifying specific genes and proteins directly involved in ethanol-induced apoptosis.
Growing evidence suggests that excessive apoptotic cell death is a major component of the pathogenesis of ethanol-induced birth defects (17-19), suggesting that therapeutic strategies directed against apoptosis are particularly valuable for the prevention of FASD. However, there is a fundamental gap in understanding how ethanol leads to apoptosis in embryos. Our long-term goal is directed toward the development of effective strategies against ethanol's teratogenesis through targeting specific genes and proteins involved in apoptosis. To reach this goal, in my laboratory, a combination of state-of-the-art approaches, including quantitative real-time PCR, RNA interference, microRNA technology and ultrasound-guide in utero microinjection are integrated with cell and whole embryo culture systems, as well as in vivo mouse models of FASD to elucidate the molecular mechanisms underlying ethanol-induced apoptosis and birth defects. We have identified a mechanism of action for a transcription factor, Siah1, in ethanol-induced apoptosis and teratogenesis. We have also found for the first time that microRNAs (miRNAs), miR-34a and miR-125b, are involved in ethanol-induced apoptosis.

Siah1 is a member of a family of highly conserved RING domain proteins, which regulate a variety of cellular functions, including cell cycle arrest and apoptosis. We have found that ethanol exposure significantly increased Siah1 protein levels in NCCs. The translocation of Siah1 and GAPDH from the cytosol to the nucleus was also evidenced in the NCCs exposed to ethanol. In addition, we have found that the inhibition of Siah1 function with siRNA prevents ethanol-induced apoptosis, strongly suggesting that Siah1 protein is involved in ethanol-induced apoptosis in NCCs (20). Furthermore, we have demonstrated that Siah1 mediates ethanol-induced apoptosis in NCCs by activation of p53 pathway (21). These results provide insights into the role of Siah1 in mediating ethanol-induced teratogenesis.

miRNAs are a recently discovered class of small 18-23 nucleotide non-coding RNA molecules. miRNAs introduce a novel concept of regulatory control over gene expression. Recent studies have revealed that miRNAs play a pivotal role in the most critical biological events including development, proliferation, differentiation and apoptosis. We have recently initiated a study to define the role of miRNAs in modulating ethanol-induced apoptosis and teratogenesis and to establish miRNA as a feasible target for the prevention of FASD. We found that treatment with ethanol resulted in a significant decrease in miR-125b expression in NCCs. Exposure to ethanol in vivo or in whole embryo culture also significantly decreased miR-125b expression in mouse embryos. In addition, overexpression of miR-125b in NCCs by transfection with miR-125b mimic significantly reduced ethanol-induced caspase-3 activation and apoptosis, whereas miR-125b inhibitor increased caspase-3 activation and apoptosis in ethanol-exposed cells, indicating that miR-125b is involved in ethanol-induced apoptosis in NCCs. Using three algorithms for miRNA target prediction, we found that Bcl-2-modifying factor (Bmf), Bcl-2 antagonist killer 1 (Bak1) and p53-upregulated modulator of apoptosis (PUMA) are the direct targets of miR-125b, which has been validated in NCCs using luciferase reporter assay. Notably, overexpression of miR-125b significantly reduced ethanol-induced increase in Bak1 protein expression in NCCs (22).

One key approach to understanding the genetic mechanisms underlying ethanol-induced birth defects includes overexpression or downregulation of target genes in specific regions of developing embryos. The combination of siRNA, miRNA, and microinjection technology with the whole embryo culture technique constitutes a practical approach to obtaining silencing of gene expression in post-implantation mouse embryos. The availability of this model system as well as the experience with utilization of this model system provides us with a unique opportunity to test the possible function of candidate genes involved in ethanol-induced apoptosis and teratogenesis. Using this sophisticated approach, our recent studies have shown that microinjection of miR-125b mimic resulted in a significant increase in miR-125b expression and a significant reduction in the Bak1 and PUMA protein expression in ethanol-exposed mouse embryos. In addition, overexpression of miR-125b significantly decreased ethanol-induced caspase-3 activation and diminished ethanol-induced apoptosis in cultured mouse embryos (22). This is the first demonstration that miR-125b can prevent ethanol-induced apoptosis and that microinjection of miRNA mimic can prevent ethanol-induced embryotoxicity. These findings suggest an avenue for the development of novel strategy for the prevention of human FASD based on the regulation of miRNA. We are excited that our laboratory has recently purchased an ultrasound in vivo micro-
imaging system. This system has made it possible for direct in utero manipulations through high-resolution ultrasound-guided microinjections and provided us with unique opportunity to explore the possible function of candidate genes involved in ethanol-induced apoptosis and birth defects.

In summary, our studies have provided important information regarding the mechanisms underlying FASD and identified several candidates for the attenuation of embryotoxicity associate with prenatal alcohol exposure. The research has also clearly shown the effectiveness of a number of agents, including antioxidants, the peptides NAP and SAL, and microRNA mimics, in the prevention of alcohol-induced apoptosis and subsequent structural abnormalities in mouse embryos. Although translating these findings to the clinical treatment poses challenges, these findings, along with the studies from other investigators, are expected to validate possible molecular targets and yield innovative strategies for the prevention of FASD. I hope that, ultimately, antioxidants, certain peptides or microRNA mimics could lessen the effects of prenatal alcohol exposure in the children of women who are unable or unwilling to curtail their alcohol abuse while pregnant.

Acknowledgements

I would like to thank Dr. Kathleen Sulik for providing mentoring and strong support that have allowed me to develop my career so far and for her great contributions to the research described here.

I would also like to thank Dr. Michael Charness for a very fruitful collaboration and for his invaluable support. In addition, I would like to thank my collaborators, postdoctoral associates and other research staff who all work very hard to make this research possible. This research has been funded by grants from the NIH/National Institute on Alcohol Abuse and Alcoholism (AA08204, AA11605, AA12974, AA013908, AA 017446 and AA021434).

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Back to Table of Contents
Although it is widely accepted that heavy alcohol consumption during pregnancy is harmful to the fetus, this is not the case for light drinking. In certain regions of the world, such as some Mediterranean countries, consumption of a glass of wine or beer with meals during pregnancy is a common occurrence [1]. In the U.S.A., the Surgeon General advises pregnant women and women who may become pregnant to abstain from alcohol consumption. However, some physicians and health care providers across the globe are unaware of the potential dangers of light drinking during pregnancy and think it is safe for their patients to have a glass of wine occasionally or even on a daily basis (for example, see [2]). A recent study found that 40% of U.S. obstetricians believe that a pregnant woman can consume 1-3 drinks/week or 1-3 drinks per occasion without risk of adverse pregnancy outcomes [3]. The issue of light drinking during pregnancy has become the focus of significant attention in recent years, in part, because of the publication of studies based on the UK Millenium Cohort Study suggesting that drinking up to 1-2 drinks per week or per occasion during pregnancy does not increase the risk of behavioural or cognitive deficits in children at 3 or 5 years of age; in fact, results showed that children born to light drinkers have higher cognitive scores than those born to mothers who did not drink during pregnancy [4, 5]. As acknowledged by the authors of these papers, a potential explanation for these results is that light alcohol consumption during pregnancy was related to higher socioeconomic status in the population under study. It is possible that light alcohol exposure did have an effect on the development of these children but that socioeconomic factors attenuated these effects (e.g., better nutrition, access to better schools, etc.). Another recent study based on data from the Danish National Birth Cohort found no statistically significant effects of light alcohol consumption during pregnancy (1-4 drinks/week) on general intelligence, attention, and executive function (i.e., cognitive abilities that regulate other behaviours) in 5 year-old children [6]. The results of these studies must be interpreted with caution because the adverse effects of light drinking during pregnancy could be subtle, manifesting at later stages of development. Moreover, the findings of these European studies may not be applicable to human populations in other parts of the globe. For example, in a population cohort with low socioeconomic status and mixed ethnicity (46% Caucasian and 54% African-American) moderate alcohol exposure during the first trimester of pregnancy was associated with significant deficits in verbal learning at age 14 [7]. Other studies with different human populations have demonstrated a link between light drinking and behavioural and cognitive problems during childhood and/or adolescence, including alterations in working memory, attention and social interactions [8-12]. It can be concluded from these studies that light drinking during pregnancy can have a long-lasting impact on brain function and that the nature and severity of the alterations depend on several factors, including socio-economic status.

An issue that is often overlooked is that studies with animal models of fetal alcohol spectrum disorders (FASDs) have convincingly demonstrated long-lasting effects of moderate alcohol exposure on brain functioning [13]. An advantage of this type of study over studies with humans is that confounding variables can be better controlled for and the dose and pattern of alcohol exposure can be more precisely defined. Adult offspring of pregnant rats who consumed low levels of alcohol displayed deficits in behavioural tests of learning and memory [14, 15]. Alterations in the strength of transmission of information between neurons were identified as a potential factor responsible for these deficits in learning and memory [16]. Importantly, it was found that an investigational agent (known as ABT-239) that regulates the actions of a key neurochemical (histamine) essential for normal brain functioning, ameliorated the learning and
memory deficits in the animals exposed to moderate alcohol levels in utero, suggesting that this agent or related agents may be potentially useful in the treatment of FASDs [15, 16]. In addition, it was discovered that moderate alcohol exposure affects the generation of new neurons in brain regions important for learning and memory, and this could also contribute to the deficits observed in the exposed offspring [17-20]. Exposure of pregnant macaque monkeys to moderate alcohol levels has also been shown to impair motor coordination and delayed response speed in infant offspring (reviewed in [21]). Similarly, offspring of pregnant mice exposed to moderate levels of alcohol displayed significant deficits on motor coordination that could be a consequence of alterations in the communication between cerebellar neurons [22]. Long-lasting alterations in social behaviour were recently demonstrated in adult offspring of rats exposed to moderate alcohol levels during pregnancy; alcohol exposed rats exhibited increases in social investigation and wrestling behaviour [23]. Moderate alcohol exposure increased preference and consumption of alcohol-containing solutions in adult offspring; adult rats from the ethanol group also exhibited increased cocaine and amphetamine consumption after cocaine exposure [24, 25]. This moderate prenatal alcohol exposure may increase the risk of developing alcoholism and other addiction-related disorders. A study with primates showed a reduction in aversive responses to repetitive tactile stimulation in young adult monkeys exposed to low levels of alcohol throughout gestation that could result in impaired control of sensory input [21, 26].

In conclusion, the collective evidence from human and animal studies strongly suggests that light drinking during pregnancy can produce significant long-lasting alterations in the offspring's brain. In light of these findings, we should redouble efforts to educate the public and health care professionals on the potential dangers of any level of alcohol consumption during pregnancy. Given the current state of the scientific evidence on the effects of light drinking during pregnancy, the safest course of action is to advise pregnant women and women that may become pregnant to avoid drinking alcohol, even at low levels.

References
VI. PREVENTING FASD IN RUSSIA

Tatiana Balachova

Preventing FASD in Russia I: How We Got Involved

This began with a request from Dr. Kathleen Michels of NIH Fogarty International Center (FIC) asking us to provide a brief statement of the most significant issues affecting the health of children in Russia for the purpose of planning a new research programme on Brain Disorders Across the Lifespan. We investigated several issues and realized that alcohol consumption during pregnancy which could lead to Fetal Alcohol Syndrome (FAS) and Alcohol Related Neurodevelopmental Disorders (ARND) appeared to be the most pressing health issue. Prenatal alcohol consumption can result in a range of adverse pregnancy outcomes including stillbirth and Fetal Alcohol Spectrum Disorders (FASD). Russia is a country with one of the highest alcohol consumption levels in the world (1) and increasingly hazardous drinking in women (2). Data about alcohol-exposed pregnancies (AEP) and prevention of FASD in Russia was not available. FAS was not recognized and prevalence of the disorder was unknown, although it could be expected that the
rates would be high as in other countries with high alcohol consumption in women and limited knowledge about FASD.

Conversations: Why did you decide to participate?

Dr. Barbara Bonner: A Russian psychologist who completed a Postdoctoral Fellowship in paediatric psychology and child abuse and neglect at the University of Oklahoma Health Sciences Center (OUHSC) described the widespread traditions of holiday drinking, deep historical roots of alcohol use described in literature (3), and her clinical experience working with alcohol dependent men and women and street children in Russia. That has led to several years of very interesting work, international collaboration, and extremely successful and productive research. The formula is: Fogarty “Brain Disorders Across the Lifespan” + a Russian psychologist involved in child maltreatment in the U.S. = a research programme in the prevention of FASD in Russian children

Dr. Tatiana Balachova: Before speaking about FAS, I always acknowledge that Russia is a beautiful country with an amazing history and people. During my Postdoctoral Fellowship at OUHSC, in 1999, I attended a workshop conducted by Dr. Ann Streissguth, a psychologist and pioneer in research on the effects of alcohol on development and throughout the lifespan. Dr. Streissguth was a member of the interdisciplinary team which first identified and published the first article describing FAS (4). In her presentation, I saw a picture of a boy who looked like the twin brother of a child that I had recently evaluated in Russia. I conducted a psychological evaluation of a 14-year-old boy form a large family with five children, who was currently living at a shelter in St. Petersburg. V. had begun smoking at age 5 and had never attended school. For as long as he could remember, he was earning money by begging on streets. He gave most of that money to his parents who spent it primarily on alcohol. At the age of twelve, he lived on the streets for about a year until he was caught stealing and brought to a shelter by police. He demonstrated good behaviour and a positive attitude at the shelter. He was eager to do any job and was kind and willing to share and help others. He attended 1st grade at the shelter at age 12. He was very persistent; he could stay focused on a simple task for a long time.

Despite his interest and exemplary behavior in the classroom, after several months of schooling, he demonstrated no academic progress. His reading and writing were very poor and he was referred for a psychological evaluation. His measured I.Q. indicated mental retardation. His responses on the tests reflected his life experiences prior to the shelter and indicated his limited understanding of social norms. Q: What does the word KNIFE mean? V.: “Knife? It is for... to kill a woman. Married... is bored by her... have killed.” Q: What does the word FUR mean? V. “Fur...that is taken from a dog. The dog is led to a basement...is killed... fur is taken.” His tone of voice was the same as if he were describing what he had for breakfast. Such a low IQ and the lack of understanding of social norms were shocking for the staff and would not have been expected based on his positive behaviour at the shelter.

I realized then, that I saw FAS features in children at shelters and in children of alcohol-dependent patients, but the disorder and the cause of the problem were undiagnosed. In 2000, I served as an advisor for WHO and conducted training of Russian paediatricians. Well-educated and caring doctors did not know about FAS and believed that alcohol withdrawal in newborns would be the most serious complication of maternal drinking during pregnancy. At that time, I realized that FAS was still largely unknown in Russia. I knew that there is a drinking culture in Russia; it is a culture that includes drinking as an essential part of everyday life when heavy drinking is socially accepted and even expected. No one spoke to me about drinking during pregnancy. I have two children and my children were just lucky that I had never been a good drinker. Many children in Russia were not as lucky. This is how I became interested in FAS, I was privileged to receive the knowledge and felt responsible to pass this knowledge on to others.

When a call for grant proposals was issued by FIC, we knew what we wanted to study. We discussed designing an FAS prevalence study to identify affected children and develop programmes for them; however, we knew that funds would be limited and decided to focus on
prevention. I approached Dr. Galina Isurina, a colleague and friend at St. Petersburg State University (SPSU) about collaborating in FAS prevention research.

Dr. Galina Isurina: My first reaction was “No”. I was an expert in neuroses, psychotherapy, and training in therapy and counselling methods; FAS was not my area. We had a long talk and finally Tatiana said: “FAS is no one’s area in Russia, so what could we do?” I agreed and have participated in FAS prevention research as a leader of FAS research at SPSU since that time. FASD prevention research and training have become “my area”. Dr. Larissa Tsvetkova, Dean of Psychology College (Faculty) at St. Petersburg State University (SPSU) [Currently Vice President, SPSU] supported the idea readily and became an advocate for FASD prevention and a leader in health behaviour prevention research at SPSU and in Russia.

Since 2003, the University of Oklahoma Health Sciences Center (OUHSC) has developed an international research collaboration with St. Petersburg State University (SPSU) and Nizhny Novgorod State Pedagogical University (NNSPU). The collaboration resulted in establishing the Prevent FAS in Russia Research Group (PFAS) and designing and implementing a line of research, training, and capacity building projects aimed at developing FASD prevention in Russia. An assessment-based strategy was used to translate knowledge and develop culturally appropriate FASD prevention in Russia. The studies involved mixed methods including 1) formative assessment to collect data critical to developing FASD prevention, 2) development of FASD education and evaluating materials in randomised educational trials, and 3) designing and evaluating a prevention intervention in a randomised controlled trial.

The principal investigators are Dr. Tatiana Balachova and Dr. Barbara Bonner (OUHCS) and Dr. Larissa Tsvetkova (SPSU). Dr. Galina Isurina (SPSU) and Dr. Elena Volkova (NNSPU) supervise the study at the universities. PFAS research group includes faculty members and consultants from medical schools and universities in Russia and the U.S., including Dr. Alexander Palchik and Dr. Vladimir Shapkaitz of St. Petersburg Pediatric Academy, Dr. Oleg Erishev and Dr. Ksenia Ribakova of St.Petersburg Bekhterev Psychoneuropsychological Research Institute, Dr. Alla Shaboltas of SPSU, Dr. Mark Chaffin and Dr. Karen Beckman of OUHSC, Dr. Jacqueline Bertrand of the Centers for Disease Control and Prevention, and Dr. Linda Sobell of Nova Southeastern University. Dr. Elena Varavikova of the Russian Federal Research Institute for Health Organization and Informatics (CNIIOIZ), Dr. John Mulvihill, Dr. Kevin Rudeen, and Dr. Mark Wolraich of OUHSC, Dr. Sheldon Levy of the University of Miami School of Medicine, and Dr. Edward Riley of San Diego State University have served on the advisory board. Larissa Skitnevskaya and Elena Kosyh of NNSPU, Maria Potapova and Alexandra Regentova of SPSU, and other graduate students from SPSU, NNSPU, and OUHSC have served as project coordinators, research assistants, and data collectors.

There has been strong support from the international research community and we have received help and invaluable contributions from wonderful professionals around the world. Research projects have been supported by Fogarty International Center (FIC) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH) and the National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC) 2-4. Most recently, funding was received from NIH and the Russian Foundation for Basic Research (RFB)5 (Pis Balachova and Shaboltas) to expand research to interdisciplinary HIV prevention study to identify gender and culturally appropriate prevention approaches for reducing HIV sexual transmission among women who are at-risk for AEP in the general population.

Preventing FASD in Russia II: What We Have Done

Tatiana Balachova, PhD, Barbara Bonner, PhD, and Galina Isurina, Larissa Tsvetkova, PhD, Elena Volkova, PhD, Katerian Burina, and Prevent FAS Research Group.

Work on developing a prevention programme includes a number of stages:
Research Phase 1. (2003-2005) The first study involved focus groups and a cross-sectional survey exploring knowledge, attitudes, behaviours, and receptivity to prevention among women and physicians in two regions in Russia. This was a large scale collection of data critical to developing FAS prevention. Results: We learned that the majority of non-pregnant women consume alcohol and that binge drinking is a major concern. Among nonpregnant women, 89% reported consuming alcohol and 65% reported binge drinking in the last three months, including 38% reporting binges at least monthly. Among women who were trying to conceive, 67% reported binge drinking. On a positive note, there was a significant decline in drinking after pregnancy identification; however, 20% of pregnant women reported alcohol use after pregnancy identification and 6% in St. Petersburg (SBP) (none in the Nizhny Novgorod Region, NNR) reported binge drinking.

Although many Russian women reduced alcohol consumption after pregnancy identification, only few recognised the risks involved in combining alcohol use with the potential to become pregnant. Among nonpregnant women, 43% were not using contraception consistently along with at-risk drinking, posing a high risk for AEP. Approximately one-third of women in SPB and more than half in NNR were at high risk for AEP because of lack of contraception and at-risk drinking. The popularity of binge drinking among Russian women who might or are trying to become pregnant constitutes a significant public health problem. Russian women have indicated that advice by their OB/GYN physicians would be the most trustful source of information about health behaviours and alcohol consumption during pregnancy (Balachova et al., 2007). The survey reported a lack of FASD knowledge among women and physicians. Printed FASD information for the general public and training materials for physicians were not available in Russia. Therefore, the study identified a necessity in developing education materials for the general public and physicians.

Research Phase 2. (2006-2008) The second study was focused on the development and evaluation of FASD education materials for women and training for physicians (paediatricians and OB/GYN). We developed educational materials for women and health professionals and the materials were evaluated in clinical trials with women and educational trials at CME courses for paediatricians and OB/GYN.

The first FASD educational website in the Russian language was developed (www.netFAS.net) to disseminate information to the general public and provide a web-based training for professionals. It is divided into a section for the general public and one for health professionals. The first contains information about the effects of alcohol on the fetus, information on FAS and other FASD, and brochures and materials that can be downloaded or printed. The section for professionals includes training on FASD designed for physicians, psychologists, and other professionals which they can complete online and receive a certificate.

Research Phase 3. (2007-2012) Based on the study initial findings, a pre-conception intervention targeting women at risk for AEP was indicated. The intervention components were drawn from a brief physician intervention (5,6,7) and a motivational dual-focused AEP prevention intervention (8) to design a dual-focused (alcohol use/pregnancy planning) brief physician prevention intervention (DFBPI) that can be delivered by OB/GYN physicians during routine women’s health clinic visits. Training in the intervention was evaluated in Phase 2 and physicians who were trained in DFBPI demonstrated significantly improved skills and competency in DFBPI. Currently, a randomised clinical trial is being conducted at 20 women’s clinics in SPB and NNR to evaluate the effectiveness of a DFBPI in preventing fetal alcohol exposure during pregnancy. A total of 1,914 childbearing age women were screened and 764 were enrolled in the study in SPB and NNR. Data collection has been completed and data are currently being analyzed. The study is the first randomised trial targeted at reducing the risk for fetal alcohol exposure and preventing FASD in Russian children.

Dissemination and capacity building

The Prevent FAS international research group (PFAS) is highly active in presenting the projects at

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41
different international conferences, consulting and disseminating knowledge to students and academicians, mentoring students in research, and providing training to physicians. PFAS faculty have given over 60 presentations at national and international meetings since 2003 and a number of materials have been produced by PFAS including eleven manuscripts published in peer-reviewed journals, five education brochures and manuals, and 31 published peer-reviewed abstracts.

The projects have included substantial capacity building activities. Lectures and research seminars on FASD and prevention, behavioural research, grant writing and obtaining funding for research, and other research topics have been conducted at SPSU, NNSPU, CNIIOIZ, and at professional meetings in Russia. Training seminars in ethics and human subject protection in research have been conducted at SPSU and NNSPU. In addition, the first behavioral Ethical Committee has been established at St. Petersburg State University with assistance from Dr. Karen Beckman, Chair of IRB at OUHSC who serves as a consultant on PFAS.

PFAS includes researchers from psychology, medicine, and public health and participation in PFAS research studies has provided an excellent interdisciplinary research learning experience for students. Several PhD dissertations and Master research projects focused on various aspects of our research and FASD have been completed under PFAS faculty supervision at SPSU, NNSPU, and OUHSC and to date, seven have been defended. PFAS faculty have provided training and assistance in developing research at universities and medical schools in Russia. Dr. Palchik has established an FAS training and research programme at St. Petersburg Pediatric Academy and is a national expert in FAS diagnosis and research. FASD education and research programmes have been growing; for example, Dr. Anait Maruanan of Irkutsk Medical University has begun FASD training for her students and works on developing a training curriculum for medical students and establishing an FASD prevention training and research programme at her university.

The PFAS group work goes beyond the universities and more than 2,000 women and physicians have participated in our research since 2003. In addition, physicians and students have been trained by the project faculty. There is evidence of increasing knowledge regarding FASD in Russia. In 2005, there was only one article on the internet about FAS in the Russian language. In 2011, a search indicated 3,852 results on FASD information in the Russian language on the internet, and in 2012, there were 12,700 search results. Although the development of the internet between 2003 and 2012 certainly contributed to this tremendous increase and other sources of information may become available, the significant proportion of FAS information in the Russian language on the internet cite PFAS research and include materials developed by the group.

Recently, Médecins du Monde association (France) and Julia Krikorian, General Coordinator in Russia showed an interest in the PFAS research. Several seminars and working meetings were held during 2011 and 2012 with support from Médecins du Monde including the first FAS School held on January 23-24, 2012 in Moscow. This notable event was a collaborative effort of CNIIOIZ, Médecins du Monde, and PFAS research group. We shared working materials, such as brochures, measures, and training materials. Médecins du Monde plans continuing collaboration with PFAS to educate physicians, train trainers, and implement FASD prevention in services to women who are heavy or hazardous drinkers. A Coordination Council for Prevention of FAS/FASD and Alcohol Harm was established at the Russian Federal Research Institute for Health Organization and Informatics (CNIIOIZ) in 2011. The Council lead by Academic Vladimir Starodubov and Dr. Elena Varavikova called for interdisciplinary cooperation and establishing mechanisms to implement FASD prevention in the Russian health care system (9). This is a very important step toward a National FASD prevention programme in Russia. PFAS will continue collaboration with the Council, Médecins du Monde, with other organizations, and will continue to provide consultation, training, and assistance in developing research.

**What to Do Next?**

The research collaboration highlights the importance of formative assessment for international
translational research. We have learned and demonstrated that assessment driven translational research is a promising approach for developing prevention interventions. But, there is still more to do. Increasingly hazardous drinking in women indicates that prevention of AEP is an important public health issue in Russia. We can’t ignore the fact that FASD information is still limited and the risk for fetal alcohol exposure is significant. The PFAS plans to continue research on investigating FASD prevention strategies and the risk in alcohol-dependent women, identifying better strategies to implement prevention, conducting research with children where prenatally affected by alcohol, and extending efforts to address women’s tobacco use and risky behaviours associated with HIV risk.

The FAS prevention group would like to thank the international community and our colleagues from Russia, USA, Denmark, France and other countries for their interest and the support they have provided to our research and dissemination efforts. Their commitment is important and essential for us to continue our research.

Commentary

Tatiana Balachova, PhD

Recently, the Russian government has implemented measures to increase population growth such as incentives for families to increase birth rates. It is essential that FASD prevention accompany these measures to reduce the risk of fetal alcohol exposure and insure the best possible birth outcomes in children. The Russian government has expressed concerns about the harmful effects of alcohol on the population and developed a national plan to reduce per capita alcohol consumption by half by 2020 (10). This is a call to change the alcohol culture. Reducing the risk for alcohol-exposed pregnancies can be the first step on the road to reaching society, changing the alcohol culture, and reducing the harmful effects of alcohol in order to improve the health of future generations. FASD has not been mentioned by the government directly yet; but, I hope it will be soon.

There is hope for women and the children who will be born. However, there is currently little hope for children with FASD in Russia. Estimated numbers of children with FAS are significant. Studies conducted by Dr. Palchik (11), Dr. Kenneth Jones, Dr. Edward Riley and their colleagues (12), and Dr. Miller and Boston-Murmansk Orphanage Research Team (13) indicated high rates of FAS among children in baby homes and orphanages for children with disabilities. There are limited diagnostic and support services for children and adults with FASD and their families. I believe in the power of knowledge and, more importantly, in power of knowledgeable and caring people around the world. I hope we can reach these children in Russia and around the world and pass a strong message to prevent further damage.

“FAS is our life and a tragedy of our society” a Paediatrician said in a focus group in 2004. I believe that can be changed. It has been changing.

Acknowledgments

1Authors wish to acknowledge all PFAS research group members, consultants, graduate students from SPSU and NNSPU, physicians who conducted interventions in St. Petersburg and the Nizhny Novgorod Region, and thank physicians and women who participated in the studies. A number of professionals have provided consultation and contributed to the developing of measures, study design, implementation, and other aspects of the international studies. We wish to thank colleagues from Russia (Academic Vladimir I. Starodubov, Vice President, Russian Academy of Medical Science and Director of the Russian Federal Research Institute for Health Organization and Informatics (CNIIOIZ), Denmark (Dr. Ulrick Kesmodel of the University of Aarhus), France (Ms. Julia Krikorian of Médecins du Monde in Russia), and the U.S. (Dr. Marcia Russell of the Prevention Research Center, Dr. Robert Sokol of Wayne State University School of Medicine, Dr. Lee Ann Kaskutas of the Alcohol Research Group, Dr. Michael Fleming, of the University of
Wisconsin-Madison (currently at Northwestern University), Dr. Ken Warren, Dr. Peggy Murray, Dr. Marcia Scott, and Dr. Kendall Bryant of NIAAA; Dr. Kathleen Michels and Dr. Marya Levintova of NIH Fogarty International Center, Louise Floyd and Elizabeth Parra Dang of CDC NCBDDDD).

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References:


Back to Table of Contents

VII. EPGENETIC APPROACH TO UNDERSTAND THE ETIOLOGY OF FASD

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She is establishing a research group of Environmental Epigenetics and Development in the Department of Medical Genetics, Haartman Institute, University of Helsinki, Finland.

The third component
We all are composed by our genes and environmental factors. Due to the rapid progression of genetic research, the nucleotide sequence of human DNA has almost been completed. Consequently, we understand the basic function of single genes, their promoter regions and the production of proteins, and we know more and more disorders inherited in a Mendelistic way. Despite these steps forward, our knowledge about the regulation of gene expression and the etiology of complex disorders is still scant.

How does the nerve cell know to maintain the activity of nerve cell specific genes and silence the unnecessary ones? And how about complex genetic disorders like dyslexia: if the heritability of dyslexia has been estimated to be around 40-70 percent, what consists the remaining 30-60 percent?

The biologist Klaus Gärtner investigated the role of environment in the degree of phenotypic variation and carried out his classic experiments in the 1970s and 1980s (Gärtner, 1990). He studied genetically identical mice housed in rigorously controlled or in highly variable environments for several generations. He observed that the phenotypic variation between these two experimental groups was surprisingly small compared to the phenotypic differences among mice in the same group. In addition to the genetic and environmental factors alone, there seemed to be a third component contributing to the phenotype. Studies of identical twins support this conclusion: there are phenotypic differences in twins who share identical genes and similar environment. This third component is now called “the epigenetic factor” and the phenotype can be considered as a result of the interactions between genome, epigenome and environment.

Epigenetic information regulates the gene expression in the absence of changes in DNA sequence. In other words, the activity of a single gene can be silenced or enhanced by epigenetic marks, although no DNA mutations have occurred. The epigenetic marks consist of methylations, histone modifications and small RNAs. These marks modulate the structure of chromatin and thus the activity of gene expression by various mechanisms. Epigenetics is involved in all crucial events in the life cycle of higher organisms: cell proliferation, differentiation, development and reproduction. However, the epigenetic marks are probably more dynamic than it has been believed. The epigenetic variation is caused by stochastic factors such as errors in maintaining the
methylation through DNA replication, as well as environmental factors. In addition to the mitotic inheritance of epigenetic information to daughter cells, there is evidence of transgenerational inheritance in mammals (Daxinger and Whitelaw, 2012). This means that, in some animal studies, an altered epigenetic mark has been transmitted from a parent to offspring via the gametes. The possibility that epigenetic information could be meiotically inheritable and transmitted across generations is fascinating, and even a “Lamarckian” point of view has been introduced by implying that some of these epigenetic factors could be acquired by the parent during the lifetime. Epigenetic effects can also be transmitted from the parent to the offspring via other mechanisms than gametes like through the egg cytoplasm, placenta, breast milk or behavioural interactions between the mother and offspring (Youngson and Whitelaw, 2008). These effects include the mother’s nutrition or exposure to toxins during pregnancy, for example. The molecular basis of these mechanisms is unclear.

**Environmental epigenetics**

It is well known that environmental factors affect the phenotype. Previous animal studies have shown that an epigenetic component is involved, but the mechanisms are unclear. These environmentally induced changes can occur during the whole life span, but previous studies have shown that the most sensitive periods are the early stages of development. According to the Barker’s developmental origin hypothesis, environmental stimuli during critical periods of development can change developmental pathways and cause permanent changes in gene expression. Epigenetic changes in the early pregnancy can have far-reaching consequences for the embryo, and the effects can become apparent later in life. These changes can be advantageous and improve the adaptation to the environment, but unfortunately there are many harmful environmental factors around us. To avoid the transmission of potential harmful epigenetic changes caused by environment, efficient epigenetic reprogramming between generations is vital. It consists of two rounds of demethylations and remethylations of the epigenome: the first reprogramming occurs in germ cells and the second in the early embryo. This reprogramming is needed to erase and reset all the epigenetic marks and thus maintain the totipotency of zygote, enabling its differentiation to all cell types that are needed to form an organism (Reik et al. 2001).

Our study focuses on the effects of gestational alcohol exposure, which is a significant environmental insult to the offspring. The aim is to understand the etiology of fetal alcohol spectrum disorders, and we believe that ethanol-induced changes in the epigenetic marks have a significant role in it. Previous studies have shown that the genetic factors, dose, time and duration of ethanol exposure are critical, and variation in these causes the wide phenotype of fetal alcohol spectrum disorders. According to previous studies, developmental periods of preconception, preimplantation and gastrulation are particularly sensitive to teratogenic effects of ethanol (Haycock 2009, Haycock and Ramsay 2009). Interestingly, these are also the periods of dynamic epigenetic reprogramming. The molecular mechanism is not clear, but alterations in the methionine-homocysteine cycle that cause changes in DNA methylation and gene expression patterns have been suggested (O’Neil et al. 2007, Sulistyoningrum et al. 2010).

**Mouse models for ethanol exposure**

To understand the mechanism of gestational ethanol exposure we developed a mouse model of fetal alcohol syndrome (FAS) and a model of maternal ethanol exposure before fertilization (EBF) with Dr Suyinn Chong and Professor Emma Whitelaw (Epigenetics Laboratory, Queensland Institute of Medical Research, Brisbane, Australia). By using an inbred mouse model it is possible to eliminate genetic and environmental variation and focus on the epigenome. In our study we are concentrating on the preconceptional period of development (EBF) and the eight first days of pregnancy, which consists of the preimplantation period of development and the beginning of gastrulation (FAS). In our study we have used an epigenetically sensitive allele *Agouti viable yellow* (*A<sup>vy</sup>*) as a biomarker. The DNA methylation state of the regulation region inversely correlates with transcriptional activity of *Agouti* gene (Morgan et al. 1999). Inbred mice that carry this allele show variable coat colours, ranging from yellow to dark brown. The regulation region of yellow mice is hypomethylated and *Agouti* gene is active. Brown mice have highly methylated region and thus the gene is silent. By using this allele it is possible to detect if a specific environmental factor is capable of changing the epigenetic marks and the gene expression in
Our mouse model of fetal alcohol syndrome
Our model of FAS is based on voluntary maternal consumption of 10% (v/v) ethanol for eight days after fertilization. This is the period of dynamic epigenetic reprogramming in the early embryo. We use the strain C57BL/6J and C57BL/Rcc, which are known to have a strong drinking preference for 10% ethanol over water. We have estimated that the peak blood alcohol level in our model is approximately 0.12%, which is a realistic human exposure. In comparison to other mouse models, ours would be considered a chronic, moderate level of ethanol exposure, and our analyses have been done on mice aged 3-4 weeks, not on fetuses. In our mouse model we observed changes in the expression of an A\textsuperscript{vy} in the offspring. We found that gestational exposure to ethanol increases methylation of A\textsuperscript{vy} in the offspring, consequently silencing transcription at this locus, which can be observed as darker mouse coat colour. This demonstrated, for the first time, that ethanol caused permanent changes on the phenotype by altering the epigenotype of the early embryo. We also detected variable postnatal growth restriction and craniofacial dysmorphology, including microcephaly and changes on the midface and palate, which were reminiscent of human FAS (Kaminen-Ahola et al. 2010a, Kaminen-Ahola et al. 2010b).

At the moment we are focusing on brain tissue. We are investigating changes in the gene expression and epigenome in the brain of 28 days old mice. According to earlier studies of FAS phenotypes, corpus callosum, hippocampus, cerebellum and frontal cortex are the most interesting brain structures in the mouse to start with.

Ethanol exposure before fertilization
In addition to the mouse model of fetal alcohol syndrome, we have developed a model for ethanol exposure before fertilization. This model involves 10% ethanol consumption for four days per week for ten weeks immediately prior to fertilization; a period that encompasses multiple cycles of oocyte maturation and ovulation. In our previous study we showed that this exposure also increased transcriptional silencing and hypermethylation of the A\textsuperscript{vy} allele in the offspring (Kaminen-Ahola et al. 2010a). In this study we want to clarify the mechanism that is probably different compared to the gestational ethanol exposure: the A\textsuperscript{vy} allele is paternally derived and not present in unfertilized oocytes.

Future plans
The strength of our study is the combination of mouse models and human studies. We have established co-operation with Finnish clinicians and specialists to collect the first set of samples of ethanol-exposed individuals in Finland. We will collect a set of samples (eg. cord blood and samples of placenta) at the time of delivery, as well as samples of meconium to determine the gestational ethanol exposure. When children are at the age of six, we will perform neuropsychological tests to determine the phenotype. Our aim is to find correlation between epigenetic changes and the phenotype of the affected child. Our long-term goal is to find biomarkers for FAS diagnosis and to develop new diagnostic criteria. If the alcohol-induced molecular changes occur very early in the development prior to the differentiation of the three germ layers, they should be present in all tissue types including blood. Because prevention of FAS is often impossible, early diagnosis and appropriate treatment have an important role in the therapy of FAS children.

References
Reproduction 81:618-627.


Back to Table of Contents
1. EFFECTS OF NEONATAL ALCOHOL DOSE AND EXPOSURE WINDOW ON LONG DELAY AND TRACE EYEBLINK CONDITIONING IN JUVENILE RATS

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ABSTRACT

Classical eyeblink conditioning has been used to assess learning and memory impairments in both humans and animal model studies of fetal alcohol spectrum disorders (FASD). Gestational exposure to alcohol in humans and its equivalent in rats severely impairs various eyeblink conditioning tasks, but less is known about how these effects are influenced by variables, such as the timing and dose of alcohol exposure. In a series of four experiments, we systematically examine how varying the timing and dose of alcohol exposure impact long delay and trace eyeblink conditioning in juvenile rats, tasks that both depend on a brainstem-cerebellar circuit but differ in that trace conditioning additionally recruits the hippocampus and prefrontal cortex. Using a “third-trimester-equivalent” alcohol exposure model, rats were exposed to a high binge dose of alcohol at one of two alcohol doses over postnatal days (PD) 4–9 or PD 7–9, windows of exposure thought to differentially target the cerebellum and hippocampus. Sham-intubated and untreated rats served as controls. As juveniles, rats from each treatment condition were trained in either a long delay or trace eyeblink conditioning task. Alcohol-exposed rats demonstrated general conditioning impairments compared to controls during long delay conditioning, with more robust impairments in rats exposed to the higher alcohol dose (5.25 g/kg/day) than those that received the lower dose (4.66 g/kg/day). Alcohol-exposed rats showed trace conditioning impairments compared to controls only when the high dose of alcohol was administered over PD 4–9 or PD 7–9. These findings indicate significant learning and memory impairments following neonatal alcohol exposure at both PD 4–9 and PD 7–9. The pattern of impairments across delay and trace conditioning suggest that alcohol disrupts processes that are common to both tasks. These findings are consistent with studies of delay and trace eyeblink conditioning in children with FASD. Future studies of the mechanisms underlying these deficits will further our understanding of brain injury and memory impairments resulting from developmental alcohol exposure.

Read Full Article,

Back to Table of Contents

2. DIFFERENT PATTERNS OF REGIONAL PURKINJE CELL LOSS IN THE CEREBELLAR VERMIS AS A FUNCTION OF THE TIMING OF PRENATAL ETHANOL EXPOSURE IN AN OVINE MODEL

Sawant OB, Lunde ER, Washburn SE, Chen WJ, Goodlett CR, Cudd TA.
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College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas, USA, 77843.

ABSTRACT

Studies in rat models of fetal alcohol spectrum disorders have indicated that the cerebellum is...
particularly vulnerable to ethanol-induced Purkinje cell loss during the third trimester-equivalent, with striking regional differences in vulnerability in which early-maturing regions in the vermis show significantly more loss than the late-maturing regions.

The current study tested the hypothesis that the sheep model will show similar regional differences in fetal cerebellar Purkinje cell loss when prenatal binge ethanol exposure is restricted to the prenatal period of brain development equivalent to the third trimester and also compared the pattern of loss to that produced by exposure during the first trimester-equivalent. Pregnant Suffolk sheep were assigned to four groups: first trimester-equivalent saline control group, first trimester-equivalent ethanol group (1.75g/kg/day), third trimester-equivalent saline control group, and third trimester-equivalent ethanol group (1.75g/kg/day). Ethanol was administered as an intravenous infusion on 3 consecutive days followed by a 4-day ethanol-free interval, to mimic a weekend binge drinking pattern. Animals from all four groups were sacrificed and fetal brains were harvested on gestation day 133. Fetal cerebellar Purkinje cell counts were performed in an early-maturing region (lobules I-X) and a late-maturing region (lobules VIc-VII) from mid-sagittal sections of the cerebellar vermis. As predicted, the third trimester-equivalent ethanol exposure caused a significant reduction in the fetal cerebellar Purkinje cell volume density and Purkinje cell number in the early-maturing region, but not in the late-maturing region. In contrast, the first trimester-equivalent ethanol exposure resulted in significant reductions in both the early and late-maturing regions. These data confirmed the previous findings in rat models that third trimester-equivalent prenatal ethanol exposure resulted in regionally-specific Purkinje cell loss in the early-maturing region of the vermis, and further demonstrated that first trimester ethanol exposure caused more generalized fetal cerebellar Purkinje cell loss, independent of the cerebellar vermal region. These findings support the idea that prenatal ethanol exposure in the first trimester interferes with the genesis of Purkinje cells in an unselective manner, whereas exposure during the third trimester selectively kills post-mitotic Purkinje cells in specific vermal regions during a vulnerable period of differentiation and synaptogenesis.


Back to Table of Contents
4. **ANOTHER PERSPECTIVE ON ‘THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID PREGNANCY ON THE CHILD’S INTELLIGENCE, ATTENTION, AND EXECUTIVE FUNCTION’**

S Astley1, T Grant2

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2 Department of Psychiatry & Behavioral Sciences, and Fetal Alcohol and Drug Unit (http://depts.washington.edu/fadu/), University of Washington, WA, USA

**ABSTRACT**

No abstract is available for this article.

**Read Full Article,**

**Back to Table of Contents**

5. **LOW AND MODERATE ALCOHOL CONSUMPTION DURING PREGNANCY: EFFECTS ON SOCIAL BEHAVIOUR AND PROPENSITY TO DEVELOP SUBSTANCE ABUSE IN LATER LIFE**

MO Parker, CH Brennan

School of Biological and Chemical Sciences, Queen Mary University of London, London, UK

**ABSTRACT**

No abstract is available for this article.

**Read Full Article,**

**Back to Table of Contents**

6. **THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID-PREGNANCY**

O Garcia-Algar1,2, D Black2, C Guerri2,3, S Pichini2,4

1 URIE, Institut Mar d’Investigacions Mèdiques (IMIM), Barcelona, Spain
2 European FASD Alliance, Landskrona, Sweden
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4 Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy

**www.nofas-uk.org**
7. **Danish Studies Suggesting Low and Moderate Prenatal Alcohol Exposure Has No Adverse Effects on Children Aged 5 Years Did Not Use Appropriate or Effective Measures of Executive Functioning**

G Powell
Retired Diplomate American Board of Psychiatry and Neurology and also American Board of Clinical and Anatomic Pathology, Fort Mill, SC, USA

**ABSTRACT**
No abstract is available for this article.

**Read Full Article,**

**Back to Table of Contents**

8. **Ontogeny of Contextual Fear Memory Formation, Specificity, and Persistence in Mice**

Akers KG, Arruda-Carvalho M, Josselyn SA, Frankland PW.
Neurosciences and Mental Health, Hospital for Sick Children, Toronto, ON, Canada, M5G 1X8.

**ABSTRACT**

Pinpointing the precise age when young animals begin to form memories of aversive events is valuable for understanding the onset of anxiety and mood disorders and for detecting early cognitive impairment in models of childhood-onset disorders. Although these disorders are most commonly modeled in mice, we know little regarding the development of learning and memory in this species because most previous studies have been restricted to rats.

Therefore, in the present study, we constructed an ontogenetic timeline of contextual fear memory ranging from infancy to adulthood in mice. We found that the ability of mice to form long-term context-shock associations emerged ~13-14 d of age, which is several days earlier than previously reported for rats. Although the ability to form contextual fear memories remained stable from infancy into adulthood, infant mice had shorter-lasting memories than adolescent and adult mice.

Furthermore, we found that mice subjected to fetal alcohol exposure showed a delay in the developmental emergence of contextual fear memory, illustrating the utility of this ontogenetic
approach in detecting developmental delays in cognitive function stemming from maladaptive early life experience.

Read Full Article,

Back to Table of Contents

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Krans EE, Davis MM, Schwarz EB.
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ABSTRACT
Objective: To determine the impact of prenatal counseling regarding psychosocial risk factors on maternal behavior.

Study Design: We analyzed data from 198,323 women participating in the Pregnancy Risk Assessment Monitoring System (PRAMS). Chi-square and logistic regression analyses assessed the relationship between psychosocial risk, prenatal counseling and maternal behavior.

Results: The odds of receiving risk-appropriate prenatal counseling were significantly greater for participants who used alcohol (OR=1.13;95% CI 1.08-1.17) and tobacco (2.02;1.91-2.13). After receiving counseling, women quit using alcohol (72.9% vs. 27.1%;p<0.01) and tobacco (79.9% vs. 20.1%;p<0.01) at a significantly greater rate and women with unintended pregnancies were more likely to use postpartum contraception (83.6% vs. 16.4%;p<0.01) than women who were not counseled. However, no significant differences were found in the rates of IPV during pregnancy (56.1% vs. 43.9%; p=0.09) between women who did and did not receive counseling.

Conclusion: Counseling regarding psychosocial risk factors during pregnancy may positively impact maternal behavior.

Read Full Article,

Back to Table of Contents

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10. AFFECTIVE DECISION-MAKING ON THE IOWA GAMBLING TASK IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDERS
Kully-Martens K, Treit S, Pei J, Rasmussen C.
1 Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada.

ABSTRACT
Individuals with fetal alcohol spectrum disorders (FASD) have difficulties with cognitive-based executive function (EF) tasks. The goal of the present study was to determine if children with FASD have impairments on the Iowa Gambling Task (IGT), which measures affective EF (i.e., decision-making and risk-taking). Individuals with FASD (n = 31) and healthy controls (n = 31), aged 8-17 completed the IGT. Children with FASD were significantly impaired on the IGT compared to controls. Over the course of the task, control scores improved, whereas children with FASD...
exhibited an overall decrease in scores. Scores increased significantly with age in the control group but did not differ significantly with age for FASD participants. Children with FASD exhibited decision-making and risk-taking impairments on a hot EF task. Children with FASD did not appear to learn from negative experiences and shift to making more positive decisions over time and their performance did not improve with age. The implications of poor task performance and a lack of age-related findings in children with FASD are discussed. (JINS, 2012, 18, 1-8).


Back to Table of Contents


11. FETAL ALCOHOL EXPOSURE AND IQ AT AGE 8: EVIDENCE FROM A POPULATION-BASED BIRTH-COHORT STUDY
School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom.

ABSTRACT
Background: Observational studies have generated conflicting evidence on the effects of moderate maternal alcohol consumption during pregnancy on offspring cognition mainly reflecting problems of confounding. Among mothers who drink during pregnancy fetal alcohol exposure is influenced not only by mother's intake but also by genetic variants carried by both the mother and the fetus. Associations between children's cognitive function and both maternal and child genotype at these loci can shed light on the effects of maternal alcohol consumption on offspring cognitive development.

Methods: We used a large population based study of women recruited during pregnancy to determine whether genetic variants in alcohol metabolising genes in this cohort of women and their children were related to the child's cognitive score (measured by the Weschler Intelligence Scale) at age 8.

Findings: We found that four genetic variants in alcohol metabolising genes in 4167 children were strongly related to lower IQ at age 8, as was a risk allele score based on these 4 variants. This effect was only seen amongst the offspring of mothers who were moderate drinkers (1-6 units alcohol per week during pregnancy (per allele effect estimates were -1.80 (95% CI=-2.63 to -0.97) p=0.00002, with no effect among children whose mothers abstained during pregnancy (0.16 (95%CI=-1.05 to 1.36) p=0.80), p-value for interaction =0.009). A further genetic variant associated with alcohol metabolism in mothers was associated with their child's IQ, but again only among mothers who drank during pregnancy.

Click here to read Full Article

Back to Table of Contents


12. STEM CELL THERAPY: SOCIAL RECOGNITION RECOVERY IN A FASD MODEL
Shirasaka T, Hashimoto E, Ukai W, Yoshinaga T, Ishii T, Tateno M, Saito T.
Department of Neuropsychiatry, School of Medicine, Sapporo Medical University, Chuo-ku, Sapporo, Japan.

ABSTRACT
To better understand the cellular pathogenetic mechanisms of fetal alcohol spectrum disorder
(FASD) and the therapeutic benefit of stem cell treatment, we exposed pregnant rats to ethanol followed by intravenous administration of neural stem cells (NSCs) complexed with atelocollagen to the new born rats and studied recovery of GABAergic interneuron numbers and synaptic protein density in the anterior cingulate cortex, hippocampus and amygdala. Prenatal ethanol exposure reduced both parvalbumin-positive phenotype of GABAergic interneurons and postsynaptic density protein 95 levels in these areas. Intravenous NSC treatment reversed these reductions. Furthermore, treatment with NSCs reversed impaired memory/cognitive function and social interaction behavior. These experiments underscore an important role for synaptic remodeling and GABAergic interneuron genesis in the pathophysiology and treatment of FASD and highlight the therapeutic potential for intravenous NSC administration in FASD utilizing atelocollagen.


Back to Table of Contents


13. EXPERT EVIDENCE BY MENTAL HEALTH PROFESSIONALS: THE COMMUNICATION CHALLENGE POSED BY EVIDENCE ABOUT AUTISM SPECTRUM DISORDER, BRAIN INJURIES, AND HUNTINGTON'S DISEASE

Freckelton I.
Senior Counsel, Victorian Bar, Australia; Professor of Law, Forensic Medicine, and Forensic Psychology, Monash University, Victoria, Australia. Electronic address: I.Freckelton@vicbar.com.au

ABSTRACT
By drawing upon mental health assessment issues about three non-mainstream conditions - Autism Spectrum Disorder, brain injuries, including Foetal Alcohol Syndrome, and Huntington's Disease - the author argues for the need for subtle, empathic and informed expert evidence about the potential nexus between such conditions and accused persons' criminal responsibility and culpability. He contends that what is forensically required is enhancement of the capacity of triers of fact to appreciate informally and authentically, sometimes in a nuanced way, how persons with different, damaged or deteriorating brains experience situations and others' behaviour so that accused persons' conduct can fairly be evaluated without imposition of assumptions or expectations in respect of "normal persons" that may not be apposite.


Back to Table of Contents


14. WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN CHILDREN WITH PRENATAL METHAMPHETAMINE/POLYDRUG EXPOSURE

Colby JB, Smith L, O’Connor MJ, Bookheimer SY, Van Horn JD, Sowell ER.
Department of Neurology, University of California Los Angeles (UCLA), Los Angeles, CA, USA; Interdepartmental Program for Biomedical Engineering, UCLA, Los Angeles, CA, USA; Developmental Cognitive Neuroimaging Laboratory, Children's Hospital Los Angeles, Los Angeles, CA, USA.

ABSTRACT
Little is known about the effects of prenatal methamphetamine exposure on white matter
microstructure, and the impact of concomitant alcohol exposure. Diffusion tensor imaging and neurocognitive testing were performed on 21 children with prenatal methamphetamine exposure (age 9.8±1.8 years; 17 also exposed to alcohol), 19 children with prenatal alcohol but not methamphetamine exposure (age 10.8±2.3 years) and 27 typically developing children (age 10.3±3.3 years). Whole-brain maps of fractional anisotropy (FA) were evaluated using tract-based spatial statistics. Relative to unexposed controls, children with prenatal methamphetamine exposure demonstrated higher FA mainly in left-sided regions, including the left anterior corona radiata (LCR) and corticospinal tract (P<0.05, corrected). Post-hoc analyses of these FA differences showed they likely result more from lower radial diffusivity (RD) than higher axial diffusivity (AD). Relative to the methamphetamine-exposed group, children with prenatal alcohol exposure showed lower FA in frontotemporal regions - particularly the right external capsule (P<0.05, corrected). We failed to find any group-performance interaction (on tests of executive functioning and visuomotor integration) in predicting FA; however, FA in the right external capsule was significantly associated with performance on a test of visuomotor integration across groups (P<0.05). This report demonstrates unique diffusion abnormalities in children with prenatal methamphetamine/polydrug exposure that are distinct from those associated with alcohol exposure alone, and illustrates that these abnormalities in brain microstructure are persistent into childhood and adolescence - long after the polydrug exposure in utero.


15. THREE-DIMENSIONAL SURFACE DEFORMATION-BASED SHAPE ANALYSIS OF HIPPOCAMPUS AND CAUDATE NUCLEUS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS
Joseph J, Warton C, Jacobson SW, Jacobson JL, Molteno CD, Eicher A, Marais P, Phillips OR, Narr KL, Meintjes EM. MRC/UCT Medical Imaging Research Unit, Faculty of Health Sciences, University of Cape Town, South Africa; Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa. jesuinmit@gmail.com

ABSTRACT
Surface deformation-based analysis was used to assess local shape variations in the hippocampi and caudate nuclei of children with fetal alcohol spectrum disorders. High-resolution structural magnetic resonance imaging images were acquired for 31 children (19 controls and 12 children diagnosed with fetal alcohol syndrome/partial FAS). Hippocampi and caudate nuclei were manually segmented, and surface meshes were reconstructed. An iterative closest point algorithm was used to register the template of one control subject to all other shapes in order to capture the true geometry of the shape with a fixed number of landmark points. A point distribution model was used to quantify the shape variations in terms of a change in co-ordinate positions. Using the localized Hotelling T(2) method, regions of significant shape variations between the control and exposed subjects were identified and mapped onto the mean shapes. Binary masks of hippocampi and caudate nuclei were generated from the segmented volumes of each brain. These were used to compute the volumes and for further statistical analysis.

The Mann-Whitney test was performed to predict volume differences between the groups. Although the exposed and control subjects did not differ significantly in their volumes, the shape analysis showed the hippocampus to be more deformed at the head and tail regions in the alcohol-exposed children. Between-group differences in caudate nucleus morphology were dispersed across the tail and head regions. Correlation analysis showed associations between the degree of compression and the level of alcohol exposure. These findings demonstrate that shape analysis using three-dimensional surface measures is sensitive to fetal alcohol exposure and provides
additional information than volumetric measures alone.

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Back to Table of Contents


16. **FATTY ACID ETHYL ESTERS (FAEES) AS MARKERS FOR ALCOHOL IN MECONIUM: METHOD VALIDATION AND IMPLEMENTATION OF A SCREENING PROGRAM FOR PRENATAL DRUG EXPOSURE**

Hastedt M, Krumbiegel F, Gapert R, Tsokos M, Hartwig S.
Institute of Legal Medicine and Forensic Sciences, Charité, University Medicine Berlin, Berlin, Germany.

**ABSTRACT**
Alcohol consumption during pregnancy is a widespread problem and can cause severe fetal damage. As the diagnosis of fetal alcohol syndrome is difficult, the implementation of a reliable marker for alcohol consumption during pregnancy into meconium drug screening programs would be invaluable. A previously published gas chromatography mass spectrometry method for the detection of fatty acid ethyl esters (FAEEs) as alcohol markers in meconium was optimized and newly validated for a sample size of 50 mg. This method was applied to 122 cases from a drug-using population. The meconium samples were also tested for common drugs of abuse. In 73% of the cases, one or more drugs were found. Twenty percent of the samples tested positive for FAEEs at levels indicating significant alcohol exposure. Consequently, alcohol was found to be the third most frequently abused substance within the study group. This re-validated method provides an increase in testing sensitivity, is reliable and easily applicable as part of a drug screening program. It can be used as a non-invasive tool to detect high alcohol consumption in the last trimester of pregnancy. The introduction of FAEEs testing in meconium screening was found to be of particular use in a drug-using population.

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Back to Table of Contents


17. **DOES ANTENATAL TOBACCO OR ALCOHOL EXPOSURE INFLUENCE A CHILD’S CEREBRAL PALSY? A POPULATION-BASED STUDY**

Kyriakopoulos P, Oskoui M, Dagenais L, Shevell MI.
Division of Pediatric Neurology, Montreal Children’s Hospital-McGill University Health Center, Montreal, Quebec, Canada.

**ABSTRACT**
Antenatal tobacco and alcohol exposure are established risk factors for premature birth and an independent risk factor for cerebral palsy. Both exert adverse effects on fetal development. In children with cerebral palsy, whether antenatal exposure to tobacco or alcohol is associated with a difference in clinical profile remains unknown. The Quebec Cerebral Palsy Registry was used to compare neurologic subtypes, gross motor functional impairment, and comorbidities in children with cerebral palsy who were or were not prenatally exposed to alcohol or tobacco. Information on in utero exposure was available in 249 children with cerebral palsy born from 1999-2002, of whom 77 were exposed to alcohol and 62 to tobacco in utero. No association was evident between exposure to tobacco or alcohol during pregnancy and neurologic subtype, Gross Motor Function
Classification System score, mean number of comorbidities experienced, or each of eight comorbidities explored. Adjusting for prematurity or low birth weight exerted no effect on these results. In utero exposure to tobacco or alcohol does not assist in predicting clinical profiles of cerebral palsy.

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18. THE TREATMENT OF ALCOHOL AND OPIOID DEPENDENCE IN PREGNANT WOMEN
Heberlein A, Leggio L, Stichtenoth D, Hillemacher T. A Department of Psychiatry, Social Psychiatry and Psychotherapy, Center for Addiction Research (CARe), Hannover Medical School, Hannover, Germany bCenter for Alcohol and Addiction Studies, Brown University, Providence, Rhode Island, USA cDepartment of Clinical Pharmacology, Hannover Medical School, Hannover, Germany.

ABSTRACT
Purpose of review: This article addresses the question of 'best treatment options', which clinicians face when treating pregnant women with alcohol and opioid dependence.

Recent Findings: Studies show that alcohol consumption is associated with fetal abnormalities and long-term cognitive problems depending on the amount consumed, drinking pattern, and time of gestation. Screening and evaluation of specific interventions are important to reduce alcohol consumption during pregnancy and associated problems in infants. Opioid detoxification is only recommended beyond the first trimester and only in those pregnant women who refuse opioid maintenance therapy. Methadone is the most established treatment of pregnant opioid-dependent women, though recent results indicate some advantages of buprenorphine, slow-release oral methadone and diamorphine compared with methadone.

Summary: Benzodiazepines seem to be the most recommendable option for managing alcohol withdrawal, and psychosocial interventions succeed in reducing alcohol consumption or in maintaining abstinence in alcohol-dependent pregnant women. Regarding opioid dependence, current results suggest that factors like the health status of the mother, the need for additional medications (e.g. treatment for HIV), comorbid drug dependence, and concurrent drug use need to be considered in order to find the 'best opioid substitute'.

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19. THE DETECTION AND QUANTIFICATION OF ETHYL GLUCURONIDE IN PLACENTAL TISSUE AND PLACENTAL PERFUSATE BY HEADSPACE SOLID-PHASE MICROEXTRACTION COUPLED WITH GAS CHROMATOGRAPHY-MASS SPECTROMETRY
Matlow JN, Aleksa K, Lubetsky A, Koren G.

ABSTRACT
Background: Ethyl glucuronide (EtG) is arising as a promising biomarker of heavy prenatal
alcohol exposure, however its transfer across the human placenta is still unclear and is currently being investigated using the ex vivo placental perfusion model. This model allows for sampling from placental tissue and placental perfusate, which is a surrogate to plasma.

**Objective:** To develop a method for detecting and quantifying EtG in placental perfusate and tissue using headspace solid-phase microextraction (HS-SPME) coupled with gas chromatography-mass spectrometry (GC-MS).

**Methods:** A method was optimized by manipulation of the following components to attain the highest peak counts for the quantifying ions of EtG and its deuterated internal standard on the mass spectrum: cartridges used for solid phase extraction, injection method, derivatizing agent, pre-injection parameters, SPME fiber, GC ramp speed, and GC column flow.

**Results:** The final method utilized involved solid phase extraction of standards via UCT CleanScreen Cartridges, derivatization with heptafluorobutyric acid, and introduction into the GC via HS-SPME with adsorption to a polydimethylsiloxane fiber. The method has improved sensitivity over other methods that quantify EtG in blood using GC-MS, with detection limits of 1.6 ng/mL and 13.7 ng/g for placental perfusate and tissue, respectively. The method was applied to samples collected from the fetal reservoir during the ex vivo placental perfusion model and EtG was detected in the fetal circulation after 20 minutes of perfusion, indicating transfer of EtG.

**Conclusions:** The present method is sensitive and can be used to quantify EtG transfer during ex vivo placental perfusion experiments.


Back to Table of Contents


20. **A LONGITUDINAL STUDY OF THE LONG-TERM CONSEQUENCES OF DRINKING DURING PREGNANCY: HEAVY IN UTERO ALCOHOL EXPOSURE DISRUPTS THE NORMAL PROCESSES OF BRAIN DEVELOPMENT**


Department of Neurology, University of California at Los Angeles, Los Angeles, California 90095-1769, University of Southern California Keck School of Medicine, Department of Pediatrics, Children's Hospital of Los Angeles, Los Angeles, California 90027, Department of Psychology, San Diego State University, San Diego, California 92182-4611, Department of Pediatrics, University of California at San Diego, La Jolla, California 92123-5109, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa, Department of Nutrition, Gillings School of Global Public Health, Nutrition Research Institute, University of North Carolina, Chapel Hill, North Carolina 27599-7461, and Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, California 90095.

**ABSTRACT**

Exposure to alcohol in utero can cause birth defects, including face and brain abnormalities, and is the most common preventable cause of intellectual disabilities. Here we use structural magnetic resonance imaging to measure cortical volume change longitudinally in a cohort of human children and youth with prenatal alcohol exposure (PAE) and a group of unexposed control subjects, demonstrating that the normal processes of brain maturation are disrupted in individuals whose mothers drank heavily during pregnancy. Trajectories of cortical volume change within children and youth with PAE differed from those of unexposed control subjects in posterior brain regions, particularly in the parietal cortex. In these areas, control children appear to show a particularly plastic cortex with a prolonged pattern of cortical volume increases followed by equally vigorous
volume loss during adolescence, while the alcohol-exposed participants showed primarily volume loss, demonstrating decreased plasticity. Furthermore, smaller volume changes between scans were associated with lower intelligence and worse facial morphology in both groups, and were related to the amount of PAE during each trimester of pregnancy in the exposed group. This demonstrates that measures of IQ and facial dysmorphology predict, to some degree, the structural brain development that occurs in subsequent years. These results are encouraging in that interventions aimed at altering “experience” over time may improve brain trajectories in individuals with heavy PAE and possibly other neurodevelopmental disorders.


Back to Table of Contents


21. THE EFFECT OF ETHYL ALCOHOL ON THE FUNCTION OF SPATIAL MEMORY IN RATS
Department of Pharmacoeconomics and Social Pharmacy, Poznan University of Medical Sciences.

ABSTRACT
Alcoholism is a mental disease in the course of which depression, anxiety, and cognitive function deficits may appear, and these symptoms can be aggravated by comorbid schizophrenia. The aim of this study was to find whether spatial memory (Morris Water Maze) function impairment is found in prenatally stressed rats (PSG) (prenatal stress paradigm - animal model of schizophrenia) and whether aripiprazole ARI and olanzapine OLA modify these functions. It was also important to study the effect of ethyl alcohol administered to rats. Behavioural tests showed that ARI and OLA improved spatial memory in the non-stressed control group (NSCG) and in the PSG. Moreover, spatial memory in the non-stressed alcohol group (NSAG) improved significantly compared to the NSCG, while in the prenatally stressed alcohol group (PSAG) spatial memory improved both in comparison to the NSCG and PSG. No statistically significant differences were found by comparing groups which received ethyl alcohol (NSAG, PSAG).


Back to Table of Contents


22. CONSENSUS DIAGNOSTIC CRITERIA FOR FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA: A MODIFIED DELPHI STUDY.
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia.

ABSTRACT
Objective: To evaluate health professionals’ agreement with components of published diagnostic criteria for fetal alcohol spectrum disorders (FASD) in order to guide the development of standard diagnostic guidelines for Australia.

Design: A modified Delphi process was used to assess agreement among health professionals
with expertise or experience in FASD screening or diagnosis. An online survey, which included 36 Likert statements on diagnostic methods, was administered over two survey rounds. For fetal alcohol syndrome (FAS), health professionals were presented with concepts from the Institute of Medicine (IOM), University of Washington (UW), Centers for Disease Control (CDC), revised IOM and Canadian diagnostic criteria. For partial FAS (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD), concepts based on the IOM and the Canadian diagnostic criteria were compared.

**Setting/Participants:** 130 Australian and 9 international health professionals.

**Results:** Of 139 health professionals invited to complete the survey, 103 (74.1%) responded, and 74 (53.2%) completed one or more questions on diagnostic criteria. We found consensus agreement among participants on the diagnostic criteria for FAS, with the UW criteria most commonly endorsed when compared with all other published criteria for FAS. When health professionals were presented with concepts based on the Canadian and IOM diagnostic criteria, we found consensus agreement but no clear preference for either the Canadian or IOM criteria for the diagnosis of PFAS, and no consensus agreement on diagnostic criteria for ARND. We also found no consensus on the IOM diagnostic criteria for ARBD.

**Conclusions:** Participants indicated clear support for use of the UW diagnostic criteria for FAS in Australia. These findings should be used to develop guidelines to facilitate improved awareness of, and address identified gaps in the infrastructure for, FASD diagnosis in Australia.


Back to Table of Contents
serve as a biomarker for fetal alcohol spectrum disorder.

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24. EFFECT OF PREDICTIVE CUING ON RESPONSE INHIBITION IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE
Department of Psychology, Center for Behavioral Teratology, San Diego State University, San Diego, California.

ABSTRACT
Background: Heavy prenatal exposure to alcohol leads to widespread cognitive deficits, including problems with attention and response inhibition. This study examined blood oxygen level-dependent response in children with and without histories of heavy prenatal alcohol exposure during a task of response inhibition consisting of cued and noncued trials.

Methods: Children and adolescents (ages 8 to 18 years) with (alcohol-exposed [AE] = 20) and without (control [CON] = 15) histories of heavy prenatal exposure to alcohol underwent functional magnetic resonance imaging while performing a go/no-go task. Unbeknownst to subjects, a predictive cue preceded the no-go stimulus in 87% of trials.

Results: Groups were matched on demographic variables and did not differ on most measures of task performance. However, following cued stimuli, the AE group demonstrated a lower hit rate to go stimuli and more conservative response bias than the CON group. AE participants demonstrated more activation during no-go trials (inhibition) relative to go trials in the left precuneus, cingulate gyrus, anterior cingulate, and right medial frontal gyrus. During cue-dependent response inhibition, the AE group demonstrated less activation in the left precentral and postcentral gyrus compared to the CON group.

Conclusions: Consistent with previous studies of response inhibition, the AE group demonstrated greater frontal and parietal activation when attempting to inhibit prepotent responses than the CON group, despite similar rates of commission errors. This study further demonstrated that the AE group had impaired behavioral performance on no-go trials and demonstrated less activation in precentral and postcentral gyri relative to the CON group on these trials. This investigation provides evidence of impaired behavioral and neural processing of sequential information in fetal alcohol spectrum disorders, which can help improve inhibition in typical populations.

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25. CHOLECALCIFEROL ATTENUATES PERSEVERATIVE BEHAVIOR ASSOCIATED WITH DEVELOPMENTAL ALCOHOL EXPOSURE IN RATS IN A DOSE-DEPENDENT MANNER
Idrus NM, Happer JP, Thomas JD.  
Center for Behavioral Teratology, Dept. Psychology, San Diego State University, 6330 Alvarado Court, Ste 100, San Diego, CA, 92120, USA. Electronic address: nidrus@projects.sdsu.edu

ABSTRACT
Alcohol is a known teratogen that is estimated to affect 2-5% of the births in the U.S. Prenatal
alcohol exposure can produce physical features such as facial dysmorphology, physiological alterations such as cell loss in the central nervous system (CNS), and behavioral changes that include hyperactivity, cognitive deficits, and motor dysfunction.

The range of effects associated with prenatal alcohol exposure is referred to as fetal alcohol spectrum disorders (FASD). Despite preventative measures, some women continue to drink while pregnant. Therefore, identifying interventions that reduce the severity of FASD is critical. This study investigated one such potential intervention, vitamin D(3), a nutrient that exerts neuroprotective properties. The present study determined whether cholecalciferol, a common vitamin D(3) nutritional supplement, could serve as a means of mitigating alcohol-related learning deficits. Using a rat model of FASD, cholecalciferol was given before, during, and after 3(rd) trimester equivalent alcohol exposure. Three weeks after cholecalciferol treatment, subjects were tested on a serial spatial discrimination reversal learning task. Animals exposed to ethanol committed significantly more errors compared to controls. Cholecalciferol treatment reduced perseverative behavior that is associated with developmental alcohol exposure in a dose-dependent manner. These data have important implications for the treatment of FASD and suggest that cholecalciferol may reduce some aspects of FASD.


Back to Table of Contents


26. ADEQUACY OF MATERNAL IRON STATUS PROTECTS AGAINST BEHAVIORAL, NEUROANATOMICAL, AND GROWTH DEFICITS IN FETAL ALCOHOL SPECTRUM DISORDERS
Rufer ES, Tran TD, Attridge MM, Andrzejewski ME, Flentke GR, Smith SM.
Molecular and Environmental Toxicology Center, University of Wisconsin-Madison, Madison, Wisconsin, United States of America; Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, Wisconsin, United States of America.

ABSTRACT
Fetal alcohol spectrum disorders (FASD) are the leading non-genetic cause of neurodevelopmental disability in children. Although alcohol is clearly teratogenic, environmental factors such as gravity and socioeconomic status significantly modify individual FASD risk despite equivalent alcohol intake. An explanation for this variability could inform FASD prevention. Here we show that the most common nutritional deficiency of pregnancy, iron deficiency without anemia (ID), is a potent and synergistic modifier of FASD risk. Using an established rat model of third trimester-equivalent binge drinking, we show that ID significantly interacts with alcohol to impair postnatal somatic growth, associative learning, and white matter formation, as compared with either insult separately. For the associative learning and myelination deficits, the ID-alcohol interaction was synergistic and the deficits persisted even after the offsprings' iron status had normalized.

Importantly, the observed deficits in the ID-alcohol animals comprise key diagnostic criteria of FASD. Other neurobehaviors were normal, showing the ID-alcohol interaction was selective and did not reflect a generalized malnutrition. Importantly ID worsened FASD outcome even though the mothers lacked overt anemia; thus diagnostics that emphasize hematological markers will not identify pregnancies at-risk. This is the first direct demonstration that, as suggested by clinical studies, maternal iron status has a unique influence upon FASD outcome. While alcohol is unquestionably teratogenic, this ID-alcohol interaction likely represents a significant portion of FASD diagnoses because ID is more common in alcohol-abusing pregnancies than generally appreciated. Iron status may also underlie the associations between FASD and parity or
socioeconomic status. We propose that increased attention to normalizing maternal iron status will substantially improve FASD outcome, even if maternal alcohol abuse continues. These findings offer novel insights into how alcohol damages the developing brain.

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Back to Table of Contents


27. **A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF SPATIAL WORKING MEMORY IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE: CONTRIBUTION OF FAMILIAL HISTORY OF ALCOHOL USE DISORDERS**

Norman AL, O'Brien JW, Spadoni AD, Tapert SF, Jones KL, Riley EP, Mattson SN

**ABSTRACT**

**Background:** Heavy prenatal alcohol exposure leads to widespread cognitive deficits, including problems with spatial working memory (SWM). Neuroimaging studies report structural and functional abnormalities in fetal alcohol spectrum disorders (FASD), but interpretations may be complicated by the co-occurrence of a family history of alcoholism. Since this history is also linked to cognitive deficits and brain abnormalities, it is difficult to determine the extent to which deficits are unique to prenatal alcohol exposure.

**Methods:** Age-matched subjects selected from 2 neuroimaging studies underwent functional imaging while engaging in a task assessing memory for spatial locations relative to a vigilance condition assessing attention. Pairwise comparisons were made for the following 3 groups: children with histories of heavy prenatal alcohol exposure (ALC, n = 18); those with no prenatal alcohol exposure, but a confirmed family history of alcoholism (FHP, n = 18); and nonexposed, family history negative controls (CON, n = 17).

**Results:** Relative to CON and FHP, the ALC group showed increased blood oxygen level dependent (BOLD) response in the left middle and superior frontal gyri for the SWM condition relative to the vigilance condition (SWM contrast). Additionally, the ALC group showed unique BOLD response increases in the left lingual gyrus and right middle frontal gyrus relative to CON, and left cuneus and precuneus relative to FHP. Both ALC and FHP showed greater activation compared to CON in the lentiform nucleus and insular region.

**Conclusions:** These results confirm previous studies suggesting SWM deficits in FASD. Differences between the ALC group and the CON and FHP groups suggest the left middle and superior frontal region may be specifically affected in alcohol-exposed children. Conversely, differences from the CON group in the lentiform nucleus and insular region for the ALC and FHP groups may indicate this region is associated with family history of alcoholism rather than specifically with prenatal alcohol exposure.

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Back to Table of Contents
28. **ETHICAL CONSIDERATIONS WHEN COMMUNICATING A DIAGNOSIS OF A FETAL ALCOHOL SPECTRUM DISORDER TO A CHILD**

Michelle Todorow, Karrela Paris, Ellen Fantus

**ABSTRACT**

Maternal alcohol consumption during pregnancy may result in Fetal Alcohol Spectrum Disorder (FASD), which is an umbrella term used to describe a range of conditions that are associated with significant neurodevelopmental impairments.

Communicating an FASD diagnosis to a child is a complex and difficult task that requires a great deal of care, particularly due to the sensitive nature of the etiology of these disorders. To the best of our knowledge, there are no formal guidelines or published materials that outline the ethical considerations specifically associated with disclosing an FASD diagnosis to a child.

This paper discusses a number of ethical principles and situational factors that should be considered when communicating an FASD diagnosis, as well as some of the potential risks and benefits associated with disclosure. We also provide recommendations to assist clinicians in communicating the diagnosis in a manner that increases understanding and minimizes harm to the child. Future recommendations include the development of formalized guidelines in order to aid clinicians in carrying out this sensitive task.

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Back to Table of Contents

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29. **CDON MUTATION AND FETAL ETHANOL EXPOSURE SYNERGIZE TO PRODUCE MIDLINE SIGNALING DEFECTS AND HOLOPROSENCEPHALY SPECTRUM DISORDERS IN MICE**

Hong M, Krauss RS.

Department of Developmental and Regenerative Biology, Mount Sinai School of Medicine, New York, New York, United States of America.

**ABSTRACT**

Holoprosencephaly (HPE) is a remarkably common congenital anomaly characterized by failure to define the midline of the forebrain and midface. HPE is associated with heterozygous mutations in Sonic hedgehog (SHH) pathway components, but clinical presentation is extremely variable and many mutation carriers are unaffected. It has been proposed that these observations are best explained by a multiple-hit model, in which the penetrance and expressivity of an HPE mutation is enhanced by a second mutation or the presence of cooperating, but otherwise silent, modifier genes. Non-genetic risk factors are also implicated in HPE, and gene-environment interactions may provide an alternative multiple-hit model to purely genetic multiple-hit models; however, there is little evidence for this contention. We report here a mouse model in which there is dramatic synergy between mutation of a bona fide HPE gene (Cdon, which encodes a SHH co-receptor) and a suspected HPE teratogen, ethanol. Loss of Cdon and in utero ethanol exposure in 129S6 mice give little or no phenotype individually, but together produce defects in early midline patterning, inhibition of SHH signaling in the developing forebrain, and a broad spectrum of HPE phenotypes. Our findings argue that ethanol is indeed a risk factor for HPE, but genetically predisposed individuals, such as those with SHH pathway mutations, may be particularly...
susceptible. Furthermore, gene-environment interactions are likely to be important in the multifactorial etiology of HPE.

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30. **L1 CELL ADHESION MOLECULE SIGNALING IS INHIBITED BY ETHANOL IN VIVO**
Littner Y, Tang N, He M, Bearer CF

**ABSTRACT**

**Background:** Fetal alcohol spectrum disorder is an immense public health problem. In vitro studies support the hypothesis that L1 cell adhesion molecule (L1) is a target for ethanol (EtOH) developmental neurotoxicity. L1 is critical for the development of the central nervous system. It functions through signal transduction leading to phosphorylation and dephosphorylation of tyrosines on its cytoplasmic domain. The function of L1 is also dependent on trafficking through lipid rafts (LRs). Our hypothesis is that L1 is a target for EtOH neurotoxicity in vivo. Our objective is to demonstrate changes in L1 phosphorylation/dephosphorylation and LR association in vivo.

**Methods:** Rat pups on postnatal day 6 are administered 4.5, 5.25, and 6 g/kg of EtOH divided into 2 doses 2 hours apart, then killed. Cerebella are rapidly frozen for assay. Blood is analyzed for blood EtOH concentration. L1 tyrosine phosphorylation is determined by immunoprecipitation and dephosphorylation of tyrosine 1176 determined by immunoblot. LRs are isolated by sucrose density gradient, and the distribution of L1 in LRs is determined.

**Results:** EtOH at all doses reduced the relative amount of Y1176 dephosphorylation as well as the relative amount of L1 phosphorylated on other tyrosines. The proportion of L1 present in LRs is significantly increased in pups who received 6 g/kg EtOH compared to intubated controls.

**Conclusions:** L1 is a target for EtOH developmental neurotoxicity in vivo.

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http://www.unboundmedicine.com/medline/ebm/record/23050935/abstract/L1_Cell_Adhesion_Molecule_Signaling_Is_Inhibited_by_Ethanol_In_Vivo

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31. **NEUROPROTECTIVE PEPTIDES INFLUENCE CYTOKINE AND CHEMOKINE ALTERATIONS IN A MODEL OF FETAL ALCOHOL SYNDROME**
Robin Roberson, Thea Kuddo, Ines Benassou, Daniel Abebe, Catherine Y. Spong
UPDN DIR NICHD NIH, Bethesda, MD

**ABSTRACT**

**Objective:** Fetal alcohol syndrome (FAS) is associated with intellectual disability and neurodevelopmental abnormalities. Neuroprotective peptides NAPVSIPQ (NAP) and SALLRSIPA (SAL) can prevent some of the alcohol-induced teratogenesis including fetal death, growth abnormalities and learning impairment in part by preventing alcohol-induced alterations in NMDA
receptor gene expression in a mouse model for FAS. We evaluated a panel of cytokines and chemokines to determine if NAP+SAL work through a cytokine/chemokine mediated pathway in preventing these alterations.

**Study Design:** Using a well-characterized FAS model, timed, pregnant C57BL6/J mice were treated on gestational day 8 (E8) with alcohol (0.03 mL/g), placebo or alcohol+peptides. Embryos were evaluated at two timepoints: after 6 hours and 10 days later at E18. A panel of cytokines/chemokines was measured using a microsphere-based multiplex immunoassay (Luminex xMAP, Millipore). Statistical analysis included Kruskal-Wallis, with P<.05 considered significant.

**Results:** Six hours after treatment, IL-6 and Keratinocyte chemoattractant cytokine (KC) were not detectable in the control embryos. Alcohol treatment resulted in detectable levels and significant increases in IL-6 (median 15.7, range 10.1-45.9 pg/ml) and KC (median 45.9, range 32.5-99.1 pg/ml). Embryos exposed to alcohol+NAP+SAL, had undetectable IL-6 and KC (both P<.003), similar to control. Alcohol exposure resulted in significant increase of granulocyte colony-stimulating factor (G-CSF) (P<.003) as compared to control, treatment with NAP+SAL prevented the alcohol-induced increase. IL-13 and IL-1β were decreased 6hr after alcohol exposure, exposure to alcohol+NAP+SAL did not completely ameliorate the decrease. At E18, 10 days after exposure, these alterations were no longer present. Several analytes (RANTES, TNF-α, IFN-γ, and IL4) were not detectable at either timepoint in any of the groups.

**Conclusion:** Prenatal alcohol exposure acutely results in a significant elevation of IL6, G-CSF and the KC which are known to affect NMDA receptors. NAP+SAL treatment prevented alcohol-induced increases. This provides additional insight into the mechanism of alcohol damage in FAS and NAP+SAL prevention of neurodevelopmental anomalies.

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32. GESTATIONAL NALTREXONE AMELIORATES FETAL ETHANOL EXPOSURES ENHANCING EFFECT ON THE POSTNATAL BEHAVIORAL AND NEURAL RESPONSE TO ETHANOL

Youngentob SL, Kent PF, Youngentob LM. Department of Psychiatry and Behavioral Sciences, State University of New York Upstate Medical University, Syracuse.

**ABSTRACT**

The association between gestational exposure to ethanol and adolescent ethanol abuse is well established. Recent animal studies support the role of fetal ethanol experience-induced chemosensory plasticity as contributing to this observation. Previously, we established that fetal ethanol exposure, delivered through a dam's diet throughout gestation, tuned the neural response of the peripheral olfactory system of early postnatal rats to the odor of ethanol. This occurred in conjunction with a loss of responsiveness to other odorants. The instinctive behavioral response to the odor of ethanol was also enhanced. Importantly, there was a significant contributory link between the altered response to the odor of ethanol and increased ethanol avidity when assessed in the same animals. Here, we tested whether the neural and behavioral olfactory plasticity, and their relationship to enhanced ethanol intake, is a result of the mere exposure to ethanol or whether it requires the animal to associate ethanol's reinforcing properties with its odor attributes. In this later respect, the opioid system is important in the mediation (or modulation) of the
reinforcing aspects of ethanol. To block endogenous opiates during prenatal life, pregnant rats received daily intraperitoneal administration of the opiate antagonist naltrexone from gestational day 6-21 jointly with ethanol delivered via diet. Relative to control progeny, we found that gestational exposure to naltrexone ameliorated the enhanced postnatal behavioral response to the odor of ethanol and postnatal drug avidity.

Our findings support the proposition that in utero ethanol-induced olfactory plasticity (and its relationship to postnatal intake) requires, at least in part, the associative pairing between ethanol’s odor quality and its reinforcing aspects. We also found suggestive evidence that fetal naltrexone ameliorated the untoward effects of gestational ethanol exposure on the neural response to non-fetal-exposure odorants. Thus, gestational naltrexone may also have a neuroprotective and/or neuroprotective impact on olfactory development.


33. AUTISM CHARACTERISTICS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS

Stevens SA, Nash K, Koren G, Rovet J.
a Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, Ontario, Canada.

ABSTRACT

Background: Children with fetal alcohol spectrum disorders (FASD) exhibit difficulties in many cognitive and behavioral domains and also have high comorbidity with other disorders such as attention deficit/hyperactivity disorder (ADHD) and conduct disorder as well as autism. Although the FASD profile is shown to be distinct from ADHD and conduct disorder, far less is known about the commonalities with autism. The current study used a parent-rated questionnaire containing an autism subscale to explore the autistic-like features that children with FASD exhibit. Methods: Studied were 25 children with FASD (age: M = 10.3 years) and 17 normal controls (NCs; age: M = 10.2 years). As part of a larger study, all parents/caregivers completed the Social Skills Improvement System (SSIS; Gresham & Elliot, 2008), which in addition to evaluating social skills and behavior problems globally, includes an Autism subscale.

Results: Between-group comparisons showed the FASD group not only scored significantly lower in social skills and significantly higher in behavior problems than the NC group but children with FASD also scored significantly higher on the Autism subscale. Item analysis revealed they showed the most difficulty in terms of social and communicative functioning and the least in repetitive and restrictive behaviors.

Conclusion: Current findings signify that FASD and autism share similarities with regard to social and communicative functioning. These findings, which further our knowledge of the FASD phenotype, may be useful in specifying the particular interventions these children need.

34. ETHANOL DISRUPTS AXON OUTGROWTH STIMULATED BY NETRIN-1, GDNF, AND L1 BY BLOCKING THEIR CONVERGENT ACTIVATION OF SRC FAMILY KINASE SIGNALING

Chen S, Charness ME.
VA Boston Healthcare System and Department of Neurology, Harvard Medical School, West Roxbury, MA, USA.

ABSTRACT
Pre-natal alcohol exposure causes fetal alcohol spectrum disorders (FASD), the most common, preventable cause of developmental disability. The developing cerebellum is particularly vulnerable to the effects of ethanol. We reported that ethanol inhibits the stimulation of axon outgrowth in cerebellar granule neurons (CGN) by NAP, an active motif of activity-dependent neuroprotective protein (ADNP), by blocking NAP activation of Fyn kinase and its downstream signaling molecule, the scaffolding protein Cas. Here, we asked whether ethanol inhibits the stimulation of axon outgrowth by diverse axon guidance molecules through a common action on the Src family kinases (SFK). We first demonstrated that netrin-1, glial cell line-derived neurotrophic factor (GDNF), and neural cell adhesion molecule L1 stimulate axon outgrowth in CGNs by activating SFK, Cas, and extracellular signal-regulated kinase 1 and 2 (ERK1/2). The specific SFK inhibitor, PP2, blocked the stimulation of axon outgrowth and the activation of the SFK-Cas-ERK1/2 signaling pathway by each of these axon-guidance molecules. In contrast, brain-derived neurotrophic factor (BDNF) stimulated axon outgrowth and activated ERK1/2 without first activating SFK or Cas. Clinically relevant concentrations of ethanol inhibited axon outgrowth and the activation of the SFK-Cas-ERK1/2 pathway by netrin-1, GDNF, and L1, but did not disrupt BDNF-induced axon outgrowth or ERK1/2 activation. These results indicate that SFK, but not ERK1/2, is a primary target for ethanol inhibition of axon outgrowth. The ability of ethanol to block the convergent activation of the SFK-Cas-ERK1/2 pathway by netrin-1, GDNF, L1, and ADNP could contribute significantly to the pathogenesis of FASD.

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Back to Table of Contents

Wiley Online Library - Alcoholism: Clinical and Experimental Research
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35. FETAL ALCOHOL-RELATED GROWTH RESTRICTION FROM BIRTH THROUGH YOUNG ADULTHOOD AND MODERATING EFFECTS OF MATERNAL PREPREGNANCY WEIGHT

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www.nofas-uk.org 69
ABSTRACT

Background: Fetal alcohol-related growth restriction persists through infancy, but its impact later in life is less clear. Animal studies have demonstrated important roles for maternal nutrition in fetal alcohol spectrum disorders, but the impact of prenatal maternal body composition has not been studied in humans. This study examined the effects of prenatal alcohol exposure on longitudinal growth from birth through young adulthood and the degree to which maternal weight and body mass index (BMI) moderate these effects.

Methods: Nearly 480 mothers were recruited at their first prenatal clinic visit to overrepresent moderate-to-heavy use of alcohol during pregnancy, including a 5% random sample of low-level drinkers and abstainers. They were interviewed at every prenatal visit about their alcohol consumption using a timeline follow-back approach. Their children were examined for weight, length/height, and head circumference at birth, 6.5 and 13 months, and 7.5, 14, and 19 years.

Results: In multiple regression models with repeated measures (adjusted for confounders), prenatal alcohol exposure was associated with longitudinal reductions in weight, height, and weight-for-length/BMI that were largely determined at birth. At low-to-moderate levels of exposure, these effects were more severe in infancy than in later childhood. By contrast, effects persisted among children whose mothers drank at least monthly and among those born to women with alcohol abuse and/or dependence who had consumed ≥ 4 drinks/occasion. In addition, effects on weight, height, and head circumference were markedly stronger among children born to mothers with lower prepregnancy weight.

Conclusions: These findings confirm prior studies demonstrating alcohol-related reductions in weight, height, weight-for-height/BMI, and head circumference that persist through young adulthood. Stronger effects were seen among children born to mothers with smaller prepregnancy weight, which may have been because of attainment of higher blood alcohol concentrations in smaller mothers for a given amount of alcohol intake or to increased vulnerability in infants born to women with poorer nutrition.


36. BRIEF INTERVENTION TO REDUCE RISKY DRINKING IN PREGNANCY: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL


ABSTRACT:

Background: Risky drinking in pregnancy by UK women is likely to result in many alcohol-exposed pregnancies. Studies from the USA suggest that brief intervention has promise for alcohol risk reduction in antenatal care. However, further research is needed to establish whether this evidence from the USA is applicable to the UK. This pilot study aims to investigate whether pregnant women can be recruited and retained in a randomized controlled trial of brief intervention aimed at reducing risky drinking in women receiving antenatal care.

Methods: The trial will rehearse the parallel-group, non-blinded design and procedures of a subsequent definitive trial. Over 8 months, women aged 18 years and over (target number 2,742) attending their booking appointment with a community midwife (n = 31) in north-east England will be screened for alcohol consumption using the consumption questions of the Alcohol Use Disorders Identification Test (AUDIT-C). Those screening positive, without a history of substance use or alcohol dependence, with no pregnancy complication, and able to give informed consent.
will be invited to participate in the trial (target number 120). Midwives will be randomized in a 1:1 ratio to deliver either treatment as usual (control) or structured brief advice and referral for a 20-minute motivational interviewing session with an alcohol health worker (intervention). As well as demographic and health information, baseline measures will include two 7-day time line follow-back questionnaires and the EuroQoL EQ-5D-3 L questionnaire. Measures will be repeated in telephone follow-ups in the third trimester and at 6 months post-partum, when a questionnaire on use of National Health Service and social care resources will also be completed. Information on pregnancy outcomes and stillbirths will be accessed from central health service records before the follow-ups. Primary outcomes will be rates of eligibility, recruitment, intervention delivery, and retention in the study population, to inform power calculations for a definitive trial. The health-economics component will establish how cost-effectiveness will be assessed, and examine which data on health service resource use should be collected in a main trial. Participants' views on instruments and procedures will be sought to confirm their acceptability.

Discussion: The study will produce a full trial protocol with robust sample-size calculations to extend evidence on effectiveness of screening and brief intervention.

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37. ALCOHOL-RELATED DEVELOPMENTAL ORIGIN OF ADULT HEALTH - POPULATION STUDIES IN POLAND AMONG MOTHERS AND NEWBORNS (2010-2012)  
Wojtyła A, Kapka-Skrzypczak L, Diatczyk J, Fronczak A, Paprzycki P.  
Department of Health Promotion, Food and Nutrition, Institute of Rural Health, Lublin, Poland.

ABSTRACT  
Alcohol related harm is a global problem for public health where frequent consumption of large amounts of alcohol constitutes a serious health risk, particularly to vulnerable groups such as adolescents, pregnant women and newborns. The epidemiological study on health-lifestyle behaviour, especially alcohol consumption, was performed on a randomised group of post-partum women's health behaviour during pregnancy, covering drinking habits, was undertaken in 2010, 2011 and 2012, \((n=8,237)\) according to the PRAMS model including effects on the foetus and newborn; women being selected from obstetric and gynaecological wards. In this Polish study, only 14% of women did not consume alcohol before becoming pregnant while 15% of women drank alcohol throughout the entire period of pregnancy. In addition, awareness of the harmful effects of alcohol consumed, especially of small amounts, before and during pregnancy is low among Polish women. It is also alarming that more than 55% of physicians who provide care for pregnant women do not discuss with them the harmful effect of alcohol on the organism of the mother and foetus, whereas over 2% of doctors even recommend the consumption of alcohol in pregnancy. With reference to the Barker's Foetal Origin of Diseases Hypothesis, the authors suggest such alcohol drinking behaviour of women during their reproductive ages and while pregnant may exert negative health effects on offspring, mainly in the form of susceptibility to contracting chronic diseases. Such findings pose a risk to future generations in Poland and require remedial/educational action targeted on health care professionals and public like.

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Back to Table of Contents
38. INTERACTIONS AMONG ALCOHOL DEPENDENCE, PERINATAL COMMON MENTAL DISORDERS AND VIOLENCE IN COUPLES IN RURAL VIETNAM: A CROSS-SECTIONAL STUDY USING STRUCTURAL EQUATION MODELING

Tran TD, Tran T, Wynter K, Fisher J.

ABSTRACT

Background: There is increasing recognition that perinatal common mental disorders (PCMDs) are prevalent in women in low and lower-middle income countries and emerging evidence that PCMDs and alcohol abuse occur in men in these settings. Domestic violence is associated with PCMDs in both women and men. The aim of this study was to examine the relationships among PCMDs, alcohol abuse and domestic violence in couples in a rural, low-income setting.

Methods: A cross-sectional, population-based study was undertaken in randomly selected communes in Ha Nam and Hanoi, Vietnam. All women in the selected study sites who were at least 28 weeks pregnant or were mothers of 4 -- 6 week old babies in the recruitment period were eligible. The husbands of the women who consented to join the study were also invited to participate. Data sources were study-specific questions and standardised measures: PCMDs were assessed by psychiatrist-administered Structured Clinical Interviews for DSM IV disorders, and alcohol dependence (AD) by the CAGE questionnaire (cut-off of >= 2). Structural Equation Modeling was used to test direct, indirect and mutual relationships simultaneously in the hypothesised model.

Results: In total 364/392 (93%) eligible women agreed to participate. Of these, 360 were married, and 230 (64%) of their husbands also participated to yield a sample of 230 couples for analyses. Overall, in 7.4% (95% CI: 4.6-11.6) of couples both wife and husband were diagnosed with a PCMD; and 41.2% (95% CI: 35.1-47.8) of couples at least one member had a PCMD. Comorbid PCMD and AD were observed in 6.9% (95% CI: 4.3-11.0) of men, but did not occur in women. After controlling for other psychosocial risk factors comorbid PCMD and AD in husbands increased by 4.7 times the probability of PCMDs in their wives via intimate partner violence. PCMDs in wives did not increase the probability of PCMDs or AD in husbands.

Conclusions: These data provide evidence that comorbid PCMD and AD in husbands have a significant adverse effect on the mental health of their wives in rural areas of Vietnam. This indicates that strategies to prevent and treat PCMDs in women will be more effective if paired with initiatives to reduce alcohol dependence and violent behaviours in men.

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Back to Table of Contents
the fetus have been largely confined to the postnatal period, after exposure to alcohol has finished. This study explored the brain function of the fetus, at the time of exposure to alcohol, to examine its effect on information processing and stability of performance.

**Methods:** Five groups of fetuses, defined by maternal alcohol consumption patterns, were examined: control (no alcohol); moderate (5 to 10 units/wk either drunk evenly across the week or as a binge, in 2 to 3 days); heavy (20+ units/wk drunk evenly or as a binge). Fetal habituation performance was examined on 3 occasions, separated by 7 days, beginning at 35 weeks of gestation. The number of trials required to habituate on each test session and the difference in performance across test sessions were recorded.

**Results:** Fetuses exposed to heavy binge drinking required significantly more trials to habituate and exhibited a greater variability in performance across all test sessions than the other groups. Maternal drinking, either heavily but evenly or moderately as a binge, resulted in poorer habituation, and moderate binge drinking resulted in greater variability compared with no, or even, drinking.

**Conclusions:** Decreased information processing, reflected by poorer habituation, and increased variability in performance may reflect the initial manifestations of structural damage caused by alcohol to the brain. These results will lead to a greater understanding of the effects of alcohol on the fetus's brain, enable the antenatal identification of fetal alcohol spectrum disorders, and lead to the early implementation of better management strategies.


Back to Table of Contents

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40. THE BRAIN IN THE BELLY: WHAT AND HOW OF FETAL NEUROIMAGING?

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¹ Department of Neuroradiology, Hopital Timone, Marseille, France
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**ABSTRACT**

This work reviews magnetic resonance imaging in the developing human brain. It focuses on fetal brain imaged in vivo and in utero with complementary sections on abnormalities seen in clinical settings, and on potential of diffusion tensor imaging and of proton magnetic resonance spectroscopy. The main purposes are to illustrate the normal fetal developing brain and its abnormalities commonly encountered in utero, and to emphasize the potential role of adjunct techniques such as diffusion imaging and spectroscopy that may help elucidate fetal brain maturation and its abnormalities.


Back to Table of Contents
41. THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON PSYCHOPATHOLOGY AND BEHAVIOR


ABSTRACT

Background: This study examined prevalence of psychiatric disorders and behavioral problems in children with and without prenatal alcohol exposure (AE) and attention-deficit/hyperactivity disorder (ADHD).

Methods: Primary caregivers of 344 children (8 to 16 years, M = 12.28) completed the Computerized Diagnostic Interview Schedule for Children-IV (C-DISC-4.0) and the Child Behavior Checklist (CBCL). Subjects comprised 4 groups: AE with ADHD (AE+, n = 85) and without ADHD (AE-, n = 52), and nonexposed with ADHD (ADHD, n = 74) and without ADHD (CON, n = 133). The frequency of specific psychiatric disorders, number of psychiatric disorders (comorbidity), and CBCL behavioral scores were examined using chi-square and analysis of covariance techniques.

Results: Clinical groups had greater frequency of all psychiatric disorders, except for anxiety, where the AE- and CON groups did not differ. There was a combined effect of AE and ADHD on conduct disorder. For comorbidity, children with ADHD had increased psychiatric disorders regardless of AE, which did not have an independent effect on comorbidity. For CBCL scores, there were significant main effects of AE and ADHD on all scores and significant AE × ADHD interactions for Withdrawn/Depressed, Somatic Complaints, Attention, and all Summary scores. There was a combined effect of AE and ADHD on Externalizing, Total Problems, and Attention Problems.

Conclusions: Findings indicate that ADHD diagnosis elevates children's risk of psychiatric diagnoses, regardless of AE, but suggest an exacerbated relation between AE and ADHD on conduct disorder and externalizing behavioral problems in children. Findings affirm a poorer behavioral prognosis for alcohol-exposed children with ADHD and suggest that more than 1 neurobehavioral profile may exist for individuals with AE.


Back to Table of Contents


42. FURTHER DEVELOPMENT OF A NEUROBEHAVIORAL PROFILE OF FETAL ALCOHOL SPECTRUM DISORDERS

Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Adnams CM, Jones KL, Riley EP. Center for Behavioral Teratology, San Diego State University, San Diego, California; Department of Psychology, San Diego State University, San Diego, California.

ABSTRACT

Background: Heavy prenatal alcohol exposure (AE) results in a broad array of neurobehavioral deficits. Recent research has focused on identification of a neurobehavioral profile or profiles that will improve the identification of children affected by AE. This study aimed to build on our preliminary neurobehavioral profile to improve classification accuracy and test the specificity of the
resulting profile in an alternate clinical group.

**Methods:** A standardized neuropsychological test battery was administered to 3 groups of children: subjects with AE (n = 209), typically developing controls (CON, n = 185), and subjects with attention-deficit/hyperactivity disorder (ADHD, n = 74). We assessed a large sample from 6 sites in the United States and South Africa, using standardized methodology. Data were analyzed using 3 latent profile analyses including (i) subjects with fetal alcohol syndrome (FAS) and controls, (ii) subjects with AE without FAS and controls, and (iii) subjects with AE (with or without FAS) and subjects with ADHD.

**Results:** Classification accuracy was moderate but significant across the 3 analyses. In analysis 1, overall classification accuracy was 76.1% (77.2% FAS, 75.7% CON). In the second analysis, overall classification accuracy was 71.5% (70.1% AE/non-FAS, 72.4% CON). In the third analysis, overall classification accuracy was 73.9% (59.8% AE, 75.7% ADHD). Subjects that were misclassified were examined for systematic differences from those that were correctly classified.

**Conclusions:** The results of this study indicate that the neuropsychological effects of AE are clinically meaningful and can be used to accurately distinguish alcohol-affected children from both typically developing children and children with ADHD. Further, in combination with other recent studies, these data suggest that approximately 70% of children with heavy prenatal alcohol exposure are neurobehaviorally affected, while the remaining 30% are spared these often-devastating consequences, at least those in the domains under study. Refining the neurobehavioral profile will allow improved identification and treatment development for children affected by prenatal alcohol exposure.


Back to Table of Contents

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43. **DETERMINANTS OF PREGNANT WOMEN'S COMPLIANCE WITH ALCOHOL GUIDELINES: A PROSPECTIVE COHORT STUDY**


**ABSTRACT**

**Background:** In 2009, Australian alcohol guidelines for pregnancy changed from low to no alcohol intake. Previous research found a high proportion of pregnant Australian women drank during pregnancy; however, there has been limited investigation of whether pregnant women comply with 2009 alcohol guidelines. The purpose of this study was to provide an assessment of pregnant women's compliance with 2009 Australian alcohol guidelines and identify predictors of such compliance, including previous drinking behaviour.

**Methods:** Cross-sectional analysis of prospective data from the 1973--1978 cohort of the Australian Longitudinal Study on Women's Health was conducted. Women aged 30--36 years who were pregnant at the 2009 survey and had data on alcohol use were included (n = 837). Compliance with 2009 alcohol guidelines for pregnancy was defined as no alcohol intake. Predictors of compliance were analysed using multivariate logistic regression, controlling for area of residence, in three separate models to account for multicollinearity between measures of previous alcohol intake (compliance with 2001 guidelines; frequency and quantity; bingeing). Private health insurance, household income, and illicit drug use were entered into all models and retained if significant.

**Results:** 72% of pregnant women did not comply with the 2009 alcohol guidelines and 82% of these women drank less than seven drinks per week, with no more than one or two drinks per drinking day. The odds of complying with abstinence increased by a factor of 3.48 (95% CI 2.39-5.05) for women who previously complied with the 2001 alcohol guidelines and decreased by a
factor of 0.19 (95% CI 0.08-0.66) if household incomes were $36,400 or more. In other models the odds of complying were lower for women who consumed alcohol before pregnancy at least weekly (OR = 0.40, 95% CI 0.25-0.63) or binged (OR >= 0.18, 95% CI 0.10-0.31) and were higher for those who abstained (OR = 45.09; 95% CI 8.63-235.49) prior to pregnancy.

**Conclusion:** Most pregnant women did not comply with alcohol guidelines promoting abstinence. Prior alcohol behaviour was the strongest predictor of compliance during pregnancy, suggesting alcohol use should be addressed in women of child-bearing age. The study is limited by the relatively short timeframe between the official introduction of the 2009 guidelines and the date the surveys were sent out. Widespread dissemination of the guidelines may be necessary to help increase guideline compliance by pregnant women.

**Read Full Article,**

Back to Table of Contents

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**44. BLOOD ALCOHOL LEVELS FOR AMERICAN INDIAN MOTHERS AND NEWBORNS**
Kvigne VL, Randall B, Simanton EG, Brenneman G, Welty TK.
MBA, PO Box 54, Centerville, SD 57014. valborg.kvigne@gmail.com

**ABSTRACT**
Very little is known about the alcohol elimination rates of newborns who have had chronic alcohol exposure in utero. In these case reports, blood alcohol levels were taken immediately before delivery, at delivery, and postdelivery for 2 mothers who drank alcohol during their pregnancies and 3 single-birth newborns. Newborn A1 of Mother A had no physical characteristics of fetal alcohol syndrome (FAS). The initial blood alcohol level for this newborn was 38.4 mg/dL 129 minutes after birth, with a subsequent blood alcohol level of 5.5 mg/dL 304 minutes after delivery, resulting in an alcohol elimination rate of 11.3 mg/dL per hour. The blood alcohol level for Mother A was 87.4 mg/dL 66 minutes before delivery. Newborn A2 of mother A had FAS. Sixty minutes after delivery, the blood alcohol level for this newborn was 39.5 mg/dL, and the alcohol level of the mother was 42.1 mg/dL. Newborn B1 of mother B had FAS. At 67 minutes after birth, newborn B1 had a blood alcohol level of 246.5 mg/dL, which dropped to 178.7 mg/dL 302 minutes after birth, resulting in an alcohol elimination rate of 17.3 mg/dL per hour. This alcohol elimination rate is within the metabolism range (15-49 mg/dL per hour) of adults with alcoholism. The maternal blood alcohol level was 265.9 mg/dL 27 minutes before delivery. Blood alcohol levels drawn on both the mother and newborn at delivery and 2 or 3 hourly follow-up levels can provide evidence that fetal alcohol dehydrogenase activity is induced by chronic maternal alcohol use.

**Read Full Article,**

Back to Table of Contents

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**45. INDUCTION OF BRAIN CYP2E1 BY CHRONIC ETHANOL TREATMENT AND RELATED OXIDATIVE STRESS IN HIPPOCAMPUS, CEREBELLUM, AND BRAINSTEM**
Department of Pharmacology, Basic Medical School of Wuhan University, Wuhan 430071, China.

**ABSTRACT**
Ethanol is one of the most commonly abused substances, and oxidative stress is an important
causative factor in ethanol-induced neurotoxicity. Cytochrome P450 2E1 (CYP2E1) is involved in ethanol metabolism in the brain.

This study investigates the role of brain CYP2E1 in the susceptibility of certain brain regions to ethanol neurotoxicity. Male Wistar rats were intragastrically treated with ethanol (3.0g/kg, 30 days). CYP2E1 protein, mRNA expression, and catalytic activity in various brain regions were respectively assessed by immunoblotting, quantitative quantum dot immunohistochemistry, real-time RT-PCR, and LC-MS. The generation of reactive oxygen species (ROS) was analyzed using a laser confocal scanning microscope. The hippocampus, cerebellum, and brainstem were selectively damaged after ethanol treatment, indicated by both lactate dehydrogenase (LDH) activity and histopathological analysis.

Ethanol markedly increased the levels of CYP2E1 protein, mRNA expression, and activity in the hippocampus and cerebellum. CYP2E1 protein and activity were significantly increased by ethanol in the brainstem, with no change in mRNA expression. ROS levels induced by ethanol paralleled the enhanced CYP2E1 proteins in the hippocampus, granular layer and white matter of cerebellum as well as brainstem. Brain CYP2E1 activity was positively correlated with the damage to the hippocampus, cerebellum, and brainstem.

These results suggest that the selective sensitivity of brain regions to ethanol neurodegeneration may be attributed to the regional and cellular-specific induction of CYP2E1 by ethanol. The inhibition of CYP2E1 levels may attenuate ethanol-induced oxidative stress via ROS generation.


Back to Table of Contents


46. ALCOHOL-INDUCED ALTERATIONS IN MATERNAL UTERINE ENDOTHELIAL PROTEOME: A QUANTITATIVE iTRAQ MASS SPECTROMETRIC APPROACH

Ramadoss J, Magness RR. Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX 77555, USA. Electronic address: jaramado@utmb.edu

ABSTRACT

Objective: To quantitate alcohol-induced alterations in the maternal uterine endothelial proteome utilizing iTRAQ-based mass spectrometry.

Study design: Uterine artery endothelial cells from third trimester pregnant ewes were FAC sorted, validated and treated without or with binge-like alcohol. Lysates were trypsin digested, iTRAQ-labeled, and analyzed using nano LC MS/MS.

Results: Alcohol significantly upregulated 14 and downregulated 17 proteins (P<0.05) including those related to cell structure, transcription/translation regulation, histones, Ca(2+)/NO, and redox balance. Gene Ontology and ArrayTrack analyses revealed alterations to protein processing, binding, and nutrient metabolism pathways. Further, alcohol altered proteins previously correlated with fetal alcohol spectrum disorders (FASD) and those that regulate epigenetic, transcriptional, and translational processes.

Conclusions: Alcohol differentially alters the proteome in the maternal uterine compartment at the level of the endothelium. iTRAQ mass spectrometry provides a robust high throughput platform to comprehend the multi-mechanistic actions of alcohol and develop appropriate biomarkers and
ameliorative measures for FASD.

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47. ALCOHOL AND PREGNANCY: DO ABSTINENCE POLICIES HAVE UNINTENDED CONSEQUENCES?

O'Leary CM.
Corresponding author: colleen.oleary@curtin.edu.au

ABSTRACT

Most policies and guidelines recommend that women abstain from alcohol during pregnancy. This can be difficult to achieve in developed nations where the majority of women consume alcohol and almost half of pregnancies are unplanned, leading to many pregnancies being exposed to alcohol prior to pregnancy awareness. Concerns have been raised that abstinence policies may lead women in this situation to terminate their pregnancy out of fear that they have harmed their baby; however, the evidence is limited. A recent study found that while few women reported alcohol as the reason for seeking an abortion, in almost all cases where alcohol was the reason, the women were either binge drinking or reported alcohol-related problems and the pregnancy was unplanned.

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48. DEVELOPMENT OF MULTI-ROUTE PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS FOR ETHANOL IN THE ADULT, PREGNANT, AND NEONATAL RAT

NB/TAD/NHEERL/ORD.

ABSTRACT

Biofuel blends of 10% ethanol (EtOH) and gasoline are common in the USA, and higher EtOH concentrations are being considered (15-85%). Currently, no physiologically-based pharmacokinetic (PBPK) models are available to describe the kinetics of EtOH-based biofuels. PBPK models were developed to describe life-stage differences in the kinetics of EtOH alone in adult, pregnant, and neonatal rats for inhalation, oral, and intravenous routes of exposure, using data available in the open literature. Whereas ample data exist from gavage and intravenous routes of exposure, kinetic data from inhalation exposures are limited, particularly at concentrations producing blood and target tissue concentrations associated with developmental neurotoxicity. Compared to available data, the three models reported in this paper accurately predicted the kinetics of EtOH, including the absorption, peak concentration, and clearance across multiple datasets. In general, model predictions for adult and pregnant animals matched inhalation and intravenous datasets better than gavage data. The adult model was initially better able to predict the time-course of blood concentrations than was the neonatal model. However, after accounting for age-related changes in gastric uptake using the calibrated neonate model, simulations consistently reproduced the early kinetic behavior in blood. This work provides comprehensive multi-route life-stage models of EtOH pharmacokinetics and represents a first step in development
of models for use with gasoline-EtOH blends, with additional potential applicability in investigation of the pharmacokinetics of EtOH abuse, addiction, and toxicity.

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**Back to Table of Contents**
50. **HIGH-THROUGHPUT CLASSIFICATION OF CLINICAL POPULATIONS FROM NATURAL VIEWING EYE MOVEMENTS**

Tseng PH, Cameron IG, Pari G, Reynolds JN, Munoz DP, Itti L.  
Department of Computer Science, University of Southern California, Los Angeles, CA, 90089, USA.

**ABSTRACT**

Many high-prevalence neurological disorders involve dysfunctions of oculomotor control and attention, including attention deficit hyperactivity disorder (ADHD), fetal alcohol spectrum disorder (FASD), and Parkinson's disease (PD). Previous studies have examined these deficits with clinical neurological evaluation, structured behavioral tasks, and neuroimaging. Yet, time and monetary costs prevent deploying these evaluations to large at-risk populations, which is critically important for earlier detection and better treatment. We devised a high-throughput, low-cost method where participants simply watched television while we recorded their eye movements. We combined eye-tracking data from patients and controls with a computational model of visual attention to extract 224 quantitative features. Using machine learning in a workflow inspired by microarray analysis, we identified critical features that differentiate patients from control subjects. With eye movement traces recorded from only 15 min of videos, we classified PD versus age-matched controls with 89.6 % accuracy (chance 63.2 %), and ADHD versus FASD versus control children with 77.3 % accuracy (chance 40.4 %). Our technique provides new quantitative insights into which aspects of attention and gaze control are affected by specific disorders. There is considerable promise in using this approach as a potential screening tool that is easily deployed, low-cost, and high-throughput for clinical disorders, especially in young children and elderly populations who may be less compliant to traditional evaluation tests.

Read Full Article,  

Back to Table of Contents

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51. **HIGH PREVALENCE OF VITAMIN D DEFICIENCY IN PREGNANT WOMEN: A NATIONAL CROSS-SECTIONAL SURVEY**

Vandevijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R.  
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**ABSTRACT**

An increasing number of studies suggest that vitamin D deficiency during pregnancy is associated with multiple adverse health outcomes in mothers, neonates and children. There are no representative country data available on vitamin D status of pregnant women in Europe. The aim of this study was to estimate the prevalence of vitamin D deficiency among Belgian pregnant women and to assess the determinants of vitamin D status in the first and third trimester of pregnancy. The women were selected via a multi-stage proportionate-to-size sampling design. Blood samples were collected and a questionnaire was completed face-to-face. 55 obstetric clinics were randomly selected and 1311 pregnant women participated in the study. The median serum 25-hydroxyvitamin D [25-(OH)D] concentration was significantly lower in the first trimester (20.4 ng/ml) than in third trimester (22.7 ng/ml). Of all women, 74.1% (95%CI = 71.8-76.5%) were vitamin D insufficient (25-(OH)D <30 ng/ml), 44.6% (95%CI = 41.9-47.3%) were vitamin D deficient (25-(OH)D <20 ng/ml), while 12.1% (95%CI = 10.3-13.8%) were severely vitamin D deficient (25-(OH)D <10 ng/ml). Of all women included, 62.0% reported taking vitamin D-containing
multivitamins, of which only 24.2% started taking those before pregnancy. The risk of vitamin D deficiency (25-(OH)D <20 ng/ml) was significantly higher for less educated women and women who reported not going on holidays to sunny climates. The risk of severe vitamin D deficiency (25-(OH)D <10 ng/ml) decreased for women who reported alcohol consumption during pregnancy, decreased with more frequent use of sunscreen lotion and increased for smokers and women who reported preference for shadow. In conclusion, vitamin D deficiency is highly prevalent among pregnant women in Belgium and this raises concerns about the health consequences for the mother and the offspring. A targeted screening strategy to detect and treat women at high risk of severe vitamin D deficiency is needed in Belgium and in Europe.


Back to Table of Contents


52. THE IMPACT OF ALCOHOL USE DURING PREGNANCY ON MATERNAL RESPONSES AFTER BIRTH
Pearson RM, Heron J, Melotti R, Joinson C, Evans J.
School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Clifton, Bristol, BS8 2BN, UK, Rebecca.Pearson@bristol.ac.uk

ABSTRACT
The aim of the study was to investigate the influence of alcohol exposure during pregnancy on a mother’s responsiveness towards her infant after birth. Using longitudinal data from a subsample of 687 mother-infant dyads from a UK cohort study (Avon Longitudinal Study of Parents and Children), we investigated the influence of alcohol use during mid- and late pregnancy on observed mother-infant interactions after birth. We found that women who drank one or more glasses of alcohol a week during their mid-trimester of pregnancy were 19 % (95 % CI, 1 to 40 %; p = 0.033) more likely to show non-responsive behaviour towards their infant 12 months after birth. In contrast, we found that alcohol use during late pregnancy was not associated with later maternal responsiveness. This study adds to the growing evidence for the importance of factors during pregnancy on later maternal responsiveness. Further research is needed to replicate these findings and to examine potential mechanisms linking maternal responsiveness to alcohol use during pregnancy.


Back to Table of Contents


53. ETHANOL-INDUCED FACE-BRAIN DYSMORPHOLOGY PATTERNS ARE CORRELATIVE AND EXPOSURE-STAGE DEPENDENT
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ABSTRACT
Prenatal ethanol exposure is the leading preventable cause of congenital mental disability. Whereas a diagnosis of fetal alcohol syndrome (FAS) requires identification of a specific pattern of
craniofacial dysmorphology, most individuals with behavioral and neurological sequelae of heavy prenatal ethanol exposure do not exhibit these defining facial characteristics. Here, a novel integration of MRI and dense surface modeling-based shape analysis was applied to characterize concurrent face-brain phenotypes in C57Bl/6J fetuses exposed to ethanol on gestational day (GD)7 or GD8.5. The facial phenotype resulting from ethanol exposure depended upon stage of insult and was predictive of unique patterns of corresponding brain abnormalities. Ethanol exposure on GD7 produced a constellation of dysmorphic facial features characteristic of human FAS, including severe midfacial hypoplasia, shortening of the palpebral fissures, an elongated upper lip, and deficient philtrum. In contrast, ethanol exposure on GD8.5 caused mild midfacial hypoplasia and palpebral fissure shortening, a shortened upper lip, and a preserved philtrum. These distinct, stage-specific facial phenotypes were associated with unique volumetric and shape abnormalities of the septal region, pituitary, and olfactory bulbs. By demonstrating that early prenatal ethanol exposure can cause more than one temporally-specific pattern of defects, these findings illustrate the need for an expansion of current diagnostic criteria to better capture the full range of facial and brain dysmorphology in fetal alcohol spectrum disorders.


Back to Table of Contents


54. ALCOHOL, TOBACCO AND DRUG USE AS REASONS FOR ABORTION
Roberts SC, Avalos LA, Sinkford D, Foster DG.
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ABSTRACT
Aims: Concern about the effects of alcohol and drug use during pregnancy is intertwined with debates about abortion. There is concern that alcohol abstinence recommendations lead women using low levels of alcohol to terminate otherwise wanted pregnancies. This study examines how women describe alcohol, tobacco and/or drug use (ATOD) as reasons for deciding to have abortions and assesses the differences between women reporting and not reporting ATOD as reasons for deciding to have an abortion.

Methods: Data come from the UCSF Turnaway Study which recruited 956 women seeking an abortion at one of 30 US clinics between 2008 and 2010. Mixed methods were used and data were analyzed through thematic coding and logistic regression.

Results: Nearly 5% reported ATOD as a reason for abortion. Women worried that their ATOD had affected their baby's health and that their or their partner's ATOD would influence parenting. Most women (84%) who reported alcohol as a reason binge drank or had an alcohol-problem symptom in the month before discovering their pregnancy. Sixty-one percent who reported drugs as a reason used drugs, with 88% using more than once/week. Although two-thirds smoked tobacco, no woman reported tobacco alone as a reason. Ninety-eight percent of women reporting ATOD as a reason had unintended pregnancies.

Conclusion: Women reporting ATOD as a reason drink at levels exceeding a low threshold and do not appear to be terminating otherwise wanted pregnancies. Thus, findings are inconsistent with hypotheses that abstinence recommendations and punitive policies lead women using low levels of alcohol or using drugs to terminate otherwise wanted pregnancies.


Back to Table of Contents

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SEVERE GASTROESOPHAGEAL REFLUX DISEASE ASSOCIATED WITH FOETAL ALCOHOL SYNDROME

Sujay NK, Jones M, Whittle E, Murphy H, Auth MK.
Department of Paediatric Gastroenterology, Alder Hey Children's NHS Foundation Trust, Liverpool L12 2AP, UK.

ABSTRACT

Prenatal alcohol exposure may have adverse effects on the developing foetus resulting in significant growth restriction, characteristic craniofacial features, and central nervous system dysfunction. The toxic effects of alcohol on the developing brain are well recognised. However, little is known about the effects of alcohol on the developing gastrointestinal tract or their mechanism. There are few case reports showing an association between foetal alcohol syndrome and gastrointestinal neuropathy. We report a rare association between foetal alcohol syndrome and severe gastrooesophageal reflux disease in an infant who ultimately required fundoplication to optimise her growth and nutrition. The child had failed to respond to maximal medical treatment (domperidone and omeprazole), high calorie feeds, PEG feeding, or total parenteral nutrition. The effect of alcohol on the developing foetus is not limited to the central nervous system but also can have varied and devastating effects on the gastrointestinal tract.


Back to Table of Contents
emerging generalized deficit conceptualization of children with PAE to those higher functioning individuals without global intellectual disability.

Read Full Article, 

Back to Table of Contents


57. Prenatal Ethanol Exposure Alters Synaptic Plasticity in the Dorsolateral Striatum of Rat Offspring via Changing the Reactivity of Dopamine Receptor
Zhou R, Wang S, Zhu X.
Department of Physiology, Nanjing Medical University, Nanjing, Jiangsu, China. zhou-rong@hotmail.com

ABSTRACT
Prenatal exposure to high-level ethanol (EtOH) has been reported to produce hyperlocomotion in offspring. Previous studies have demonstrated synaptic plasticity in cortical afferent to the dorsolateral (DL) striatum is involved in the pathogenesis of hyperlocomotion. Here, prenatal EtOH-exposed rat offspring were used to investigate whether maternal EtOH exposure affected synaptic plasticity in the DL striatum. We found high-frequency stimulation (HFS) induced a weaker long-term potentiation (LTP) in EtOH rats than that in control rats at postnatal day (PD) 15. The same protocol of HFS induced long-term depression (LTD) in control group but still LTP in EtOH group at PD 30 or PD 40. Furthermore, enhancement of basal synaptic transmission accompanied by the decrease of pair-pulse facilitation (PPF) was observed in PD 30 EtOH offspring. The perfusion with D1-type receptors (D1R) antagonist SCH23390 recovered synaptic transmission and blocked the induction of abnormal LTP in PD 30 EtOH offspring. The perfusion with D2-type receptors (D2R) agonist quinpirole reversed EtOH-induced LTP into D1R- and metabotropic glutamate receptor-dependent LTD. The data provide the functional evidence that prenatal ethanol exposure led to the persistent abnormal synaptic plasticity in the DL striatum via disturbing the balance between D1R and D2R.

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Back to Table of Contents

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58. Effects of Heavy Prenatal Alcohol Exposure and Iron Deficiency Anemia on Child Growth and Body Composition Through Age 9 Years
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4 Department of Human Biology, University of Cape Town, Cape Town, South Africa

www.nofas-uk.org 84
ABSTRACT

Background: Prenatal alcohol exposure has been associated with pre- and postnatal growth restriction, but little is known about the natural history of this restriction throughout childhood or the effects of prenatal alcohol on body composition. The objective of this study was to examine the effects of heavy prenatal alcohol exposure on longitudinal growth and body composition.

Methods: Eighty-five heavy drinking pregnant women (≥2 drinks/d or ≥4 drinks/occasion) and 63 abstaining and light-drinking controls (<1 drink/d, no binging) were recruited at initiation of prenatal care in an urban obstetrical clinic in Cape Town, South Africa and prospectively interviewed during pregnancy about alcohol, smoking, drug use, and demographics. Among their children, length/height, weight, and head circumference were measured at 6.5 and 12 months and at 5 and 9 years. Percent body fat (BF) was estimated at age 9 years using bioelectric impedance analysis.

Results: In multiple regression models with repeated measures (adjusted for confounders), heavy alcohol exposure was associated with reductions in weight (0.6 SD), length/height (0.5 SD), and head circumference (0.9 cm) from 6.5 months to 9 years that were largely determined at birth. These effects were exacerbated by iron deficiency in infancy but were not modified by iron deficiency or measures of food security at 5 years. An alcohol-related postnatal delay in weight gain was seen at 12 months. Effects on head circumference were greater at age 9 than at other age points. Although heavy alcohol exposure was not associated with changes in body composition, children with fetal alcohol syndrome (FAS) and partial fetal alcohol syndrome (PFAS) had lower percent BF than heavy exposed nonsyndromal and control children.

Conclusions: Heavy prenatal alcohol exposure is related to prenatal growth restriction that persists through age 9 years and an additional delay in weight gain during infancy. FAS and PFAS diagnoses are associated with leaner body composition in later childhood.


59. ALCOHOL INTAKE IN PREGNANCY INCREASES THE CHILD’S RISK OF ATOPIC DERMATITIS. THE COPSAC PROSPECTIVE BIRTH COHORT STUDY OF A HIGH RISK POPULATION

Carson CG, Halkjaer LB, Jensen SM, Bisgaard H.
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ABSTRACT

Background: Atopic dermatitis has increased four-fold over the recent decades in developed countries, indicating that changes in environmental factors associated with lifestyle may play an important role in this epidemic. It has been proposed that alcohol consumption may be one contributing risk factor in this development.

Objective: To analyze the impact of alcohol intake during pregnancy on the development of atopic dermatitis during the first 7 years of life.

Method: The COPSAC cohort is a prospective, longitudinal, birth cohort study of 411 children born to mothers with a history of asthma, followed up for 7 years with scheduled visits every 6 months as well as visits for acute exacerbations of atopic dermatitis. Risk of atopic dermatitis from any...
alcohol consumption during pregnancy was analyzed as time-to-diagnosis and adjusted for known risk factors.

**Results:** 177 of 411 children developed atopic dermatitis before age 7 years. We found a significant effect of alcohol intake during pregnancy on atopic dermatitis development (HR 1.44, 95% CI 1.05-1.99 p=0.024). This conclusion was unaffected after adjustment for smoking, mother's education and mother's atopic dermatitis.

**Limitations:** The selection of a high-risk cohort, with all mothers suffering from asthma, and all children having a gestational age above 35 weeks with no congenital abnormality, systemic illness, or history of mechanical ventilation or lower airway infection.

**Conclusion:** Alcohol intake by pregnant women with a history of asthma, is significantly associated with an increased risk for the child for developing atopic dermatitis during the first 7 years of life.


Back to Table of Contents

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60. SLEEP PROBLEMS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS.

Chen ML, Olson HC, Picciano JF, Starr JR, Owens J.

Department of Pediatrics, Division of Pulmonary and Sleep Medicine, University of Washington School of Medicine, Seattle, WA, USA. maida.chen@seattlechildrens.org

**ABSTRACT**

**Study objectives:** Sleep problems in children with fetal alcohol spectrum disorders (FASD) are reportedly common but not well characterized. Objectives were to: (1) assess sleep concerns in children with FASD using a caregiver-report survey, the Children's Sleep Habits Questionnaire (CSHQ); (2) compare CSHQ results with those of previously reported community sample; and (3) describe pilot polysomnography findings in children with FASD.

**Methods:** Children with FASD were recruited from a behavioral intervention study, and participating caregivers completed the CSHQ. CSHQ results were compared with the original data from a previously published community sample of similar age. Participants with FASD and elevated CSHQ scores were offered overnight polysomnography.

**Results:** Thirty-three children with FASD (4.1-12.1 years) were enrolled; 85% of children with FASD scored above the clinical cutoff Total Score of 41, reflecting marked sleep disturbance. Elevated subdomain scores occurred primarily in areas concerning for pediatric insomnia. Those with comorbid ADHD had elevated CSHQ on additional subdomains with no difference in Total Scores. Compared with the community sample, children with FASD had higher Total Scores on the CSHQ (52 vs. 39, p < 0.001). Polysomnography, completed in 5 subjects, revealed mild sleep disordered breathing and fragmented sleep with elevated non-respiratory arousal indices.

**Conclusions:** Clinically significant sleep problems are present in children with FASD on both subjective and objective measures. Further investigation is needed to better describe these sleep disturbances and their impact on overall health and daytime neurobehavioral problems in this clinical population.


Back to Table of Contents
61. MATERNAL ALCOHOL USE DURING PREGNANCY, BIRTH WEIGHT AND EARLY BEHAVIORAL OUTCOMES

Chen JH.
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ABSTRACT
Aims: To examine the effect of maternal alcohol use during pregnancy on infant behavioral outcomes and birth weight, and to investigate the differential susceptibility of infant behavioral outcomes and birth weight to prenatal alcohol exposure.

Methods: Data on children born to women taking part in the United States National Longitudinal Survey of Youth (NLSY) (n = 1618) were analyzed using the sibling fixed-effects model, which helps adjust for maternal, genetic and social confounders when examining effects of pre-natal exposure to possible toxins such as alcohol. Mothers were classified as non-drinkers, light-to-moderate drinkers and heavy drinkers according to their frequency of alcohol use during pregnancy. Infants' behavioral outcomes were assessed using the modified Rothbart Infant Behavior Questionnaire in the NLSY, which measures three dimensions of behavioral outcomes: positive mood, fearfulness and difficultness.

Results: Estimates from the model indicated that drinking during pregnancy was positively associated with infant difficultness, but not with positive mood or fearfulness. Further analysis by frequency of alcohol use suggested that both light-to-moderate and heavy drinking were associated with an increase in infant difficultness. Additionally, while low-to-moderate drinking during pregnancy was associated with infant difficultness, drinking at this level was not associated with low birth weight.

Conclusion: The findings suggest that maternal alcohol use during pregnancy is a risk factor for infant behavioral outcomes, after taking into account many confounding factors. Infant behavioral outcomes appear to be more vulnerable to light-to-moderate levels of alcohol use during pregnancy than birth weight is.


Back to Table of Contents

62. HEALTH CARE BURDEN AND COST ASSOCIATED WITH FETAL ALCOHOL SYNDROME: BASED ON OFFICIAL CANADIAN DATA

Popova S, Lange S, Burd L, Rehm J.
Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Lana.Popova@camh.ca

Abstract
Background: Fetal Alcohol Spectrum Disorder (FASD) is a group of disorders caused by prenatal alcohol exposure. From this group, Fetal Alcohol Syndrome (FAS) is the only disorder coded in the International Classification of Diseases, version 10 (ICD-10). This coding was used to gain an understanding on the health care utilization and the mortality rate for individuals diagnosed with FAS, as well as to estimate the associated health care costs in Canada for the most recent available fiscal year (2008-2009).
**Methods**: Health care utilization data associated with a diagnosis of FAS were directly obtained from the Canadian Institute for Health Information (CIHI). Mortality data associated with a diagnosis of FAS were obtained from Statistics Canada.

**Results**: The total direct health care cost of acute care, psychiatric care, day surgery, and emergency department services associated with FAS in Canada in 2008-2009, based on the official CIHI data, was about $6.7 million. The vast majority of the most responsible diagnoses, which account for the majority of a patient's length of stay in hospital, fall within the ICD-10 category Mental and Behavioural Disorders (F00-F99). It was evident that the burden and cost of acute care hospitalizations due to FAS is increasing by 1.6 times greater in 2008-2009, compared to 2002-2003. The mortality data due to FAS, obtained from Statistics Canada (2000-2008), may be underreported, and are likely invalid.

**Discussion**: The official data on the utilization of health care services by individuals diagnosed with FAS are likely to be underreported and therefore, the reported cost figures are most likely underestimated. The quantification of the health care costs associated with FAS is crucial for policy developers and decision makers alike, of the impact of prenatal alcohol exposure, with the ultimate goal of initiating preventive interventions to address FASD.


Back to Table of Contents

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63. **ALCOHOL-INDUCED PREMATURE PERMEABILITY IN MOUSE PLACENTA-YOLK SAC BARRIERS IN VIVO**


**Source**
University of Oulu, Department of Internal Medicine, Oulu, Finland; Biocenter Oulu, Oulu, Finland; Clinical Research Center, Oulu University Hospital, Oulu, Finland.

**ABSTRACT**

**Objective**: Acute alcohol exposure induces malformation and malfunction of placenta-yolk sac tissues in rodents, reducing the labyrinth zone in the placenta and altering the permeability and fluidity of the cell membrane. During normal mouse placentation the cells line up in an optimal way to form a hemotrichorial placenta where layers II and III are connected through gap junctions. These act as molecular sieves that limit the passage of large molecules. PlGF is a developmentally regulated protein that controls the passage of molecules in the vasculosyncytial membranes and media of large blood vessels in the placental villi. In addition to the chorioallantoic placenta, rodents also have another type of placenta that consists of Reichert's membrane within the trophoblast cell layer on the maternal side and the parietal endodermal cells on the embryonic site. This forms a separate materno-fetal transport system. We study here whether alcohol affects these two placental barriers, leading to placental malfunction that in turn diminishes the nutrient supply to the embryo.

**Study design**: CD-1 mice received two intraperitoneal injections of 3 g/kg ethanol at 4 h intervals at 8.75 days post coitum (dpc). The placentas were collected on 9.5, 11.5 and 14.5 dpc and used for histopathological protein studies. Hemotrichorial cell layer structure interactions through connective tissue and gap junction were analyzed by electron microscopy. The permeability of the feto-maternal barrier was visualized with Evans Blue.

**Results**: VEGF, a permeability inducer, was found to be up-regulated in the mouse placenta after acute alcohol exposure, and permeability was also affected by altered structures in the barriers
that separate the feto-maternal blood circulation which destroyed the gap junctions in the hemotrichorial cell layer, reduced the thickness of Reichert's membrane and interfered with Reichert's trophoblast/Reichert's parietal interaction. These defects together could have caused the permeability malfunction of the placenta-yolk sac tissues as visualized and quantified here by Evans Blue leakage.

**Conclusions:** An altered PIGF/VEGF ratio together with barrier malformation may contribute to placental malfunction by altering the permeability of the feto-maternal barriers. Further studies are needed in order to show whether premature permeability is involved in the intrauterine growth restriction observed in human FAS embryos.

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**64. ADVANCED GESTATIONAL AGE INCREASES SERUM CARBOHYDRATE-DEFICIENT TRANSFERRIN LEVELS IN ABSTINENT PREGNANT WOMEN**
Bakhireva LN, Cano S, Rayburn WF, Savich RD, Leeman L, Anton RF, Savage DD. Corresponding author. lbakhireva@salud.unm.edu

**ABSTRACT**

**Aims:** Carbohydrate-deficient transferrin (%CDT) is a well-established and highly specific biomarker for sustained heavy consumption of alcohol. However, in pregnant women, the specificity of this biomarker might be affected by advanced gestational age, even after accounting for increased transferrin concentrations in pregnancy. The goal of this prospective study was to assess the variability in %CDT during pregnancy among alcohol-abstaining patients.

**Methods:** Patients were recruited during one of the first prenatal care visits and followed-up to term. Abstinence was confirmed by maternal self-report and by alcohol biomarkers. Biomarkers assessed in the mother included serum gamma-glutamyltranspeptidase, urine ethyl glucuronide and ethyl sulfate, and whole blood phosphatidylethanol (PEth). In addition, PEth was measured in a dry blood spot card obtained from a newborn. For %CDT analysis, serum samples were collected at baseline and at term and analyzed by an internationally validated high-performance liquid chromatography and spectrophotometric detection method.

**Results:** At recruitment (mean gestational age 22.6 ± 7.3 weeks), the mean %CDT concentration was 1.49 ± 0.30%, while at term, it increased to 1.67 ± 0.28% (P = 0.001). Using a conventional cutoff concentration %CDT >1.7%, 22.9 and 45.7% of the sample would be classified as 'positive' for this biomarker at recruitment and at term, respectively (P = 0.011).

**Conclusion:** These results suggest that a conventional cutoff of 1.7% might be too low for pregnant women and would generate false-positive results. We propose that %CDT >2.0% be used as a cutoff concentration indicative of alcohol exposure in pregnant women. The sensitivity of %CDT at this cutoff for heavy drinking during pregnancy needs to be assessed further.

**Read Full Article,**
A REVIEW OF EXECUTIVE FUNCTION DEFICITS AND PHARMACOLOGICAL MANAGEMENT IN CHILDREN AND ADOLESCENTS.

Hosenbocus S, Chahal R.
Department of Psychiatry, Royal Inland Hospital, Kamloops, British Columbia.

ABSTRACT

Objective: To review both the functions and dysfunction of the executive system (ES) focusing on the extent of executive function (EF) deficits in most psychiatric disorders in children and adolescents and the possibility of such deficits acting as markers for pharmacological management.

Method: A LITERATURE REVIEW WAS CONDUCTED USING MEDLINE, PSYCHINFO, CINAHL, PSYCHARTICLES AND PUBMED WITH THE FOLLOWING KEYWORDS: executive function or dysfunction, pediatric or children or adolescents, psychopharmacology, psychotropic medications, attention deficit hyperactivity disorder (ADHD), depression, obsessive compulsive disorder, anxiety disorders, bipolar disorder, schizophrenia, autism spectrum disorders (ASD), fetal alcohol spectrum disorders (FASD). Due to the limited amount of specific information obtained for some childhood disorders, the search was broadened to include relevant adult literature where information was extrapolated.

Results: Abundant literature was found on the nature of the ES and the executive dysfunctions in most psychiatric disorders in children and adolescents, but not so much on the use of medication. EF deficits were found to be more consistent in disorders such as ADHD, ASD and FASD than in the other disorders but were not specific enough for use as clinical markers for those disorders. For children with ADHD and ASD there was adequate information on the use of psychotropic medications and impact on some EF domains but information on the impact of medication on EF in the other disorders in children and adolescents was fairly limited. Medications acting on the dopaminergic system also showed positive effects on EF deficits and are commonly used in the treatment of EF disorders such as ADHD, ASD and FASD.

Conclusion: Existing literature indicates that EF deficits underlie most psychiatric disorders in children and adolescents. However, there are so many executive functions linked to so many activities and circuits in the brain that it is hard to quantify them in a particular disorder for use as specific markers for that disorder. The ES uses dopamine as its main neurotransmitter and this has implications for clinical management. Dopamine agonists (e.g. stimulants) and antagonists (e.g. neuroleptics) are medications that have direct impact on the ES and are commonly used to treat EF disorders in children and adolescents while serotonergic medications e.g. selective serotonin reuptake inhibitors (SSRIs) have not been very successful in treating such disorders. Identifying EF deficits early could be useful in guiding management including the use of medication in those disorders.


Back to Table of Contents
relation to alcohol-specific risk pathways of intergenerational transmission of alcohol use is not well understood. Further, the roles of alcohol-specific contextual influences on children's early alcohol use have been little examined. In a 20-year prospective, multimethod study of 83 fathers and their 125 children, we considered the predictors of child alcohol use by age 13 years. The predictors included fathers' adolescent antisocial behavior and alcohol use, both parents' adult alcohol use, norms about and encouragement of child use, parental monitoring, child-reported exposure to intoxicated adults, and parent-reported child externalizing behaviors. Path models supported an association between fathers' adolescent alcohol use and children's use ($\beta = 0.17$) that was not better explained by concurrent indicators of fathers' and children's general problem behavior. Fathers' and mothers' adult alcohol use uniquely predicted child use, and exposure to intoxicated adults partially mediated the latter path. Other family risk mechanisms were not supported. However, parental alcohol use and child alcohol use were linked in expected ways with family contextual conditions known to set the stage for alcohol use problems later in adolescence.


Back to Table of Contents

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67. CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE EXPERIENCE REDUCED CONTROL OF ISOTONIC FORCE
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³ Motor Control Laboratory, School of Exercise and Nutritional Sciences, San Diego State University, San Diego, California

ABSTRACT
Background: Heavy prenatal alcohol exposure can result in diverse and extensive damage to the central nervous system, including the cerebellum, basal ganglia, and cerebral cortex. Given that these brain regions are involved in the generation and maintenance of motor force, we predicted that prenatal alcohol exposure would adversely affect this parameter of motor control. We previously reported that children with gestational alcohol exposure experience significant deficits in regulating isometric (i.e., constant) force. The purpose of this study was to determine whether these children exhibit similar deficits when producing isotonic (i.e., graded) force.

Methods: Children with heavy prenatal alcohol exposure and typically developing children completed a series of isotonic force contractions by exerting force on a load cell to match a criterion target force displayed on a computer monitor. Two levels of target force (5 or 20% of maximum voluntary force) were investigated in combination with varying levels of visual feedback.

Results: Compared with control children, children with heavy prenatal alcohol exposure generated isotonic force signals that were less accurate, more variable, and less complex in the time domain. Specifically, interactions were found between group and visual feedback for response accuracy and signal complexity, suggesting that these children have greater difficulty altering their motor output when visual feedback is low.

Conclusions: These data suggest that prenatal alcohol exposure produces deficits in regulating isotonic force, which presumably result from alcohol-related damage to developing brain regions involved in motor control. These children will most likely experience difficulty performing basic motor skills and daily functional skills that require coordination of finely graded force. Therapeutic
strategies designed to increase feedback and, consequently, facilitate visual-motor integration could improve isotonic force production in these children.

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68. **OMEGA-3 SUPPLEMENTATION CAN RESTORE GLUTATHIONE LEVELS AND PREVENT OXIDATIVE DAMAGE CAUSED BY PRENATAL ETHANOL EXPOSURE**

Patten AR, Brocardo PS, Christie BR.
Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada; Department of Biology, University of Victoria, Victoria, British Columbia, Canada.

**ABSTRACT**
Prenatal ethanol exposure (PNEE) causes long-lasting deficits in brain structure and function. In this study, we have examined the effect of PNEE on antioxidant capacity and oxidative stress in the adult brain with particular focus on four brain regions known to be affected by ethanol: cerebellum, prefrontal cortex and hippocampus (cornu ammonis and dentate gyrus subregions). We have utilized a liquid diet model of fetal alcohol spectrum disorders that is supplied to pregnant Sprague-Dawley rats throughout gestation. To examine the therapeutic potential of omega-3 fatty acid supplementation, a subset of animals were provided with an omega-3-enriched diet from birth until adulthood to examine whether these fatty acids could ameliorate any deficits in antioxidant capacity that occurred due to PNEE. Our results showed that PNEE caused a long-lasting decrease in glutathione levels in all four brain regions analyzed that was accompanied by an increase in lipid peroxidation, a marker of oxidative damage. These results indicate that PNEE induces long-lasting changes in the antioxidant capacity of the brain, and this can lead to a state of oxidative stress. Postnatal omega-3 supplementation was able to increase glutathione levels and reduce lipid peroxidation in PNEE animals, partially reversing the effects of alcohol exposure, particularly in the dentate gyrus and the cerebellum. This is the first study where omega-3 supplementation has been shown to have a beneficial effect in PNEE, reducing oxidative stress and enhancing antioxidant capacity.

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69. **ETHANOL-INDUCED DISRUPTION OF GOLGI APPARATUS MORPHOLOGY, PRIMARY NEURITE NUMBER AND CELLULAR ORIENTATION IN DEVELOPING CORTICAL NEURONS**

Powrozek TA, Olson EC.
Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY 13210, USA; Developmental Exposure Alcohol Research Center, SUNY Binghamton University, Binghamton, NY 13902, USA.

**ABSTRACT**
Prenatal ethanol exposure disrupts cortical neurite initiation and outgrowth, but prior studies have
reported both ethanol-dependent growth promotion and inhibition. To resolve this ambiguity and better approximate in vivo conditions, we quantitatively analyzed neuronal morphology using a new, whole hemisphere explant model. In this model, Layer 6 (L6) cortical neurons migrate, laminate and extend neurites in an organotypic fashion. To selectively label L6 neurons, we performed ex utero electroporation of a GFP expression construct at embryonic day 13 and allowed the explants to develop for 2 days in vitro. Explants were exposed to (400 mg/dL) ethanol for either 4 or 24 h prior to fixation. Complete 3-D reconstructions were made of >80 GFP-positive neurons in each experimental condition.

Acute responses to ethanol exposure included compaction of the Golgi apparatus accompanied by elaboration of supernumerary primary apical neurites, as well as a modest (∼15%) increase in higher order apical neurite length. With longer exposure time, ethanol exposure leads to a consistent, significant disorientation of the cell (cell body, primary apical neurite, and Golgi) with respect to the pial surface. The effects on cellular orientation were accompanied by decreased expression of cytoskeletal elements, microtubule-associated protein 2 and F-actin.

These findings indicate that upon exposure to ethanol, developing L6 neurons manifest disruptions in Golgi apparatus and cytoskeletal elements which may in turn trigger selective and significant perturbations to primary neurite formation and neuronal polarity.

Read Full Article,

Back to Table of Contents


70. ACUTE AND CHRONIC EXPOSURE OF CHICK EMBRYO TO ETHANOL ALTERS BRAIN NEUROSTEROID LEVELS
Taherianfard M, Davazdahemamy M, Shojaeifard M, Sharifi M.
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ABSTRACT
Neurosteroids are modulators of neuronal function that may play important role in brain maturation. The aim of the present investigation was to study the effect of prenatal exposure to acute and chronic ethanol on brain progesterone, estradiol, and testosterone concentration on 10th and 15th days following egg incubation. Eggs were exposed to ethanol at 10 % in chronic treatment and 70 % in acute treatment. Progesterone, estradiol, and testosterone were assayed by radioimmunoassay method. It was shown that brain progesterone level was significantly decreased (P < 0.05) in chronic ethanol group on embryonic day 10, but it was significantly increased (P < 0.05) in acute and chronic groups on embryonic day 15. Brain estradiol level was significantly increased (P<0.05) in chronic ethanol group on embryonic day 10, and it was decreased (P < 0.05) in acute and chronic groups of ethanol on embryonic day 15.

Brain testosterone was significantly increased (P < 0.05) in acute and chronic ethanol-exposed groups on embryonic days 10 and 15. Our observations suggest that ethanol may modulate neurosteroid synthesis in the brain.

Read Full Article,

Back to Table of Contents
71. BIOCHEMICAL AND GENETIC ANALYSES OF CHILDHOOD ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Emrah Caylak
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ABSTRACT
Attention deficit/hyperactivity disorder (ADHD) in children is a neurobehavioral disorder characterized by inattention, hyperactivity, and/or impulsivity. The biochemical abnormalities and genetic factors play significant roles in the etiology of ADHD. These symptoms affect the behavior performance and social relationships of children in school and at home. Recently, many studies about biochemical abnormalities in ADHD have been published. Several research groups have also suggested the genetic contribution to ADHD, and attempted to identify susceptibility and candidate genes for this disorder through the genetic linkage and association studies. To date, these studies have reported substantial evidence implicating several genes (dopaminergic: DRD4, DAT1, DRD5, COMT; noradrenergic: DBH, ADRA2A; serotonergic: 5-HTT, HTR1B, HTR2A; cholinergic: CHRNA4, and central nervous system development pathway: SNAP25, BDNF) in the etiology of ADHD. Understanding the biochemistry and genetics of ADHD will allow us to provide a useful addition with other treatment procedures for ADHD.


Back to Table of Contents

72. MICROGLIA PLAY A ROLE IN ETHANOL-INDUCED OXIDATIVE STRESS AND APOPTOSIS IN DEVELOPING HYPOTHALAMIC NEURONS

Boyadjieva NI, Sarkar DK.
Endocrine Program, Department of Animal Sciences (NIB, DKS), Rutgers, The State University of New Jersey, New Brunswick, New Jersey.

ABSTRACT
Background: Animals exposed to alcohol during the developmental period develop many physiological and behavioral problems because of neuronal loss in various brain areas including the hypothalamus. Because alcohol exposure is known to induce oxidative stress in developing neurons, we tested whether hypothalamic cells from the fetal brain exposed to ethanol (EtOH) may alter the cell-cell communication between neurons and microglia, thereby leading to increased oxidative stress and the activation of apoptotic processes in the neuronal population in the hypothalamus.

Methods: Using enriched neuronal and microglial cells from fetal rat hypothalami, we measured cellular levels of various oxidants (O2 -, reactive oxygen species, nitrite), antioxidants (glutathione [GSH]), antioxidative enzymes (glutathione peroxidase [GSH-Px], catalase, superoxide dismutase) and apoptotic death in neurons in the presence and absence of EtOH or EtOH-treated microglial culture medium. Additionally, we tested the effectiveness of antioxidative agents in preventing EtOH or EtOH-treated microglial conditioned medium actions on oxidative stress and apoptosis in neuronal cell cultures.

Results: Neuronal cell cultures showed increased oxidative stress, as demonstrated by higher cellular levels of oxidants but lower levels of antioxidant and antioxidative enzymes, as well as, increased apoptotic death following treatment with EtOH. These effects of EtOH on oxidative stress and cell death were enhanced by the presence of microglia. Antioxidative agents protected developing hypothalamic neurons from oxidative stress and cellular apoptosis which is caused by EtOH or EtOH-treated microglial culture medium.

Conclusions: These data suggest that exposure of developing hypothalamic neurons to EtOH increases cellular apoptosis via the effects on oxidative stress of neurons directly and via increasing production of microglial-derived factor(s).


Back to Table of Contents


73. A PROSPECTIVE COHORT STUDY OF THE PREVALENCE OF GROWTH, FACIAL, AND CENTRAL NERVOUS SYSTEM ABNORMALITIES IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE

Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; Bethesda, Maryland Department of Pediatrics, National Capital Consortium, Bethesda, Maryland.

ABSTRACT

Background: Most children who are exposed to large quantities of alcohol in utero do not develop fetal alcohol syndrome (FAS). Population-based prospective data on the risk of developing components of fetal alcohol spectrum disorders (FASD), however, are limited.

Methods: This was a prospective cohort study of 9,628 women screened during their first prenatal appointment in Chile, which identified 101 who consumed at least 4 drinks/d (exposed) matched with 101 women with no reported alcohol consumption during pregnancy (unexposed). Detailed alcohol consumption data were collected during the pregnancy. Children were evaluated up to 8.5 years of age by clinicians masked to exposure status.

Results: One or more functional central nervous system abnormalities were present in 44.0% (22/50) of the exposed children compared to 13.6% (6/44) of the unexposed (p = 0.002). Growth restriction was present in 27.2% (25/92) of the exposed and 12.5% (12/96) of the unexposed (p = 0.02). Abnormal facial features were present in 17.3% (14/81) of the exposed children compared to 1.1% (1/89) of the unexposed children (p = 0.0002) by direct examination. Of the 59 exposed children with data available to detect at least 1 abnormality, 12 (20.3%) had no abnormalities. Binge drinking from conception to recognition of pregnancy (OR = 1.48 per day, 95% CI: 1.15 to 1.91, p = 0.002) and after recognition of pregnancy (OR = 1.41 per day, 95% CI: 1.01 to 1.95, p = 0.04) and total number of drinks consumed per week from conception to recognition of pregnancy (OR = 1.02 per drink, 95% CI: 1.01 to 1.04, p = 0.0009) were significantly associated with abnormal child outcome.

Conclusions: After exposure to heavy alcohol consumption during pregnancy, 80% of children had 1 or more abnormalities associated with alcohol exposure. Patterns of alcohol use that posed the greatest risk of adverse outcomes were binge drinking and high total weekly intake. Functional neurologic impairment occurred most frequently and may be the only sign to alert physicians to
prenatal alcohol exposure.

Read Full Article,

Back to Table of Contents


74. EXPLANATION OF SOCIAL INEQUALITIES IN HYPERACTIVITY/INATTENTION IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE
Pfunder M, Liebig S, Feldmann R.
Sociology, University of Bielefeld, Germany.

ABSTRACT
Background: Hyperactivity and inattention are major effects of prenatal alcohol exposure (PAE). Although predominantly women from the high social class consume alcohol during pregnancy, children from the low social class are particularly affected by the adverse effects of PAE. This study aimed to test the hypothesis of a social gradient in hyperactivity/inattention in children with PAE.

Methods: Children with PAE (N=996) enrolled in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) were studied. KiGGS was designed and conducted by Robert Koch Institute (RKI) as a nationwide representative survey on the health of German children and adolescents aged 0-17 years. The data include information given by parents and adolescents on the physical and mental health, sociodemographic features, life circumstances and conditions.

Results: PAE children with a middle and low parental socioeconomic status (SES) are on a higher risk of developing hyperactivity/inattention compared to those with high parental SES. Cultural-behavioral factors had the strongest effect in the explanation of social inequalities in hyperactivity/inattention among children with PAE.

Conclusions: Cultural-behavioral factors, particularly health-related behaviors, need a significant improvement in children from the low and middle social class. To reduce social inequalities in hyperactivity in children with PAE, interventions have to focus on the dietary and television habits of the child by reaching parents from the low and middle social class.

Read Full Article,

Back to Table of Contents

[Epub ahead of print]

75. PRENATAL ALCOHOL EXPOSURE, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AND SLUGGISH COGNITIVE TEMPO
Center for Behavioral Teratology, San Diego State University, San Diego, California.

ABSTRACT
Background: Children with heavy prenatal alcohol exposure often meet criteria for attention-
deficit/hyperactivity disorder (ADHD). ADHD research has examined subtype differences in symptomatology, including sluggish cognitive tempo (SCT). This construct is defined by behavioral symptoms including hypoactivity and daydreaming and has been linked to increased internalizing behaviors. The current study examined whether similar findings are displayed in children with prenatal alcohol exposure.

Methods: As part of a multisite study, caregivers of 272 children (8 to 16 years) completed the SCT Scale and Child Behavior Checklist (CBCL). Four groups were included: alcohol-exposed children with ADHD (ALC+; n = 75), alcohol-exposed children without ADHD (ALC−; n = 35), nonexposed children with ADHD (HD; n = 60), and nonexposed children without ADHD (CON; n = 102). SCT and CBCL scores were analyzed using 2 (exposure) × 2 (ADHD) analyses of variance. Pearson’s correlations measured the relationships between SCT, CBCL, and Full Scale IQ (FSIQ). Discriminant function analysis examined whether SCT items could accurately classify groups.

Results: Analyses revealed significant main effects of exposure and ADHD on SCT and internalizing and externalizing scores and significant interaction effects on SCT and internalizing scores. SCT significantly correlated with internalizing, externalizing, and attention ratings in all groups and with FSIQ in ALC+. Discriminant function analysis indicated that specific SCT items could distinguish ALC− from CON.

Conclusions: Alcohol-exposed children exhibited elevated SCT scores. Elevations were related to increased parent ratings of internalizing and externalizing behaviors and attention. These findings are observed in alcohol-exposed children regardless of ADHD symptoms and specific SCT items proved useful in distinguishing exposed children, suggesting clinical utility for this measure in further defining the neurobehavioral profile related to prenatal alcohol exposure.


Back to Table of Contents

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76. ALCOHOL USE AND BINGE DRINKING AMONG WOMEN OF CHILDBEARING AGE--UNITED STATES, 2006-2010

Centers for Disease Control and Prevention (CDC).

ABSTRACT

Alcohol use during pregnancy is a leading preventable cause of birth defects and developmental disabilities. Alcohol-exposed pregnancies (AEPs) can lead to fetal alcohol syndrome and other fetal alcohol spectrum disorders (FASDs), which result in neurodevelopmental deficits and lifelong disability. In 2005, the Surgeon General issued an advisory urging women who are pregnant or who might become pregnant to abstain from alcohol use. Healthy People 2020 set specific targets for abstinence from alcohol use (MICH-11.1) and binge drinking (MICH-11.2) for pregnant women. To estimate the prevalence of any alcohol use and binge drinking in the past 30 days among women aged 18-44 years, CDC analyzed 2006-2010 Behavioral Risk Factor Surveillance System (BRFSS) data. Based on their self-reports, an estimated 51.5% of nonpregnant women used alcohol, as did 7.6% of pregnant women. The prevalence of binge drinking was 15.0% among nonpregnant women and 1.4% among pregnant women. Among pregnant women, the highest prevalence estimates of reported alcohol use were among those who were aged 35-44 years (14.3%), white (8.3%), college graduates (10.0%), or employed (9.6%). Among binge drinkers, the average frequency and intensity of binge episodes were similar, approximately three times per month and six drinks on an occasion, among those who were pregnant and those who were not. Clinical practices that advise women about the dangers associated with drinking while pregnant, coupled with community-level interventions that reduce alcohol-related harms, are necessary to
mitigate AEP risk among women of childbearing age and to achieve the Healthy People 2020 objectives.

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77. NORTHERN BRITISH COLUMBIAN ABORIGINAL MOTHERS: RAISING ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDER
Johnston S, Boyle JS.

ABSTRACT
This interpretive ethnographic study describes the experiences of northern British Columbian Aboriginal mothers raising adolescents with fetal alcohol spectrum disorder (FASD) and provides an understanding of how the mothers interpreted and responded to their adolescents' FASD. The all-encompassing theoretical perspectives of postcolonialism provided the conceptual guide for this study. This ontological stance facilitates discourse on the social and historical context of this research focused on northern British Columbian Aboriginal mothers. Using semi-structured interviews and participant observation, eight participants were interviewed three times over a period of several months. Data were analyzed using an interpretive analysis to generate an overarching cultural theme, Mothering from the Margins. The theme conveyed how study participants understood FASD and how they were raising their adolescents within the social and historical context unique to postcolonial societies.

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78. DIAGNOSING FETAL ALCOHOL SYNDROME: NEW INSIGHTS FROM NEWER GENETIC TECHNOLOGIES
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ABSTRACT
Objective: A genetic opinion is frequently requested in the assessment of a child with suspected fetal alcohol spectrum disorders (FASD). We studied the outcome of genetic assessment of 80 children referred to a regional genetics centre between 2004 and 2010 to identify the value of the genetic assessment in cases of suspected FASD.

Design: Retrospective case series.

Patients: 80 patients, aged between 1 month and 26 years.

Methods: Data from the medical records was abstracted, entered onto a standard study pro forma, recorded in an Excel spreadsheet and analysed using simple frequency analysis.
Results: In 20% of cases fetal alcohol syndrome was confirmed at the genetic consultation. The most common facial features were thin upper lip (86.6%) and short palpebral fissures (82%). A lip-philtrum score of 4 or 5 was identified in two-thirds of cases. The most common alternative diagnosis was a chromosome disorder, representing 8.75% of the FASD referrals.

Setting: A regional genetics service in the North West of England.

Conclusions: Genetic assessment was of particular value in excluding other diagnoses and providing information to carers. Two-thirds of the children referred were subject to a care order increasing the difficulty to obtain a family and alcohol exposure history. Classification of FASD was difficult in children under a year old when data on growth and development were limited. Structural malformations were not common in the group overall and some previously reported diagnostic signs were not found to be reliable markers of FASD. Chromosome disorders showed phenotypic overlap with FASD and are an important differential diagnosis.


79. ATTENUATION OF OXIDATIVE STRESS, NEUROINFLAMMATION, AND APOPTOSIS BY CURCUMIN PREVENTS COGNITIVE DEFICITS IN RATS POSTNATALLY EXPOSED TO ETHANOL

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Pharmacology Research Laboratory, University Institute of Pharmaceutical Sciences, UGC Center of Advanced Study, Panjab University, Chandigarh, 160014, India.

ABSTRACT
Rationale: Clinical and experimental evidence have demonstrated that alcohol consumption during pregnancy can disrupt brain development, leading to a variety of behavioral alterations including hyperactivity, motor dysfunction, and cognitive deficits in offsprings. Alcohol-induced neurocognitive deficits are associated with activation of oxidative-inflammatory cascade coupled with extensive apoptotic neurodegeneration in different brain regions.

Objectives: The present study was designed with an aim to investigate the protective effect of curcumin, a principal curcuminoid present in the Indian spice turmeric, against alcohol-induced cognitive deficits, neuroinflammation, and neuronal apoptosis in rat pups postnatally exposed to ethanol.

Methods And Results: Male Wistar rat pups were administered ethanol (5 g/kg, 12 % v/v) by intragastric intubation on postnatal days (PD) 7, 8, and 9 and were treated with curcumin (30 and 60 mg/kg) from PD 6 to 28. Performance of ethanol-exposed pups that did not receive curcumin was significantly impaired as evaluated in both Morris water maze and elevated plus maze tasks recorded by using computer tracking. Cognitive deficit was associated with enhanced acetylcholinesterase activity, increased neuroinflammation (oxidative-nitrosative stress, TNF-α, IL-1β, and TGF-β1), and neuronal apoptosis (NF-κβ and caspase 3) in both cerebral cortex and hippocampus of ethanol-exposed pups. Chronic treatment with curcumin significantly ameliorated all the behavioral, biochemical, and molecular alterations in different brain regions of ethanol-exposed pups.

Conclusions: The current study demonstrates the possible involvement of oxidative-inflammatory cascade-mediated apoptotic signaling in cognitive deficits associated with postnatal ethanol exposure and points towards the neuroprotective potential of curcumin in mitigating alcohol-induced behavioral, biochemical, and molecular deficits.

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80. ALCOHOL BIOMARKERS
Ingall GB.
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ABSTRACT
Excessive alcohol consumption poses a wide variety of significant immediate and long-term health risks. Ethanol biomarkers have clinical utility for detection, diagnosis, and treatment of alcohol use disorders as well as for screening for fetal alcohol exposure. Indirect biomarkers are those that reflect the toxic effects of ethanol on organs, tissues, or body biochemistry, whereas direct biomarkers are products of ethanol metabolism. Liver enzymes, carbohydrate deficient transferrin and mean corpuscular volume are discussed as examples of indirect markers of alcohol use. Commentary on the direct ethanol markers includes the following: acetaldehyde adducts, ethyl glucuronide, ethyl sulfate, phosphatidylethanol and fatty acids ethyl esters.

81. PRENATAL ETHANOL EXPOSURE IMPAIRS PASSIVE AVOIDANCE ACQUISITION AND ENHANCES UNCONDITIONED FREEZING IN RAT OFFSPRING
Ohta K, Sakata-Haga H, Fukui Y.
Department of Anatomy and Developmental Neurobiology, Institutes of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan.

ABSTRACT
Previous studies have suggested that ethanol exposure during brain development affects responses to fear and anxiety after maturity. To clarify in detail the impaired behavior related to fear and anxiety seen in rat offspring prenatally exposed to ethanol, their behaviors were observed using an elevated T-maze (ETM) test, which allows assessment of passive avoidance acquisition and one-way escape separately, and an elevated open platform (EOP) test for the assessment of unconditioned freezing against innate fear. The ETM test revealed that acquisition of passive avoidance was significantly inhibited in prenatally ethanol-exposed rats, while their escape behavior was not altered. In the EOP test, the duration of the freezing behavior was significantly elongated in prenatally ethanol-exposed offspring. Thus, we concluded that prenatal ethanol exposure could impair acquisition of passive avoidance, while it could facilitate a response related to unconditioned fears in rat offspring.
82. INHIBITION OF HISTONE ACETYLATION BY CURCUMIN REDUCES ALCOHOL-INDUCED EXPRESSION OF HEART DEVELOPMENT-RELATED TRANSCRIPTION FACTORS IN CARDIAC PROGENITOR CELLS

Heart Centre, Children's Hospital of Chongqing Medical University, Chongqing, PR China.

ABSTRACT
Alcohol exposure during pregnancy may cause congenital heart disease (CHD). In our previous studies, we found that alcohol selectively increased acetylation of histone H3 at lysine 9 (H3K9) and enhanced the expression of heart development-related genes in cardiac progenitor cells. The objective of this study is to investigate the protective effects of histone acetyltransferases (HATs) inhibitor, curcumin, on histone hyperacetylation and the over-expression of heart development genes induced by alcohol. Western blot analysis was employed to detect the acetylation levels of histone H3K9 and real-time PCR was applied to measure the expressions of heart development-related transcription factors, GATA4, Mef2c and Tbx5 (GMT). Our results showed that alcohol increased the acetylation of H3K9 by 2.76-fold (P<0.05) and significantly enhanced the expression of GATA4 and Mef2c (P<0.05). When cells were treated with alcohol plus 25 μM curcumin, the hyperacetylation of H3K9 and over-expression of GATA4 and Mef2c by alcohol was reversed. These data indicate that curcumin can correct the over-expression of cardiac genes by reversing the alcohol induced hyperacetylation of histone H3 at lysine 9 in cardiac progenitor cells, suggesting that curcumin is protective against alcohol-induced cardiac gene over-expression that may result in heart malformations.

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83. USE OF THE DIAGNOSTIC CLASSIFICATION OF MENTAL HEALTH AND DEVELOPMENTAL DISORDERS OF INFANCY AND EARLY CHILDHOOD: REVISED EDITION (DC:0–3R) WITH CANADIAN INFANTS AND YOUNG CHILDREN PRENATALLY EXPOSED TO SUBSTANCES

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2York University
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ABSTRACT
The current study examined the mental health diagnostic profiles of infants and young children prenatally exposed to substances using the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood, Revised (DC:0–3R) diagnostic system. Participants were 46 biological mother–infant dyads who were engaged in a clinical program for mothers with substance-use problems and their young children (aged 10–41 months). Diagnostic information was reported for each of the five axes listed in the DC:0–3R diagnostic system based on file reviews. In addition, the children's socioemotional and adaptive behaviors were assessed using the Child Behavior Checklist, Infant–Toddler Social Emotional Assessment, the Social-
Emotional Scale, and the Adaptive Behavior Assessment System (2nd ed.). In this sample of young children with prenatal substance exposure, a broad range of socioemotional symptoms were evident, with almost one third of the children meeting criteria for at least one Axis I mental health diagnosis. In addition, the majority of dyads demonstrated features of a disordered relationship. Children in more problematic relationships demonstrated higher levels of socioemotional and adaptive functioning difficulties and were more likely to have an Axis I diagnosis than were children in adapted relationships. The importance of early intervention efforts aimed at infants with prenatal substance exposure and their biological mothers is highlighted, with a particular focus on enhancing the quality of the mother–child relationship.


84. PARADOXICAL EFFECTS OF ALCOHOL AND THIAMINE DEFICIENCY ON THE EYE OPENING IN RAT PUPPS
Bâ A.
Université de Cocody, UFR Biosciences, Côte d’Ivoire.

ABSTRACT

Objective: The present study attempts to determine whether developmental thiamine (B1 vitamin) deficiency and developmental ethanol exposure disturb eye opening in Wistar rat pups.

Methods: During gestation and lactation, Wistar rat dams were exposed to the following treatments: (1) Prenatal thiamine-deficient dams; (2) perinatal thiamine-deficient dams; (3) postnatal thiamine-deficient dams; (4) 12% alcohol/water drinking mothers; (5) mothers drinking 12% alcohol/water + thiamine hydrochloride mixture; (6) ad libitum control dams.

Pair-feeding treatments controlled malnutrition related to thiamine deficiency: (7) Prenatal pair-fed dams; (8) perinatal pair-fed dams; (9) postnatal pair-fed dams and included also the control of alcohol consummation: (10) pair-fed saccharose dams. After birth, from postnatal day 10 (P10) to P18, eye opening was observed in the pups bred by ten different experimental dams.

Results: The present experiments showed eye opening to be delayed strongly in perinatal thiamine-deficient pups only. Consequently, our study suggests perinatal thiamine deficiency to interfere with photoreceptors differentiation in the rat retina. In addition, our results reveal that developmental alcohol exposure-induced premature eye opening contrasted paradoxically with perinatal thiamine deficiency-induced delayed opening.

Conclusions: The results suggest differential actions of alcohol and thiamine deficiency on cellular genesis in the rat retina.

85. PROGRAMMED CELL DEATH 4 (PDCD4): A NOVEL PLAYER IN ETHANOL-MEDIATED SUPPRESSION OF PROTEIN TRANSLATION IN PRIMARY CORTICAL NEURONS AND DEVELOPING CEREBRAL CORTEX

Madhusudhanan Narasimhan¹,², Marylatha Rathinam¹, Amanjot Riar¹, Dhyanesh Patel¹, Srinivas Mummidi³,⁴, Hsin-Shen Yang⁵, Nancy H. Colburn⁶, George I. Henderson¹,², Lenin Mahimainathan¹,²
¹ Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, Lubbock, Texas
² South Plains Alcohol and Addiction Research Center, Texas Tech University Health Sciences Center, Lubbock, Texas
³ Center for Personalized Medicine, South Texas Veterans Health Care System, San Antonio, Texas
⁴ School of Medicine (SM), University of Texas Health Science Center at San Antonio, San Antonio, Texas
⁵ Graduate Center for Toxicology and Markey Cancer Center, University of Kentucky, Lexington, Kentucky
⁶ Laboratory of Cancer Prevention (NHC), National Cancer Institute, Frederick, Maryland

ABSTRACT

Background: Prenatal exposure to ethanol (EtOH) elicits a range of neuro-developmental abnormalities, microcephaly to behavioral deficits. Impaired protein synthesis has been connected to pathogenesis of EtOH-induced brain damage and abnormal neuron development. However, mechanisms underlying these impairments of protein synthesis are not known. In this study, we illustrate the effects of EtOH on programmed cell death protein 4 (PDCD4), a tumor and translation repressor.

Methods: Primary cortical neurons (PCNs) were treated with 2.5 and 4 mg/ml EtOH for different time points (4 to 24 hours), and PDCD4 expression was detected by Western blotting. Protein synthesis was determined using [35S] methionine incorporation assay. Methyl cap pull-down assay was performed to establish the effect of EtOH on association of eukaryotic initiation factor 4A (eIF4A) with capped mRNA. Luciferase assay was performed to determine the in vivo translation. A 2-day acute 5-dose binge model with EtOH (4 g/kg body wt, 25% v/v) was performed in Sprague–Dawley rats at 12-hour intervals and analyzed for PDCD4, eIF4A, and eIF4A–methyl cap association.

Results: EtOH increased PDCD4 expression in a time- and dose-dependent manner in PCNs, which inhibited the association of eIF4A with methyl cap. EtOH and ectopic PDCD4 expression suppressed in vivo translation in PCNs and RNAi targeting of PDCD4 blocked the inhibitory effect of EtOH on protein synthesis. In utero exposure of pregnant rats to EtOH resulted in a significant increase in PDCD4 in fetal cerebral cortex along with the inhibition of methyl cap–associated eIF4A, compared with isocaloric controls. Increased PDCD4 also occurred in pooled fractions of remaining brain regions.

Conclusions: Our data, for the first time, illustrate that PDCD4 mediates inhibitory effects of EtOH on protein synthesis in PCNs and developing brain.

Read Full Article,

Back to Table of Contents
ABSTRACT

**Background:** Exposure to alcohol in utero is a known cause of mental retardation. Although a certain degree of motor impairment is always associated with fetal alcohol spectrum disorder, little is known about the neurobiological basis of the defective motor control. We have studied the striatal interneurons containing parvalbumin in a rat model of fetal alcohol spectrum disorder.

**Methods:** Newborn rats received ethanol by inhalation from postnatal day two through six and parvalbumin striatal neurons were labeled by immunohistochemistry on postnatal day 60. The spatial distribution of parvalbumin interneurons was studied using Voronoi spatial tessellation and their dendritic trees were completely reconstructed.

**Results:** Parvalbumin interneurons of ethanol-treated animals showed a clustered spatial distribution similar to that observed in control animals. The dendritic tree of parvalbumin interneurons was significantly reduced in ethanol-treated animals, as compared with controls.

**Conclusions:** Striatal parvalbumin interneurons are crucial components of the brain network serving motor control. Therefore, the shrinkage of their dendrites could contribute to the motor and cognitive symptoms observed in fetal alcohol spectrum disorder.


Back to Table of Contents
88. **ALCOHOL USE PATTERN IN PREGNANT WOMEN CARED FOR IN A PUBLIC UNIVERSITY HOSPITAL AND ASSOCIATED RISK FACTORS**

Souza LH, Santos MC, Oliveira LC. Universidade Presidente Antônio Carlos, Araguari, MG, Brasil.

**ABSTRACT**

**Purpose:** To determine the pattern of alcohol use before and during pregnancy and associated risk factors in puerperal women hospitalized in a public university hospital in Southeastern Brazil.

**Methods:** Between June and September 2009, 493 puerperae were consecutively evaluated. Those with cognitive impairment were excluded from the study. The AUDIT and CAGE questionnaires were used to diagnose alcohol use/abuse before pregnancy, in addition to the T-ACE during pregnancy. Another questionnaire was applied to collect sociodemographic data, such as age, educational level, marital status, and household income. The $\chi^2$ test was used in the statistical analysis and the Odds Ratio (OR) and 95% confidence interval (95%CI) were calculated. A p-value <0.05 was considered to be significant.

**Results:** Before pregnancy, the CAGE was positive in 50/405 (12.3%) women and the AUDIT identified alcohol use in 331 (67.1%), which was of low risk in 233 (47.3%), risky in 73 (14.8%), and harmful or indicating possible alcohol dependence in 25 (5%). During pregnancy, the CAGE was positive in 53/405 (13.1%) women and the T-ACE in 84 (17%); the AUDIT identified alcohol use in 114 women, which was of low risk in 73 (14.8%), risky in 27 (5.5%), and harmful or indicating possible alcohol dependence in 14 (2.8%). During pregnancy, alcohol use was more frequent (OR=2.8; 95%CI 1.2 - 6.2) among women with a lower educational level (8.8 versus 3.3%) and more frequent (OR=3.8; 95%CI 1.3 - 11.1) among those who did not cohabit with a partner (6 versus 1.7%). Among pregnant women who drank alcohol, 49/114 (43%) were advised to stop drinking.

**Conclusions:** Alarming alcohol use was observed during pregnancy, especially among pregnant women with a lower educational level and those who did not cohabit with a partner. There was a low frequency of counseling aimed at abstinence and the AUDIT was the instrument that most frequently diagnosed alcohol consumption.


[Back to Table of Contents](#)
something that is "uniquely Indian."

Read Full Article,

Back to Table of Contents


90. ANOTHER STEP FORWARD IN RELATING FACIAL AND BRAIN DYSMORPHOLOGIES ASSOCIATED WITH PRENATAL ALCOHOL EXPOSURE

Fryer SL. Department of Psychiatry, University of California, San Francisco, CA 94121, USA. susanna.fryer@ucsf.edu

ABSTRACT
Abstract not available

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Back to Table of Contents


91. EFFECTS OF EXPOSURE TO MODERATE LEVELS OF ETHANOL DURING PRENATAL BRAIN DEVELOPMENT ON DENDRITIC LENGTH, BRANCHING, AND SPINE DENSITY IN THE NUCLEUS ACCUMBENS AND DORSAL STRIATUM OF ADULT RATS

Rice JP, Suggs LE, Lusk AV, Parker MO, Candelaria-Cook FT, Akers KG, Savage DD, Hamilton DA. Department of Psychology, University of New Mexico, Albuquerque, NM 87131, USA.

ABSTRACT
Reductions in measures of dendritic morphology in the agranular insular cortex have been identified as consequences of prenatal exposure to moderate levels of ethanol in the rat. Motivated by the strong connectivity between this region of frontal cortex and the striatum and a growing body of data linking specific components of the mesocortical/limbic system to effects of ethanol and ethanol self-administration, the current study investigated the effects of moderate fetal ethanol exposure on the dendritic morphology of medium spiny neurons (MSNs) in several regions of the striatum. Throughout gestation, pregnant rat dams either consumed a saccharin solution (control) or achieved average daily blood ethanol concentrations of 84 mg% via voluntary consumption of a 5% ethanol solution. The brains of adult male offspring were extracted and processed for Golgi- Cox staining. MSNs from the dorsomedial striatum, dorsolateral striatum and the nucleus accumbens core and shell were sampled for analysis. Relative to saccharin controls, robust reductions in dendritic length and branching, but not spine density, were observed in the shell of the nucleus accumbens in fetal-ethanol-exposed rats. No significant prenatal ethanol effects were found in the other regions of the striatum. These findings suggest that exposure to moderate levels of ethanol in utero can have profound effects on brain regions related to reward processing and provide possible clues relevant to understanding increased self-administration of drugs of abuse in animals exposed to ethanol during brain development.

Read Full Article,

Back to Table of Contents
92. PRENATAL ETHANOL EXPOSURE STIMULATES NEUROGENESIS IN HYPOTHALAMIC AND LIMBIC PEPTIDE SYSTEMS: POSSIBLE MECHANISM FOR OFFSPRING ETHANOL OVERCONSUMPTION

Chang GQ, Karatayev O, Liang SC, Barson JR, Leibowitz SF. Laboratory of Behavioral Neurobiology, The Rockefeller University, New York, NY, USA.

ABSTRACT

Exposure to ethanol during the prenatal period contributes to increased alcohol consumption and preference in rodents and increased risk for alcoholism in humans. With studies in adult animals showing the orexigenic peptides, enkephalin (ENK), galanin (GAL) and orexin (OX), to stimulate ethanol consumption, the question addressed here is whether prenatal ethanol alters the development in utero of specific neurons that express these peptides. With reports describing suppressive effects of high doses of ethanol, we examined the offspring of dams gavaged from embryonic day 9 to parturition with a control solution or lower ethanol doses, 1 and 3g/kg/day, known to promote ethanol consumption in the offspring. To understand underlying mechanisms, measurements were taken in postnatal offspring of the expression of ENK in the hypothalamic paraventricular nucleus (PVN) and nucleus accumbens (NAC), GAL in the PVN, and OX in the perifornical lateral hypothalamus (PFLH) using real-time qPCR and in situ hybridization, and also of the cell proliferation marker, 5-bromo-2-deoxyuridine (BrdU), and its double-labeling with either neuronal nuclei (NeuN), a marker of mature neurons, or the peptides. On postnatal day 15 (P15), after two weeks without ethanol, the offspring showed increased expression of ENK in the PVN and NAC core but not shell, GAL in the PVN, and OX in the PFLH. In these same areas, prenatal ethanol compared to control increased the density at birth (P0) of neurons expressing these peptides and at P0 and P15 of neurons double-labeling BrdU and NeuN, indicating increased neurogenesis. These BrdU-positive neurons were found to express ENK, GAL and OX, indicating that prenatal ethanol promotes neurogenesis in these specific peptide systems. There were no changes in gliogenesis or apoptosis. This increase in neurogenesis and density of peptide-expressing neurons suggests the involvement of these hypothalamic and accumbal peptide systems in mediating the increased alcohol consumption observed in prenatal ethanol-exposed offspring.


Back to Table of Contents

93. OVEREXPRESSION OF SERUM RESPONSE FACTOR IN ASTROCYTES IMPROVES NEURONAL PLASTICITY IN A MODEL OF EARLY ALCOHOL EXPOSURE

Paul AP, Medina AE. Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, Richmond, VA 23298-0709, USA.

ABSTRACT

Neuronal plasticity deficits underlie many of the cognitive problems seen in fetal alcohol spectrum disorders (FASD). We have developed a ferret model showing that early alcohol exposure leads to a persistent disruption in ocular dominance (OD) plasticity. Recently, we showed that this deficit could be reversed by overexpression of serum response factor (SRF) in the primary visual cortex during the period of monocular deprivation (MD). Surprisingly, this restoration was observed throughout the extent of visual cortex and most of the cells transfected by the virus were positive...
for the astrocytic marker GFAP rather than the neuronal marker NeuN. Here we test whether overexpression of SRF exclusively in astrocytes is sufficient to restore OD plasticity in alcohol-exposed ferrets. To accomplish that, first we exposed cultured astrocytes to Sindbis viruses carrying either a constitutively active form of SRF (SRF+), a dominant negative (SRF-) or control Green Fluorescent Protein (GFP). After 24h, these astrocytes were implanted in the visual cortex of alcohol-exposed animals or saline controls one day before MD. Optical imaging of intrinsic signals showed that alcohol-exposed animals that were implanted with astrocytes expressing SRF, but not SRF- or GFP, showed robust restoration of OD plasticity in all visual cortex. These findings suggest that overexpression of SRF exclusively in astrocytes can improve neuronal plasticity in FASD.

Read Full Article,  


94. RECORDING A HISTORY OF ALCOHOL USE IN PREGNANCY: AN AUDIT OF KNOWLEDGE, ATTITUDES AND PRACTICE AT A CHILD DEVELOPMENT SERVICE

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Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, Australia. Raewyn.mutch@health.wa.gov.au

ABSTRACT

Aims: To assess the effectiveness of alcohol documentation, examining medical correspondence and medical files of patients referred to the State Child Development Service (SCDS) and (ii) To measure the knowledge, attitudes and clinical practice of health practitioners working at the child development service (CDS) in relation to asking about alcohol use in pregnancy.

Methods: Written documentation for children attending the State Child Development Centre (SCDC) in Western Australia were examined for documentation of alcohol use during pregnancy; a random sample of 40 medical records were examined and all correspondence authored by every paediatrician for the calendar year 2006 (n=210) were reviewed. (ii) A survey was completed of staff at the CDS, to assess their knowledge, attitudes, and clinical practice and their perceived importance of asking about alcohol and other drug use.

Results: Review of all written documentation, of both files and paediatric correspondence, found only three letters recording alcohol use in pregnancy; two of the letters recorded the index child displaying stigmata consistent with prenatal alcohol exposure, yet Fetal Alcohol Spectrum Disorders (FASD) were not considered within the concluding differential diagnoses. 56% of responding CDS staff (73% response) agreed it was important to ask about alcohol use when taking a pregnancy history, 20% indicated they routinely asked about alcohol exposure and 35% of staff said they never asked about alcohol use. 60% of the CDS staff completing the survey would welcome a proven technique to ask about alcohol use.

Conclusions: There is a gap in clinical practice within this CDS in asking and/or recording information about alcohol use in pregnancy. The majority of CDS staff who completed the survey agreed that asking about alcohol use in pregnancy was important and welcomed a proven technique to do so.

Read Full Article,  

Back to Table of Contents
95. VASCULAR EFFECTS OF MATERNAL ALCOHOL CONSUMPTION

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ABSTRACT
Maternal alcohol consumption during pregnancy is a significant field of scientific exploration primarily because of its negative effects on the developing fetus, which is specifically defined as fetal alcohol spectrum disorders. Though the effects on the mother are less explored compared with those on the fetus, alcohol produces multiple effects on the maternal vascular system. Alcohol has major effects on systemic hemodynamic variables, endocrine axes, and paracrine factors regulating vascular resistance, as well as vascular reactivity. Alcohol is also reported to have significant effects on the reproductive vasculature including alterations in blood flow, vessel remodeling, and angiogenesis. Data presented in this review will illustrate the importance of the maternal vasculature in the pathogenesis of fetal alcohol spectrum disorders and that more studies are warranted in this field.


Back to Table of Contents

96. AUSTRALIA'S DOUBLE STANDARD ON THAILAND'S ALCOHOL WARNING LABELS

O'Brien P.
Melbourne Law School, University of Melbourne, Melbourne, Victoria, Australia.

ABSTRACT
Introduction and aims: Since 2010, members of the World Trade Organization (WTO), including Australia, have opposed Thailand's proposal for graphic warnings on alcohol containers. This paper aims to provide an account of the arguments for/against Thailand and to examine the arguments' legal and political validity.

Design and methods: This paper reviews primary WTO records in relation to Thailand's proposal to reveal the arguments for/against Thailand's proposal. The paper analyses these arguments in light of WTO cases to identify the legal strengths and weaknesses of Thailand's position. The paper then considers whether the attacks on Thailand by Australia are justified in light of the Australian Government's position on (i) alcohol warning labels in Australia and (ii) tobacco plain packaging.

Results: The legal arguments against Thailand are: only harmful alcohol consumption should be prevented; there is no evidence that graphic warning labels can reduce alcohol-related harm; the labels unnecessarily restrict international trade. There are some legal weaknesses in Thailand's proposal. Yet, Australia's opposition to Thailand cannot be justified whilst Australia is (i) mandating pregnancy-related alcohol warnings in Australia and (ii) defending its plain packaging law against similar WTO attacks.

Discussion: No WTO member is obliged to challenge another member for being non-compliant. The case tests the willingness of WTO members like Australia to respect the autonomy of other countries to pursue their public health goals and trial novel interventions.

www.nofas-uk.org
Conclusions: Australia’s actions suggest it is willing to protect its alcohol industry at the expense of public health in Thailand.


Back to Table of Contents


97. THE EFFECT OF DIFFERENT ALCOHOL DRINKING PATTERNS IN EARLY TO MID PREGNANCY ON THE CHILD’S INTELLIGENCE, ATTENTION, AND EXECUTIVE FUNCTION

Kesmodel US, Bertrand J, Støvring H, Skarpness B, Denny CH, Mortensen EL; Lifestyle During Pregnancy Study Group. Department of Public Health, Section of Epidemiology, Aarhus University, Aarhus, Denmark. ukes@soci.au.dk

ABSTRACT
Objective: To conduct a combined analysis of the estimated effects of maternal average weekly alcohol consumption, and any binge drinking, in early to mid pregnancy on general intelligence, attention, and executive function in 5-year-old children.

Design: Follow-up study.

Setting: Neuropsychological testing in four Danish cities 2003-2008.

Population: A cohort of 1628 women and their children sampled from the Danish National Birth Cohort.

Methods: Participants were sampled based on maternal alcohol consumption during early pregnancy. At age 5 years, the children were tested for general intelligence, attention, and executive function. The three outcomes were analysed together in a multivariate model to obtain joint estimates and P values for the association of alcohol across outcomes. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy were adjusted for a wide range of potential confounding factors.

Main Outcome Measures: Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), the Test of Everyday Attention for Children at Five (TEACH-5), and the Behavior Rating Inventory of Executive Functions (BRIEF) scores.

Results: Multivariate analyses showed no statistically significant effects arising from average weekly alcohol consumption or any binge drinking, either individually or in combination. These results replicate findings from separate analyses of each outcome variable.

Conclusions: The present study contributes comprehensive methodological and statistical approaches that should be incorporated in future studies of low to moderate alcohol consumption and binge drinking during pregnancy. Furthermore, as no safe level of drinking during pregnancy has been established, the most conservative advice for women is not to drink alcohol during pregnancy. However, the present study suggests that small volumes consumed occasionally may not present serious concern.


Back to Table of Contents
98. **SAFETY CONCERNS REGARDING BINGE DRINKING IN PREGNANCY: A REVIEW**

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**ABSTRACT**

**Background:** There is ongoing debate about the risks to the fetus associated with maternal binge drinking. This makes it difficult to counsel patients about the potential risks associated with their use of alcohol during pregnancy.

**Methods:** This article reviews the literature on animal and human studies regarding binge drinking (four to five drinks at one time in humans, or the equivalent in laboratory animals).

**Results:** Animal studies provide evidence that high doses of alcohol over a short period of time can be more damaging than lower doses over a long period of time. Human data are more inconsistent, especially in terms of the association with malformations. Although neurobehavioral effects are the most commonly reported adverse outcome, some studies do not find such an association. Conclusions are confounded by the design of many studies, which fail to document pattern and total amount of alcohol consumption at one time. In addition, it has been suggested there is a bias against the null effect in publications.

**Conclusion:** Although the evidence in humans is not conclusive, the incidence of binge exposures in pregnancy is high, and it appears prudent to counsel patients to avoid this exposure whenever possible. Women inadvertently exposed to a single binge episode of alcohol early in the first trimester before pregnancy recognition can be reassured that the risks for adverse effects in their baby are likely low if they are able to discontinue use for the duration of the pregnancy. Unfortunately, there may be some residual fetal risk.


Back to Table of Contents

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99. **PROTECTIVE EFFECT OF EXOGENOUS NUCLEOTIDES ON THE DEVELOPMENTAL TOXICITY OF ALCOHOL**

Dong WH, Zhao J, Zhang JX, Xu LL, Xu YJ.
Department of Nutrition and Food Hygiene, Peking University School of Public Health, Beijing, China.

**ABSTRACT**

**Objective:** To investigate the preventive effect of exogenous nucleotide (EN) on the developmental toxicity of alcohol.
Methods: C57BL/6J pregnant mice were divided into 6 groups randomly: the control group, the alcohol group, the low (0.01%EN), middle (0.04%EN), high (0.16%EN) and higher (0.64% EN) intervention groups. From the 6th gestational days (GD) to the 15th GD, pregnant animals except those in the control group were administrated with 5 g (per kg body weight) alcohol intragastrically. Normal mouse forage was provided to the animals in the control group and alcohol group, while forage containing different quantities of EN was provided to the animals in the intervention groups. On GD 18, all the dams were killed, their blood samples were collected for further analysis, and fetal developmental indexes were observed.

Results: Compared with the animals in the alcohol group, offspring's body weight and placenta weight of EN intervention groups improved a lot; superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity increased significantly (P<0.05), malondialdehyde (MDA) levels decreased significantly (P<0.01); the live birth rate of animals in the interventions groups has increased significantly and the absorbed embryo rate of them has decreased significantly (P<0.01); the forepaw phalanges, hindpaw phalanges and caudal vertebrae ossification point increased significantly (P<0.01); the anomalies of both occipital and sternum have decreased significantly in 0.04%EN group (P<0.05).

Conclusion: EN has a significant protective effect on the developmental toxicity of alcohol.


Back to Table of Contents


100. PATHWAYS TO ALCOHOL-INDUCED BRAIN IMPAIRMENT IN YOUNG PEOPLE: A REVIEW


ABSTRACT

Classically, disorders associated with 'alcohol-related brain damage' (ARBD) occur as a result of chronic excessive alcohol misuse and confer significant physical and psychological disability to the individual as well as to the community. These phenotypes are often difficult to detect at early stages and therefore early intervention and treatment is limited. It remains unresolved as to whether there are neurobiological markers of the early stages of such brain damage in young 'at-risk' drinkers, who probably experience 'alcohol-induced brain impairment' prior to the onset of ARBD, per se. This review focuses on neurobiological (in particular, neuropsychological and neuroimaging) markers that are associated with alcohol misuse in young people (13-24 years of age). The findings from this review suggest that a clearer understanding of alcohol misuse (particularly with regards to binge drinking) is needed. Despite this, neurocognitive profile along with supporting neuroimaging evidence appears to be particularly important in the early detection of brain changes that result from excessive alcohol use.

In young alcohol misusers, these preventable and potentially reversible deficits may be progressive but if left unresolved such deficits eventually become major contributors to poor outcome (long term) and hamper adherence to treatment. We address five key themes in this review: (i) there are specific drinking patterns in young people; (ii) youth represents a critical period in brain development that is particularly vulnerable to alcohol misuse; (iii) the extent to which there are pre-existing versus alcohol-induced neurobiological changes remains unclear; (iv) vulnerability markers may be mediated by mental health and substance use comorbidities; and (v) cognitive remediation
would be a likely candidate for early prevention and treatment as it could help to develop efficient meta-cognitive skills to prevent relapse in young drinkers.

Read Full Article,

Back to Table of Contents


101. ROLE OF NON-CODING RNAs IN THE NEUROADAPTATION TO ALCOHOLISM AND FETAL ALCOHOL EXPOSURE
Reilly M.
Division of Neuroscience and Behavior, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health Rockville, MD, USA.

ABSTRACT
No Abstract Available

Read Full Article,

Back to Table of Contents


102. ETHANOL EXPOSURE ALTERS PROTEIN EXPRESSION IN A MOUSE MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS
Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

ABSTRACT
Alcohol exposure during development can result in variable growth retardation and facial dysmorphology known as fetal alcohol spectrum disorders. Although the mechanisms underlying the disorder are not fully understood, recent progress has been made that alcohol induces aberrant changes in gene expression and in the epigenome of embryos. To inform the gene and epigenetic changes in alcohol-induced teratology, we used whole-embryo culture to identify the alcohol-signature protein profile of neurulating C6 mice. Alcohol-treated and control cultures were homogenized, isoelectrically focused, and loaded for 2D gel electrophoresis. Stained gels were cross matched with analytical software. We identified 40 differentially expressed protein spots (P < 0.01), and 9 spots were selected for LC/MS-MS identification. Misregulated proteins include serotransferrin, triosephosphate isomerase and ubiquitin-conjugating enzyme E2 N. Misregulation of serotransferrin and triosephosphate isomerase was confirmed with immunologic analysis. Alteration of proteins with roles in cellular function, cell cycle, and the ubiquitin-proteasome pathway was induced by alcohol. Several misregulated proteins interact with effectors of the NF-κB and Myc transcription factor cascades. Using a whole-embryo culture, we have identified misregulated proteins known to be involved in nervous system development and function.

Read Full Article,

Back to Table of Contents
**103. EFFECTS OF THIRD TRIMESTER-EQUIVALENT ETHANOL EXPOSURE ON CL(-) CO-TRANSPORTER EXPRESSION, NETWORK ACTIVITY, AND GABAERGIC TRANSMISSION IN THE CA3 HIPPOCAMPAL REGION OF NEONATAL RATS**

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Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA.

**ABSTRACT**
Fetal alcohol spectrum disorders are often associated with structural and functional hippocampal abnormalities, leading to long-lasting learning and memory deficits. The mechanisms underlying these abnormalities are not fully understood. Here, we investigated whether ethanol exposure during the 3rd trimester-equivalent period alters spontaneous network activity that is involved in neuronal circuit development in the CA3 hippocampal region. This activity is driven by GABA(A) receptors, which can have excitatory actions in developing neurons as a consequence of greater expression of the Cl(-) importer, NKCC1, with respect to expression of the Cl(-) exporter, KCC2, resulting in high [Cl(-)](i). Rat pups were exposed to ethanol vapor from postnatal day (P) 2-16 (4 h/day). Weight gain was significantly reduced in pups exposed to ethanol compared to control at P15 and 16. Brain slices were prepared immediately after the end of the 4-h exposure on P4-16 and experiments were also performed under ethanol-free conditions at the end of the exposure paradigm (P17-22). Ethanol exposure did not significantly affect expression of KCC2 or NKCC1, nor did it affect network activity in the CA3 hippocampal region. Ethanol exposure significantly decreased the frequency (at P9-11) and increased the amplitude (at P5-8 and P17-21) of GABA(A) receptor-mediated miniature postsynaptic currents. These data suggest that repeated in vivo exposure to ethanol during the 3rd trimester-equivalent period alters GABAergic transmission in the CA3 hippocampal region, an effect that could lead to abnormal circuit maturation and perhaps contribute to the pathophysiology of fetal alcohol spectrum disorders.

**Read Full Article,**

**Back to Table of Contents**

---

**104. HEALTH PROFESSIONALS’ PERCEPTIONS ABOUT THE ADOPTION OF EXISTING GUIDELINES FOR THE DIAGNOSIS OF FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA**

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, Australia. rwatkins@ichr.uwa.edu.au

**ABSTRACT**
Background: Despite the availability of five guidelines for the diagnosis of fetal alcohol spectrum disorders (FASD), there is no national endorsement for their use in diagnosis in Australia. In this study we aimed to describe health professionals' perceptions about the adoption of existing guidelines for the diagnosis of FASD in Australia and identify implications for the development of national guidelines.

Methods: We surveyed 130 Australian and 9 international health professionals with expertise or involvement in the screening or diagnosis of FASD. An online questionnaire was used to evaluate participants’ familiarity with and use of five existing diagnostic guidelines for FASD, and to assess...
their perceptions about the adoption of these guidelines in Australia.

**Results:** Of the 139 participants surveyed, 84 Australian and 8 international health professionals (66.2%) responded to the questions on existing diagnostic guidelines. Participants most frequently reported using the University of Washington 4-Digit Diagnostic Code (27.2%) and the Canadian guidelines (18.5%) for diagnosis. These two guidelines were also most frequently recommended for adoption in Australia: 32.5% of the 40 participants who were familiar with the University of Washington 4-Digit Diagnostic Code recommended adoption of this guideline in Australia, and 30.8% of the 26 participants who were familiar with the Canadian guidelines recommended adoption of this guideline in Australia. However, for the majority of guidelines examined, most participants were unsure whether they should be adopted in Australia. The adoption of existing guidelines in Australia was perceived to be limited by: their lack of evidence base, including the appropriateness of established reference standards for the Australian population; their complexity; the need for training and support to use the guidelines; and the lack of an interdisciplinary and interagency model to support service delivery in Australia.

**Conclusions:** Participants indicated some support for the adoption of the University of Washington or Canadian guidelines for FASD diagnosis; however, concerns were raised about the adoption of these diagnostic guidelines in their current form. Australian diagnostic guidelines will require evaluation to establish their validity in the Australian context, and a comprehensive implementation model is needed to facilitate improved diagnostic capacity in Australia.

Read Full Article,  

Back to Table of Contents

Epub 2012 Jun 12.

105. PRENATAL ETHANOL EXPOSURE LEADS TO GREATER ETHANOL-INDUCED APPETITIVE REINFORCEMENT

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**ABSTRACT**

Prenatal ethanol significantly heightens later alcohol consumption, but the mechanisms that underlie this phenomenon are poorly understood. Little is known about the basis of this effect of prenatal ethanol on the sensitivity to ethanol's reinforcing effects. One possibility is that prenatal ethanol exposure makes subjects more sensitive to the appetitive effects of ethanol or less sensitive to ethanol's aversive consequences. The present study assessed ethanol-induced second-order conditioned place preference (CPP) and aversion and ethanol-induced conditioned taste aversion (CTA) in infant rats prenatally exposed to ethanol (2.0 g/kg) or vehicle (water) or left untreated. The involvement of the κ opioid receptor system in ethanol-induced CTA was also explored. When place conditioning occurred during the ascending limb of the blood-ethanol curve (Experiment 1), the pups exposed to ethanol in utero exhibited greater CPP than untreated controls, with a shift to the right of the dose-response curve. Conditioning during a later phase of intoxication (30-45 min post-administration; Experiment 2) resulted in place aversion in control pups exposed to vehicle during late gestation but not in pups that were exposed to ethanol in utero. Ethanol induced a reliable and similar CTA (Experiment 3) in the pups treated with vehicle or ethanol during gestation, and CTA was insensitive to κ antagonism. These results suggest that brief exposure to a moderate ethanol dose during late gestation promotes ethanol-mediated reinforcement and alters the expression of conditioned aversion by ethanol. This shift in the motivational reactivity to ethanol may be an underlying basis of the effect of prenatal ethanol on
later ethanol acceptance.

Read Full Article,

Back to Table of Contents


106. REDUCED SLEEP AND IMPAIRED SLEEP INITIATION IN ADULT MALE RATS EXPOSED TO ALCOHOL DURING EARLY POSTNATAL PERIOD

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Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. dvolgin@vet.upenn.edu

ABSTRACT

Prenatal alcohol exposure (AE) is associated with cognitive and neurobehavioral abnormalities, such as increased motor activity and elevated anxiety, that may last a lifetime. Persistent sleep disruption may underlie these problems. Using a rat model, we investigated long-term alterations of sleep-wake behavior following AE during a critical early developmental period. Male rats received 2.6 g/kg of alcohol intragastrically twice daily on postnatal days (PD) 4-9, a developmental period equivalent to the third trimester of human pregnancy (AE group), or were sham-intubated (S group). On PD52-80, they were instrumented for tethered electroencephalogram and nuchal electromyogram recording and habituated to the recording procedures. Sleep-wake behavior was then recorded during one 24 h-long session. Wake, slow-wave sleep (SWS) and rapid eye movement sleep (REMS) were scored in 10 s epochs during 6h of the lights-on (rest) and 6h of the lights-off (active) periods. During the active period, REMS percentage was significantly lower (4.7 ± 0.9 (SE) vs. 8.2 ± 0.9; p < 0.02) and the percentage of SWS tended to be lower (p = 0.07) in AE than S rats (N = 6/group). During the rest period, sleep and wake amounts did not differ between the groups, but AE rats had longer latency to both SWS and REMS onset (p = 0.02 and 0.003, respectively). Our data demonstrate that, in a rat model of prenatal AE, impaired sleep-wake behavior persists into the adulthood. Disordered sleep may exacerbate cognitive and behavioral disorders seen in human victims of prenatal AE.

Read Full Article,

Back to Table of Contents


107. SUPPLEMENTAL CHOLINE DURING THE PERIWEANING PERIOD PROTECTS AGAINST TRACE CONDITIONING IMPAIRMENTS ATTRIBUTABLE TO POST-TRAINING ETHANOL EXPOSURE IN ADOLESCENT RATS

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ABSTRACT

Supplemental choline during early stages of development can result in long-lasting improvements to memory function. In addition, pre- or postnatal choline has been shown to be protective against some of the adverse effects of early alcohol exposure. The present experiment examined whether supplemental choline given to rats would protect against the effects of posttraining alcohol administration on trace fear conditioning. Posttraining alcohol exposure in adolescent rats results in poor performance in this hippocampus-dependent task, although delay conditioning is unaffected.
Here, rats were given an s.c. injection of either saline or choline chloride daily on postnatal days (PD) 15-26. On PD 30 subjects were trained in a trace fear conditioning procedure. For the next 3 days animals were administered 2.5 g/kg ethanol or water control, and conditional stimulus (CS)-elicited freezing was measured on PD 34. Results indicated that posttraining alcohol disrupted the expression of trace conditioning and that supplemental choline on PD 15-26 was protective against this effect. That is, choline-treated animals subsequently given posttraining ethanol performed as well as animals not given ethanol. These results indicate that supplemental choline given during the periweaning period protects against ethanol-induced impairments in a hippocampus-dependent learning task. Findings contribute to the growing literature showing improvements in learning and memory in subjects given extra dietary choline during critical periods of brain development.


108. ALCOHOL DELAYS THE EMERGENCE OF THE FETAL ELICITED STARTLE RESPONSE, BUT ONLY TRANSIENTLY

Hepper PG, Dornan JC, Lynch C, Maguire JF.
Fetal Behaviour Research Centre, School of Psychology, The Queen's University of Belfast, Belfast, BT7 INN, UK.

ABSTRACT
Prenatal exposure to alcohol may exert a significant detrimental effect on the functioning of the individual's brain, however few studies have examined this before birth. This longitudinal study examined the effect of maternal alcohol consumption on the elicited startle response of the fetus. Two groups of fetuses were examined: one whose mothers drank alcohol (approximately 10 units per week); the other whose mothers did not drink alcohol. Fetuses were examined at 29, 32 and 35 weeks gestation and their startle response observed using ultrasound in response to 2 presentations of a pink noise (70-250Hz) at 90dB(A) separated by 30s. Fetuses exposed to alcohol exhibited a weaker startle response at 29 weeks gestation than did fetuses not exposed to alcohol. There was no difference in the response at 32 and 35 weeks gestation. To ensure that the effects were not due to a more general effect of alcohol on fetal movement, a second experiment compared the spontaneous movements (observed on ultrasound for 45 min) of fetuses whose mothers drank alcohol and fetuses of mothers who didn't drink alcohol. There were no differences in movements exhibited by the fetuses. The results suggest that exposure to alcohol delays the emergence of the elicited startle response at 29 weeks gestation but this delay has disappeared by 32 weeks gestation. The possible role of altered neural development, acute exposure to alcohol and disruptions to the fetus's behavioural repertoire, in mediating these effects are discussed.


109. IMPACT OF CHRONIC ETHANOL INTAKE OF RAT MOTHERS ON THE SEIZURE SUSCETIBILITY OF THEIR IMMATURE MALE OFFSPRING

Riljak V, Maresova D, Jandova K, Borrelova J, Pokorny J.
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ABSTRACT
The aim of present study was to examine the impact of prenatal ethanol exposure on seizure
susceptibility of the offspring. Pregnant Wistar rats were compelled to drink either 10% or 20% ethanol solution, as the only drinking fluid since conception up to the weaning of their offspring at the age of 28 days. Pregnant and nursing rats of the control group drank water. Electrophysiological experiments (repeated electrical stimulation and analysis of cortical afterdischarges duration) were than performed on their immature offspring. Rat pups were tested on postnatal day 18, 25, and 35. Shortening of afterdischarges duration was observed in 18-day-old animals (mothers drank 20% ethanol) when compared with age matched controls and failure of post-ictal depression phenomenon was found in 25- and 35-day-old animals. Our findings signalize that ethanol exposure during pregnancy influences seizure susceptibility by acting on excitatory/inhibitory brain systems and this effect is dose- and age-dependent.


Back to Table of Contents
111. COMPARISON OF SPATIAL WORKING MEMORY IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE AND THOSE DIAGNOSED WITH ADHD; A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY
Department of Physiology, University of Manitoba, 432 Basic Medical Sciences Bldg, 745 Bannatyne Ave, Winnipeg, MB R3E 0J9, Canada. Malisza@cc.umanitoba.ca.

ABSTRACT
Background: Alcohol related neurodevelopmental disorder (ARND) falls under the umbrella of fetal alcohol spectrum disorder (FASD), but individuals do not demonstrate the facial characteristics associated with fetal alcohol syndrome (FAS), making diagnosis difficult. While attentional problems in ARND are similar to those found in attention-deficit/hyperactivity disorder (ADHD), the underlying impairment in attention pathways may be different.

Methods: Functional magnetic resonance imaging (fMRI) of a working memory (1-back) task of 63 children, 10 to 14 years old, diagnosed with ARND and ADHD, as well as typically developing (TD) controls, was conducted at 3 T. Diffusion tensor imaging (DTI) data were also acquired.

Results: Activations were observed in posterior parietal and occipital regions in the TD group and in dorsolateral prefrontal and posterior parietal regions in the ARND group, whereas the ADHD group activated only dorsolateral prefrontal regions, during the working memory component of the task (1-back minus 0-back contrast). The increases in frontal and parietal activity were significantly greater in the ARND group compared to the other groups. This increased activity was associated with reduced accuracy and increased response time variability, suggesting that ARND subjects exert greater effort to manage short-term memory load. Significantly greater intra-subject variability, demonstrated by fMRI region-of-interest analysis, in the ADHD and ARND groups compared to the TD group suggests that moment-to-moment lapses in attention contributed to their poorer task performance. Differences in functional activity in ARND subjects with and without a diagnosis of ADHD resulted primarily from reduced activation by the ARND/ADHD + group during the 0-back task. In contrast, children with ADHD alone clearly showed reduced activations during the 1-back task. DTI analysis revealed that the TD group had significantly higher total tract volume and number of fibers than the ARND group. These measures were negatively correlated with errors on the 1-back task, suggesting a link between white matter integrity and task performance.

Conclusions: fMRI activations suggest that the similar behavior of children with ARND and ADHD on a spatial working memory task is the result of different cognitive events. The nature of ADHD in children with ARND appears to differ from that of children with ADHD alone.

Back to Table of Contents

112. EFFECTS OF ALCOHOL, LITHIUM, AND HOMOCYSTEINE ON NONMUSCLE MYOSIN-II IN THE MOUSE PLACENTA AND HUMAN TROPHOBLASTS
Han M, Neves AL, Serrano M, Brinez P, Huhta JC, Acharya G, Linask KK.
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ABSTRACT
Objective: Mouse embryonic exposure to alcohol, lithium, and homocysteine results in intrauterine
growth restriction (IUGR) and cardiac defects. Our present study focused on the placental effects. We analyzed the hypothesis that expression of nonmuscle myosin (NMM)-II isoforms involved in cell motility, mechanosensing, and extracellular matrix assembly are altered by the 3 factors in human trophoblast (HTR8/SVneo) cells in vitro and in the mouse placenta in vivo.

**Study design:** After exposure during gastrulation to alcohol, homocysteine, or lithium, ultrasonography defined embryos exhibiting abnormal placental blood flow.

**Results:** NMM-IIA/NMM-IIB are differentially expressed in trophoblasts and in mouse placental vascular endothelial cells under pathological conditions. Misexpression of NMM-IIA/NMM-IIB in the affected placentas continued stably to midgestation but can be prevented by folate and myoinositol supplementation.

**Conclusion:** It is concluded that folate and myoinositol initiated early in mouse pregnancy can restore NMM-II expression, permit normal placentation/embryogenesis, and prevent IUGR induced by alcohol, lithium, and homocysteine.


113. MOTION PERCEPTION IN CHILDREN WITH FOETAL ALCOHOL SYNDROME

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**ABSTRACT**

**Aim:** To evaluate the visual magnocellular pathway by a coherent motion perception test in children with foetal alcohol syndrome (FAS).

**Methods:** Eighty-nine children (49 with verified FAS and 40 without FAS) aged from 10 to 16 years were included into the study. Both the study and the control group were children living in orphanages. A coherent motion perception test was used. The test consisted of 150 white moving dots on a black background presented in different signal-to-noise ratio conditions. The task was direction detection of the coherently moving dots whose percentage decreased at each step.

**Results:** A significant difference between the two groups was found (p = 0.018). Children with FAS had lower coherent motion perception ability in all the signal-to-noise ratio conditions. A significant difference between difficulty levels (p < 0.001) was found for all subjects in both groups – decreasing the stimulus signal-to-noise level decreased the motion perception score. In both groups, the motion perception score differed for vertical and horizontal stimuli (p = 0.003) with better performance with vertical stimuli.

**Conclusion:** Impaired motion perception in FAS children could be indicative of a dorsal stream developmental dysfunction resulting from alcohol brain damage.

114. MATERNAL SMOKING AND ALCOHOL CONSUMPTION DURING PREGNANCY AS RISK FACTORS FOR SUDDEN INFANT DEATH

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ABSTRACT
A population based case control study was conducted to examine alcohol consumption and maternal smoking during pregnancy and the risk of SIDS in an Irish population. Each SIDS case (n = 287) was compared with control infants (n = 832) matched for date and place of birth for infants born from 1994 to 2001. Conditional logistic regression was used to investigate differences between Cases and Controls establishing Odds Ratio's (OR) and 95% Confidence Intervals (CI). Mothers who smoked were 3 times more likely to have a SIDS Case, and a dose response effect was apparent, with mothers smoking 1-10 cigarettes/day OR 2.93 (CI 1.50-5.71), and those smoking > 10 cigarettes/day OR 4.36 (CI 2.50-7.61). More Case mothers consumed alcohol during pregnancy than Control mothers and, within drinkers, the amount of alcohol consumed was also greater (p < 0.05). A dose response with frequency of drinking was apparent. The adjusted odds ratio for those consuming alcohol in all three trimesters was 3.59 (CI:1.40-9.20). Both of these risk factors are modifiable and need to be incorporated into antenatal education from a SIDS point of view.

Link to the Article, 

Back to Table of Contents

115. ELEVATION OF GM2 GANGLIOSIDE DURING ETHANOL-INDUCED APOPTOTIC NEURODEGENERATION IN THE DEVELOPING MOUSE BRAIN

Mitsuo Saito1,5, Goutam Chakraborty2, Relish Shah2, Rui-Fen Mao2, Asok Kuma3,5, Dun-Sheng Yang3,5, Kostantin Dobrenis4, Mariko Saito2,5
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ABSTRACT
GM2 ganglioside in the brain increased during ethanol-induced acute apoptotic neurodegeneration in 7-day-old mice. A small but a significant increase observed 2 h after ethanol exposure was followed by a marked increase around 24 h. Subcellular fractionation of the brain 24 h after ethanol treatment indicated that GM2 increased in synaptic and non-synaptic mitochondrial fractions as well as in a lysosome-enriched fraction characteristic to the ethanol-exposed brain.
Immunohistochemical staining of GM2 in the ethanol-treated brain showed strong punctate staining mainly in activated microglia, in which it partially overlapped with staining for LAMP1, a late endosomal/lysosomal marker. Also, there was weaker neuronal staining, which partially colocalized with complex IV, a mitochondrial marker, and was augmented in cleaved caspase 3-positive neurons. In contrast, the control brain showed only faint and diffuse GM2 staining in neurons. Incubation of isolated brain mitochondria with GM2 in vitro induced cytochrome c release in a manner similar to that of GD3 ganglioside. Because ethanol is known to trigger mitochondria-mediated apoptosis with cytochrome c release and caspase 3 activation in the 7-day-old mouse brain, the GM2 elevation in mitochondria may be relevant to neuroapoptosis. Subsequently, activated microglia accumulated GM2, indicating a close relationship between GM2 and ethanol-induced neurodegeneration.

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116. PREGNANT WOMEN AND ALCOHOL USE IN THE BOSOMTWI DISTRICT OF THE ASHANTI REGION-Ghana
Adusi-Poku Y, Edusei AK, Bonney AA, Tagbor H, Nakua E, Otupiri E.
District Health Directorate, Offinso North, Ashanti-Ghana.

ABSTRACT
Drinking alcohol in pregnancy is a serious public health concern worldwide. This study sought to determine the magnitude and socio-demographic characteristics of pregnant women attending Antenatal clinic in the Bosomtwe district, Ghana who drank alcohol and to assess their general knowledge about the effects of alcohol in pregnancy. The study, a descriptive cross-sectional, was conducted in all the ten health facilities providing reproductive health care with a sample size of 397 pregnant women using structured questionnaires. The findings of the study were that 20.4% of pregnant women drank alcohol. The 25-29 year group 26 (34.0%), married 50 (61.7%) and Junior High School Educated 37 (45.7%) as well as Christians 69 (85.0%) and traders 28 (34.6%) drank most. Majority 77 (33.5%) heard about the detrimental effects of alcohol at Antenatal Clinics (ANC). The District Health Management Team (DHMT) should strengthen health education on alcohol at ANC and through the radio as well as the DHMT collaborating with the Ghana Education Service to embark on education of school pupils and students on the harmful effects of alcohol in pregnancy.

Link to the Article,

117. EFFECTS OF ETHANOL EXPOSURE ON NERVOUS SYSTEM DEVELOPMENT IN ZEBRAFISH
Cole GJ, Zhang C, Ojiaku P, Bell V, Devkota S, Mukhopadhyay S.
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ABSTRACT
Alcohol (ethanol) is a teratogen that adversely affects nervous system development in a wide
range of animal species. In humans numerous congenital abnormalities arise as a result of fetal alcohol exposure, leading to a spectrum of disorders referred to as fetal alcohol spectrum disorder (FASD). These abnormalities include craniofacial defects as well as neurological defects that affect a variety of behaviors. These human FASD phenotypes are reproduced in the rodent central nervous system (CNS) following prenatal ethanol exposure. While the study of ethanol effects on zebrafish development has been more limited, several studies have shown that different strains of zebrafish exhibit differential susceptibility to ethanol-induced cyclopia, as well as behavioral deficits. Molecular mechanisms underlying the effects of ethanol on CNS development also appear to be shared between rodent and zebrafish. Thus, zebrafish appear to recapitulate the observed effects of ethanol on human and mouse CNS development, indicating that zebrafish can serve as a complimentary developmental model system to study the molecular basis of FASD. Recent studies examining the effect of ethanol exposure on zebrafish nervous system development are reviewed, with an emphasis on attempts to elucidate possible molecular pathways that may be impacted by developmental ethanol exposure. Recent work from our laboratories supports a role for perturbed extracellular matrix function in the pathology of ethanol exposure during zebrafish CNS development. The use of the zebrafish model to assess the effects of ethanol exposure on adult nervous system function as manifested by changes in zebrafish behavior is also discussed.

Read Full Article,  

Back to Table of Contents


118. DISORDERS OF NEUROGENESIS OF CORTICAL AND SUBCORTICAL STRUCTURES IN RAT BRAIN LIMBIC SYSTEM DURING FETAL ALCOHOL SYNDROME FORMATION
Svanidze IK, Museridze DP, Didimova EV, Sanikidze TV, Gegenava LG, Gvinadze NN.

ABSTRACT
Disorders of neurogenesis of cortical and subcortical structures in rat brain limbic system were studied in the offspring of rats that received ethanol during pregnancy. The methods used included the staining of histological sections with cresyl violet, in vitro culture, and electron paramagnetic resonance. Prenatal alcohol intoxication was shown to induce the disturbances in proliferative activity of granular layer cells in the hippocampal dentate gyrus, neuron- and glioblast migration, enhancement of free NO and lipoperoxide production and cell death. This resulted in the changes in the number of neurons in cortical and subcortical structures of rat brain limbic system and in fetal alcohol syndrome formation.

Link to the Article,  

Back to Table of Contents


119. A RODENT MODEL OF LOW- TO MODERATE-DOSE ETHANOL CONSUMPTION DURING PREGNANCY: PATTERNS OF ETHANOL CONSUMPTION AND EFFECTS ON FETAL AND OFFSPRING GROWTH
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ABSTRACT
It is unknown whether low to moderate maternal alcohol consumption adversely affects postnatal
The aim of the present study was to develop a rodent model of low-moderate-dose prenatal ethanol (EtOH) exposure. Sprague-Dawley rats were fed a liquid diet with or without 6% v/v EtOH throughout gestation and the pattern of dietary consumption determined. Fetal bodyweights and hepatic alcohol-metabolising gene expression were measured on embryonic Day (E) 20 and offspring growth studied until 1 year. At E8 the plasma EtOH concentration was 0.03%. There was little difference in dietary consumption between the two treatment groups. At E20, EtOH-exposed fetuses were significantly lighter than controls and had significantly decreased ADH4 and increased CYP2E1 gene expression. Offspring killed on postnatal Day (PN) 30 did not exhibit any growth deficits. Longitudinal repeated measures of offspring growth demonstrated slower growth in males from EtOH-fed dams between 7 and 12 months of age; a cohort of male pups killed at 8 months of age had a reduced crown-rump length and kidney weight. In conclusion, a liquid diet of 6% v/v EtOH fed to pregnant dams throughout gestation caused a 3-8% reduction in fetal growth and brain sparing, with growth differences observed in male offspring later in life. This model will be useful for future studies on the effects of low-moderate EtOH on the developmental origins of health and disease.


120. PREGNANT WOMEN AND MOTHERS USING ALCOHOL, TOBACCO AND ILLEGAL DRUGS
Nechanská B, Mravčík V, Sopko B, Velebil P.

ABSTRACT
This analysis is focused on use of addictive substances among women hospitalised during delivery or puerperium. Analysed data come from National Registry of Mothers at Childbirth and from National Registry of Newborns, which are managed by the Institute of Health Information and Statistics. Goal: To describe the prevalence of addictive substances use among women during gestation and to study its relation to health complications during pregnancy, delivery or puerperium and to health status of foetus and newborns. Methods and materials: The reporting to registries is provided in the Report on mother at childbirth and in the Report on newborn. Both registers provide basic socio-demographic information about mother, information about previous pregnancies and abortions, about current pregnancy, course of delivery, birth and neonatal treatment and health of newborn during hospitalization of mother during delivery or puerperium. Use of addictive substances is monitored in the National Registry of Mothers at Childbirth since 2000. Addictive substances are divided to tobacco, alcohol and drugs. Descriptive analysis of data was performed and binary logistic regression was used to test association of substance use with education and marital status (adjusted for age), analysis of variance was used to test association of substance use with selected health complications of pregnancy, delivery or puerperium and with health status of foetus/newborns (adjusted for age, education, marital status and interaction between addictive substances).Results: In 2000-2009, 1,008,821 mothers were reported of whom 60,502 women were registered as cigarette smokers, 1,528 used alcohol and 1,836 used other (illegal) drugs. Total of 1,027,200 newborns were reported. The average age of mothers using addictive substances were about 0.5-3 years lower in comparison with nonusers, in average mothers using illegal drugs were the youngest. Mothers using addictive substances were more often unmarried and had lower education than nonusers - almost 2/3 of mothers using addictive substances were unmarried or didn’t live in permanent partnership and more than 82% of mothers-users have lower education (primary or secondary school without a diploma). The association between substance use and induced and spontaneous abortions was observed only in smokers. Serious complications of pregnancy were associated with all monitored addictive substances - in mothers-smokers, a probability of serious complications were about 40 %, in users of illicit drugs about 13 % and in alcohol users about 5 % higher as compared to nonusers. Substance use showed almost no
association with problems during childbirth. Alcohol and illegal drugs use increased probability of complications in puerperium. Health status of foetus/newborn was negatively significantly altered mainly in those born to mothers-smokers in almost all observed characteristics. Mothers alcohol use during pregnancy was associated primarily with the overall health status of foetus immediately after delivery, congenital anomalies, stillbirth or need for treatment of newborn in the theatre. Infants of mothers using addictive substances had higher probability of consequent hospitalization after discharge from the neonatal department, transfer to infant home and death of infant. Conclusion: Association between complications during pregnancy, delivery and puerperium and health status of newborns and substance use of mothers during pregnancy was found mainly in cigarette smoking. Alcohol use was found significant in some (but serious) health problems of mothers and newborns. The association between illegal drugs and monitored indicators wasnt found. Following the results of this work, criteria for reporting of illegal drug use in mothers during pregnancy should be improved.

**Link to the Article,**

[Back to Table of Contents]
1. SECOND EUROPEAN CONFERENCE ON FASD  
European FASD Alliance  
Presented on October 21-24, 2012

Read Full Article,  
http://www.cjcp.ca/pubmed.php?articleId=390

Back to Table of Contents

2. THE POWER OF NETWORKING – HIGHLIGHTS OF THE WORK OF CANADA’S NETWORK ACTION TEAM ON FASD PREVENTION FROM A WOMEN’S HEALTH DETERMINANTS PERSPECTIVE

Poole, N  
BC Centre of Excellence for Women’s Health and the Canada FASD Research Network

ABSTRACT

Background: The aim of this presentation is to profile Canadian examples of FASD prevention activities from across research, policy, and practice which are linked through a Network Action Team (NAT) on FASD Prevention, funded by the Canada FASD Research Network. This poster will provide an overview of the virtual community of practice (CoP) model and illustrate the strategies that have allowed the NAT to work collaboratively across time and geographies.

Methods: Over the past six years, the NAT has been building a virtual network of over 40 researchers, health care/other service providers, community based advocates and parents, and decision makers/health system planners from across Canada. Team members lead academic and community-based research projects, hospital and community based programs, evaluation studies, a blog on women, alcohol, and pregnancy, and other local and national initiatives.

Results: The NAT has utilized a virtual Community of Practice model as a mechanism for knowledge exchange, engaging researchers, policy makers, civil servants, clinicians, community-based service providers, advocates, and women concerned with FASD prevention.

As the Network continues to grow with interest from new communities and stakeholders, additional strategies for maintaining effective working relationships and for ensuring the smooth uptake of knowledge into program and policy development are being explored.

Conclusion: Virtual and collaborative approaches to promoting women’s health can be an effective strategy for preventing FASD and allows researchers, policy makers, and advocates from multiple sectors to better address the range of proximal and distal factors that influence alcohol consumption during pregnancy.

Keywords: Virtual Community of Practice model, FASD prevention, collaborative and community-based programming

Source of funding for the study: Canada FASD Research Network

ARTICLE ABSTRACTS
3. NOW YOU SEE ME, NOW YOU DON’T – SERVICE DELIVERY TO FASD OFFENDERS IN SASKATCHEWAN COMMUNITY CORRECTIONS

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ABSTRACT

Background: FASD offenders involved in community corrections come with a variety of challenges. One of the challenges facing community corrections practitioners is how to best provide service to FASD offenders. What would the components of a service delivery program include in order to most effectively meet the needs of FASD offenders receiving existing services from Saskatchewan Community Corrections?

Methods: Utilizing case study methodology, this research explored the intersection of present day service delivery practice and proposed future practices as demonstrated by the Strategic Training Initiative in Community Supervision (STICS) project. Interview sampling of two sub-groups of research participants was employed. Conducting one-on-one interviews with those involved in the STICS project and the implementation of community corrections policies comprised the first sub-group. Interviews with those involved in the criminal justice system with FASD expertise (ie. lawyers, judges, police, etc.) comprised the second.

Results/Conclusion: Using a thematic network as a thematic analysis tool for qualitative data, this research identified limitations within community corrections and the STICS project that would need to be addressed to ensure success in providing community corrections service to FASD offenders.

Keywords: Community Corrections, Case Study, Thematic Analysis, Strategic Training Initiative in Community Supervision (STICS)

Source of funding: None

Conflict of Interest: The author declares no conflict of interest.

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Link to the Article, http://www.cjcp.ca/pubmed.php?articleId=382

Back to Table of Contents
EVERYDAY MEMORY IMPAIRMENTS IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDER

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ABSTRACT

Background: Everyday memory (EM) allows one to successfully perform real-world tasks across a variety of domains. An important component to successful use of EM involves an intrinsic motivational factor rooted in social cognition, such as not wanting to let someone down or understanding how another would feel. However, these social cognitive skills are often impaired in youth with FASD.

Despite its critical functional relevance, EM has received limited attention in relation to youth with FASD and may underlie some of the social difficulties that they experience. The current study explored whether significant differences exist in EM between youth with an FASD diagnosis compared with a typically developing control group.

Methods: A secondary analysis was conducted on scores of EM as measured by the Everyday Memory Questionnaire from youth between the ages of 9 and 15 years with an FASD diagnosis (N = 41) and a typically developing control group (N = 47). Non-parametric Mann-Whitney U Tests were performed for between group comparisons.

Results: Significantly lower scores were found across all domains of EM measured in youth with FASD, including retrieval memory, task monitoring, conversational monitoring, spatial memory, and memory for everyday activities (p<0.01 for all comparisons).

Conclusions: Poorer performance across a variety of EM skills were evident in youth with FASD compared with controls. Insight gained from this study will allow for a better understanding of the specific cognitive challenges faced by these youth and can have implications for guiding treatment and interventions to promote social functioning.

Keywords: Secondary data analysis, everyday memory, social cognition

Source of funding: Canadian Institute for Health Research (CIHR)

Conflicts of Interest: The authors declare no conflict of interest.

Student/Trainee: Presenting author Sabrina Agnihotri is a full-time Ph.D. student.

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Link to the Article,
http://www.cjcp.ca/pubmed.php?articleId=382

Back to Table of Contents
5. CORTICAL MORPHOLOGY IN CHILDREN WITH ALCOHOL RELATED NEURODEVELOPMENTAL DISORDER

Rajaprakash M¹,², Chakravarty MM¹,⁴,⁵, Lerch JP¹,³, Rovet J¹,²
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ABSTRACT

Background: Children exposed to alcohol in utero show reduced cortical volumes. However, the underlying determinants of these reductions have not been investigated in alcohol-related neurodevelopmental disorder (ARND), a prevalent fetal alcohol spectrum disorder subgroup that lacks marked facial dysmorphologies.

Methods: T1-weighted magnetic resonance imaging scans were obtained from 121 participants (8-16 years), 57 diagnosed with ARND and 64 typically developing controls. Scans were submitted to the CIVET pipeline (version 1.1.10). Group differences in cortical thickness, surface area, and gyrification were analyzed using a general linear model covaried for age, sex, acquisition protocol, and handedness.

Results: Groups did not differ significantly in cortical thickness. However, the ARND group showed reduced total brain volumes (p = 0.001); reduced grey matter volumes in bilateral frontal lobes (p = 0.002, p = 0.002), bilateral parietal lobes (p = 0.006, p < 0.001), and the right temporal lobe (p = 0.001); smaller surface areas in the bilateral frontal (p = 0.001, p < 0.001) and temporal lobes (p < 0.001, p < 0.001); and reduced total gyrification. Local reductions in surface area were observed in the right temporal lobe (p = 0.009), particularly in the right superior temporal gyrus and the right temporop-occipital region. A significant interaction between sex and group on global cortical grey matter volume (p = 0.048) and surface area (p = 0.034) was observed.

Conclusion: ARND is characterized by global reductions in cortical surface area and gyrification and females are more vulnerable than males to the teratogenic effects of alcohol.

Keywords: ARND, cortical thickness, MRI, surface area

Source of funding: Canadian Institutes of Health Research (200810MOP-203919, 101009MOP-229653, and NET-54014) to JR, and Hospital for Sick Children RESTRACOMP scholarship to MR.

Conflict of Interest: The authors declare no conflict of interest.

Student/Trainees: Meghna Rajaprakash is a Full-time MSc student at the University of Toronto

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Link to the Article,  
http://www.cjcp.ca/pubmed.php?articleId=382

Back to Table of Contents
6. SERVICE UTILIZATION PATTERNS AMONG CHILDREN AND ADOLESCENTS WITH PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDER

Kully-Martens K¹, Wyper K¹, Andrew G², Zwaigenbaum L², Tough S³, Rasmussen C²
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Department of Pediatrics, University of Alberta²;
Department of Pediatrics and Community Health Sciences, University of Calgary³

ABSTRACT

Background/Objectives: Although receiving services for developmental disabilities is a strong protective factor against negative outcomes in FASD, there is little research on service utilization patterns among individuals with FASD. The goal of the current study was to examine rates of service utilization among children with FASD and those with confirmed prenatal alcohol exposure (PAE) without an FASD diagnosis. Service utilization patterns were compared across diagnostic group, diagnostic assessment before age six vs. after age six, and residential location (urban vs. rural).

Methods: Caregivers of 46 children with FASD and 26 with PAE were interviewed using the Services for Children and Adolescents Parent Interview (SCAPI). The SCAPI collects information about child medication, individual child therapy, parent/family therapy, education services, parenting classes/groups, and parent medication. Questions about respite and early intervention were added.

Results: The most frequently used services among both diagnostic groups were education services, child medication, child therapy, and parenting classes. The groups differed in access to educational support (accessed more by FASD) and parenting classes/groups (accessed more by PAE). Children assessed before age 6 had better service access than those diagnosed later in areas of early intervention, parent/family therapy, and parent medication whereas a greater proportion of those diagnosed after age 6 accessed respite. Service access did not differ between urban and rural participants.

Conclusions: An FASD diagnosis instead of just confirmed PAE does not generally seem to increase overall rates of service utilization. Furthermore, geographic location has little effect on service utilization. However, being diagnosed before age six appears to be associated with better service access.

Keywords: FASD, prenatal alcohol exposure, service use

Source of funding: Canadian Institutes of Health Research (CIHR)

Conflict of Interest: The authors declare no conflict of interest

Student/Trainee: K. Kully-Martens is a Master's student at the University of Alberta

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Link to the Article, http://www.cjcp.ca/pubmed.php?articleId=382

Back to Table of Contents
7. EXAMINING THE VALIDITY OF THE ASANTE FASD SCREENING AND REFERRAL TOOL FOR YOUTH PROBATION OFFICERS IN JUSTICE INVOLVED YOUTH

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Simon Fraser University²

ABSTRACT

Background: The need for FASD assessment and diagnostic services is high in justice settings where rates of prenatal alcohol exposure (PAE) appear prevalent. However, diagnostic capacity and resources are scarce, underscoring the need for valid screening tools to identify individuals appropriate for complete assessments.

Objective: To assess the sensitivity, specificity, and predictive values of the Asante FASD Screening and Referral Tool (AST) in justice involved youth.

Method: The AST was completed for 100 justice-involved youth ages 12 – 23 (M = 17.53, SD = 1.59, 81.0% male), 50 with an FASD diagnosis and 50 without PAE, by unblinded raters. Sensitivity and specificity coefficients were calculated according to the AST referral algorithm (one social factor plus ≥ two personal factors, or, no social factors plus ≥ three personal factors).

Results: Of the 50 youth diagnosed with FASD, 46 screened positive for further assessment using the AST referral decision tree, while 15 youth without PAE screened positive. Sensitivity and specificity values for the AST were 92% (CI .80 -.97) and 70% (.55 - .82), respectively, producing a positive predictive value of .75 (CI .62 -.85), negative predictive value of .90 (CI .75 -.97), false positive rate of .25 (CI .15 -.38), and false negative rate of .10 (CI .03 -.25).

Conclusions: Overall, findings suggest the AST showed strong clinical utility in identifying youth with a confirmed diagnosis of FASD. Results support the need for further efforts to validate the AST prospectively using full assessments following screening.

Keywords: Diagnostic screening; FASD; Youth justice

Source of funding: Canadian Foundation on Fetal Alcohol Research; Social Sciences and Humanities Research Council of Canada, Michael Smith Foundation for Health Research; BC Mental Health and Addictions

Conflict of Interest: The authors declare no conflict of interest

Student/Trainee: No (Postdoctoral Fellow).

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Link to the Article, http://www.cjcp.ca/pubmed.php?articleId=382

Back to Table of Contents
8. IMPROVING OUTCOMES FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER IN CARE

McHenry SA, Cheng J, Popham J, Muhajarine N
University of Saskatchewan

ABSTRACT

Background/Objectives: Foster parents frequently experience challenges associated with parenting children with FASD that may result in negative outcomes such as instability and multiple placements. In Saskatchewan, there is a need for foster parents to have a better understanding of FASD in order to improve the outcomes of children in care.

Methods: The Saskatchewan FASD Support Network developed and initiated a half-day training on FASD for foster/adoptive parents. A program evaluation using mixed methods was conducted to identify baseline measures and to determine the efficacy of the program. A pre/post test was administered to parents to establish the short-term impact of the program. Phone interviews and focus groups were conducted two months later to illustrate the experiences of parents as they utilized the skills gained during the training.

Results: A total of 67 participants attended training sessions. Only 36% had received any training prior to the program and the majority of parents rated their current knowledge of FASD as fair or poor. The training session improved parent’s knowledge in several important areas: general knowledge of FASD; the lived experience of FASD; primary and secondary disabilities; and building supports and strategies. During the focus groups, parents also indicated that they were interested in learning more about agespecific behavioral strategies and ways in communicating about FASD with others.

Conclusion/Discussion: The results from the program evaluation will be used to develop recommendations for best practices and improve outcomes for children with FASD in foster care further developing their training program.

Keywords: FASD, Program evaluation, Health education

Source of funding: Mitacs, Saskatchewan FASD Support Network

Acknowledgement: The work of the Saskatchewan FASD Support Network and contributions by Sarah Nordin, Lisa Mooney and Fleur Macqueen Smith are gratefully acknowledged.

Conflict of Interest: The authors declare no conflict of interest

Student/Trainee: Full-time students

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Back to Table of Contents
9. UNDERSTANDING THE EFFICACY OF TREATMENT OF SLEEP DISORDERS AMONG CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER AND PRENATAL ALCOHOL EXPOSURE
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University of Saskatchewan

ABSTRACT

Background/Objectives: The prevalence of sleep disturbances (SD) among children with FASD is significantly higher than those without. Due to the intricate relationship between the CNS and sleep processes, high rates are not surprising. SDs are strongly linked to cognitive, psychiatric, behavioural, and physical health problems. Parents with children with SDs have been found to have higher stress levels.

Methods: A systematic search of research was performed using popular research databases, and a hand/reference list search. Original reference criteria for inclusion in the review were: publication date (2001+), language (English/French/German), human, study population (FASD), design (clinical/epidemiological/genetic/pharmaceutical), and outcomes (quality of life/drug effect/psychiatric or behavioural impact/adverse impacts/family functioning). Due to a low number of articles included in the review, criteria relaxed to include: population (FASD/PAE), study (human/animal), and topic (SDs).

Results: The original search produced n=159 articles. Of these, only n=3 met criteria. In the secondary search of human studies n=10 of n=157 possible articles and n=14 out of n=60 animal articles were reviewed. The majority of human articles were descriptive, focusing on prevalence and sleep characteristics. The most rigorous human study found a relationship between sensory problems and increased levels of SDs. Findings from animal studies tended to focus on disruptions to the circadian system.

Conclusion/Discussion: Research established that children with FASD/PAE have a higher likelihood of SDs. Preliminary evidence indicates interventions emphasizing circadian rhythm systems and sensory processing difficulties may be effective. Overall, little empirical research exists and future research should rigorously study outcomes/validate practical strategies that are most significant with individuals with FASD/caregivers/families.

Keywords: FASD/PAE, review, sleep disorders

Source of funding: NeuroDevNet Knowledge Translation Core

Conflict of Interest: The authors declare no conflict of interest

Student/Trainee: Full-time students

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Back to Table of Contents
ABSTRACT

**Background/Objectives:** Among those most vulnerable lacking identification as well as access to services for special learning needs are children with FASD. Overarching research questions initially proposed by the interdisciplinary research team and community partners are: (1) what are effective screening tools for FASD and literacy for use in educational contexts in Saskatchewan and (2) how to collaboratively develop a methodology using screening tools to determine the prevalence of patterns of reading and literacy skills in students with FASD. Active case ascertainment prevalence data are required in planning access to diagnosis as well as to interventions in order to ameliorate adverse outcomes for learners with FASD. With further team collaboration, research objectives were refined as follows: (1) to review and evaluate literacy screening tools suitable for learners with diagnoses within FASD; and (2) to develop capacity to pilot and implement a methodology to estimate the prevalence and patterns of dynamic, multimodal literacy skills in learners with FASD with which to inform learning and life skills interventions.

**Methods:** An interactive, multi-modal, dynamic literacy assessment protocol and scoring rubric was proposed as an optimal diagnostic screening tool for grades three to six students having existing FASD diagnoses. This qualitative protocol was selected due to its demonstrated capacity to accommodate challenges with memory, sequencing, abstractions, sensory issues, and attention which often characterize these students.

**Conclusion/Discussion:** Collaborative planning and communication among researchers, community members, Aboriginal Elders, school personnel and parents or caregivers were found to be key to planning, piloting and beginning to implement this project, and to future research collaborations.

**Source of funding:** Saskatchewan Health Research Foundation (SHRF) Phase I Development Grant

**Conflict of Interest:** The authors declare no conflict of interest

**Student/trainee:** Post-Doctoral researcher full time

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**Link to the Article,**
http://www.cjcp.ca/pubmed.php?articleId=382

[Back to Table of Contents]
A. FETAL ALCOHOL EXPOSURE AFFECTS BRAIN STRUCTURE IN CHILDREN

CHICAGO – Children exposed to alcohol during fetal development exhibit changes in brain structure and metabolism that are visible using various imaging techniques, according to a new study being presented today at the annual meeting of the Radiological Society of North America (RSNA).

Alcohol use by expectant mothers can lead to problems with the mental and physical development of their children—a condition known as fetal alcohol syndrome. Research suggests an incidence of 0.2 to 1.5 per 1,000 live births, according to the Centers for Disease Control and Prevention. Costs for care of individuals affected by fetal alcohol syndrome in the U.S. have been estimated at $4 billion annually.

Advancements in magnetic resonance imaging (MRI) are affording unprecedented insights into the effects of alcohol on the central nervous systems of children whose mothers drank alcohol during their pregnancy. Recently, researchers in Poland used three different MRI techniques to better define these effects.

The study group included 200 children who were exposed to alcohol during their fetal stage and 30 children whose mothers did not drink while pregnant or during lactation. Researchers used MRI to evaluate the size and shape of the corpus callosum, the bundle of nerve fibers that forms the major communication link between the right and left halves of the brain, in the two groups. Prenatal alcohol exposure is the major cause of impaired development or complete absence of the corpus callosum.

The MRI results showed statistically significant thinning of the corpus callosum in the children exposed to alcohol compared with the other group.

"These changes are strongly associated with psychological problems in children," said Andrzej Urbanik, M.D., chair of the Department of Radiology at Jagiellonian University in Krakow, Poland.

Dr. Urbanik and colleagues also used diffusion weighted imaging (DWI) to study six areas of the central nervous system in the children. DWI maps the diffusion process of water and can be a more sensitive means than traditional MRI for detecting tissue abnormalities.

Children in the alcohol group exhibited statistically significant increases in diffusion on DWI compared with the other children.

"The increase of diffusion indicates neurological disorders or damage to the brain tissue," Dr. Urbanik said.

To noninvasively study metabolism in the brains of the children, the researchers used proton (hydrogen) magnetic resonance spectroscopy (HMRS), a common adjunct to structural MRI studies. HMRS results showed a complex collection of metabolic changes.

"In individual cases, we found a high degree of metabolic changes that were specific for particular locations within the brain," Dr. Urbanik said.
Coauthors are Teresa Jadczak-Szumiło, M.Sc., Monica Nardzewska-Szczechpanik, M.D., Paulina Karcz, M.Sc., and Justyna Kozub, M.Sc.

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Link to the Article,

By Brian Kelly, Sault Star
Saturday, November 17, 2012 9:34:51 EST AM

B. COLLEGE LAUNCHES FETAL ALCOHOL PROGRAM

Sault College will offer the first post-graduate certificate for professionals who work with people with fetal alcohol spectrum disorder.

The one-year program will be available online through the college's continuing education department starting in September 2013.

It targets health, education, social services, child care and criminal justice workers, vice-president academic Leo Tiberi told the college's board of governors on Thursday.

FASD is the most common disability in Canada with about 130,000 affected in Ontario alone, he said. It's caused when women drink during pregnancy and can result in their children developing physical, mental, cognitive and behavioural disabilities.

Most training available now is done by service organizations through workshops and seminars.

"There is no standardized formal curriculum offered by colleges or universities," Tiberi told the board during his presentation.

Sault College began exploring the program offering in 2006 when it began talks with various agencies. A partnership with the North Bay-based Anishinabek Educational Institute started in June 2011 helped develop the post-graduate certificate.

"There is a need in our province to provide education that will enhance FASD prevention and better prepare Ontario professionals to support individuals and families living with FASD," said Tiberi.

"This is a groundbreaking interdisciplinary initiative for educating persons working (in the fields of) health, education, child care, social services and criminal justice."

Courses include FASD overview, brain and behaviour, developmental and learning disabilities, support strategies and practicum.

On the web: www.saultcollege.ca
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Back to Table of Contents
C. TWO CHICAGO STUDENTS DEVELOP NOVEL TREATMENT METHOD FOR FETAL ALCOHOL SYNDROME

Two Chicago high school students have developed a novel treatment method to reduce the negative effects of Fetal Alcohol Syndrome (FAS) and a new understanding of genetics behind the disease. This research is being presented at the 2012 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition in Chicago, Ill., Oct. 14 - 18. More than 8,000 attendees are expected at the largest conference dedicated to the pharmaceutical sciences.

Ayana Jamal and Ariella Hoffman-Peterson, 2012 graduates of Niles North High School in Skokie, Ill., represent two of the youngest researchers presenting at the conference. Jamal, a freshman at University of Illinois, and Hoffman-Peterson, a freshman at Northwestern University, worked alongside F. Bryan Pickett, M.A., Ph.D., associate professor at Loyola University Chicago, to complete their FAS research projects in high school.

Jamal's research, which determined a novel way to reduce the negative effects of alcohol on a zebrafish's development, concluded that there is strong evidence that retinoic acid can be used as a potential FAS treatment. While not in the lab during her summers or weekends, Jamal participated in several other activities, including playing softball, writing for her student newspaper, mentoring freshmen and teaching Sunday school.

"I first became interested in doing my own science research with the encouragement of one of my teachers during freshman year," said Jamal. "I'm excited to be able to experience a professional scientific meeting like AAPS, and to be among scientists who conduct this pharmaceutical research every day."

Hoffman-Peterson also conducted her research in zebrafish embryos. She studied the RALDH2 gene, whose function is closely tied to FAS because alcohol competes for the activity of this gene. She looked at the nearby so-called "junk DNA" to explore whether it had an active role in the gene's pathways. Outside of the science classroom, Hoffman-Peterson was on her school’s dance team and taught at religious school.

"I always knew I wanted to work in the science and medical field. My inspiration came from my grandfather who was a doctor," said Hoffman-Peterson. "I've presented my research at different student competitions, but this is my first experience at AAPS."

Source: American Association of Pharmaceutical Scientists

Link to the Article,

Back to Table of Contents
Fetal Alcohol Exposure and IQ at Age 8: Evidence from a Population-Based Birth-Cohort Study

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Abstract

Background: Observational studies have generated conflicting evidence on the effects of moderate maternal alcohol consumption during pregnancy on offspring cognition mainly reflecting problems of confounding. Among mothers who drink during pregnancy fetal alcohol exposure is influenced not only by mother’s intake but also by genetic variants carried by both the mother and the fetus. Associations between children’s cognitive function and both maternal and child genotype at these loci can shed light on the effects of maternal alcohol consumption on offspring cognitive development.

Methods: We used a large population based study of women recruited during pregnancy to determine whether genetic variants in alcohol metabolising genes in this cohort of women and their children were related to the child’s cognitive score (measured by the Weschler Intelligence Scale) at age 8.

Findings: We found that four genetic variants in alcohol metabolising genes in 4167 children were strongly related to lower IQ at age 8, as was a risk allele score based on these 4 variants. This effect was only seen amongst the offspring of mothers who were moderate drinkers (1–6 units alcohol per week during pregnancy (per allele effect estimates were $-1.80 \ (95\% CI = -2.63 to -0.97) p = 0.00002$, with no effect among children whose mothers abstained during pregnancy $(0.16 \ (95\% CI = -1.05 to 1.36) p = 0.80)$. A further genetic variant associated with alcohol metabolism in mothers was associated with their child’s IQ, but again only among mothers who drank during pregnancy.


Introduction

The public health burden associated with alcohol use includes any adverse outcomes experienced by children whose mothers used alcohol during pregnancy. The deleterious effects of heavy maternal alcohol use on offspring outcomes are well established [1] however effects of more moderate use are less clear. Official guidelines on safe drinking during pregnancy appear contradictory on this point, with some advocating complete abstinence and others suggesting that moderate use is safe (http://www.icap.org/Table/InternationalGuidelinesOnDrinkingAndPregnancy).

A recent systematic review of findings from observational studies found no consistent evidence of adverse effects from low-to-moderate prenatal alcohol consumption [2], as did an even more recent study of a population-based cohort examining this issue [3,4]. Interpreting observational evidence on effects of maternal alcohol use on offspring outcomes is complicated by the issue of confounding. In particular, complete abstinence from alcohol is often associated with other maternal characteristics that may adversely influence offspring outcomes [5] whilst moderate alcohol use is often associated with characteristics that may exert independent beneficial effects. Statistical adjustment for confounding of this nature is notoriously difficult. The alternative of a randomized controlled trial (RCT) would be unethical, unless this were an RCT of an intervention to stop drinking during pregnancy and then there would be uncertainty surrounding its effectiveness. Quasi experimental designs may be useful to progress the evidence in this area. One novel approach, Mendelian randomization, provides an alternative method for investigating the causal nature of early life influences on later diseases [6,7]. Associations between genetic variants and disease are not generally susceptible to confounding by lifestyle factors [8] and genetic variants which influence exposure to alcohol by affecting the ability to metabolise alcohol, should not be subject to confounding by smoking, diet and other lifestyle factors.

The conversion of ethanol to acetaldehyde is catalysed primarily by a group of 5 alcohol dehydrogenases (ADH) enzymes (ADH1A,
ADH1B, ADH1C, ADH4, ADH7), which are expressed in a tissue and time specific manner. The genes encoding these enzymes are clustered together in a 380 kb region on the long arm of chromosome 4. Genetic variation has been reported in these genes leading to differences in the ability to metabolise ethanol [9]. In slow metabolisers, peak alcohol levels may be higher and persist for longer than in fast metabolisers. It is hypothesized that alleles which result in “fast” metabolism of ethanol will protect against abnormal brain development in infants. The importance of peak which result in “fast” metabolism of ethanol will protect against abnormal brain development in infants. The importance of peak blood alcohol concentration has been demonstrated in animal and human studies of neuro-behavioural outcomes in offspring exposed to ethanol during fetal life [10–12]. Until recently there had only been a handful of studies which have looked at associations of ADH genotypes and alcohol-related infant outcomes. These studies have tended to focus on mothers who drank heavily during pregnancy and possibly due to very small sample sizes have produced conflicting results [13–18].

The principal exposure to alcohol in young children is likely to have occurred during fetal life. If the alcohol dose reaching the fetus is influenced by ADH genotype as discussed above then it should be possible to detect genotype effects on cognitive outcomes. Such effects should only be seen in offspring of women who report alcohol use during pregnancy (assuming such reporting is accurate) and their presence if detected in moderate alcohol users would provide further evidence that even moderate alcohol use can adversely affect childhood cognition. Because we do not know the relative contributions of maternal and fetal enzymes in metabolising alcohol in fetal life and it is likely that both contribute to overall alcohol exposure, we studied the effects of both maternal and child genotype on childhood cognitive outcomes. Analyses were stratified according to whether mothers consumed low-to-moderate amounts of alcohol during pregnancy or whether they abstained. This was done to test our hypothesis that an association between ADH genotype and cognitive outcomes would only exist in the former group, but would not be present in mothers who did not drink.

Methods

Ethics Statement

Ethical approval came from the Avon Longitudinal Study of Parents And Children (ALSPAC) Law and Ethics Committee (IRB 00003312) and the four Local Research Ethics Committees (LREC), Southmead, Frenchay and Bristol and Weston Health Authorities. Informed written consent was obtained from participants in this study, and from the parents of children in this study.

Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based prospective study investigating environmental and other factors that affect the health and development of children. The study methods are described in detail on the study website (http://www.alspac.bris.ac.uk). In brief, pregnant women living in three health districts centred in and around the city of Bristol, England who had an expected date of delivery between the start of April 1991 and the end of December 1992 were eligible. 14,541, approximately 85% of those eligible [19], enrolled in the study, and of these, 13,622 (95%) had a singleton, live born child. Detailed information was obtained from the mother throughout pregnancy and information on both the mother and child has been collected at regular intervals, and is ongoing.

Measurement of Alcohol Intake

At 18 weeks’ gestation women were asked to complete a questionnaire, which included questions on their average amount and frequency of alcohol consumption before the current pregnancy, during the first trimester and in the previous 2 weeks or at the time when they first felt the baby move. One drink was specified as one unit of alcohol (corresponding to an ethanol content of approximately 8 grams), and women were asked to recall their frequency of drinking as never, <1 unit/week, ≥1 unit/week, 1–2 units/day, 3–9 units/day, or 10+ units/day. Around 32 weeks of gestation women completed another questionnaire in which they were asked about their average weekday and weekend alcohol consumption, from which weekly intake was derived. Any woman who reported drinking even if it was less than 1 unit/week either in the first trimester or when they felt the baby first move was classified as drinking during pregnancy. Women who reported drinking some alcohol at 32 weeks were also classified as drinkers, however women for whom this questionnaire was missing were not excluded from the stratified analysis, but coded according to their drinking status during the first trimester and when the baby first moved. At approximately 18 and 32 weeks of pregnancy women were also asked on how days during the past month they had drank 2 pints of beer (or the equivalent amount of alcohol), any women who reported doing this on at least one occasion was classified as a binge drinker in our analysis of the association between genotype and binge drinking. We excluded 269 women who reported drinking >6 units per week at any point during pregnancy from our main stratified analyses, because we were interested in the effect of moderate alcohol intake of the mothers during pregnancy on child IQ scores rather than the effects of heavy drinking.

Measurement of Cognition

Cognitive testing was carried out during a clinic visit of children at age 8 year using a shortened version (which is described in detail elsewhere [20]) of the Wechsler Intelligence Scale for Children (WISC-III) from which an overall age adjusted total score was derived [21].

Measurement of Potential Confounders

Data on selected characteristics from mothers and their partners was used to conduct a sensitivity analysis adjusting for potential confounding factors. Maternal age at delivery was calculated from dates of birth of the mother and baby. Other data were obtained by questionnaires administered to the mother during pregnancy. Family social class was derived as the highest social class of the mother or her partner, which was based on occupation and determined according to the 1991 British Office of Population Statistics classification. This was dichotomised as manual or lower versus higher. Mother’s education was dichotomised as at most Ordinary Level (O-level) or equivalent versus higher. The O-level was an exam-based qualification for students aged 14–16 years, which was replaced by the General Certificate of Secondary Education (GCSE) in 1988 in the UK. Further details are available at http://www.direct.gov.uk/en/EducationAndLearning/QualificationsExplained/DG_10039924.

Genotyping

Ten Single Nucleotide Polymorphisms (SNPs) in 4 ADH genes (ADH1A rs4699714, rs3763894, rs1448834, ADH1A rs2866151, rs975833, rs1229966, ADH1B rs2066701, rs147536, rs1229984 and ADH7 rs284779) were selected for genotyping on the basis of literature searches either because they had previously been shown
to be associated with alcohol metabolism, intake or dependency or because they were haplotype tagging SNPs. SNPs were genotyped by KBioscience [http://www.kbioscience.co.uk] using the KASPar chemistry, a competitive allele-specific PCR system using FRET quencher cassette oligos [http://www.kbioscience.co.uk/ genotyping/genotyping-chemistry.html]. Blind duplicates and Hardy-Weinberg equilibrium tests were used as quality control checks. Genotyping success rate was above 93.3% and error rate from duplicates was below 0.25% for all SNPs.

Ethnicity of Participants

Women and children of white-European origin only were included to avoid population stratification, as many polymorphisms in the ADH genes differ markedly across different populations [22], and patterns of alcohol drinking are culturally dependent. Ethnicity was available from self-report or had been imputed from five genetic ancestry-informative markers [23].

Statistical Analysis

Deviation of genotype counts from Hardy Weinberg equilibrium (HWE) was tested by Pearson’s χ² test using the genhwi command in STATA. For all our rs1229984-outcome analyses we grouped rare homozygotes and heterozygotes together and assumed a dominant effect (as the minor allele frequency (MAF) for rs1229984 was <0.05), our previous analysis of this SNP on alcohol intake suggested this was appropriate [23]. All other SNPs were consistent with a per rare allele effect and so we report per allele effects. Associations between maternal genotype and drinking at 18 weeks of pregnancy have been presented in our earlier paper [23] so we also looked at the effects of FET scores as the outcome. A likelihood ratio test of interaction between number of risk alleles and maternal genotype and maternal binge drinking at 18 weeks to determine whether any effects we detected were due to metabolism or due to changes in alcohol intake. We tested associations between overall WISC score at age 8 and genotype using linear regression models, as WISC score was found to be approximately normally distributed. We looked at mother’s genotype and child’s genotype separately as we did not know which was more important in determining the exposure of the fetus to alcohol. This analysis was stratified by whether or not mothers reported drinking alcohol during pregnancy.

Sensitivity Analyses

The potential for confounding was determined by carrying out sensitivity analyses in which our models were adjusted by the following factors: mother’s education, mothers’ smoking, gestational age of the child, age of the mother at delivery, mother’s marital status, parity, mother’s partners alcohol consumption, social class of the mother and her partner, and also by 5 ancestry informative markers with established population-specific allelic distributions—rs715598 and rs1726966 in TAS2R38 [24], rs4988235 in MCM6 [25], A44771G in ASPM [26] and rs930557 in CPB1 [26].

Stepwise Selection of Genetic Variants

Overall exposure to alcohol in utero is likely to be determined not by a single genetic variant in this region, but by several maternal and/or offspring genetic variants within this pathway. In order to account for this and for linkage disequilibrium in the area, which may lead to confounding between genotypes, we used Akaica’s Information Criterion [27] to carry out a backwards stepwise selection of all child genotypes based on WISC score at age 8, in which all genotypes were initially entered into the model and then eliminated in turn based on the goodness of fit of the model, the purpose of which was to find the minimum set of markers which were associated with WISC score after taking into account linkage disequilibrium between the SNPs. Moreover, since offspring genotype is determined by alleles inherited from the mother and from the father and so will reflect mother’s genotype to a certain extent we repeated this stepwise selection including all mother and child genotypes in the model, to determine the minimal set of genetic variants (whether from the mother or the fetus) which were independently associated with overall WISC score at age 8.

Linkage Disequilibrium Analysis

Pair-wise linkage disequilibrium (LD) across the SNPs was computed in mothers using haplview [http://www. broadinstitute.org/scientific-community/science/programs/ medical-and-population-genetics/haplview/haplview] [28].

Test of Interaction between Number of Risk Alleles and Alcohol Intake in the Mothers

We took the four SNPs which were selected as being related to WISC score among children using Akaica’s Information Criterion (ADH17 rs284779, ADH1B rs4147536 ADH1A rs975833 and ADH1A rs2866151) and constructed a genotype score based on the number of rare alleles a child carried across the four loci, given that at each loci a child could carry zero, one or two rare alleles. We carried out an analysis of this score on WISC at age 8 stratified by alcohol intake (any versus none) during pregnancy. When we had constructed our genotype score we found that most children (3939/4167, 94.5%) had a total of two, three or four ‘risk’ alleles across these sites, only eight out of 4167 children had no ‘risk’ alleles at this site, with 195 children having one risk allele and only 25 having five risk alleles, no one had more than five ‘risk’ alleles. For our analysis, children were grouped as having less than or equal to two risk alleles, three risk alleles or greater than or equal to four alleles. We excluded mothers who reported drinking more than one unit per day during pregnancy, leaving 4167 women and their children who had provided sufficient data and were eligible for this analysis. The association between this score and total WISC score was tested using a linear regression model. In addition, an analysis of gene-environment interaction was carried out using this score and ever drank during pregnancy as the exposures and WISC score as the outcome. A likelihood ratio test was carried out to compare a model with no interaction term against one with an interaction term.

Results

14541 women were originally recruited into ALSPAC. However, we restricted our analysis to live singleton births, which were first ALSPAC births and excluded women and children of known non-white ethnic origin and those with missing ethnicity data, which left us with 11086 eligible mother-child pairs. Not all of these children and their mothers had data on all genotypes or on all observational variables. Numbers for the separate analyses are provided in the tables. The mean age-adjusted WISC score among the 6196 eligible children who completed the test at age 8 was 104.7 (SD = 16.3). This was slightly higher among those participants who also had genotype data available (mean = 105.1 SD = 16.2). Genotype distributions however, did not differ by whether participants also had alcohol data and WISC scores. The proportion of mothers drinking during pregnancy was higher in all those eligible for whom this data was available (77.6%, 7168/
mothers reported drinking during pregnancy. Among children of all of these effects was generally weak.

The ADH1B rs1229984 SNP among mothers was found to be associated with binge drinking at 18 weeks of pregnancy (as previously reported [23]). In addition, the rare alleles of ADH4 rs4699714 and ADH1B rs2066701 were more common among children of mothers who reported binge drinking at 18 weeks of pregnancy after adjustment for mothers genotype at these loci (OR = 1.17 (95% CI = 1.01–1.36), p = 0.03 and OR = 1.19 (95% CI = 1.03–1.38), p = 0.02 respectively).

Univariate analyses of mother and child genotypes and WISC score at age 8 (Table 1) stratified by whether mothers reported moderate alcohol use (<1–6 units per week) during pregnancy or not suggested a decrease in WISC score with the presence of the rare allele at ADH7 SNP rs284779 among children and mothers. The rare allele at ADH4 rs414884 in mothers was also associated with a decrease in IQ score among their children as was the rare allele at ADH1A rs2836615 and the common allele at rs1229966. All of these effects were only present among children whose mothers reported drinking during pregnancy. Among children of non-drinking mothers ADH4 rs4699714 and rs414884 were associated with WISC scores, and there seemed to be an effect of mother’s genotype at ADH1B rs1229984 although evidence for these effects was generally weak.

Because overall in-utero exposure to alcohol will be determined by genotypes at several loci within ADH genes and by interactions between mother and child genotypes, and to account for confounding by linkage disequilibrium a backwards stepwise selection based on Akaike’s information criterion was used to select the best fitting genetic model for predicting child’s IQ. When only child’s genotypes were entered in the model, the following SNPs were identified as being independently associated with WISC score: ADH1A rs2866151, rs975833, ADH7 rs284779 and ADH1B rs4147536. Further analyses to uncover the nature of interactions between genotypes at these SNPs found that the 2 SNPs in ADH1A were in complete linkage disequilibrium (LD) (D’ = 1, r² = 0.28, chi² = 1967 df = 1) with each other, such that individuals who had the rare homozygote genotype at one site always had the common homozygote genotype at the other site. However, individuals with no rare alleles at these 2 sites had a greater WISC score than those with any 1 rare allele with those having any 2 rare alleles (whether rare homozygotes at one site or heterozygotes at both sites) having the lowest WISC score. In addition, strong, but not complete, LD exists between these ADH1A sites and ADH1B rs4147536 (rs2866151- rs4147536, D’ = 0.91, r² = 0.18, > chi² = 1284 df = 1, rs975833-rs4147536, D’ = 0.95, r² = 0.07, chi² = 514, df = 1). Adding rs4147536 to a model containing both ADH1A SNPs strengthened the association with the ADH1 SNPs, and we found that having any 3 alleles across the ADH1A and ADH1B SNPs rs2866151, rs975833 rs4147536 was associated with the lowest WISC score, although no-one in our study was found to have more than 3 rare alleles across these 3 sites. Rs204779 in ADH7 is not in LD with the other 3 SNPs mentioned above, but it did show evidence of interaction with a composite score of the other 3 SNPs.

The results of 2 logistic regression models (one model including children of mother’s who drank during pregnancy and 1 including children of mothers who did not drink) with mutual adjustment for genotype at all of the four loci above are given in Table 2. When all mother and child genotypes were entered into the model the above 4 genotypes in the children were identified as important in predicting WISC score plus additionally ADH4 rs414884 in both the mothers and the children, results are not shown here, but can be provided on request. However, in this model the results of for ADH4 rs414884 were complex with the rare allele in mother’s being associated with a decrease in child’s IQ and the rare allele in children being associated with an increase in child’s IQ, as indicated in the unadjusted analyses in Table 1.

In our analysis of genotype score (based on adding together the number of rare alleles present across 4 SNPs listed in Table 4) and WISC (Table 3), we found strong evidence of a dose-response between number of risk alleles and total WISC score (Effect estimate = −1.20 (95% CI = −1.89 to −0.52) per allele p = 0.001), with WISC score decreasing with increasing number of risk alleles. We found that this effect was limited to the children of mothers who reported drinking during pregnancy (Effect estimate = −1.90 (95% CI = −2.63 to −0.97) p = 2×10⁻⁶), and there was evidence of an interaction between number of risk alleles and mother’s drinking behaviour on WISC score at age 8 (pinteraction = 0.009). In addition, the effect of genotype score among children of drinking mothers was strengthened after adjustment for amount drank at 32 weeks of pregnancy (adjusted effect estimate = −2.63 (95% CI = −3.75 to −1.54) p = 2.8×10⁻⁶).

This effect did not change in a sensitivity analysis excluding all women who reported binge drinking (≥4 units of alcohol) either at 10 weeks or 32 weeks of pregnancy (question asked at these time points but refers to the preceding month) (p = 0.005). For all categories of allele score, drinking during pregnancy was associated with a higher IQ score in the child. We also looked at the effect of genotype score on offspring IQ among the 269 women excluded from our main analysis due to drinking ≥6 units per week during pregnancy. 192 of these women drank 1–2 units per day during pregnancy and 77 women drank more than 2 units per day during pregnancy. We found that among those women drinking 1–2 units per day there was no evidence that the effect of genotype score was any different from mothers drinking ≤1 unit per day (per allele effects for these women were −1.08, 95% CI = −4.23 to 2.06 p = 0.5), whereas for the 77 women drinking more than 2 units per day the effect of genotype appeared to be double that among moderate drinkers (per allele effect = −3.52 (95% CI = −7.96 to 0.93, p = 0.12). However, reflecting the small number of women in these groups, the evidence for these effects is weak and the confidence intervals are wide.

We did not find evidence of an association between fetal genotype score and alcohol intake among the pregnant women in this study, suggesting that the above effects are due to metabolism of alcohol rather than alcohol intake.

Adjustment of analyses for five ancestry informative markers, and adjustment for potential confounders made no difference to the results (data not shown), but these variables have previously been shown not to be associated with the genotypes analysed here [23].
Table 4 shows mothers age, educational level and socio-economic group according to drinking status and child’s genotype score, for the mothers with data on both. Mothers who drank moderately during pregnancy were older, better educated and less likely to be from a manual socio-economic group. However, these factors were not associated with genotype score.

Discussion

Purpose of the Study and Overall Result

Observational studies have suggested that whilst heavy alcohol drinking during pregnancy causes fetal alcohol syndrome, there are no apparent adverse effects associated with moderate drinking [3,4]. This has led to a disparity between scientific evidence and

Table 1. Results for associations between mother and child genotypes and total WISC score at age 8.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP-rs number</th>
<th>Rare allele freq</th>
<th>HWE p-value</th>
<th>Mothers drinking (&lt;1–6 units per week)</th>
<th>Mothers not drinking during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>Per allele effect on WISC (SE) P-value</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH4</td>
<td>rs4699714</td>
<td>0.27</td>
<td>0.05</td>
<td>2344</td>
<td>0.14 (0.52)</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs3762894</td>
<td>0.16</td>
<td>0.44</td>
<td>2352</td>
<td>0.63 (0.64)</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs4148884</td>
<td>0.08</td>
<td>0.85</td>
<td>2351</td>
<td>−1.53 (0.84)</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs2866151</td>
<td>0.46</td>
<td>0.44</td>
<td>2304</td>
<td>−1.23 (0.48)</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs975833</td>
<td>0.24</td>
<td>0.13</td>
<td>2323</td>
<td>0.93 (0.57)</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs1229966</td>
<td>0.36</td>
<td>0.22</td>
<td>2330</td>
<td>1.18 (0.50)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs2066701</td>
<td>0.29</td>
<td>0.43</td>
<td>2294</td>
<td>0.43 (0.54)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs4147536</td>
<td>0.22</td>
<td>0.70</td>
<td>2326</td>
<td>0.49 (0.58)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs1229984*</td>
<td>0.03</td>
<td>0.57</td>
<td>2346</td>
<td>−1.27 (1.62)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs284779</td>
<td>0.45</td>
<td>0.91</td>
<td>2343</td>
<td>−1.40 (0.48)</td>
</tr>
</tbody>
</table>

Child

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP-rs number</th>
<th>Rare allele freq</th>
<th>HWE p-value</th>
<th>Per allele effect on WISC score &amp;95% confidence intervals</th>
<th>P-value</th>
<th>Per allele effect on WISC score &amp;95% confidence intervals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH4</td>
<td>rs4699714</td>
<td>0.28</td>
<td>0.56</td>
<td>-0.30 (0.47)</td>
<td>0.52</td>
<td>1456 (0.66)</td>
<td>0.03</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs3762894</td>
<td>0.17</td>
<td>0.01</td>
<td>0.38 (0.55)</td>
<td>0.49</td>
<td>1458 (0.80)</td>
<td>0.91</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs4148884</td>
<td>0.08</td>
<td>0.75</td>
<td>0.21 (0.76)</td>
<td>0.78</td>
<td>1474 (1.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs2866151</td>
<td>0.47</td>
<td>0.16</td>
<td>-0.45 (0.42)</td>
<td>0.29</td>
<td>1433 (0.61)</td>
<td>0.89</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs975833</td>
<td>0.24</td>
<td>0.74</td>
<td>-0.32 (0.50)</td>
<td>0.52</td>
<td>1450 (0.69)</td>
<td>0.94</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs1229966</td>
<td>0.37</td>
<td>0.39</td>
<td>0.40 (0.44)</td>
<td>0.36</td>
<td>1461 (0.62)</td>
<td>0.87</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs2066701</td>
<td>0.29</td>
<td>0.43</td>
<td>0.02 (0.47)</td>
<td>0.97</td>
<td>1429 (0.66)</td>
<td>0.92</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs4147536</td>
<td>0.20</td>
<td>0.49</td>
<td>0.13 (0.53)</td>
<td>0.80</td>
<td>1453 (0.73)</td>
<td>0.78</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs1229984*</td>
<td>0.03</td>
<td>0.57</td>
<td>-1.06 (1.26)</td>
<td>0.40</td>
<td>1702 (1.61)</td>
<td>0.21</td>
</tr>
<tr>
<td>ADH7</td>
<td>rs284779</td>
<td>0.45</td>
<td>0.01</td>
<td>-1.27 (0.41)</td>
<td>0.002</td>
<td>1465 (0.60)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

A linear regression model was used for this analysis, *Dominant effect.

doi:10.1371/journal.pone.0049407.t001

Table 2. Results for adjusted model including 4 child variants.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP-rs number</th>
<th>Maternal drinking during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;1–6 units per week N = 2792</td>
</tr>
<tr>
<td>Child</td>
<td></td>
<td>Per allele effect on WISC score &amp;95% confidence intervals</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs2866151</td>
<td>−1.95 (−3.29 to −0.61)</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs975833</td>
<td>−1.72 (−3.23 to −0.21)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs4147536</td>
<td>−1.47 (−2.97 to 0.02)</td>
</tr>
<tr>
<td>ADH7</td>
<td>rs284779</td>
<td>−1.27 (−2.10 to −0.44)</td>
</tr>
</tbody>
</table>

A linear regression model was used for this analysis, *Dominant effect.

doi:10.1371/journal.pone.0049407.t002
current advice given to pregnant women. The purpose of this study was to determine whether exposure to moderate levels of alcohol during gestation influences child's cognition. We investigated associations between genetic variants in alcohol metabolising enzymes in mothers and their children, in a population based study of women, many of whom drank in moderation during pregnancy to determine whether these variants were related to IQ scores in the child at age 8. We found strong evidence that four such variants among children were related to differences in IQ and that this effect was only present in children of mothers who drank some alcohol during pregnancy. Such gene-environment interactions can be taken as providing evidence supporting a causal relationship between maternal alcohol intake and offspring IQ.

### Genetic Variation in ADH Genes and Alcohol Metabolism

There is considerable between-individual variation in blood alcohol concentrations achieved following ingestion of a standard weight-adjusted amount of alcohol [30]. Variation in the ADH region is thought to contribute substantially to this variation [9], with the largest effect on breath and blood alcohol levels due to enzymes which act early in the time course of alcohol metabolism, soon after ingestion when hepatic concentrations are highest [9]. Another recent study by Birley [31] has identified a region in ADH7 as being the one most strongly associated with alcohol consumption [32,33]. ADH1A is particularly interesting in relation to fetal exposure to alcohol as this is expressed from the first trimester of fetal life and is active in the liver from the second trimester and gradually increases in activity, such that in adults this locus is responsible for most of the liver ADH activity [35]. ADH4 is expressed in the liver and may account for 40% of alcohol oxidation at intoxicating levels [36]. There are very few extensive studies of SNPs in ADH genes and alcohol metabolism, thus the relevant polymorphisms (apart from a couple of rare exceptions) along with the direction and size of effect is still not clear. However, we have summarized what is known about the genetic variants we selected in Text Box S1.

### Genetic Variation and Offspring IQ Score

Given the level of complexity of this pathway and the amount of redundancy due to the fact that five ADH genes are all catalysing the same reaction, we hypothesised that any one SNP would have only a minor effect on metabolism of alcohol and that interactions between SNPs across this region would be important. Previous studies have shown that interactions between SNPs across these genes are apparent in the risk of alcoholism, in particular between ADH1B and ADH7 and between ADH4 and ADH1A [40,41]. In line with this a multivariate model which included several SNPs across this region showed that after adjustment for variants at other sites rare alleles at ADH1A rs2866151 and rs975833, ADH1B rs4147536 and ADH7 rs284779 among children were associated with decreased IQ scores at age 8, whereas, aside from the SNP in ADH7, these SNPs were not associated with IQ in univariate models suggesting interactions between SNPs. When mother’s genotype as well as child’s genotype was entered into the model, we were able to confirm the results with reduced bias.

### Table 3. IQ score by number of risk alleles stratified by maternal alcohol intake during pregnancy.

<table>
<thead>
<tr>
<th>Mother’s drinking status</th>
<th>Number of risk alleles*</th>
<th>Effect estimate and 95% CI</th>
<th>P-value (dose response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinkers</td>
<td>≤2</td>
<td>N=519 Mean = 103.1 (SD = 16.7)</td>
<td>0.16 (~1.05 to 1.36)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>N=628 103.5 (15.7)</td>
<td>0.16 (~1.05 to 1.36)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>N=328 103.2 (15.8)</td>
<td>0.16 (~1.05 to 1.36)</td>
</tr>
<tr>
<td>Drinking during pregnancy (≤1–6 units per week)</td>
<td>≤2</td>
<td>N=1139 107.5 (16.3)</td>
<td>-1.80 (~2.63 to -0.97)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>N=1171 105.4 (16.1)</td>
<td>-1.80 (~2.63 to -0.97)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>N=482 104.0 (15.8)</td>
<td>-1.80 (~2.63 to -0.97)</td>
</tr>
<tr>
<td>All women</td>
<td>≤2</td>
<td>N=1658 106.1 (16.6)</td>
<td>-1.20 (~1.89 to -0.52)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>N=1799 104.7 (16.0)</td>
<td>-1.20 (~1.89 to -0.52)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>N=710 103.8 (15.8)</td>
<td>-1.20 (~1.89 to -0.52)</td>
</tr>
</tbody>
</table>

P-value for interaction between number of risk alleles and drinking during pregnancy = 0.009

*Total number of risk alleles in ADH1A rs2866151 rs975833, ADH1B rs4147536 and ADH7 rs284779.

doi:10.1371/journal.pone.0049407.t003

### Table 4. Mothers age, educational level and socio-economic group by genotype score and drinking behaviour during pregnancy.

<table>
<thead>
<tr>
<th>Mother’s characteristics</th>
<th>Genotype score (Number of risk alleles*)</th>
<th>Mothers drinking during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≤2</td>
<td>&lt;1–6 units per week Abstainers</td>
</tr>
<tr>
<td></td>
<td>29.2±4.6</td>
<td>29.7±4.4</td>
</tr>
<tr>
<td></td>
<td>29.4±5.5</td>
<td>28.4±4.5</td>
</tr>
<tr>
<td>Education (%O-level or higher)</td>
<td>44.6</td>
<td>47.0</td>
</tr>
<tr>
<td></td>
<td>43.4</td>
<td>37.5</td>
</tr>
<tr>
<td>Socio-economic group (% Non-manual occupation)</td>
<td>58.7</td>
<td>61.7</td>
</tr>
<tr>
<td></td>
<td>57.7</td>
<td>51.8</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0049407.t004
ADH4 rs4148884 was also important with opposing effects for mother and child genotype at this loci.

The mutually adjusted effects at ADH1A rs2866151 and rs975833 and ADH1B rs417536 are greater than the unadjusted effects at this site. The explanation for this could be that there is evidence of strong linkage disequilibrium (possibly due to selection) across these loci which means that individuals in this study did not have more than three out of six possible rare allele across the three sites, this coupled with the finding that there seems to be an additive effect across the three sites such that individuals with no rare alleles had the highest WISC score followed by those with any 1 rare allele, followed by those with any two rare alleles and those with any three rare alleles had the lowest score. ADH7 rs284779 was not in LD with the above SNPs but there was evidence of an interaction between the ADH7 SNP and SNPs at ADH1A and ADH1B.

Relative Importance of Fetal and Maternal Genotypes on Fetal Exposure to Alcohol

There is very little published on the relative importance of fetal and maternal ADH enzymes in determining alcohol exposure of the fetus. We anticipated that enzymes in both the fetus and the mother may play a role, thus we looked at the effect of maternal genetic variation, fetal genetic variation, and because the fetal genotype is a combination of alleles inherited from both the mother and the father, we used stepwise selection of all maternal and fetal genotypes to determine which (mother or child) were having an independent effect on child’s IQ. Most of the genetic variants which we found to predict child’s IQ among offspring exposed to alcohol were child genotypes. This is in line with evidence that ADH1A is expressed at high levels in the fetus with ADH1B being expressed from the second trimester onwards with very minor roles for these enzymes in alcohol metabolism later in life [34].

Consistency with Previous Studies

To our knowledge this is the first population-based study to investigate the role of ADH variants in children and their mothers in a study in which most of the mother’s drank in moderation during pregnancy. A handful of very small studies have been carried-out among heavy drinking mothers and their children to look at the effects of ADH enzymes on the presence of fetal alcohol syndrome with mixed results due to a lack of power [13–19]. Many studies including our own have looked at the association between maternal alcohol intake measured by questionnaire and offspring IQ [42–44] most showing as we do in Alati et al [43] that moderate alcohol intake during pregnancy is associated with an increase in child’s IQ relative to non drinking. However, moderate drinking in our study was found to be strongly associated with an increase in maternal age, increase in maternal educational level and a higher social class all of which are associated with a higher IQ among children. Thus observed associations are probably due to confounding by socio-economically clustered factors. Conversely genotype is not on the whole associated with these factors and therefore associations between genotype and IQ are unlikely to be confounded by lifestyle factors [8].

Once we had excluded women with missing data (the main reason being lack of DNA) we were left with a much smaller subset of the original ALSPAC study. However our genotype and our WISC scores correspond well with larger samples of women with any of the above data. In addition, whilst missing exposure or phenotype data could possibly bias observational results, for example if there were a tendency for women who drank alcohol not to take part in the study or to be lost to follow-up (which is what we found), then this may bias any association between alcohol intake and child’s IQ. However, such selection is unlikely to have biased the genotype results as genotype is not associated with missingness.

One concern when using genetic variants to make inferences about associations between exposures and outcomes is pleiotropy [45]. This is the phenomenon whereby the gene may act on a number of pathways and thus may influence an outcome by a mechanism other than that involving the exposure of interest. ADH enzymes are involved in the metabolism of retinoic acid, a compound which is extremely important in fetal development. In addition, as well as influencing alcohol levels, variants in ADH will also have an effect on acetaldehyde levels, the primary substrate of alcohol. However, whilst the precise mechanism by which ADH genes influence child’s cognition needs further investigation the finding that these effects are limited to children of women who drank during pregnancy indicates that alcohol is the important exposure in this pathway. It is not established whether the genetic variants of ADH which were associated with child’s IQ in this study are associated with “fast” or “slow” metabolism of alcohol. We assume, based on the results of this study and on our previous work that these variants predispose to “slow” alcohol metabolism.

Public Health Implications

If real these results could have important public health consequences, because cognitive ability has implications for social trajectories and health. It is well documented that individuals with lower IQ have lower socio-economic positions and poorer adult health and even higher mortality rates compared with those with higher IQs [46–48]. Whilst the effects of genotype appear modest, 3.5 points difference on the WISC scale for those children with ≤2 risk alleles compared to those with >4 risk alleles, it is important to remember that these are effects for genotypes which are likely to result in very small differences in peak alcohol levels and alcohol exposure, and these subtle metabolic effects are among women drinking less than 1 unit of alcohol per day. Larger causal effects are anticipated for more substantial differences in fetal alcohol exposure levels, for example the differences existing between offspring of mothers with moderate alcohol consumption and mothers abstaining.

Conclusion

Five variants in genes involved in alcohol metabolism amongst children and their mothers were associated with child’s cognitive ability at age 8 in a population-based study.

 Associations between child’s genotype and outcome were only present among those whose mothers reported drinking alcohol in moderation during pregnancy. This suggests that, even amongst women drinking moderate amounts of alcohol, subtle changes in exposure to alcohol due to an ability to metabolise the substrate may be important, and offers some support to the hypothesis that even small amounts of alcohol in utero have an effect on future cognitive outcomes.

Supporting Information

Text Box S1 (DOCX)

Acknowledgments

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.
Author Contributions
Conceived and designed the experiments: SJL RG GDS JG. Performed the experiments: S. Ring SJL. Analyzed the data: SJL LZ S. Rodriguez. Wrote the paper: SJL JM LZ RG. Contributed towards the analysis plan and to discussions on the interpretation of the data: ESD MB RA KS JM GDS RG JG.

References
Prenatal Ethanol Exposure Alters Synaptic Plasticity in the Dorsolateral Striatum of Rat Offspring via Changing the Reactivity of Dopamine Receptor

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Introduction

Heavy ethanol (EtOH) consumption during pregnancy has grave and multifaceted consequences for child development [1]. The most far-reaching consequence of prenatal EtOH exposure is its effect on the brain brings the ensuing behavioral alterations [2,3]. Numerous clinical investigations have found that children, boys in particular, exposed to EtOH in utero display hyperlocomotion, which may not be diagnosed until their educational years, and this deficit may increase in severity during the adult stage [4–6]. Similarly, this behavioral abnormality observed clinically could be widely mirrored by prenatal EtOH exposed animal models [7–10]. Although there is a considerable amount of data regarding the morphological and behavioral effects associated with prenatal EtOH exposure [11], the mechanisms underlying developmental defects caused by maternal EtOH consumption remain unclear.

The striatum, especially the dorsolateral (DL) subregion, appears to play a critical role in assisting voluntary motor behaviors in humans, other primates and rodents [12,13]. The neocortex provides major glutamatergic inputs to striatal medium spiny projection neurons. Plasticity at corticostriatal synapses is thought to provide a cellular basis for striatum-dependent behaviors [14,15]. Two forms of synaptic plasticity can be induced by high frequency stimulation (HFS) in the DL striatum: long-term depression (LTD) and long-term potentiation (LTP) [16–20]. Partridge et al. (2000) have reported that in the developing rat DL striatum, the conversion from LTP to LTD occurs during the period of the postnatal 3rd week [21]. Morphological and electrophysiological properties of striatal neurons have been reported to become mature after the postnatal 3rd weeks [22]. Until recently, few experiments have been conducted to study whether prenatal EtOH exposure affects synaptic plasticity of the postnatal developing DL striatum.

Dopaminergic projection from midbrain nuclei is another important input in striatum. Earlier studies on the striatum have shown that dopamine system participates in the change of striatal synaptic plasticity during the early postnatal development via both pre- and post-synaptic mechanisms [23]. Dopamine-mediated action is achieved by its interaction with two types of G protein-coupled receptor, D1-type receptors (D1 or D5, termed here D1R) and D2-type receptors (D2, D3 or D4, termed here D2R) [24,25]. The down-regulation or knockout of D1R prevents either the induction of LTD or LTP [20,26,27] and reduces spontaneous motor activity [28,29]. Interestingly, in D2R-knockout mice, HFS of corticostriatal fibers induces LTP instead of LTD [30]. Previous studies have indicated that prenatal EtOH exposure results in a long-lasting perturbation of central dopamine receptor sensitivity [5,31]. It has been reported that prenatal EtOH exposure enhances the reactivity of D1R in the rat brain [5,32]. Hence, we pose a hypothesis that prenatal EtOH exposure affects dopami-
nergic systems leading to the changes of synaptic plasticity in the DL striatum.

This study investigated whether prenatal exposure to a relatively high-dose EtOH affected synaptic plasticity in the DL striatum of rat offspring, and if so, whether the functions of dopamine receptors were involved in the alteration of synaptic plasticity and basal synaptic properties.

Materials and Methods

Ethics Statement

The present studies were approved by Animal Care and Use Committee of Nanjing Medical University (ID: 2008031911). The protocols used here were in accordance with the guidelines published in the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize the number of animals and their suffering.

Preparation of prenatal EtOH exposed animal model

**Subjects.** Pregnant Sprague-Dawley rats ( Oriental Bio Service Inc., Nanjing) were delivered to our laboratory on gestation day (GD) 2. The morning that vaginal plugs were found was designated as GD 0, and births were expected on GD 21–22. Females were housed individually in polyethylene maternity cages (44×25×20 cm) under environmentally controlled conditions (7:00 am lights on, 7:00 pm lights off; ambient temperature at 20–23°C). The pregnant dams and their offspring were monitored with regard to body weight gain. The day of birth was referred to as postnatal day 0 (PD 0). The dams were allowed to nurse the own young before weaning occurred at PD 21. Litters were then culled to a maximum of 10 pups by sex. One male offspring was randomly selected from each litter as the object of study.

**Treatment.** On gestational day (GD) 7, pregnant dams were divided into control and EtOH group. Starting from GD 7 throughout GD 20, dams from EtOH group were daily administrated with 6 g EtOH/kg body weight, with ad libitum access to laboratory chow and water. Animals in control group received the same volume of isocaloric sucrose solution as EtOH. The EtOH/sucrose solution was delivered by intragastric intubations. Binge-like regime of EtOH administration was chosen as producing higher blood EtOH concentration (BEC) [33,34] and thus being more damaging as compared to the liquid diet. To determine BECs for EtOH-treated dams on GD 20, 20 μl of blood was taken from each subject and rapidly analyzed by gas-liquid chromatography [35].

Electrophysiological analysis

**Slice preparation.** The procedure used was similar to that described previously [21]. Animals were killed by decapitation, their brains were immediately removed and placed in ice-cold (−3°C) modified artificial cerebrospinal fluid (ACSF) containing the following substances (in mM): 124 NaCl, 2 CaCl₂, 4.5 KC1, 1.0 MgCl₂, 26 NaHCO₃, 1.2 NaH₂PO₄, and 10 D-glucose and adjusted to pH 7.4 by bubbling with 95% O₂/5% CO₂. Coronal brain slices (400 μm) were cut using a vibrating microtome (Microslicer DTK 1500, Dousaka EM Co, Kyoto, Japan) in ice-cold oxygenated ACSF. The slices containing the DL striatum were stored for a minimum of 1 h prior to recording in oxygenated ACSF maintained at room temperature.

**Field potential recording.** For recording, slices were transferred to a chamber continuously perfused with oxygenated ACSF (2 ml/min) maintained at 30±1°C. Stimulation consisted of monophasic wave pulses delivered through a stainless steel electrode placed in the white matter overlying the DL striatum. The stimulation-evoked population spike (PS) was recorded from the DL striatum through glass micropipettes filled with 2 M NaCl (4–5 MΩ) connected with a differential AC amplifier (A-M Systems, model 1700, Seattle, WA). The experimental control, data acquisition, and analysis were performed using pCLAMP software (Molecular Devices, Union City, CA). The PS amplitude was defined as the average of the amplitude from the beginning to the peak negativity, and the amplitude from peak negativity to the end. Input-output (I/O) curves were constructed to examine basal synaptic transmission by delivering an ascending series of 11 stimulus intensities (0.03–0.68 mA) that ranged from sub-threshold intensity for elicitation of a PS to that eliciting maximal response. Test stimulus which induced 50% of a maximum of PS amplitude was required for the followed procedures. Paired-response pulse of PS was evoked by pair test stimulus at corticostriatal afferent fibers. The same recordings as those before HFS continued for 60 min after HFS. Each PS amplitude pre- or post-HFS was normalized to the percentage of the mean pre-HFS value. Because HFS induced small change of PS response (<20%) is not stable and persistent, the successful induction of LTD or LTP requires the decrease or increase of PS amplitude post-HFS during the stable phase (>30 min post-HFS) exceeds a minimum of 20% [36–38].

**Drug administration.** SCH23390, L-sulpiride, quinpirole, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), d-2-amino-5-phosphonopentanoic acid (D-AP5) used in the present study were all obtained from Sigma-Aldrich (St. Louis, MO). L-sulpiride, quinpirole, MPEP, D-AP5 were dissolved to their final concentrations in ACSF. SCH23390 was dissolved in ACSF containing 0.1% DMSO. Drug solutions entered the recording chamber within 40 s after a three-way tap had been turned on. They were applied in the bath for at least 30 min starting from 15 min pre-HFS.

**Data analysis/statistics.** Data were retrieved and processed with the software Micro cal Origin 6.1. The group data were expressed as the means ± standard error (SE). Experimental results were compared among treatment groups by ANOVAs followed by Bonferroni’s post hoc test or t test. Statistical analysis was performed using Stat 7 software (STATA Corporation, USA). P<0.05 was considered statistically significant. For statistical purposes, only one slice was studied per rat in electrophysiological analysis.

Results

Prenatal EtOH exposure analysis

The mean BECs for EtOH-treated dams were 302.89±19.5 and 331.21±28.9 mg/dl, 2 and 3 h after the last intubation on GD 20 (n = 20), respectively, suggesting binge-like EtOH administration during gestation results in maternal high-level BEC which corresponded with the previous reports [37]. Prenatal EtOH exposure had no effect on the length of gestation, average litter size, or the distribution of male and female offspring (data not shown).
The disturbed conversion of striatal synaptic plasticity in EtOH offspring

To determine whether prenatal EtOH exposure affected synaptic plasticity in the DL striatum of rat offspring, synaptic plasticity at PD 15, PD 30 and PD 40 was recorded and compared between control and EtOH offspring. As shown in Figure 1A, HFS caused a significantly persistent potentiation of PS (133.49 ± 4.83% at 60 min post-HFS; n = 14) in PD 15 control offspring, showing a representative sample of LTP. By contrast, the same HFS protocols induced a mild increase of PS amplitude in the same-aged EtOH offspring (115.59 ± 5.70%; n = 16). In PD 30 control offspring, HFS induced the depression of PS amplitude for over 60 min (70.67 ± 3.89%; n = 10), indicating the successful induction of LTD (Fig. 1B). Interestingly, the same mode of HFS induced LTP but not LTD in the slices from PD 30 EtOH offspring (127.71 ± 3.31%; n = 10; Fig. 1B). The similar results to that in Figure 1B were obtained in PD40 control and EtOH offspring (control group: 67.63 ± 2.92%; n = 10; EtOH group: 130.58 ± 2.80%; n = 10; Fig. 1C). In addition, there was no significant difference in the size of striatum between control and EtOH offspring at any of three postnatal ages (data not shown). Consistent with the present findings about control rats, Partridge et al. (2000) have reported that LTP is the dominating form during PD12–14, while LTD replaces LTP during PD24–32 in the developing rat DL striatum [21]. The results obtained from EtOH offspring suggested the possibility that prenatal EtOH exposure led to the impairment of reversal development of synaptic plasticity in the DL striatum. It has been reported that adult-typical behaviors of rats are completely established during PD21–23 [32]. Hereafter, we paid great attention on the mechanisms underlying HFS-induced LTP instead of LTD in the DL striatum of PD 30 EtOH offspring.

Enhancement of basal synaptic transmission with the increase in presynaptic glutamate release at corticostriatal pathway of EtOH offspring

I/O curves were constructed to identify whether prenatal EtOH exposure influenced basal synaptic transmission in striatum. Two-way ANOVA analysis indicated statistically significant effects with EtOH exposure (F(1,22) = 10.481; P = 0.001), stimulation intensity (F(1,22) = 65.812; P < 0.00001; Fig. 2A). Post-hoc analysis using Bonferroni’s test further revealed PS amplitudes in EtOH offspring were significantly higher than those in control offspring at the same stimulation intensity when stimulation intensity ranged from 0.22 mA to 0.46 mA (∆ control group: n = 10, EtOH group: n = 12; P < 0.05). At higher or lower stimulation intensity, there was no significant difference in PS amplitude between two groups (P > 0.05). Paired-pulse facilitation (PPF) was introduced to detect whether presynaptic glutamate release participates in the potentiation of basal synaptic transmission in EtOH rats. PPF is well known as a special phenomenon that the second stimulus evoked PS with enlarged amplitude with paired-pulse stimulation of striatum. PPF is always expressed as the ratio of the second PS amplitude to the first one and regarded to have negative correlation with presynaptic glutamate release. The data of PPF were collected corresponding to paired-pulse stimulation with different inter-pulse intervals (IPIs) from 25 to 500 msec. As shown in Figure 2B, two-way ANOVA analysis on PPF revealed significant effects with EtOH exposure (F(1,22) = 10.744; P = 0.001) and IPIs (F(1,22) = 10.188; P < 0.00001). Bonferroni’s post-hoc test further indicated PPF in EtOH rats was significantly less than that in control rats at the same IPIs when IPIs ranged from 50 msec to 100 msec (control group: n = 10, EtOH group: n = 12; P < 0.05). Taken together, the findings indicate that the potentiation of basal synaptic transmission in PD 30 EtOH offspring is, at least part, due to the increase in presynaptic glutamate release.

Up-regulation of D1R function is involved in EtOH-induced potentiation of basal synaptic transmission

Earlier studies have reported that D1R activation improves the presynapse release of glutamate, while D2R activation plays an opposite effect [39,40]. The D1R antagonist SCH23390 and the D2R antagonist L-sulpiride were applied to examine whether dopamine receptors were involved in the potentiation of basal synaptic transmission induced by prenatal EtOH exposure. The findings in Figure 3A showed that the perfusion with SCH23390 (10 μM) for 30 min did not affect the amplitude of test stimulus-evoked PS in the slices obtained from PD 30 control rats (basal, 0.22 ± 0.05 mV; SCH23390, 0.21 ± 0.07 mV; n = 11; t = 0.993; P = 0.928; paired t test). However, SCH23390 completely abolished the increase of test stimulus-evoked PS amplitude in PD 30 EtOH rats (basal, 0.31 ± 0.06 mV; SCH23390, 0.20 ± 0.04 mV; n = 12; t = 4.303; P = 0.001; paired t test). Similarly, the treatment with SCH23390 recovered the reduction of PPR evoked by pair-pulse stimulation with 50 msec IPI in EtOH offspring (n = 12; t = 4.966; P = 0.000001; paired t test) without changing that in control rats (n = 11; t = 0.318; P = 0.757; paired t test; Fig. 3B). However, the perfusion with 10 μM L-sulpiride for 30 min had no significant effect on either PS amplitude or PPR in control and EtOH group (Fig. 3C, 3D). In addition, application of 0.1% DMSO (the vehicle of SCH23390) alone did not affect PS amplitude in either control or EtOH offspring (data not shown). These data suggest that prenatal EtOH exposure results in the increase of glutamate release probably via up-regulation of D1R function, which, in turn, brings the potentiation of basal synaptic transmission.

Up-regulation of D1R function LTP participates in LTD instead of LTD in PD 30 EtOH offspring

In order to further investigate whether up-regulation of D1R function participated in the conversion from LTD to LTP, corticostriatal synaptic plasticity was then induced in presence of SCH23390. The findings showed that SCH23390 completely blocked the LTD induction, but failed to make it return to LTD (92.15 ± 6.43%, n = 8; Fig. 4). This result suggests D1R up-regulation is one of the possible mechanisms underlying the appearance of LTD instead of LTD in PD 30 EtOH offspring.

Down-regulation of D2R function blocks LTD induction in PD 30 EtOH rats

A large number of documents indicate that D2R, as well as D1R, plays an important role in striatal synaptic plasticity. Calabresi et al. (1997) have found that HFS at corticostriatal fibers induces LTD instead of LTD in D2R knockout mice [30]. This part of our study was performed to make clear whether D2R activation mediated the conversion from LTD to LTD in EtOH offspring. The perfusion with 10 μM L-sulpiride for 30 min blocked HFS induced LTD, but did not reverse it to LTD in control slices (100.06 ± 5.18%, n = 8; Fig. 5A). The same treatment with L-sulpiride did not alter LTD measured in EtOH offspring (123.45 ± 6.45%, n = 8; Fig. 5B). However, the application of quinpirole (10 μM), a D2R agonist, revealed the similar LTD in EtOH offspring with that in control offspring (71.21 ± 4.67%, n = 8; Fig. 5C). In control offspring the induction of LTD was sensitive to SCH23390 (99.46 ± 7.50%, n = 12). Similarly, the
quinpirole-recovered LTD in EtOH offspring was also blocked by SCH23390 (98.07±6.66%, n = 10; Fig. 5D).

Previous studies have reported that metabotropic glutamate receptor (mGluR) rather than N-methyl-D-aspartate receptor (NMDAr) is involved in HFS-LTD induction in striatum, [17,18,41]. Our results revealed that in control offspring this LTD was blocked by the mGluR antagonist MPEP (10 μM) (97.83±2.82%, n = 10; Fig. 6A), but not the NMDAr antagonist AP5 at 50 μM (68.43±6.87%, n = 8; Fig. 6B). In EtOH offspring the quinpirole-rescued LTD was also sensitive to MPEP (103.23±2.03%, n = 10; Fig. 6C) but not AP5 (70.74±4.25%; Fig. 6D). The findings indicate that D2R down-regulation together with D1R up-regulation participates in a profound shift in the direction of long-term change at corticostriatal synapses (NMDAr-
EtOH offspring showed a D1R-mediated potentiation of basal synaptic transmission through increasing presynaptic glutamate release. Third, D1R antagonist SCH23390 blocked the induction of LTP in EtOH-exposed offspring. Fourth, D2R agonist quinpirole could rescue the D1R- and mGluR-dependent LTD induction in EtOH-exposed offspring.

The present study found that LTP was induced in the DL striatum of PD 15 control rats, while LTD was elicited in PD 30 or PD 40 control rats by the same HFS protocol. Consistent with our results, Partridge et al. (2000) have reported that in the developing rat striatum, the conversion from LTP to LTD occurs during the postnatal third week [21]. Tepper and associates (1998) have shown that the third week of postnatal maturation in rat striatum is an intense period of electrophysiological and morphological change [22]. This discriminating pattern of synaptic development may give rise to functional differences in integratingafferent input during this stage of striatal development. LTP is a predominant form of plasticity when synapses are beginning to come on-line in striatum [21]. The emergence of LTD later in development is thought to help to fine-tune synaptic efficacy to refine movement and behavioral sequencing [16,42]. This is in line with the fact that LTD predominates during a time period when movement patterns are changing from more neonatal to more adult-like [21]. LTD appearing in the early development has been considered to depend on NMDAr activation [21]. Studies in the review by Costa et al. (2000) have shown prenatal EtOH exposure led to a decrease in either NMDAR expression or function in various regions of the brain [43]. Therefore, we speculated the impairment of LTP in PD15 EtOH-exposed offspring might be the consequence of NMDAr down-regulation. Furthermore, in the present study, prenatal EtOH exposure resulted in LTP but not LTD of synaptic plasticity at PD 30 even if at the older age, when LTD was generally induced in the same-aged control rats. The loss of LTD in the mature DL striatum of adult animals has been reported to be accompanied by the motor abnormality [44]. This observation, together with the findings presented here, suggests that this abnormal synaptic plasticity in the DL striatum might be the important mechanism underlying movement disorders caused by in utero exposure to EtOH.

Among mechanisms responsible for the abnormal corticostriatal synaptic plasticity in PD 30 EtOH-exposed offspring, one might be that EtOH modulates glutamatergic neurotransmission either directly or via changing other neurotransmitter systems. Calabresi et al. (1997) found that tetanic stimulation of corticostriatal afferent fibers produced NMDAr-dependent LTP in slices from D2R-mull mice [30]. Based on this finding, D2R is considered to play a key role in controlling the direction of long-term changes in synaptic efficacy in striatum. However, a different viewpoint is raised here i.e. the appearance of LTD instead of LTP in EtOH offspring is caused through EtOH-induced up-regulation of D1R and down-regulation of D2R leading to the imbalance between the function of D1R and D2R. This conclusion is suggested by the following main findings. First, D2R antagonist L-sulpiride blocked LTD induction, but not facilitated LTP expression in control offspring. Second, D1R antagonist SCH23390 did not recover LTD though it blocked LTD induction in EtOH-exposed offspring. Third, SCH23390 could recover the basal synaptic transmission via eliminating the increase of presynaptic glutamate release induced by prenatal EtOH exposure. Forth, D2R agonist quiniride reversed NMDAr-dependent LTP into mGluR-dependent LTD via adjusting the balance between D1R and D2R in EtOH-exposed offspring. A large body of evidence has established that striatal LTD induction requires the activation of both D1R and D2R [16,17,45], whereas LTP expression is only related to D1R functions in the DL striatum of young male rat mice [30]. Based on this finding, D2R is considered to play a key role in controlling the direction of long-term changes in synaptic efficacy in striatum. 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activation [26,27]. And this was also proved by two main results acquired from the present study. One is that striatal LTD in control slices was blocked by inhibiting D1R or D2R. The other is HFS induced LTP in EtOH slices could be abolished by D1R antagonist but not D2R antagonist. It has been established striatal LTD shares several characteristics with other forms of synaptic plasticity in the brain [46–48]. The induction of striatal LTD is considered to be presynaptic through decreasing glutamate release, as shown by a decrease in the frequency but not the amplitude of spontaneous EPSCs [49,50] with an increase in PPF [50]. There is general agreement that D2R plays a negative role in regulating presynaptic glutamate release [39,51]. The latest studies indicate that D2R activation evokes retrograde signal pathway via endocannabinoids leading to the reduction of glutamate release [18,30,49,52–54]. The activation of cAMP-PKA signal pathway leading to the increase of presynaptic glutamate release is one of the important mechanisms involved in D1R-dependent LTP [26]. Our findings indicate that the imbalance between the function of D1R and D2R induced by up-regulation of D1R and down-regulation of D2R might be responsible for appearance of LTP instead of LTD in EtOH-exposed offspring. Earlier studies using other methods have proved that the exposure to high-dose EtOH during prenatal and postnatal development has long-lasting effects on central dopaminergic systems linked with behavioral rewarding effects. For example, microarray analysis has demonstrated that developmental EtOH exposure causes up-regulation of D1R in the rat or mouse striatum [5,55]. Receptor binding study in rats treated prenatally with EtOH shows a significant reduction in functional D2R within the mature striatum [31,56]. Of course, further study should be necessary preformed to determine the expression and function of D1R and D2R during the develop-

**Figure 3.** Dopamine receptors are involved in EtOH induced potentiation of basal synaptic transmission at corticostratial pathway in PD 30 offspring. The hollow line represents the duration of drug perfusion. **A & B:** Effect of the D1R antagonist SCH23390 on test stimulus evoked PS and PPF in control and EtOH rats. Note that SCH23390 inhibits the potentiation of PS and the reduction of PPF in EtOH rats, but did not affect those in control rats. **C & D:** Effect of the D2R antagonist L-sulpiride on test stimulus evoked PS and PPF in control and EtOH rats. Note that the treatment with L-sulpiride had no influence on PS amplitude or PPF at 50 msec IPI in both groups. doi:10.1371/journal.pone.0042443.g003

**Figure 4.** Up-regulation of D1R participates in the facilitation of LTP in PD 30 EtOH rats. ‘†’ indicates the time point of HFS application. The hollow line represents the period of drug occurrence in ASCF. Note that SCH23390 completely blocked the potentiation of PS amplitude at 60 min post-HFS. doi:10.1371/journal.pone.0042443.g004
mental striatum to support our conclusion. In addition, the cholinergic system is another important factor involved in stratal synaptic transmission and plasticity [53,57]. Some reports have pointed out that a dysfunction of the hippocampal cholinergic system is one of important outputs for prenatal exposure to high-dose EtOH [58,59]. Therefore, the impairment of cholinergic system induced by prenatal EtOH exposure might also mediate the abnormal synaptic plasticity of striatum. Although one of the conclusions in the present that prenatal EtOH exposure has a long-lasting effect on dopamine receptors is strongly supported by a large of increased literatures. To date, it is very difficult to explain the fact why the exposure to EtOH results in opposite changes of D1R and D2R function: an up-regulation of D1R function and a down-regulation of D2R function.

Figure 5. Down-regulation of D2R leads to the shift of synaptic plasticity from LTD to LTP in PD 30 EtOH rats. ‘↑’ indicates the time point of HFS application. The hollow line represents the period of drug occurrence in ASCF. A & B: L-sulpiride completely blocked HFS induced LTD in control rats, but had no effect on HFS induced LTP in EtOH rats. C: the D2R agonist quinpirole recovered the induction of LTD in EtOH rats. D & E: SCH23390 completely blocked either the induction of LTD in control rats or quinpirole-recovered LTD in EtOH rats.

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Conclusions

The DL striatum controls motor activity by processing the flow of information arising from the cerebral cortex and projecting, via direct and indirect pathways, to the output nuclei of the basal ganglia [60]. Intrastriatal dopaminergic system takes part in this process by affecting the excitatory synaptic transmission and plasticity. Our results indicate a possible pathophysiologic mechanism underlying hyperlocomotion induced by prenatal EtOH exposure that imbalance in the function of D1R and D2R within the DL striatum impairs the development and maturation of corticostrial synaptic plasticity.
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We acknowledge that the work described is an original work and has not been previously published or under consideration for publication elsewhere in whole or in part. We declare that there is no competing financial that could be construed as influencing the results or interpretation of the reported study.

Author Contributions

Conceived and designed the experiments: RZ. Performed the experiments: RZ SW XZ. Analyzed the data: RZ SW XZ. Contributed reagents/materials/analysis tools: RZ. Wrote the paper: RZ.

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