

Neurodevelopmental Disorders Associated with Prenatal Exposure to Alcohol

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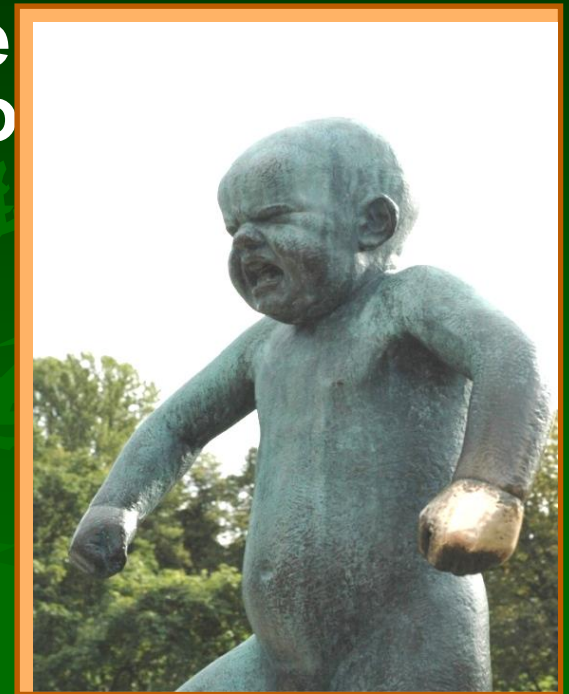
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Meharry Medical College

- When I was in medical school at Meharry Medical college taking Pediatrics in 1969, Dr. E. Perry Crump was the Chairman of the Department of Pediatrics.
- Dr. Crump taught me that the low-income children of North Nashville had a high prevalence of “mild mental retardation.”
- Dr. Crump and Julius Richmond, M.D. (President’s Johnson’s and Carter’s Surgeon General) went on to form Head Start to address this national problem).

The Critical Role of Self-Regulation

- Neuroscience and behavioral research are converging on the importance of self-regulation for successful development
- Children who do not develop the capacity to inhibit impulsive behavior, to plan, and to regulate their emotion are at high risk for behavioral and emotional difficulties



Bell CC & McBride DF. Affect Regulation and the Prevention of Risky Behaviors. Journal of the American Medical Association, Vol. 304, No. 5: 565 –566, August 4, 2010

The Critical Role of Self-Regulation

- 1979 – 88.5% (246) of the 274 children in Pupil Service Center on Chicago's Southside had Childhood Neurodevelopmental Disorders (CND)
- 1985 – 20% of inmates in Texas Department of Corrections were “mentally retarded.”
- 2011 - chart audit on 162 children in several nurse-based school clinics estimates 39% (63) of those children met the DSM-5 Condition for Further Study - “Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (NDA-PAE) a (CND).
- 2012 prior to the closure of the Community Mental Health Council, Inc. - chart audit of 330 randomly selected patients revealed that 12% (39 of 330 patients) met criteria for CND.

Social Determinants of Health

- Think about all the liquor stores in the African-American (ghettos) and Native American (reservations) communities all over the country.
- The plethora of liquor stores have a determination on the indigenous populations' health.

Neurodevelopmental Disorders

- Autism and Autism Spectrum Disorders
- ADHD
- Intellectual Disability
- Specific Learning Disorders
- Communication Disorders
- Motor Disorders
- Newly defined DSM-5 Neurodevelopmental Disorder associated with Fetal Alcohol Exposure

DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

- A. More than minimal exposure to alcohol during gestation, including prior to pregnancy recognition
 - Confirmation of gestational exposure to alcohol from
 - Maternal self-report of alcohol use in pregnancy
 - Medical or other records
 - Clinical observation (Ask for baby photos)
 - Patients report the following:
 - “I was taken from my mom when I was a baby”
 - “My mom was doing drugs”
 - “My grandmother told me my mom was drinking”
 - “I saw my mom drink when she was carrying my sister”

DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

- B. Impaired neurocognitive functioning as manifested by one or more of the following:
 1. Impairment in global intellectual performance
 - i.e. IQ of 70 or below
 2. Impairment in executive functioning
 - e.g. poor planning and organization, inflexibility, difficulty with behavioral inhibition
 3. Impairment in learning
 - e.g. lower academic achievement than expected for intellectual level; specific learning disability

DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

➤ B - Impaired neurocognitive functioning as manifested by one or more of the following:

4. Memory impairment

-e.g. problems remembering information learned recently; repeatedly making the same mistakes; difficulty remembering lengthy verbal instructions

5. Impairment in visual-spatial reasoning

-e.g. disorganized or poorly planned drawings or constructions; problems differentiating left from right

DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

➤ C. Impaired self-regulation manifested by one or more of the following:

1. Impairment in mood or behavioral regulation

-e.g. mood liability, negative affect or irritability, frequent behavioral outbursts

2. Attention deficit

-e.g. difficulty shifting attention; difficulty sustaining mental effort

3. Impairment in impulse control

-e.g. difficulty waiting turn; difficulty complying with the rules


DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

- D. Impairment in adaptive functioning as manifested by two or more of the following, one of which must be (1) or (2):
 1. Communication deficit
 - e.g. delayed acquisition of or difficulty understanding spoken language
 2. Impairment in social communication and interaction
 - e.g., overly friendly with strangers, difficulty reading social cues; difficulty understanding social consequences
 3. Impairment in daily living skills
 - e.g. delayed toileting, feeding, or bathing; difficulty managing daily schedule
 4. Impairment in motor skills
 - e.g., fine motor development; delayed attainment of gross motor milestones or ongoing deficits in gross motor function; deficits in coordination and balance.

DSM – 5: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

- E. Onset of disorder occurs in childhood.
- F. The disturbance causes clinically significant distress or impairment in social, academic, occupational or other important areas of functioning.
- G. The disorder is not better explained by the direct physiological effects associated with postnatal use of a substance (e.g. medication, alcohol or other drugs); medical condition (traumatic brain injury, delirium, dementia);

The Fetal Alcohol Exposure Picture

- Mild mental retardation
 - Specific learning disorders
 - Speech and language deficits
 - ADHD
 - Special education classes
 - Explosive emotionality
 - Low frustration tolerance / explosive temper
 - Short-lived affective outbursts wrongfully referred to as moods when the reality is their emotional stability is labile
- 

The Fetal Alcohol Exposure Picture

- Often childlike and naïve, they really want people to like them
- They have been ostracized most of their lives because they are "slow"
- Poor judgment, planning ability, capacity to foretell consequences of their behavior
- Difficulty doing simple math
 - e.g. Serial 7's: $100-7= \dots$ $93-7= \dots$ $86-7= \dots$

The Fetal Alcohol Exposure Picture

- Prior diagnoses: Bipolar, schizophrenia, ADHD, major depression
- Patients report being on a wide variety of medications that they do not find helpful.
- Patients may or may not continue to have the characteristic facial characteristics of FAE
 - widely set eyes, epicanthal folds in their eye lids, flat mid-face, short palpebral fissures, indistinct philtrum, small chin, irregularly shaped ears, small head - of course these features go away as the child ages

Discriminating
Features

Associated
Features

short palpebral
fissures

flat midface

short nose

indistinct philtrum

thin upper lip

epicanthal folds

low nasal bridge

minor ear
anomalies

micrognathia

In the Young Child

Prevalence of Drinking while Pregnant in the US

- 13% knowingly drink
- 1% drink heavily
- 3-4% binge drink (SAMHSA)
- 12% of pregnant women consume 5 or more drinks per month
- 50% of pregnancies are unplanned

FETAL ALCOHOL SPECTRUM DISORDER TERMINOLOGY

- Different organizations, different terms
 - SAMHSA, ICD-10, APA, IOM, etc.
- **FASD**: “an umbrella term describing the range of effects that can occur in an individual whose mother drank during pregnancy.”
- Growth retardation – facial dysmorphology – CNS abnormalities (OFC)
 - pFAS: partial FAS
 - NL growth vv ht/wt
 - ARND: alcohol-related neurodevelopmental dx
 - NL growth
 - ARBDs: alcohol-related birth defects
 - Major structural abnormalities

Three most common research methodologies to discover prevalence of FASD

- Clinic-based studies
- Positive surveillance of existing records often limited to a geographical area
- Active Case Ascertainment

Prevalence of Fetal Alcohol Spectrum Disorders – U.S.

- Fetal Alcohol Syndrome (FAS) occurs far more frequently than generally believed
 - 1 per 1000 live births
- Although estimates vary widely, when combined with the milder afflictions of Fetal Alcohol Spectrum Disorders (FASD), the Centers for Disease Control puts the frequency of FAS/FASD as high as 1 in 100.

Prevalence of Fetal Alcohol Spectrum Disorders – U.S.

- May et al. *Prevalence & Characteristics of Fetal Alcohol Spectrum Disorders*. *Pediatrics*, 2014, 134: 855-866.
 - Population study in a Midwestern community
 - Population = 160,000
 - Median income \$51,800
 - 11% below poverty
 - Surveyed 70% of 2,033 1st graders
 - 2.4 to 4.8% had FASD

Prevalence of Fetal Alcohol Spectrum Disorders – U.S.

- Susan Astley, Ph.D., & colleagues
 - rates of FASD in Washington state's foster care population were 10-15/1,000
- Dr. Pat Rojmahamongkol, et al
 - 17% of physicians correctly identified FAS
 - 74% were able to correctly identify Williams Syndrome
 - Williams Syndrome occurs in only 1/7,500.

Prevalence of Fetal Alcohol Spectrum Disorders – U.S.

➤ Chasnoff, et al

– 547 youth referred for severe behavioral disorders

- 50.6% African American
- 1.3% Asian
- 32.2% White
- 0.7% Native American
- 12.2% Biracial
- 3% Other/unknown

– **28.5%** of these youth had FASD

- 86.5% had never been diagnosed or were misdiagnosed
- 26.4% of these youth were misdiagnosed as having ADHD

Prevalence of Fetal Alcohol Spectrum Disorders – South Africa

- In a low SES, highly rural of South Africa in the Western Cape Province, FASD occurs in 182 – 259 per 1,000 children or 18-26 percent
 - May, et al “The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: Prevalence and characteristics.” *Drug and Alcohol Dependence* 159: 207 – 218

Prevalence of Fetal Alcohol Spectrum Disorders - Australia

- In a remote Aboriginal community of the Fitzroy Valley in Western Australia, FASD occurs in 120 per 1,000 children or 12 percent
 - Fitzpatrick et al, (2015) Prevalence of fetal alcohol syndrome in a population based sample of children living in remote Australia: The Lililwan* Project. *Journal of Paediatrics and Child Health* 51: 450-457.

Prevalence of Fetal Alcohol Spectrum Disorders - Russia

- The prevalence of FAS among adopted children from Eastern Europe/Russia) living in US 15 to 70/ 1,000
- Children Russian adoptees diagnosed ARND = 34%
- Records of alcohol-exposed pregnancy were significantly higher and constituted 19% to 41%
- Prospective adopting parents are concerned about the high risk of FASD among children adopted from Russia
 - Popova et al 2014. “What research is being done on prenatal alcohol exposure and fetal alcohol spectrum disorders in the Russian research community?” *Alcohol and Alcoholism* 49 (1): 85 – 95

Patients seen at JPH's Family Medicine
Clinic – Serving Community of 143,000
Median income \$33,809 & 95% Public Aid

| | |
|---|-----------------------|
| Total patients with Neurodevelopmental Disorders | 297 (49%) |
| Total Patients without Neurodevelopmental Disorders | 314 (51%) |
| Total | 611 (100%) |

Patients seen at Jackson Park Hospital's Family Medicine Clinic

| | |
|--|----------------------|
| Number of adult and child patients with clinical profile consistent with Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (NDA-PAE) | 237 (39%) |
| Number of adult patients <u>meeting strict criteria</u> for NDA-PAE | 87 (14%) |
| Number of adult patients meeting strict criteria for NDA-PAE minus criterion A but <u>patients are almost certain mother was drinking</u> | 40 (7%) |
| Number of adult patients meeting strict criteria for NDA-PAE minus criterion A – <u>no maternal history of drinking available</u> | 97 (16%) |

Patients seen at Jackson Park Hospital's Family Medicine Clinic

| | |
|--|---------------------|
| Number of child patients meeting strict criteria for neurobehavioral disorder associated with prenatal alcohol exposure | 11 (2%) |
| Number of child patients meeting strict criteria for neurobehavioral disorder associated with prenatal alcohol exposure minus criteria A but collaterals are almost certain the patient's mother was drinking | 2 (0.3%) |

There was no author disagreement about the children's source of neurodevelopmental disorder

Patients seen at Jackson Park Hospital's Family Medicine Clinic

| | |
|---|--------------------|
| Number of ADULT patients with other types of Neurodevelopmental Disorders | 45 (7%) |
| Number of ADULT patients where authors disagreed about the type of Neurodevelopmental Disorder | 7 (1%) |

Public Health

- Biotechnical Prevention
- Psychosocial Prevention

Biotechnical Approach

- CHOLINE 500 mg BID
- FOLATE 400 mcg BID
- OMEGA-3 500 mg BID
- VITAMIN A 2000 IU Daily

CHOLINE

- Precursor to acetylcholine, phosphatidyl choline
- Contributes to the integrity of the cell membrane

Postnatal Choline - Human Model

- Pilot study of 20 children with FASD, ages 2.5 to 5 years, who were randomly assigned (double blind) to placebo or 500mg choline supplementation per day for 9 months
- Plasma choline levels increased by 105% at month 1 and remained elevated at 6 months (105%) and 9 months (102)
- Tolerability was high with 17 participants completing the study.

Postnatal Choline Human Model

- By 6 months, the choline group showed a 9.9% increase in delayed sequential memory (a hippocampally dependent measure) compared to the placebo group which showed only a 2.2% increase (effect size 0.42).
- In the choline group, earlier age at enrolment was associated (non-significantly) with greater improvement in memory.
- At 9 months, global cognitive functioning (Mullen Scales) was increased by 8.6 points in the choline group vs. 4.3 points in the placebo group (effect size = 0.29).

Postnatal Choline – Human Model

- The greatest improvement on the Mullen was in fine motor skill (7.1 points for the active group vs 1 point for the placebo group, effect size = 0.59).
- Wozniak et al. Post-Natal Choline Supplementation in Children with FASD: Preliminary Safety and Efficacy Results; University of Minnesota

Postnatal Choline – Human Model

- Double blind, Randomized placebo-controlled pilot trial in children (aged 2.5 – 5) with FASD (N-60) who received 500mg of choline or placebo daily for 9 months.
- Choline was well tolerated.
- Choline supplementation improved the secondary outcome Elicited Imitation Memory only after immediate recall performance was controlled for, and the outcome was moderated by age.

Postnatal Choline – Human Model

- The treatment effect on EI items recalled was significant in the younger participants (2.5- to \leq 4.0 year olds); the younger choline group showed an increase of 12-14% greater than the younger placebo group or delayed recall measures during treatment.
- The pilot suggests that an additional evaluation of choline supplementation be an intervention for memory functioning in children with FASD is warranted.
- Wozniak et al. (2015 – on line). Choline supplementation in children with FASD. American Journal of Clinical Nutrition. DOI: 103945/ajcn.114.099168.

Postnatal Choline – Human Model

- Thomas J, et al. Choline Supplementation in Children With Fetal Alcohol Spectrum Disorders; San Diego State University
- Randomized, Control Trial in 5 – 10 year olds
- Changes in cognitive function as measured by performance on neuropsychological tasks of learning/memory, executive functions, and attention
- Children's Behavior Checklist (CBCL), Behavioral Rating Inventory of Executive Function (BRIEF) - Baseline and 6 weeks; Parent questionnaires about children's behavioral functioning will assess changes.

Prenatal Choline – Human RTC

- Alcohol using and non-alcohol using women randomized to one of three multivitamin/mineral supplement groups: None; multivitamins/minerals; and multivitamins/minerals plus choline.
- Children (N-367) were tested at 6 months with the Bayley Scales of Infant Development yielding standard scores for Mental Development Index (MDI), Psychomotor Development, and Behavior.
- MDI was significantly impacted by peri-conceptual alcohol dose ($p < .001$)
- Micronutrient supplementation had a protective effect ($p < .005$).
- Coles et al. Dose and Timing of Prenatal Alcohol Exposure and Maternal Nutritional Supplements. *Maternal and Child Health Journal*, On-Line July 12, 2015 – DOI 10.1007/s10995-015-1779-x

Perinatal Phosphatidylcholine

Supplementation and Early Childhood Behavior Problems: Evidence for CHRNA7

Moderation – Ross et al, JAPA in press

- $\alpha 7$ -Nicotinic receptors are involved in the final maturation of GABA inhibitory synapses before birth. Choline at levels found in the amniotic fluid is an agonist at $\alpha 7$ -nicotinic receptors.
- A double-blind placebo-controlled trial found high-dose oral phosphatidylcholine supplementation during pregnancy to increase maternal amniotic fluid choline levels and enhance fetal development of cerebral inhibition decreasing childhood behavior problems.

Perinatal Phosphatidylcholine

Supplementation and Early Childhood Behavior Problems: Evidence for CHRNA7

Moderation – Ross et al, JAPA in press

- CHRNA7, the $\alpha 7$ -nicotinic acetylcholine receptor gene, has been associated with schizophrenia, autism, and attention deficit hyperactivity disorder.
- Maternal phosphatidylcholine treatment may, by increasing activation of the $\alpha 7$ -nicotinic acetylcholine receptor, alter the development of behavior problems in early childhood that can presage later mental illness

TAKE AWAY POINTS

- Choline supplementation "can alter brain development following a developmental insult.
- Early dietary interventions may reduce the severity of some fetal alcohol effects, even when administered after birth." (Thomas)
- Educate and involve OB/Gynes, Pediatricians, Psychiatrists, schools, DCFS, prison system, and vitamin companies.

