

Prenatal Diagnosis of FASD – Is It Possible?

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Introduction

- Background
- Role of ultrasound in prenatal diagnosis
- Current research studies
- Integration with other CIFASD projects
- Future Directions
- Recap

Diagnosing Fetal Alcohol Syndrome

- Prenatal maternal alcohol use
- Growth deficiency
- Central nervous system abnormalities
- Dysmorphic features
 - Short palpebral fissures
 - Indistinct philtrum
 - Thin upper lip

Caucasian

African

Why Attempt Prenatal Diagnosis of FASD?

- Most FASD diagnosed relatively late in child's life
- Early identification of affected individuals opens possibility of early intervention
- Early interventions potentially lead to improved outcome
- Earliest opportunity to impact outcome is during fetal life

Pathways To Identification of At Risk Individuals

- Increasingly screening for substance abuse / tobacco/alcohol part of routine prenatal care
- Multiple tools in use for identification and quantification of alcohol use in pregnancy
- Use of such screening tools yields an enriched population in which secondary screening tools may be applied

Further Evaluation of At Risk Groups

- Detailed questionnaires
- Face to Face Interviews
- Counseling / Education
- Behavior Change
- Evaluation of Fetus and Newborn
 - Imaging
 - Dysmorphology
 - Developmental studies

Ultrasound As a Screening Tool

- Ultrasound allows evaluation of fetal anatomy and detection of abnormalities
- Such abnormalities may be structural:
 - Heart Defects
 - Central Nervous System Abnormalities
 - Cleft Lip & Palate etc etc
- Or may be “soft signs” such as used for detection of T21

“Soft Signs”

- Ultrasound findings that do not necessarily correspond to a structural defect
- May be temporary finding that resolves or disappears
- Examples:
 - Nuchal translucency
 - Nuchal thickening
 - Echogenic bowel
 - Absent / Short Nasal Bone

Ultrasound and Functional Assessment

- Ultrasound can be used to assess fetal well-being and behavior
- Amniotic fluid assessment
- Fetal movement
 - Spontaneous
 - Evoked
- Widely used clinically in other at risk settings – IUGR, Hypertension etc

Newborn Assessment and Diagnosis of FASD

- Why not just assess all newborns for features of FASD?
 - Is such an assessment possible?
 - How accurate is such an evaluation?
 - Don't you need special training?
 - What about infants who have FASD without structural features of FAS?

Proposed Schema

- Screen all pregnant women for substance abuse
- Evaluate all screen positive subjects in more detail
- Develop an at risk population for targeted ultrasound evaluation prenatally
- Evaluate all newborns in this enriched population
 - At birth
 - Sequentially thereafter

What Should We Look For With Ultrasound?

- Major structural defects more common in infants born to women who drink
 - Cardiac defects
 - Clefts
 - CNS abnormalities
- BUT
 - Such major anomalies still relatively rare and not adequate for use in screening for FASD

CNS Abnormalities

- Cerebral growth and development
- Cerebellar development
- Corpus Callosum Development
- Detailed evaluation requires relatively high-tech imaging and special expertise
 - MRI
 - 3DUS
- May not be amenable to being part of a screening strategy

What About Growth?

- IUGR more common in infants of women who drink
- Microcephaly more common in infants of women who drink
- BUT
 - Still not enough to detect most cases of FASD

Proposal

- Develop Ultrasound Toolset to Allow prenatal diagnosis of FASD
- Use standardized assessment of growth
- Careful evaluation of Fetal Anatomy
- Assessment of specific neurological structures
- Addition of new measures of CNS anatomy

Current Research

- In Ukraine:
 - Relatively high prevalence of alcohol use in pregnancy
 - Availability of population amenable to screening
 - Availability of adequate imaging
 - Willingness to participate and effect change

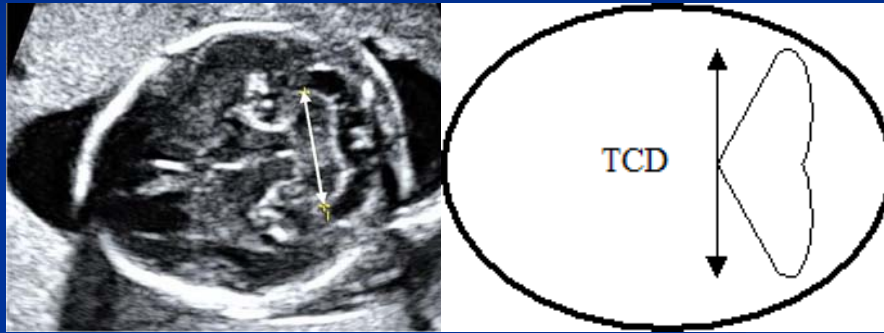
Ultrasound – Start Simple

- Routine serial ultrasound exams
- Studies at ~24 & ~34 wks compared
- Standard Two-Dimensional Ultrasound
- Routine biometry
- Routine anatomic evaluation
- Specific brain measurements

Biometry & Anatomy

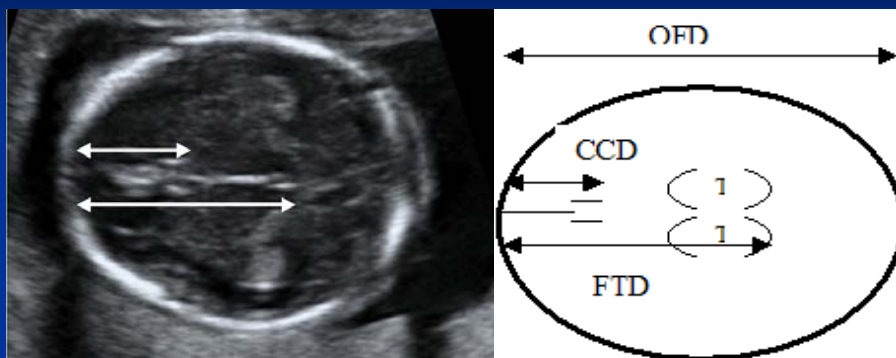
- Head Size - Biparietal Diameter & Head Circumference (BPD & HC)
- Abdominal Circumference (AC)
- Femur Length (FL)
- Estimated Fetal Weight
- Systematic Anatomic Evaluation

Specific Brain Measurements



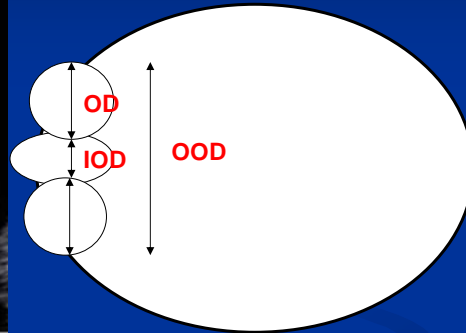
TCD = Transverse Cerebellar Diameter

Specific Brain Measurements



OFD = Occipital Frontal Diameter
CCD = Caval Calverial Distance
FTD = Frontothalamic Distance

Orbital Measurements



OD = Orbital Diameter
IOD = Inter Orbital Diameter
OOD = Outer Orbital Diameter

Current Research

- 6,745 pregnant women screened by TWEAK and AUDIT Questionnaires
- Inclusion criteria:
 - Gestational age: 10-40 wks
 - Alcohol exposed group (1-2 drinks x 10 per month)
 - Control group (1:1 ratio)

Subject Population

- 166 Subjects
 - 84 Alcohol-exposed
 - 82 Controls

Maternal Demographics

| Characteristic | Exposed (n=84) | Controls (n=82) | p-value |
|-------------------------------|----------------|-----------------|---------|
| Maternal age | 26.2 ± 5.7 | 24.7 ± 4.1 | NS |
| Marital Status: Single (%) | 10.7 | 1.2 | 0.017 |
| Low Socio-economic Status (%) | 51.2 | 31.7 | 0.006 |
| Vitamin Use (%) | 64.3 | 89.0 | 0.001 |
| Smoking (%) | 50.6 | 2.5 | 0.001 |

Alcohol Consumption Pattern Among Alcohol-Exposed & Comparison Subjects (Signs of Risk Drinking)

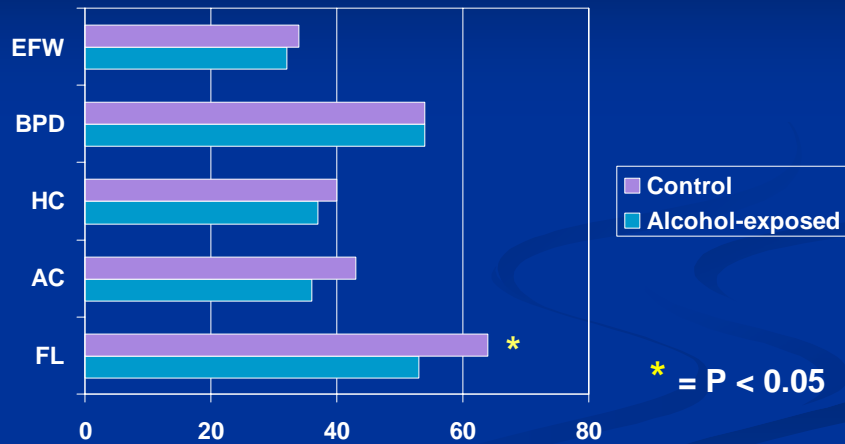
| Signs of Risk Drinking | Alcohol Exposed | No Alcohol | p-value |
|------------------------|-----------------|------------|------------------|
| | <u>%</u> | <u>%</u> | |
| Tolerance ≥ 6 | 67.1 | 1.4 | <0.001 |
| AUDIT ≥ 6 | 27.4 | 0.0 | <0.001 |
| TWEAK ≥ 6 | 69.6 | 1.4 | <0.001 |

* AUDIT & TWEAK are alcohol screening questionnaires

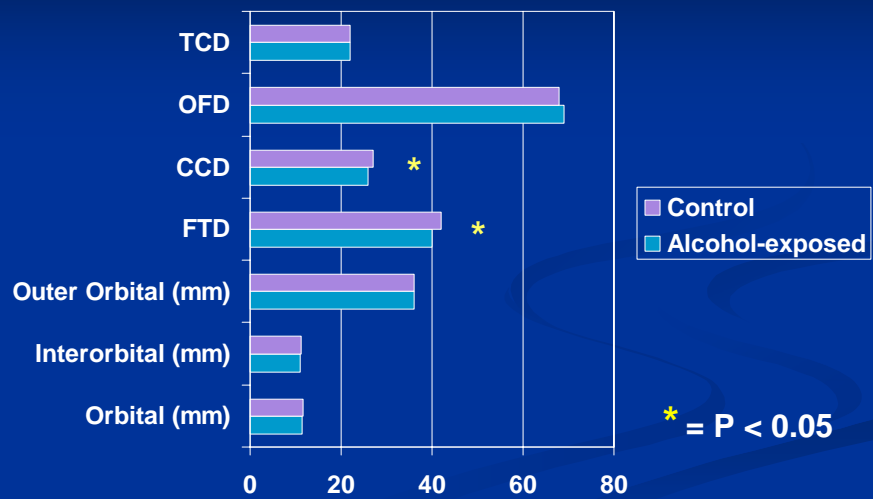
Alcohol Consumption Pattern Among Alcohol-Exposed & Comparison Subjects (Absolute Ounces of Alcohol)

| Absolute Ounces of Alcohol (AA) | Alcohol Exposed | No Alcohol | p-value |
|---------------------------------|--------------------------------|--------------------------------|------------------|
| | <u>Mean\pms.d</u> | <u>Mean\pms.d</u> | |
| <u>Periconceptual period:</u> | | | |
| AA per day | 1.07 \pm 1.4 | 0.02 \pm 0.2 | <0.001 |
| AA per drinking day | 5.01 \pm 4.6 | 2.96 \pm 4.8 | 0.399 |
| <u>Pregnancy:</u> | | | |
| AA per day | 0.14 \pm 0.3 | 0.0004 \pm 0.002 | <0.001 |
| AA per drinking day | 2.23 \pm 3.6 | 0.20 \pm 0.00 | 0.442 |

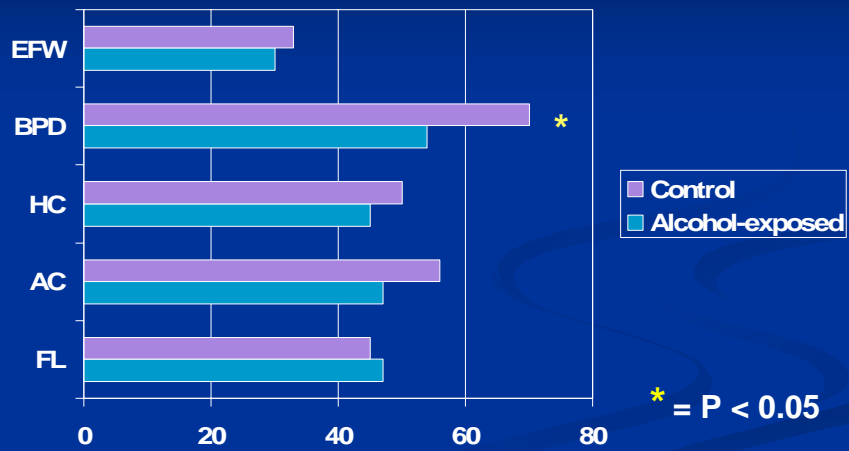
2nd Trimester Ultrasound



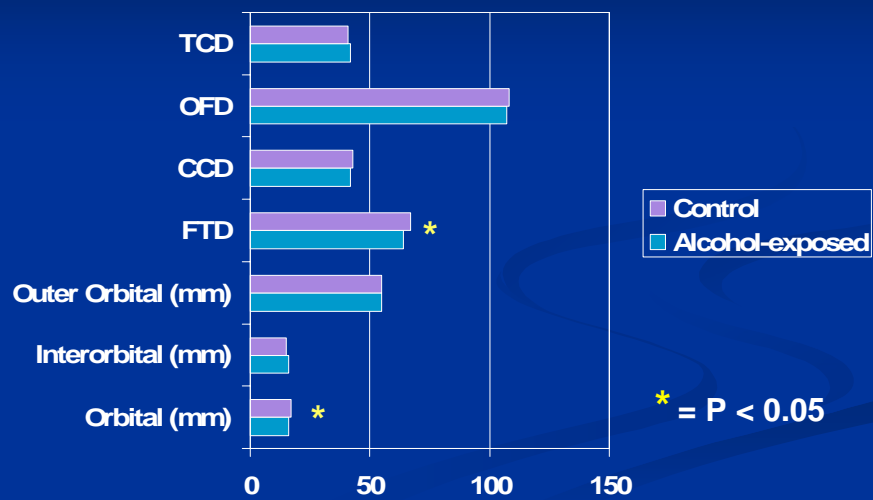
2nd Trimester Ultrasound



3rd Trimester Ultrasound



3rd Trimester Ultrasound



Summary

- Alcohol exposed fetuses have:
 - Reduced frontothalamic distance in both 2nd and 3rd trimesters
 - Reduced caval calvarial distance in 2nd trimester
 - Reduced BPD and orbital diameter in 3rd trimester

Newborn Assessment

- Physical exam for all newborns
 - FAS, not FAS, deferred – local pediatrician
 - FAS, not FAS, deferred – dysmorphologist
 - Deferred reexamined later – and FASD diagnosis based on further exam.....
- Bayley at 6/12 and 12/12

Correlation of US findings with Dysmorphology data

Pregnant Women:

- Alcohol-exposed (n=84)
moderate/heavy alcohol exposure
- Comparison (n=82)
no/minimal alcohol exposure

Newborn Children:

- FASD (n=21) (3 FAS & 18 Deferred)
- No FASD (n=121)

Fetal Growth Measures (2nd trimester) FASD vs. No FASD

| Fetal Growth Measures* | FASD (n=21) | No FASD (n=121) | p-value |
|---------------------------|----------------|--------------------|--------------|
| | Mean±sd | Mean±sd | |
| Estimated fetal wt % | 27.6±4.2 | 35.0±1.8 | 0.105 |
| Biparietal diameter % | 47.0±7.1 | 56.1±2.9 | 0.236 |
| Head circumference % | 28.5±4.4 | 41.9±1.8 | 0.006 |
| Abdominal circumference % | 27.2±7.6 | 43.3±3.2 | 0.053 |
| Femur length % | 47.0±5.4 | 62.5±2.2 | 0.010 |

* All models adjusted for smoking

Fetal Growth Measures (3rd trimester) FASD vs. No FASD

| Fetal Growth Measures* | FASD (n=21) | No FASD (n=120) | p-value |
|---------------------------|----------------|--------------------|--------------|
| | Mean±sd | Mean±sd | |
| Estimated fetal wt % | 24.2±4.0 | 33.4±2.3 | 0.054 |
| Biparietal diameter % | 48.9±7.0 | 66.7±4.2 | 0.033 |
| Head circumference % | 33.9±5.6 | 53.8±3.3 | 0.003 |
| Abdominal circumference % | 47.3±6.3 | 54.2±3.5 | 0.350 |
| Femur length % | 30.9±6.3 | 51.9±3.6 | 0.005 |

* All models adjusted for smoking

Fetal Brain Measures (3rd trimester) FASD vs. No FASD

| Brain Measure | FASD (N=21) | No FASD (N=120) | p-value* |
|--|------------------------|------------------------|---------------------|
| | Mean±s.e. | Mean±s.e. | |
| Transverse Cerebella Diameter (mm) | 40.8±0.4 | 41.9±0.5 | 0.178 |
| Occipital Frontal Diameter (mm) | 107.4±2.5 | 107.8±1.5 | 0.888 |
| Caval-Calvarial Distance (mm) | 41.6±1.0 | 43.3±0.6 | 0.127 |
| <u>Frontothalamic Distance (mm)</u> | <u>63.9±1.2</u> | <u>66.3±0.7</u> | <u>0.080</u> |
| Outer Orbital Diameter (mm) | 54.0±0.9 | 55.5±0.6 | 0.180 |
| Interorbital Distance (mm) | 14.9±0.6 | 15.6±0.3 | 0.301 |
| <u>Orbital Diameter (mm)</u> | <u>16.8±0.4</u> | <u>16.9±0.3</u> | <u>0.880</u> |

* Adjusted for gestational age & smoking in pregnancy

Summary

- Significant differences on selected somatic and brain growth measures on ultrasound between infants with some structural features of FAS and those without on newborn physical exam:
 - Head circumference percentile
 - BPD percentile (3rd trimester)
 - Abdominal circumference percentile (2nd trimester)
 - Femur length percentile
 - Frontothalamic distance (3rd trimester)

Next Steps

- **Further correlation of prenatal ultrasound findings with postnatal assessment of:**
 - **Dysmorphology**
 - **CNS imaging**
 - **Neurodevelopment**
- **Evaluation of predictive value of morphologic sonographic markers**

Next Steps (2)

- Addition of Measures of Fetal Behavior
- Correlation of Morphology with Fetal Behavior Measures
- Development of screening triage tool combining best set of measures at specific gestational ages
- Test tool in practice

Measures of Fetal Behavior

- Biophysical Profile
- Spontaneous “startles”
- Evoked startles

What next?

- Evaluate ultrasound data further
- Add in new project(s)
- The eye
- Dentition / facial skeleton
- Facial dysmorphology

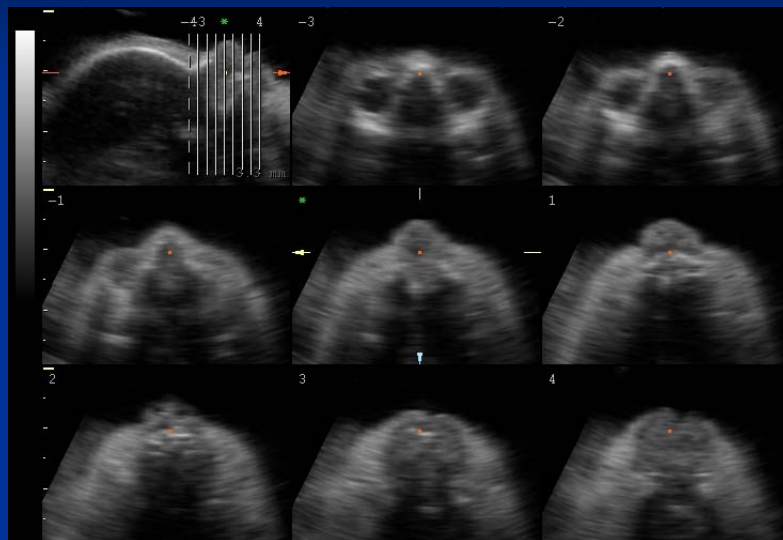
New Ultrasound Projects 1

- Effects of alcohol on development of eye
 - Prenatal measurements of orbital dimensions already in place – additional laterality measurements being recorded
 - Add In 3DUS?
 - Add in postnatal assessment of globe dimensions and structure of eye
 - Already have interest and expertise in Ukraine
 - Need specialized pediatric ophthalmic transducer

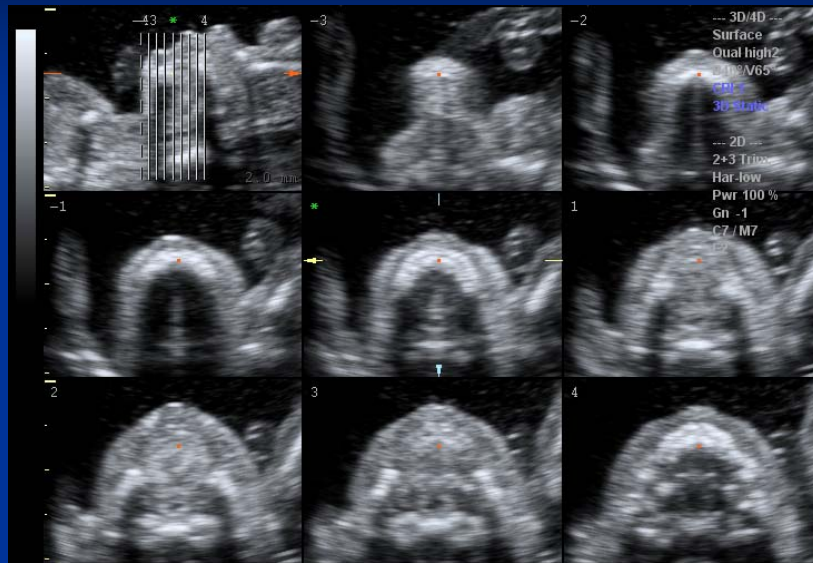
New Ultrasound Projects 2

- Effects of alcohol on dentition / facial skeleton
- Equipment in place and expertise developing to allow imaging of fetal facial skeleton using 3D/4DUS
- Can assess facial skeleton using various modalities including 3D rendering, multiplanar and multislice

Multislice Orbits to Maxilla



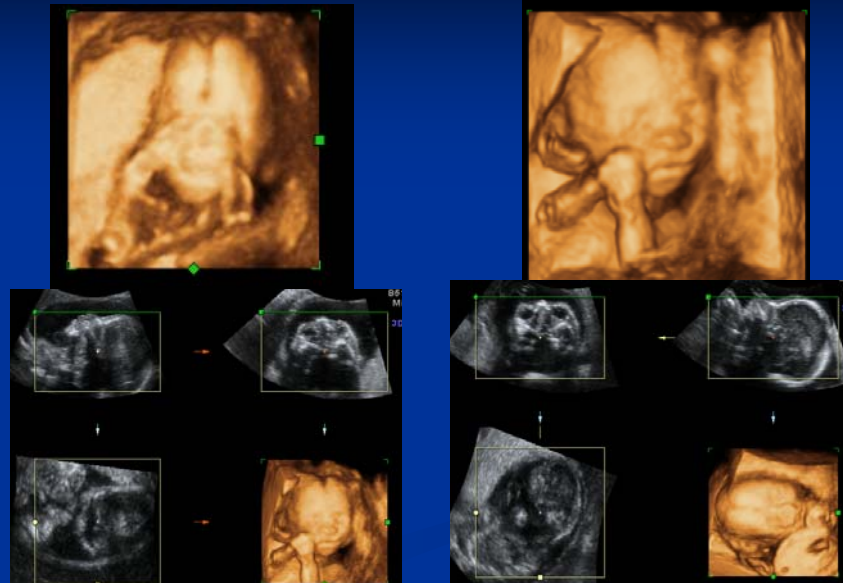
Multislice Maxilla to Mandible



New Ultrasound Projects 3

- Prenatal vs. Postnatal dysmorphology
- Equipment in place and expertise developing to allow imaging of fetal face using 3D/4DUS
- Potential for developing sonographic measures of facial structures
- Potential for comparing US and examination

Rendering & Multiplanar



Thank You

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