Impact of Maternal Obesity on Fetuses’ and Children’s Neurodevelopment

March 15th, 2023

Dr. Lynne Ausman | Dr. Tomo Tarui
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Jordan Nutrition Innovation Lab Webinar

Impact of Maternal Obesity on Fetuses’ and Children’s Neurodevelopment

Wednesday, March 15th, 2023
3:30-4:30 pm Jordan Time | 7:30-8:30 am US Eastern

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Impact of maternal obesity on fetuses' and children’s neurodevelopment

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March 15, 2023
DISCLOSURE

• No relevant financial relationships have been reported in the past 24 months with an ACGME-defined ineligible company.

• I won’t be discussing off-label uses for purposes other than that for which the food and drug administration (US) approved the product use.

• I will discuss the investigative analysis of fetal brain MRI beyond clinical practice.
OVERVIEW

1. Impact of maternal obesity pregnancy on offspring children’s neurodevelopment
2. How to assess the living fetal brain?
3. Preliminary data on the altered fetal brain development of fetuses of pregnant women with obesity
Maternal obesity [pre-pregnancy body mass index (BMI) ≥ 30 kg/m²] is an epidemiological public health risk all over the world (US 29%).

Maternal obesity has transgenerational health impacts on their offspring children’s health.

The estimated distribution of obese pregnant women—the global perspective (184 countries, 2014)

Chen et al. 2018
Strauss, 2021
NEURODEVELOPMENTAL IMPACTS OF MATERNAL OBESITY

• Offspring children of maternal obesity pregnancy have increased risks of cardiovascular, metabolic, neurodevelopmental, and psychiatric disorders.

• Large-scale national registry studies reported that maternal obesity increases the risk of various neurodevelopmental disorders (NDD) in offspring
  o Attention Deficit Hyperactivity Disorder (ADHD): + 47~89% risk
  o Autism Spectrum Disorder (ASD): 1.5~2-fold risk
  o Anxiety and depression
ADHD

- Prevalence: Jordan: 6.2 ~ 40.6% (Nafi et al. 2011, Al Azzam et al. 2016), US: 8-10%
- ADHD manifests as hyperactivity, impulsiveness, and poor attention, resulting in impairments in working memory, executive function, and impulsive behaviors.
- Causes: Genetics? Environmental?
- Four Nordic birth cohort studies found that maternal body mass index (BMI) dose-dependently increases the risk for children’s ADHD symptoms. Excessive gestational weight gain increases risk.

<table>
<thead>
<tr>
<th>Severity of maternal obesity</th>
<th>% Increased risk of ADHD in children</th>
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<tbody>
<tr>
<td>Overweight (BMI 25 ≤, &lt;30)</td>
<td>+ 23~28%</td>
</tr>
<tr>
<td>Obesity (BMI 30 ≤, &lt;35)</td>
<td>+ 47~89%</td>
</tr>
<tr>
<td>Severe obesity (BMI ≥ 35)</td>
<td>+ 88~95%</td>
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AUTISM SPECTRUM DISORDER (ASD)

- Prevalence: Jordan: ?, UAE 0.29% (29/10,000, Eapen et al. 2007), Oman 0.14% (1.4/10,000, Al-Farsi et al. 2011), US 2.3% (1/44, ADDM Network). Diagnostic factor.

- ASD manifests as difficulties in communication and interaction with other people, restricted interest, and repetitive behaviors (DSM-V, NICHD)

- Causes: Genetics? Environmental?

- Pre-pregnancy obesity increases the odds ratio for ASD in offspring by 1.3~2.05 -fold

- Excessive gestational weight gain also increases the risk for ASD in children by 10~58%
ALTERED BRAIN DEVELOPMENT IN OFFSPRING OF WOMEN WITH OBESITY

• Offspring children of maternal obesity pregnancy had structural and functional alterations in brain
  o Smaller hippocampus in school age boys (but not in girls) (Alves et al. 2020)
  o Altered white matter integrity (higher fraction anisotropy and lower mean diffusivity) in children and adults (Verdejo-Roman et al. 2019)
• Intrauterine origin? (Neonatal brain study)
  o Poorer white matter maturation in newborns (Ou et al. 2015)
  o Decreased functional connectivity in the dorsal anterior cingulate cortex (Li et al. 2016)
• Information on fetal brain development is lacking
MOUSE AND RAT STUDY

• Animal (mouse, rat) models of diet-induced obesity during pregnancy
• Maternal obesity affects offspring’s intrauterine brain development
  o Increased neuroprogenitor proliferation
  o Altered neuronal differentiation and maturation
  o Altered DNA methylation patterns
• Mechanisms
  o Altered lipid metabolism
  o Inflammation
  o Oxidative stress

Information on human fetal brain development is lacking

ASSESSING HUMAN BRAIN

Current clinical practice

Anatomic Diagnosis

- US
- MRI

Genetic Diagnosis

- Amniocentesis
- Chorionic villi sampling
- Maternal blood

L1CAM mutation+: c.2014 C>T point mutation resulting Q(Gln)672X (stop codon mutation)
DYNAMIC DEVELOPMENT OF FETAL BRAIN
VULNERABLE OR POTENTIAL?

Fetal Growth From 8 to 40 Weeks

Neurulation
- Neural plate
- Neural tube
- Day 18
- Day 20
- Day 22

Neurogenesis, Migration
- Midline formation
  (Segmentation, Regionalization)
- Gyrification,
  Sulcal development

Gyrification, Sulcal development

Novel fetal MRI technology

- **Quantitative analysis of fetal brain MRI**

  - Artifact correction
  - Segmentation
  - Volumetric analysis
  - 3D cerebral surface analysis

28 GW

Maria Murgasova, Oxford
DETERMINE IMPACT OF MATERNAL OBESITY ON REGIONAL FETAL BRAIN GROWTH

- Prospective observational study at Tufts Medical Center
  - Inclusion: Healthy pregnant women aged 15 to 45, singleton pregnancy, gestational week between 18 and 36, and both fetal sexes
  - Exclusion: Multiple pregnancies, abnormal fetal sonographic findings or MRI findings, or known chromosomal abnormalities
- Offered research fetal brain MRI scans
- Segmentation and Volumetric analysis using Freeview.
- Statistical analysis: Comparison of non-linear growth regression models between BMI groups.
BRAIN REGIONAL VOLUMETRIC ANALYSIS OF FETAL BRAIN

- Right cortical plate
- Left cortical plate
- Right subcortical parenchyma
- Left subcortical parenchyma
- Cerebellar hemispheres
- Cerebellar vermis
- Lateral ventricles
- IIIrd ventricle
- Brainstem
ACCELERATED FETAL BRAIN GROWTH IN MATERNAL OBESITY PREGNANCY

a. Left cortical plate

b. Right cortical plate

c. Whole cortical plate

d. Whole brain

e. Subcortical parenchyma

f. Cerebellum

\[ p = 0.0003^* \]

\[ p = 0.0002^* \]

\[ p = 0.0614 \]

\[ p = 0.0487^* \]

\[ p = 0.5813 \]
CORTICAL PLATE IS SPECIFICALLY BIGGER RELATIVE TO WHOLE BRAIN

- a. Left cortical plate / Whole brain
- b. Right cortical plate / Whole brain
- c. Whole cortical plate / Whole brain
- d. Whole cerebellum / Whole brain
ACCELERATED FETAL BRAIN GROWTH IN PREGNANCY COMPLICATED WITH MATERNAL OBESITY

- Maternal high BMI had increased regional brain volume cortical plate and whole cerebellum
- Cortical plate is specifically increased volume compared to the rest of the fetal brain

Limitations
- Need larger cohort study
- Longitudinal analysis (fetal to neonatal brain development)
- Association with neurodevelopmental outcomes

Infants/toddlers with ASD have larger brain
Children and adults with ASD have altered connectivity, gyrification
FETAL BRAIN DIFFUSION MRI ANALYSIS - AXONAL, CONNECTION DEVELOPMENT

- Diffusion analysis
  - Apparent Diffusion Coefficient (ADC), Fraction Anisotropy (FA) analyses
  - Diffusion tensor imaging (DTI) analysis

Reviewed in Tournier, 2019
Phillips et al, 2012

Isotropic diffusion
Anisotropic diffusion along fiber tracts
Typical ODF at fiber crossing
raw dMRI signal
fibre orientations
tractography

Reviewed in Tournier, 2019
Validation of *In utero* Tractography of Human Fetal Commissural and Internal Capsule Fibers with Histological Structure Tensor Analysis

Christian Mitter¹,²*, András Jakab³, Peter C. Brugger⁴, Gerda Ricken², Gerlinde M. Gruber⁴, Dieter Bettelheim⁵, Anke Scharrer⁶, Georg Langs³, Johannes A. Hainfellner², Daniela Prayer¹ and Gregor Kasprian¹

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sue MRI,
SULCAL PATTERN MATCHING AND SIMILARITY ANALYSIS

Calculate similarity index (SI)

Sulcal position

Compare corresponding sulcal basins

Compare inter-sulcal relationship

Template Subject

Kiho Im, PhD
FNNDSC
Boston Children’s Hospital

Fetal-Neonatal Neuroimaging
Developmental Science Center
Boston Children’s Hospital
Disorganized Patterns of Sulcal Position in Fetal Brains with Agenesis of Corpus Callosum

Tomo Tarui1,2,3,5, Neel Madan7, Nabgha Farhat1,2, Rie Kitano5, Asye Ceren Tanranitan1,2, George Graham8, Borjan Gagoski1,3, Alexa Craig9, Caitlin K. Rollins4, Cynthia Ortinau10,11, Vidya Iyer5, Rudolph Pienaar1,3, Diana W. Bianchi12, P. Ellen Grant1,2,3 and Kiho Im1,2

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Fetuses with isolated agenesis of corpus callosum have altered sulcal position
Individual variations exist in sulcal positional patterns

Tarui, Kitano, Bianchi, Grant, Im et al. 2018
FETAL CEREBRAL SURFACE ANALYSIS
REGIONAL ANALYSIS

• Cerebral cortex functional regionalization originates in fetal life

Regional Alterations in Cortical Sulcal Depth in Living Fetuses with Down Syndrome

Hyuk Jin Yun1,2, Juan David Ruiz Perez1,2, Patricia Sosa1,2, J. Alejandro Valdés1,2, Neel Madan3, Rie Kitano4, Shizuko Akiyama4, Brian G. Skotko5, Henry A. Feldman2,6, Diana W. Bianchi7, P. Ellen Grant1,2,8, Tomo Tarui9 and Kiho Im1,2

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Fetuses with Down syndrome (DS) have regional specific altered sulcal depth

1. Executive function
   Multimodal processing
2. Auditory language and memory
3. Fine motor
4. Visuomotor processing

Developmental phenotype specific to children with DS

Yun, Kitano, Akiyama, Bianchi, Tarui, Im et al. 2020
SUMMARY

- Maternal obesity increases risk of offspring’s ADHD or autism spectrum disorder by 1.5 to 2-folds
- Human brain imaging studies and animal model studies suggest intrauterine origin of altered fetal brain development
- Quantitative analysis of fetal brain MRI revealed that maternal obesity increased region-specific fetal brain growth
- Multimodal fetal brain MRI analysis can assess comprehensive human fetal brain development
- Understanding impact of maternal obesity on fetuses' and children’s neurodevelopment may open doors for prevention/intervention
FATTY ACID AS A TREATMENT OF NEURODEVELOPMENTAL DISORDERS

• LCPUFAs have been thought to play critical nutritional roles in various neurodevelopmental and psychiatric disorders

ADHD
• Studies in children and adults with ADHD found lower n-3 LCPUFA blood levels (especially DHA). Milte et al., 2015; Antalis et al., 2006; Laasonen et al., 2009
• Nine randomized control trials since 2012 tested efficacy of LCPUFAs on ADHD symptoms
  o 7/9 studies reported some improved ADHD symptoms by various forms and contents of LCPUFAs supplements
    o Milte et al., 2012; Perera et al., 2012; Richardson et al., 2012; Widenhorn-Muller et al., 2014; Bos et al., 2015; Barragan et al., 2017; Dopfner et al., 2021
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Q&A

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