Determinants of the Infant Microbiome and Childhood Obesity: Mom Matters

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The intractable challenge of obesity
To Stem Obesity, Start Before Birth

By JANE E. BRODY  JULY 11, 2016 5:43 AM  77
I. The human microbiome and the influence of pregnancy

II. The infant microbiome development: mom matters

III. Impacts on maternal-offspring transmission of microbiota and their childhood obesity risk
   I. In depth: Maternal weight, C-section and gut microbiota

IV. Restoring the missing microbes through vaginal seeding: what we know and what we don’t know

V. Conclusions
The human microbiome: An extended view of ourselves

- ~40 trillion microbes
- **Bacteria**, viruses, archaea, and fungi
- Co-evolved with us; mostly commensal
- Inhabit all barrier surfaces
- Many useful functions
  - Educate immune system
  - Regulate mucosal barrier
  - Extract energy & produce SCFAs and vitamins
- Modifiable (unlike our genome)
- Environments, lifestyle, drugs and probiotics

Gut microbiome in pregnancy

- Compared to 1\textsuperscript{st} trimester, 3\textsuperscript{rd} trimester stool microbiota (n=91 women):  
  - More abundant  
  - Less diverse  
  - Enriched in \textit{Proteobacteria}
- 3\textsuperscript{rd} trimester gut microbiota (vs. 1\textsuperscript{st}) transferred phenotype of insulin resistance obesity to GF mice\textsuperscript{1}

- \textbf{Outstanding question:} Are there programmed gut microbiota changes during pregnancy and, if so, are these changes adaptive for growth and health of mother and fetus?

1. Koren O et al \textit{Cell} 2012
Vaginal microbiome in pregnancy

- Lactobacilli most prevalent
- More stable in pregnancy than in non-pregnant state
- Non-lactobacillus dominant ecosystems tend to be more variable in pregnancy

- Large prospective studies needed to:
  - Examine pregnancy-related changes by race
  - Understand how vaginal microbiota affect maternal and offspring health
  - Identify factors (e.g., diet) to manipulate vaginal microbiota

1. DiGiulio DB et al PNAS 2015
Microbiome at the feto-placental interface?

• ‘The fetus lies in a sterile environment’—Henry Tissier of the Pasteur Institute, 1900

• 2014 study suggested unique placental microbiome1

• Bacterial DNA have also been found in amniotic fluid, fetal membranes and infant meconium, suggesting possible low-biomass maternal-fetal transfer of microbiota2

• However, a recent study showed that the findings of bacteria in the placenta may be due to contamination3

Mother provides newborn pioneering microbiota

- First *major* exposure to live microbiota comes at birth
- Exposure to maternal vaginal and fecal microbiota at birth via membrane rupture and/or vaginal delivery
- Pioneering microbiota (e.g. *bifidobacteria infantis*) are fed by human milk oligosaccharides found in breast milk

Gut microbiome is highly formative until ~3 years of age

Yatsuneko et al *Nature* 2012
Gut microbiome maturation during early life

Bokulich NA et al Sci Tran Med 2016
Altering early-life gut microbiota development has lasting metabolic consequences in mice

Cox L et al. *Cell* 2014
Prenatal Antibiotics and Risk of Offspring Obesity at Age 7 Years

Adjusted for child sex, maternal receipt of public assistance, ethnicity, maternal age, pre-pregnancy BMI, birth weight, and delivery mode

Mueller NT. et al *IJO* 2014
Birth mode alters acquisition of newborn microbiota

Vaginal Delivery

C-section Delivery

Dominguez-Bello et al PNAS 2010
The impact of C-section on the composition of infant microbiome has been shown to persist up to 2 years\textsuperscript{1,2}

C-section delivery rates have increased ~ 80% in 20 y

Cesarean Section Rates in OECD Countries: 1990, 2000 and 2009

C-section delivery has been linked to immune disorders...

**Asthma**
- Thavagnanam S et al. *Clin Exp Allergy* 2008
- Roduit C et al. *Thorax* 2009
- Sevelsted A et al. *Pediatrics* 2015
- Black M et al. 2016

**Respiratory infections**
- Sevelsted A et al. *Pediatrics* 2015
- Kristensen K et al. *Pediatr Infect Dis J* 2015
- Kristensen K et al. *J Allergy Clin Immunol* 2016

**Celiac disease**
- Decker E et al. 2010
- Marild K et al. *Gastroenterology* 2012

**Juvenile arthritis**
- Sevelsted A et al. *Pediatrics* 2015
- Kristensen K et al. *J Allergy Clin Immunol* 2016
Cesarean delivery has also been associated with higher offspring risk of childhood obesity.

Relative Risk of Childhood Obesity

Adjusted for child sex, maternal receipt of public assistance, ethnicity, maternal age, pre-pregnancy BMI, birth weight, and prenatal antibiotics

Mueller NT et al. IJO. 2014
What is the role of the maternal microbiome in the intergenerational association of obesity?

NOTES: Obesity is defined as body mass index (BMI) greater than or equal to the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.

NOTES: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates using age groups 20–39, 40–59, and 60–74. Overweight is body mass index (BMI) of 25 kg/m² or greater but less than 30 kg/m²; obesity is BMI greater than or equal to 30; and extreme obesity is BMI greater than or equal to 40. Pregnant females were excluded from the analysis.
SOURCES: NCHS, National Health Examination Survey and National Health and Nutrition Examination Surveys.
Children born to mothers carrying excess weight have markedly higher risk of developing obesity.

Adjusted for child sex, maternal receipt of public assistance, ethnicity, maternal age, and birth weight (n=323)

Excess maternal weight → Childhood obesity
Excess maternal weight → Genetics → Childhood obesity
Excess maternal weight → Genetics → Childhood obesity
Genetics → Environment / Energy Imbalance → Excess maternal weight
Excess maternal weight

**Microbiome?**

Genetics

Environment / Energy Imbalance

Childhood obesity
Might mother-to-newborn microbiota transfer play a role in the intergenerational association of obesity?
Intestinal microbiota can transfer obesity phenotype from humans to mice

Ridaura et al. Science. 2013
Walker and Parkhill. Science. 2013
Maternal gut microbiota composition in the third trimester is modified by maternal pre-pregnancy body weight status

Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women\(^1-^3\)

Maria Carmen Collado, Erika Isolauri, Kirsi Laitinen, and Seppo Salminen

- Excess pre-pregnancy weight was associated with altered shifts in maternal gut microbiota
  - ↑*Bacteroides*
  - ↑*Staphylococcus*
Maternal overweight and obesity associated with alterations in the infant gut microbiome

- Did not adjust or stratify by mode of delivery
HYPOTHESIS:

Neonates born *vaginally* to overweight/obese moms host different gut microbiota than neonates born *vaginally* to normal weight moms.
Brazilian Microbiome Birth Cohort

• 74 Babies delivered 38-42 weeks
  – Exclusions: HIV/AIDS, autoimmune diseases, diabetes, hypertension, pre-eclampsia, smokers, restrictive diets, use of antibiotics in 3rd trimester

• Data from medical records and questionnaire

• 5 g of first stool (after meconium) collected from diapers with sterile spatulas and placed in sterile tubes at 4 °C for < 6 h and stored at −80 °C until processing
Analyses of microbial populations and functions

**Samples**
Newborn Feces (n=74)

**DNA Extraction**
16S rRNA gene V4 region

**Sequencing**
Illumina MiSeq platform

**Bioinformatics analysis**

**Statistical test**
- LDA Effect Size (LEfSe)
- Factorial Kruskal-Wallis test (α <0.05)
- LDA score >3.0-fold (~P value <0.001)

**QIIME Pipeline**
- Open-ref OTUs picking
- Alpha diversity
  Taxonomy plot
- Beta diversity
  Principal Coordinate analysis (PCoA)

**Prediction of Metagenome**
- PICRUSt
- Predictive functional profiling
### Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=74)</th>
<th>Maternal Pre-pregnancy BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal (&lt;25 kg/m(^2))</td>
</tr>
<tr>
<td>Mothers age, y, mean (SD)</td>
<td>30.7 (5.0)</td>
<td>30.3 (4.9)</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>56 (75.7)</td>
<td>30 (69.8)</td>
</tr>
<tr>
<td>Vaginal delivery, n (%)</td>
<td>18 (24.3)</td>
<td>13 (30.2)</td>
</tr>
<tr>
<td>Pregnancy wt gain, kg, mean (SD)</td>
<td>13.3 (4.8)</td>
<td>13.4 (4.7)</td>
</tr>
<tr>
<td>Girls, %</td>
<td>48.7</td>
<td>53.5</td>
</tr>
<tr>
<td>Gestational age, y, mean (SD)</td>
<td>38.8 (0.8)</td>
<td>38.8 (0.9)</td>
</tr>
<tr>
<td>Birth weight, g, mean (SD)</td>
<td>3,257 (361)</td>
<td>3,235 (332)</td>
</tr>
</tbody>
</table>

*range: 25-41.1 kg/m\(^2\)
Alpha diversity of infant stool microbiota did not differ by pre-pregnancy BMI or delivery mode.

Beta diversity of microbiota in newborn feces differs by maternal BMI and delivery mode.

Weighted UniFrac distances were used to evaluate beta diversity. PERMANOVA was used to test dissimilarity.

Mueller NT et al Scientific Reports 2016
Bacteroides abundance differs by birth mode and maternal BMI within vaginally delivered

Mueller NT et al *Scientific Reports* 2016
Metabolic pathways in the predicted metagenome of neonatal stool differs by delivery mode

KO Functional Categories

<table>
<thead>
<tr>
<th>Level 2</th>
<th>P value</th>
<th>LDA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acid Metabolism</td>
<td></td>
<td>3.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrate Metabolism</td>
<td>0.001</td>
<td>3.14</td>
<td></td>
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<tr>
<td>Lipid Metabolism</td>
<td>0.005</td>
<td>3.19</td>
<td></td>
</tr>
<tr>
<td>Glycan Biosynthesis and Metabolism</td>
<td>0.009</td>
<td>3.40</td>
<td></td>
</tr>
<tr>
<td>Metabolism of Cofactors and Vitamins</td>
<td>0.006</td>
<td>3.26</td>
<td></td>
</tr>
<tr>
<td>Metabolism of Terpenoids and Polypeptides</td>
<td></td>
<td>3.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nucleotide Metabolism</td>
<td>0.014</td>
<td>3.27</td>
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</tr>
<tr>
<td>Xenobiotics Biodegradation and Metabolism</td>
<td>0.001</td>
<td>3.14</td>
<td>C-section</td>
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<tr>
<td>Enzyme Families</td>
<td></td>
<td>3.14</td>
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<td>3.14</td>
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Metabolic pathways in the predicted metagenome of stool differs by maternal pre-pregnancy BMI among vaginally delivered newborns

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<thead>
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<th>Maternal BMI &lt; 25 Kg/m² (n=13)</th>
<th>Maternal BMI ≥ 25 Kg/m² (n=5)</th>
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<tbody>
<tr>
<td><strong>Amino Acid Metabolism</strong></td>
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<tr>
<td>Lysine degradation</td>
<td>Alanine aspartate and glutamate metabolism</td>
</tr>
<tr>
<td>Tryptophan metabolism</td>
<td>Histidine metabolism</td>
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<tr>
<td>Valine, leucine and isoleucine degradation</td>
<td></td>
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<tr>
<td><strong>Butanoate metabolism</strong></td>
<td><strong>Biosynthesis of Other</strong></td>
</tr>
<tr>
<td><strong>Secondary Metabolites</strong></td>
<td><strong>Streptomycin biosynthesis</strong></td>
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<td><strong>Carbohydrate Metabolism</strong></td>
<td><strong>Amino sugar and nucleotide</strong></td>
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<td><strong>Enzyme Families</strong></td>
<td><strong>Fructose and mannose</strong></td>
</tr>
<tr>
<td>Protein kinases</td>
<td>metabolism</td>
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<td><strong>Lipid Metabolism</strong></td>
<td><strong>Galactose metabolism</strong></td>
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<td>Fatty acid metabolism</td>
<td><strong>Pentose and glucuronate</strong></td>
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<td><strong>Xenobiotics Biodegradation</strong></td>
<td><strong>interconversions</strong></td>
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<td><strong>Energy Metabolism</strong></td>
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<td><strong>Carbon fixation pathways in</strong></td>
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<td><strong>Sphingolipid metabolism</strong></td>
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<td><strong>Nucleotide Metabolism</strong></td>
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Metabolic pathways in the predicted metagenome of stool do **NOT** differ by maternal **pre-pregnancy BMI** among Cesarean delivered newborns.

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HYPOTHESIS:

Neonates born *vaginally* to overweight/obese moms host different gut microbiota than neonates born *vaginally* to normal weight moms.

![Diagram showing the difference in gut microbiota between neonates born vaginally to overweight/obese and normal weight moms.](image)

✔️ Provide supporting evidence
Does vaginal delivery modify the intergenerational association of overweight and obesity?
Associations of Cesarean Delivery and Maternal Obesity With Childhood Overweight and Obesity are Independent and Additive

Mueller NT et al IJO 2016
Does Newborn Exposure to Ruptured Membranes in Labor Modify the Association of C-section and Obesity?
Figure. Adjusted $\beta$ (95% CI) of adiposity measures in children (between age 2.8 and 16.6y) from Project Viva delivered by Cesarean compared with vaginal delivery (0 reference).
What to do about medically necessary C-sections?

Vaginal seeding at birth??
Restoring the microbiome of C-section delivered newborns

1. 1 Hr

2. Sterile Container

3. Mouth → Face → Rest of Body

Dominguez-Bello et al 2016 Nature Medicine
Inclusion criteria for patients in the observational study

- Scheduled C-section
  (maternal choice, previous C-section or malposition presentation)

- “Healthy” mothers with healthy pregnancy

- Negative for HIV, Group B *Streptococcus* (GBS),
  active primary herpes, gonorrhea, chlamydia and other STDs, bacterial vaginosis

- Vaginal pH ≤ 4.5 at time of delivery
Beta diversity of vaginal gauze microbes in relation to maternal body sites

Dominguez-Bello et al 2016 Nature Medicine
Restoration of some bacterial taxa at age 1 month

Does vaginal seeding of C-section babies protect from C-section associated diseases?
“Newborns may develop severe infections from exposure to vaginal commensals and pathogens”

“Despite the infection risks that the authors correctly associate with our procedure, **vaginal birth is the desired mode of delivery after a healthy pregnancy** even in the case of GBS-positive mothers”

“Interventions that alter natural processes such as vaginal birth should be practiced only when necessary, and **the results of our study are a first step towards reducing the potential costs associated with C-section.**”
Vaginal seeding: minimizing risks

• In the absence of evidence of benefit or guidelines to ensure the procedure is safe, we are not recommending that clinicians perform vaginal seeding.

• If mothers choose to do it themselves, clinicians should respect their autonomy but ensure they are fully informed about the potential risks.

• Parents should also be advised to mention that they performed “vaginal seeding” if their baby becomes unwell.
Perturbations to microbiome development: strategies for prevention and restoration

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 Breastfeeding  
 Pre- and probiotic supplementation of neonate |
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| Gestational, perinatal, or postnatal antibiotics | Implement robust antimicrobial stewardship programs ([link](http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria])  
Develop safe strategies that limit use of antibiotics in women in labor (e.g., rapid PCR testing for group B Streptococcus at the time of admission to the delivery unit)  
During C-section delivery, give antibiotics after cord clamping to eliminate fetal exposure to antibiotics  
Use more prudence in antibiotic administration during pregnancy | |
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Use more prudency in antibiotic administration during pregnancy | Breastfeeding  
Pre- and probiotic supplementation of mother during pregnancy and neonate after birth |
| Formula feeding                            | Adopt WHO/UNICEF Baby Friendly Hospital Initiative  
Develop other policies that incentivize breastfeeding  
Do not offer formula to newborns without request or medical indication  
Promote use of donor breast milk rather than formula when maternal milk is not an option |
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| Formula feeding                     | Adopt WHO/UNICEF Baby Friendly Hospital Initiative  
Develop other policies that incentivize breastfeeding  
Do not offer formula to newborns without request or medical indication  
Promote use of donor breast milk rather than formula when maternal milk is not an option | Reintroduce breastfeeding  
Pre- and probiotic supplementation |

Outstanding questions

- What are the key members of the maternal microbial communities that promote a healthy newborn microbiome?
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- What pathophysiological states during pregnancy lead to disrupted maternal–offspring exchange?
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- To what degree can breastfeeding restore microbes and their functions during development?
- Can we restore the vaginal microbiota to C-section-delivered babies?
- Does neonatal microbial restoration reduce the risk of microbiome-related diseases?

Summary & Conclusions

- Understanding the microbiome changes what it means to be ‘human’
- The microbiome may change during pregnancy to support the nutrition and development of the mother and her offspring
- While maternal-fetal transmission of microbiota may occur, the newborns first large exposure to microbiota occurs at delivery
- Maternal obesity, antibiotics, and C-section delivery may impact healthy maternal-offspring transmission of microbiota and the long-term health of the offspring
- Interventions targeting microbiota during pregnancy and at delivery may be an innovative way to improve offspring health
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Discussion & Contact

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