THE INFLUENCE OF PERINATAL FACTORS ON DEVELOPMENT OF THE INFANT GUT MICROBIOTA

Tiffany Weir, PhD
Associate Professor
Food Science and Human Nutrition
Colorado State University
Learning Objectives

• To describe the gut microbiota and its role in human health.
• To identify pre- and post-natal factors that influence the infant gut microbiota.
• To translate current research into practical dietary advice for improved maternal-child health.
Meet Your Microbiota!

Getting to know your gut microbiota
A huge quantity (hundreds of trillions) of bacteria and other microorganisms inhabit your intestines fulfilling key functions for your health and wellbeing.

- **Gut microbiota’s weight** can reach up to **1 to 2 Kg**
- **95%** of our bacteria located in the gastrointestinal (GI) tract
- **The GI tract surface** is as big as 2 tennis courts, **400 m²**
- Bacteria are **10 to 50 times** smaller than human cells
- In our body, microbes **outnumber** human cells by **10:1**
- Laid end to end, our body's bacteria would **circle the Earth 2.5 times**

www.gutmicrobiotawatch.org  
@gutmicrobiotaww  
www.facebook.com/GutMicrobiotaWW
WHAT ARE ALL THOSE MICROBES DOING?
Microbiota and Health

Nagpal et al. 2014 Front Med. dx.doi.org/10.3389/fmed.2014.00015
Digestion

Complex carbohydrates, like dietary fiber, feed the gut microbiota and result in production of SCFA, metabolites that regulate appetite, feed the colon, and help keep the gut barrier strong.

Gut microbes can be an important source of Vitamin K and B vitamins!

Proteins provide critical building blocks for new cell growth but should be eaten with fiber to reduce ammonia and other products released when they are metabolized by gut bacteria.

Certain members of the gut microbiota facilitate uptake of dietary fat. In addition, bile secretion can profoundly alter the microbiota composition.
Obesity

When co-housed the “lean” mice transferred their microbes and their phenotype to the “obese” animals!

Gut microbes help train and regulate the innate (panel 1) and adaptive (panel 2) immune systems. This is especially important in infancy, and the timing and amount of colonization of various microorganisms can have lifelong consequences in immune function.

Kabot et al. (2014) https://dpi.org/10.1016/j.it.2014.07.010
HOW DO WE GET THESE MICROBES?

Why birth influences and early feeding patterns are CRITICAL for a healthy microbiome.
Colonization Influences

- **Mode of delivery:** cesarean, vaginal
- **Placenta:** amniotic liquid
- **Maternal factors:** nutrition, BMI, weight gain during pregnancy, microbiota composition
- **Antibiotic exposure**
- **Breast milk and/or formula feeding**

Maternal Factors

Normal pregnancy weight gain leads to alterations in a woman’s microbiota that increase her metabolic challenges. Maternal obesity is a strong predictive factor of childhood obesity and may be due to microbiota effects.

Maternal obesity was associated with reduced gamma-proteobacteria, which are important early colonizers of the gut and help to develop and train the infant immune system.

Mode of Delivery

Table 1

<table>
<thead>
<tr>
<th>Cesarean Delivery Associated Childhood Diseases&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
</tr>
<tr>
<td>All Cesareans</td>
</tr>
<tr>
<td>Repeat Cesareans Only</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
</tr>
<tr>
<td>All Cesareans</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Female &amp; Repeat Cesarean&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Celiac Disease</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (Type 1)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Gastroenteritis</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Gastroenteritis AND Asthma</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Data from references<sup>46, 47, 50</sup>

<sup>2</sup>Odds Ratio (OR) with 95% CI versus vaginal delivery

>10% of babies are born pre-term worldwide.

25% of pre-term survivors have adverse neurodevelopmental outcomes.

Pre-term birth is associated with a microbiota profile distinct from full term. It is characterized by reduced microbial diversity and slower maturation of the microbiota. These differences persist up to 4 years.

Restoring Microbiota

Breast vs. Formula

Mother’s Milk Microbiome

Birth factors don’t affect milk microbiome

Oligosaccharides

Human
- Oligosaccharides: 32%
- Proteins: 6%
- Fats: 8%
- Lactose: 54%

Cow
- Oligosaccharides: 32%
- Proteins: 27%
- Fats: 41%

* An estimate. Oligosaccharide content varies over time and between individuals.
How they work...

Directly prevent pathogen colonization and attachment by “hiding” epithelial cells and acting as decoys.

Aldrich et al. (2013) Glycobiology 23: 664–676
MODULATING THE MICROBIOME

Care and Feeding of the Microbiota
Human Breastmilk

- Human breastmilk provides many nutrients that influence microbiota development and general gut health
  - Micro-organisms
  - HMOs
  - Immunoglobins
  - Lactoferrin
  - Omega 3-Fatty Acids
  - L-glutamine
Passive exposure to secretory IgA in breastmilk induces microbiota changes that persist into adulthood in mice.


PNAS February 25, 2014. 111 (8) 3074-3079
Lactoferrin (LF) binds iron to prevent pathogens from accessing it.

- LF can block enteric pathogens from binding to the epithelium.
- LF acts as an antimicrobial by directly binding microbes and viruses.
Omega-3 Fatty Acids

L-Glutamine

- High levels of cell proliferation are required for epithelial cell turnover (every 4-5 days).
- L-Glutamine
  - Regulates several pathways involved in cell proliferation/cell death
  - Enhances endogenous anti-oxidants and reduces cellular stress
  - Increases tight junction protein expression

Prebiotics are non-living indigestible polysaccharides (food components) that stimulate the growth of bacteria important in human health (and early development—i.e. *Bifidobacterium*).
Prebiotic Classification

Selective utilization by host microorganisms
- Prebiotic
  - CLAs and PUFAs
  - Human milk oligosaccharides
    - Oligosaccharides e.g. FOS, Inulin, GOS, MOS, XOS
  - Phenolics and phytochemicals

Substances that affect the microbiome
- Dietary fibre
  - Readily fermentable
  - Less fermentable
    - Proteins and fats
  - Antibiotics
  - Vitamins

Not Prebiotic
- Probiotics
Oligosaccharide Sources

- **Canonical prebiotics** include:
  - Fructo-oligosaccharides
  - Galacto-oligosaccharides
  - Xylo-oligosaccharides
  - Inulin

- **Diet**
  - Major dietary sources are consumed in limited amounts in a typical American diet

- **Supplements**
- **Fortification in foods**
  - Yogurt
  - Infant formula
  - Artificial sweeteners

<table>
<thead>
<tr>
<th>Foods with Prebiotics</th>
<th>Prebiotic fiber by weight</th>
<th>Amount needed for 6g serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicory Root</td>
<td>64.6%</td>
<td>9.3 g</td>
</tr>
<tr>
<td>Jerusalem Artichoke</td>
<td>31.5%</td>
<td>19 g</td>
</tr>
<tr>
<td>Dandelion greens</td>
<td>24.3%</td>
<td>24.7 g</td>
</tr>
<tr>
<td>Raw garlic</td>
<td>17.5%</td>
<td>34.3 g</td>
</tr>
<tr>
<td>Raw leek</td>
<td>11.7%</td>
<td>51.3 g</td>
</tr>
<tr>
<td>Raw onion</td>
<td>8.6%</td>
<td>69.8 g</td>
</tr>
<tr>
<td>Cooked onion</td>
<td>5%</td>
<td>120 g</td>
</tr>
<tr>
<td>Raw asparagus</td>
<td>5%</td>
<td>120 g</td>
</tr>
<tr>
<td>Raw wheat bran</td>
<td>5%</td>
<td>120 g</td>
</tr>
<tr>
<td>Whole wheat flour,cooked</td>
<td>4.8%</td>
<td>125g</td>
</tr>
<tr>
<td>Raw banana</td>
<td>1%</td>
<td>600 g</td>
</tr>
</tbody>
</table>
Resistant Starch

- Indigestible carbohydrate passes through stomach and small intestine
- Resists pancreatic and small bowel enzymatic digestion
- Reaches colon intact where beneficial bacteria easily ferment this portion of the indigestible starch
- Dominant in amylose straight-chain structure
  - Less surface area for enzyme digestion
  - Digested more slowly
  - Also contains amylopectin structures

Slide prepared by Ms. Madison Service as part of her Honors Thesis project
### Dietary Sources of Resistant Starch

#### Plaintains/Bananas

<table>
<thead>
<tr>
<th>Plantains/Bananas</th>
<th>Method</th>
<th>Amount (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantain/Green Banana</td>
<td>A/B</td>
<td>35</td>
</tr>
<tr>
<td>Plantain, cooked</td>
<td>A/B</td>
<td>3.5</td>
</tr>
<tr>
<td>Ripe Banana</td>
<td>A/B</td>
<td>0.3</td>
</tr>
<tr>
<td>Unripe Banana</td>
<td>A</td>
<td>4.7</td>
</tr>
</tbody>
</table>

#### Flours/Starches

<table>
<thead>
<tr>
<th>Flours/Starches</th>
<th>Method</th>
<th>Amount (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckwheat flour</td>
<td>B</td>
<td>16</td>
</tr>
<tr>
<td>Cassava starch</td>
<td>B</td>
<td>44.6</td>
</tr>
<tr>
<td>Corn flour</td>
<td>A/B</td>
<td>11</td>
</tr>
<tr>
<td>Potato starch</td>
<td>A/B</td>
<td>66.7</td>
</tr>
<tr>
<td>Potato starch (cooked &amp; cooled)</td>
<td>B</td>
<td>3.8</td>
</tr>
<tr>
<td>Wheat flour</td>
<td>A/B</td>
<td>13</td>
</tr>
</tbody>
</table>

#### Legumes/Nuts/Seeds

<table>
<thead>
<tr>
<th>Legumes/Nuts/Seeds</th>
<th>Method</th>
<th>Amount (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black beans, cooked</td>
<td>B</td>
<td>10.8</td>
</tr>
<tr>
<td>Cashews</td>
<td>A</td>
<td>12.9</td>
</tr>
<tr>
<td>Chickpeas, cooked and cooled</td>
<td>B</td>
<td>6.4</td>
</tr>
<tr>
<td>Navy beans</td>
<td>B</td>
<td>10</td>
</tr>
<tr>
<td>Red lentils</td>
<td>A</td>
<td>13.8</td>
</tr>
<tr>
<td>Red bean, cooked</td>
<td>B</td>
<td>10.6</td>
</tr>
<tr>
<td>Mung bean, raw</td>
<td>B</td>
<td>22.9</td>
</tr>
</tbody>
</table>

- Amount per 100 g of food
- A: In vivo method (ileostomy)
- B: In vitro method (mimic digestion in laboratory)
### Dietary Sources of Resistant Starch

<table>
<thead>
<tr>
<th>Vegetables</th>
<th>(g)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrots</td>
<td>1.1</td>
<td>B</td>
</tr>
<tr>
<td>Cassava (yucca)</td>
<td>9.69</td>
<td>B</td>
</tr>
<tr>
<td>Lesser yam</td>
<td>23.25</td>
<td>B</td>
</tr>
<tr>
<td>Parsnip</td>
<td>1.1</td>
<td>B</td>
</tr>
<tr>
<td>Potatoes (roasted &amp; cooled)</td>
<td>3.2</td>
<td>A</td>
</tr>
<tr>
<td>Potatoes (baked)</td>
<td>.16</td>
<td>A/B</td>
</tr>
<tr>
<td>Sweet potato</td>
<td>1.1</td>
<td>A/B</td>
</tr>
<tr>
<td>Taro</td>
<td>2.6</td>
<td>A/B</td>
</tr>
<tr>
<td>White yam</td>
<td>4.3</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grains</th>
<th>(g)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pumpernickel bread</td>
<td>4.5</td>
<td>A</td>
</tr>
<tr>
<td>Rye Bread</td>
<td>3.2</td>
<td>B</td>
</tr>
<tr>
<td>Corn (cooked)</td>
<td>3.85</td>
<td>B</td>
</tr>
<tr>
<td>Corn (cooked &amp; cooled)</td>
<td>4.4</td>
<td>B</td>
</tr>
<tr>
<td>Corn tortilla</td>
<td>3.12</td>
<td>B</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>3.2</td>
<td>A/B</td>
</tr>
<tr>
<td>Puffed wheat</td>
<td>6.2</td>
<td>A</td>
</tr>
<tr>
<td>Oats, rolled, (uncooked)</td>
<td>7.8</td>
<td>A/B</td>
</tr>
<tr>
<td>Whole rice (cooked, cooled)</td>
<td>5.48</td>
<td>B</td>
</tr>
<tr>
<td>Whole rice</td>
<td>2.63</td>
<td>B</td>
</tr>
</tbody>
</table>

Slide prepared by Ms. Madison Service as part of her Honors Thesis project
Microbiota Accessible Carbohydrates

Intestinal epithelial cells

Regulate lipid and glucose metabolism, intestinal homeostasis, immune responses

Regulate gene expression

Metabolized in liver

Butyrate, Propionate, Acetate
Gnotobiotic mice with characterized human gut microbiota

Dietary fiber deprivation

Infection with enteric pathogen

Fiber-rich (FR) diet

Mature mucus layer: intact barrier function

Fiber-free (FF) diet

Microbiota-eroded mucus layer: barrier dysfunction

Fiber-degrading microbiota

Mucus-degrading microbiota

Mucosal pathogen

Bacterial dietary fiber degradation

Bacterial host-secreted mucus degradation

Probiotics are live bacteria or yeast that when eaten in sufficient amounts can be beneficial for intestinal health.
Probiotic sources

- Food sources:
  - Fermented dairy foods like yogurt, kefir products, and aged cheeses
  - Some fermented non-dairy foods including kimchi, sauerkraut, and kombucha
  - Supplemented non-fermented foods: Good Belly

Slide from Katie McGirr, CSU Extension
Safety of Evivo supplementation was demonstrated in healthy, term infants by:

- No reported increase in GI distress
- Less frequent and more formed soft stools

Babies given Evivo showed:

- 79% increase in *Bifidobacteria*.
- 80% reduction of groups of potentially harmful bacteria.
- Babies high in *Bifidobacteria* had 4x lower levels of endotoxin.

https://www.evivo.com/scientific-publications
Key Points

• Disturbances in the maternal microbiota are heritable and can influence child health outcomes.

• Breastfeeding provides the infant with pre- and probiotics necessary for early immune development.

• Dietary management of the microbiota is critical for mother and child in the pre and early postnatal period.
Questions?
Mothers’ Milk Bank
Colorado Based. Nationwide Reach.

https://rmchildren.org/?gclid=CNjJhtyc4tMCFdO3wAodK78GJg