Early life nutrition and Inflammation

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and

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The process of development
Critical windows and responses to other noxious stimulants
Conditions being considered

- Lung function
- Obesity
- Possible mechanisms of changes?
Lung development and post-natal function
FIGURE 1
Inflammation and fetal lung maturation and development

Effect of intra-amniotic inflammation/infection (IAI) on fetal lung maturation (left side) and development (right side).

Asthma as an immune/inflammatory function-related disease of development
Development of the lung:
Asthma & allergic disease

Asthma
Eczema (atopic dermatitis)
Hayfever (allergic rhinoconjunctivitis)
Food allergy

Characterised by:

- Tissue inflammation
- Th2 biased immune responses (IL-4, IL-5, IL-13)
- ↑ IgE, ↑ allergen specific IgE
- ↑ eosinophils, allergen skin prick tests
Importance of antenatal influences

1). Associations between birth measurements & asthma/allergy

Godfrey et al (1994)

Children born in Preston 1935-43 detailed birth measurements

↑ IgE @ 50

Birth head circumference ↑ 0.30 inches (p=0.004) relative to trunk and limbs

Birth weight ↑ 5.6oz (p=0.04)

? Nutritional compromise: sustaining fetal head growth at expense of trunk & limbs, effects on thymus, immune development
Importance of antenatal influences

1). Associations between birth measurements & asthma/allergy

Numerous studies
- \( \downarrow \) birth weight \( \rightarrow \) \( \uparrow \) asthma
- \( \uparrow \) birth weight, \( \uparrow \) head circumference \( \rightarrow \) \( \uparrow \) hayfever, \( \uparrow \) eczema, \( \uparrow \) IgE

Mechanism unclear, not thymus development
Importance of antenatal influences

Fetal measurements at 10 weeks gestation and 5 year wheeze/asthma

Adjusted OR
(95% CI)
0.01
0.1
1
10
Q1                Q2                Q3                Q4

CRL quartiles →

Wheeze p=0.034
Asthma p=0.026

Thorax 2010; 65: 391.
Importance of antenatal influences

2). Associations between lung function at birth & asthma/wheeze

Never asthma

History of asthma

Asthma at 10 yrs

NEJM 2006; 355:1682
Importance of antenatal influences

3). Associations between cord blood immune responses & allergy (asthma)

Stimulus: PHA

Stimulus: House dust mite
Inflammatory pathways that may induce asthma

- Immune mediated inflammation associated with a Th2-type response producing IgE in response to allergens
- Neutrophilic inflammation may be important in some sub-groups
- Antigen-independent responses including innate immune cells (e.g. dendritic cells, alveolar macrophages, bronchial epithelial cells)
Maternal diet during pregnancy

Maternal nutrient intake

Several hypotheses – unfortunately don’t have time to consider properly but a couple are worth considering briefly
Maternal diet during pregnancy: nutrients

Maternal diet during pregnancy

Changing diet contributing to the increase in asthma and allergy?

Hypotheses
2. Lipid hypothesis: ↑ n-6 PUFA, ↓ n-3 PUFA (Eur Respir J 1997;10:6)
3. Vitamin D hypotheses: vitamin D supplements (Allergy 1999;54:757) vitamin D deficiency (JACI 2007;120:1031)
Cord blood 25(OH)D and allergen specific IgE 1-5 years

Tuscon birth cohort n=208

Adjusted OR (95% CI)

? U shaped association, low and high deleterious

J Allergy Clin Immunol 2011;128:1093

Rowett Institute of Nutrition and Health
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Maternal diet during pregnancy: nutrients

Maternal diet during pregnancy: Vitamin E

Maternal vitamin E intake & childhood wheeze 2-3 years

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>Lower limit</td>
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<tr>
<td>Litonjua (E11) 2006</td>
<td>0.700</td>
<td>0.478</td>
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<tr>
<td>Martindale (E12) 2005</td>
<td>0.790</td>
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<td>Miyake (E15) 2010</td>
<td>0.540</td>
<td>0.322</td>
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<tr>
<td></td>
<td>0.676</td>
<td>0.519</td>
</tr>
</tbody>
</table>

↓Maternal vitamin E: ↓ lung function, ↑ wheeze & asthma @ 5 yrs

Pilot trial of vitamin E intervention underway

J Allergy Clin Immunol 2011; 127: 724
Obesity, inflammation and pregnancy outcome
Common mechanistic pathways of developmental programming as a result of maternal over nutrition.
An overview of obesity in pregnancy and fetal outcome

- increased LGA
- increased SGA
- increased pre-eclampsia
- increased risk of obesity in offspring
- Increased risk of metabolic syndrome

Heerwagen et al, 2010 AJP R711-R722
An overview of obesity in pregnancy and fetal outcome

Heerwagen et al, 2010 AJP R711-R722
Lipotoxicity in pregnancy

Central adipose tissue
↑lipolysis
↓'safe' storage of TG
↑insulin resistance

Lower body adipose tissue
↓lipolysis
↑'safe' storage of TG
↑insulin sensitivity

NEFA

↑ ectopic fat accumulation
lipotoxicity

↑ oxidative stress
↑ oxidized lipids

maternal endothelial/
vascular stress

↓ trophoblast invasion
? uteroplacental
insufficiency

placenta

altered development, fat
metabolism & transport & ↑ inflammation

offspring obesity

above the waist

normal metabolic adaptation
to pregnancy:

normal placental transport
of nutrients and essential
fatty acids

healthy outcome

below the waist
Effect of obesity on inflammatory proteins and iron metabolism

Garcia-Valdes, Campoy and McArdle 2013
Is iron deficiency a contributor to the problems associated with obesity and pregnancy outcome?
Possible mechanisms of action of inflammation and early life nutrition
Gestational diabetes induces HIF1 expression in the placenta

Relationship between inflammation and developmental programming

Adapted from Thomson and Webb (2013) Clin Sci 125, 19-25
Pathways of activation by ROS

Adapted from Thomson and Webb (2013) Clin Sci 125, 19-25
Regulation of function by Protein, Glucose, Iron, Zinc and O2 Through mTOR Signaling

- Protein, eg BCAA
- Growth Factors
  - PI3K
  - Pdkp1
  - Thr308
  - Akt
  - Thr1462
  - PTEN
  - Thr24/32
  - FOXO
  - Ser2448
  - Rheb
  - Ser2448
  - Thr389
  - mTORC1
  - 4E-BP
  - S6K
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  - Transcription
  - Cell Size and Survival
- Translation
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Wullschleger et al, 2006
Fretham et al, 2011
Interactions between mTOR and immune cells

Soliman 2013 Nutrients 5
Epigenetics as a mechanism for inducing immune changes in early life
Effect of iron deficiency on the cell cycle

Figure 1. Nephron numbers in each diet/strain group. Data are mean ± SE. *P<0.05 between control and corresponding deficient diet. n=8 animals per group.
Cellular function may be susceptible to nutritional and other stresses that induce permanent change.

Stressors that induce permanent change may operate through inflammatory pathways.

Cytokines may be central to the balance between a mother and her developing fetus.
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