PKU and Pregnancy

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What is Maternal PhenylKetonuria? It’s about the baby

- Birth defects resulting from a toxic environment for fetal growth and development
- Caused by ↑ maternal blood PHE during pregnancy
- Damage is prenatal and cannot be reversed after birth
- Child will need special medical and educational care throughout life
MPKU: History

- In early years women with PKU severely disabled and pregnancy uncommon
- 1960s – NewBorn Screening allows early treatment of PKU – preventing intellectual disability
- NOW: women with PKU diagnosed and treated early, living normal lives – and having children
- BUT many “off diet” – risk for children affected by MPKU

“Success of NBS and treatment in preventing devastating MR of PKU could be erased by a population of babies w/ irreversible effects of MPKU” Scrivier
What Causes MPKU?

In Mother:
- Blood PHE concentrates as crosses placenta – 1.5–2 X
- ↑ blood PHE overwhelms normal transport across placenta
- Limits transport of other amino acids across placenta – needed for fetal growth

<table>
<thead>
<tr>
<th>Maternal blood</th>
<th>Fetal blood</th>
<th>Fetal brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 umol/L</td>
<td>900-1200 umol/L</td>
<td>????</td>
</tr>
</tbody>
</table>

- Maternal blood PHE: 600 umol/L
- Fetal blood PHE: 900-1200 umol/L
- Fetal brain PHE: ????
NORMAL Amino Acid Transport Across Placenta

Maternal Blood
- HIS
- ISO
- LEU
- MET
- PHE
- THR
- TRP
- TYR
- VAL

Fetal Blood
- HIS
- ISO
- LEU
- MET
- PHE
- THR
- TRP
- TYR
- VAL

PLACENTAL Amino Acid Transport
ABNORMAL Amino Acid Transport Across Placenta

Maternal Blood

Fetal Blood

PLACENTAL TRANSPORT

- HIS
- PHE
- ISO
- LEU
- MET
- PHE
- TRP
- TYR
- VAL
- THR
- PHE
What Causes MPKU?

Maternal blood  
600 umol/L

Fetal blood  
900-1200 umol/L

Fetal brain  
?????

In Fetus:

• ↑ blood PHE concentrates again crossing Blood Brain Barrier (BBB) – *neurotoxic levels*

• Limits transport of other amino acids across BBB – needed for brain development and neurotransmitters
NORMAL Amino Acid Transport Across BBB

Fetal Blood Brain Barrier

Fetal Blood
- HIS
- ISO
- LEU
- MET
- PHE
- THR
- TRP
- TYR
- VAL

Fetal Brain
- HIS
- ISO
- LEU
- MET
- PHE
- THR
- TRP
- TYR
- VAL

Fetal Blood

Fetal Brain

NORMAL Amino Acid Transport Across BBB
ABNORMAL Amino Acid Transport Across BBB

Fetal Blood Brain Barrier

Fetal Blood

ISO
MET
PHE
PHE
PHE

LEU
PHE
PHE
PHE

LEU
PHE
PHE
PHE

Fetal Brain

PHE
ISO
PHE
PHE

PHE
PHE
PHE
PHE

PHE
PHE
PHE
PHE

TYR
TRP
THR
THR

THR
THR
THR

VAL
PHE
PHE
PHE

PHE
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PHE
PHE
How Does a Baby Grow?
Organogenesis

1st Trimester
4 weeks – brain, spinal cord, heart begin to form
6 weeks – brain activity recorded, heart beating
8 weeks – all essential organs+ face forming
10-12 weeks – all body parts and organs formed

Birth defects in MPKU syndrome
- Microcephaly ➔ intellectual disability
- Congenital heart defects (CHD)
- Cleft lip/palate
- Facial defects: short/ smooth filtrum, small palpebral fissures, epicanthal folds
Birth defects in MPKU syndrome

- Poor fetal growth and low birth weight
- Poor fetal brain development continues – microcephaly
- May also have slow postnatal growth
- Consequences – and severity vary widely
- Risk lowest when maternal blood PHE nearest to normal
Early Maternal PKU Studies

Levy + Lenke International Survey – 1980

Maternal PKU Collaborative Study (MPKUCS)
- NIH study: US, Canada, Germany – 1984-2002
- 574 pregnancies, 382 women, 412 live births
- children studied 0-12 years

NIH Consensus Statement - 2001
MPKU Study Findings

Levy + Lenke survey – babies of untreated PKU mothers
Maternal blood PHE >1200 mg/dl

- 92% intellectual disability
- 73% microcephaly
- 40% poor fetal growth – IUGR
- 24% spontaneous miscarriage
- 12% CHD

MPKU Collaborative Study – babies of treated PKU mothers

- 66% of mothers had blood PHE >600 umol/L at 8 weeks
  - 47% microcephaly
  - 13% CHD
- 34% of mothers had blood PHE <600 umol/L by 8 weeks
  - 8% microcephaly
  - 0% CHD
MPKU Collaborative Study

Maternal characteristics that ↑ risk for poor brain development in child

- Maternal PHE >600 umol/L – not in control by 10 weeks

Consequences in child:
  - IQ below normal
  - Intellectual disability & poor behavior control
  - ADHD – independent of IQ
  - Poor executive function

- ▼ IQ or socioeconomic status – ↑ difficulty in adherence

- Teenage pregnancy

- Low pre-pregnancy weight + poor weight gain

- Low protein intake during pregnancy
Recommendations

MPKUCS findings – NIH Consensus Statement

1. Blood PHE in control *before conception*
   - Diet and medical food throughout life
   - PHE < 360 umol/L before and throughout pregnancy

2. If blood PHE not in control before conception:
   - Be alert to pregnancy early – call clinic
   - Start diet and formula immediately
   - PHE levels <360 umol/L rapidly

3. *Ongoing clinical relationship w/ metabolic center*
MPKU Collaborative Study

Reality Is:

Are mothers on diet? When do they start?

- **96%** are *off diet* for 6-24 years
- **35%** started diet preconception
- **50%** started diet during 1st trimester
- **14%** started diet during 2nd – 3rd trimester
- **1%** never start diet

How soon is diet effective in achieving control?

- **30%** PHE in control < 2 weeks
- **32%** PHE in control 2-20 weeks
- **7%** PHE in control 20-34 weeks
- **30%** PHE *never* stable in control range
What Does This Mean?

Risk & consequences – are dose dependent

- Higher the maternal blood PHE – and longer it is high – greater the risk and severity of birth defects
- First 10-12 weeks – organogenesis – most critical period
- Brain and fetal growth throughout pregnancy – so each week continues to be important
- Fetal damage is irreversible
- DIET for LIFE
BUT: Adherence to Diet Decreases in Adolescents and Adults

- 0–4 years (n=178), 28%
- 5–9 years (n=137), 27%
- 10–14 years (n=98), 50%
- 15–19 years (n=77), 79%

Walter, 2002
• In US: >50% of pregnancies are unplanned
• 1/2-2/3 of babies are exposed to neurotoxic maternal blood PHE levels
New Studies Show Some Improvement

But child’s normal IQ & development still dependent on:

- Maternal blood PHE in *tight* control before + throughout pregnancy – 100-240 umol/L
- Minimal fluctuation in maternal blood PHE – even when stays within control range
- Frequent clinic visits – monitoring, education, support, nutrition counseling

“…weekly visits to a nutritionist experienced in treating PKU to reinforce and make changes in the diet during pregnancy is key factor in improving blood PHE concentrations.”

Maternal PKU workgroup

• Barriers to preconception control
• Modification of diet recommendations
• Safety of adjunct therapies in pregnancy (Kuvan, LNAAs, etc.)
• Requirements during postpartum and lactation
Guidelines for Treating PKU
Recommendations 2014
GMDI – ACMG

• Maternal blood PHE 120-360 umol/L preconception
• Closely monitor:
  • Maternal weight gain
  • Blood PHE, dietary intake, nutritional status
  • Fetal development – by high-risk obstetrics
• Adjust diet and medical food as frequently as needed
• Offer sapropterin (Kuvan) on individual basis
• Avoid LNAAs in pregnancy
• Maintain treatment through postpartum and lactation
• *Individualize treatment plans!*

Phenylalanine Hydroxylase Deficiency Diagnosis and Management Guideline, Vockley, et al. Genetics and Medicine 2014
Dietary Treatment of PKU During Pregnancy

- PHE in diet limited to amount that controls blood PHE levels to 120-360 (240) umol/L 3-4 months preconception

<table>
<thead>
<tr>
<th>Dietary PHE</th>
<th>1st Trimester</th>
<th>2nd &amp; 3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>225 - 770 mg/day</td>
<td>770-2275 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

- Higher PHE tolerated in 2nd + 3rd trimesters helps!
Dietary Treatment of PKU During Pregnancy

- ↑ protein & calories for good maternal weight gain & fetal growth – needs ↑ by 50% (>70 g/d)
- Medical food and specialty low protein foods essential
  - Concentrated amino acid medical food
  - Adequate fat intake – 30-35% calories

<table>
<thead>
<tr>
<th>Pre-pregnancy</th>
<th>1st Trimester</th>
<th>2nd + 3rd Trimester</th>
<th>40 weeks</th>
<th>25-35 lbs</th>
<th>28-40 lbs</th>
<th>15-25 lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>3 ½ lbs</td>
<td>1 lb/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>5 lbs</td>
<td>1 lb/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>2 lbs</td>
<td>2/3 lb/week</td>
<td></td>
<td></td>
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Nutritional status of the mother has direct effect on how well the baby grows and develops – and is often inadequate.
## Dietary Treatment of PKU in Pregnancy

<table>
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<tr>
<th>Nutrient</th>
<th>Function</th>
<th>DRI / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12</td>
<td>DNA synthesis</td>
<td>2.6 ug (2.8 ug in lactation)</td>
</tr>
<tr>
<td>Calcium</td>
<td>Bone strength</td>
<td>1000-1300 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>O² transport proteins</td>
<td>27 mg (9 mg in lactation)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Vision, immune system, reproduction system</td>
<td>770 ug RAE (1300 ug in lactation) &amp; always &lt; 3000ug</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Ca absorption Ca/Phos balance</td>
<td>600 IU</td>
</tr>
<tr>
<td>Zinc</td>
<td>Immune function, DNA /protein building</td>
<td>11-12 mg (12 mg for lactation)</td>
</tr>
<tr>
<td>Folate/folic acid</td>
<td>DNA/protein building – prevent NTD, IUGR and prematurity</td>
<td>600 ug</td>
</tr>
<tr>
<td>DHA</td>
<td>Brain, eye, nervous system development</td>
<td>300 mg</td>
</tr>
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</table>
Normal Pregnancy Symptoms

Complicates diet adherence – ↓ appetite and intake

Early pregnancy – nausea, vomiting, smell sensitivity, food aversions
- Frequent meals/snacks – eat before rising (dry snack)
- Protein at each meal/snack
- Eat solids separate from liquids
- Cold foods and drinks – frequent fluids
- Avoid culprit foods
- Motion sickness bands
- Dried ginger/ginger tea
- Anti-nausea medications
- Hospitalization

Late pregnancy – heartburn, constipation, cravings, increased salivation
- Small frequent meals/snacks
- Avoid high fat/spicy/acidic foods
- Sit upright 90 minutes after eating/drinking
- High fiber foods, stool softener for constipation
- Increase fluids, mouthwash rinses for increased salivation
PKU Management in Pregnancy

- *Individualized dietary therapy*
- Frequent blood samples to monitor
- Frequent maternal weight + fetal growth measurements
- Frequent nutrition counseling – diet changes as needed
- Assistance w/ resources (WIC, etc.)
- High risk OB and neonatologist
  - High resolution ultrasounds
- Hospital admission?

PHE
120-240 umol/L
Postpartum and Lactation

Important to continue diet through postpartum and lactation – but 70-90% of women do not

Postpartum period – weeks after delivery
• ↑ blood PHE may increase depression, emotion swings, anxiety, difficulty w/ decision making
• May impair parenting ability
• Postpartum treatment same as for preconception

Breastfeeding: mother with PKU can safely breast feed infant who does not have PKU
• Protein and calorie needs similar to 3rd trimester
New Therapies

What we know about Kuvan

• “Class C” – means not enough research to prove safety but use if benefit outweighs any unknown risk
• No controlled studies – but clinical reports of safety
• PKUDOS MOMs – FDA mandated registry – 2013
  • Blood PHE 23% lower + more stable when on Kuvan
  • Normal babies in 81% w/ blood PHE <360 umol/L
• Kuvan appropriate for pregnant women\(^1,2\)
  • Taking Kuvan preconception
  • When cannot control blood PHE w/ diet alone
  • But best to determine response before pregnancy

Future therapies?

\(^1\) ACMG/GMDI/NIH, \(^2\) Cunningham, et al, MGM 2012
MPKU Diet: Barriers to Adherence

- Complicated: planning, food preparation, calculations
- Preparing foods different from family meals
- Expense of low protein foods, formula
- Restarting formula
- Nausea during pregnancy
- Poorly covered by insurance or public assistance
- More frequent blood sampling
- Lack of access to prenatal and genetics care
- Limited obstetrician knowledge – lack of high risk OB
- Loss of contact with metabolic clinic
- Lack of emotional support system
- Possible difficulty thinking due to ↑ blood PHE
Prevention is the Only Cure for MPKU

A woman w/ PKU coming to treatment already pregnant represents a *medical emergency*

- Stay in touch with your clinic
- **Plan pregnancies** – access to contraception
- PHE level in control – means dietary compliance from before conception through postpartum
- Optimal maternal nutrition
- Consider use of new therapies
- NPKUA support group
It’s up to us..........