



Nutritional Management of maternal patients with inborn errors of amino acid metabolism: What to consider


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June 7, 2018






Learning Objectives



- Understand general considerations when managing maternal patients with inborn errors of metabolism;
- Discuss case reports relating to maternal inborn errors of metabolism;
- Evaluate application of learnings to one's own clinical practice.



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What we've learned from pregnancies in MSUD, propionic and methylmalonic acidemia

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Disclosures


- Honoraria provided by Nutricia North America:
 - development of educational materials
 - speaker for presentations and webinars
- Honoraria provided by Met-Ed:
 - Metabolic University faculty
 - Development of educational materials
- Dietitian Advisory Board for Pegvaliase® (Biomarin Pharmaceuticals)
- PI for the following research grants funded by:
 - Galactosemia Foundation
 - Vitaflo International

□ **None pose any conflict of interest for this presentation**

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Limited experience, but some trends

| | Total # | Preeclampsia | Preterm < 37 wks | IUGR < 10% | Abnormal infant Development |
|--------------------|-----------|---------------|------------------|----------------|-----------------------------|
| MSUD | 16 | 1 | 1 | 2 | 0 |
| Propionic acidemia | 7 | 2 | 2 | 1 | 0 |
| MMA | 13 | 1 | 5 | 1 | 0 |
| TOTAL | 36 | 4 | 8 | 4 | 0 |
| % of total | | 11 % | 22 % | 11 % | 0 % |
| US Stats | | 2 – 6% | 13 % | 3 – 10% | |

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None of the infants have microcephaly or congenital heart defects seen in maternal PKU syndrome

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Mothers appear to be at higher risk than the infants


Goals for pregnancy 

1. Refer to an obstetric clinic specializing in high risk pregnancies

TEAM EFFORT:
 High Risk OB Clinic
 Metabolic Clinic
 Local OB
 Patient


Goals for pregnancy 

2. Maintain normal maternal weight gain during pregnancy

Weight gain goals same as general population 

| Pre-pregnancy BMI | Total weight gain (lbs) | Rate of gain in 2 nd and 3 rd trimesters (lbs/week) |
|-------------------|-------------------------|---|
| < 18.5 | 28 - 40 | 1 - 1.3 |
| 18.5 - 24.9 | 25 - 35 | 0.8 - 1 |
| 25 - 29.9 | 15 - 25 | 0.5 - 0.7 |
| > 30 | 11 - 20 | 0.4 - 0.6 |

First trimester: 1 to 4.5 lbs/week

Goals for pregnancy 

3. Maintain plasma amino acid concentrations within the normal or goal range

4. Anticipate a higher intact protein tolerance as pregnancy progresses

Example: MSUD Case Study



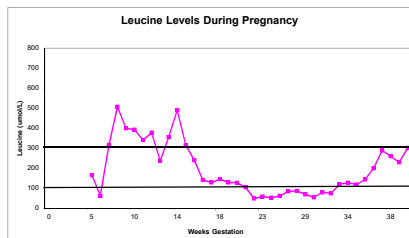
- 23 year old, homozygous for common Mennonite mutation
- Diagnosed at DOL 4 with metabolic crisis
- History of excellent metabolic control: No evidence of delays or other long-term problems associated with poor control
- Presented at 6 weeks gestation with good metabolic control
- Pre-pregnancy BMI = 24

MSUD Case Study Cont'd



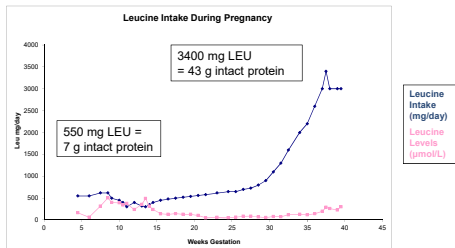
Goal: Leucine concentrations established for MSUD, not normal lab concentrations

Same for VAL and ILE




Based on: van Calcar, S. Chapter 21 in: L.E. Bernstein et al. (eds.), *Nutrition Management of Inherited Metabolic Diseases: Lessons from Metabolic University*, DOI 10.1007/978-3-319-14621-8_21, © Springer International Publishing, Switzerland, 2014.


MSUD Case Study Cont'd



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Goals for pregnancy 

5. Avoid over-restriction of intact protein sources to prevent reduced fetal growth

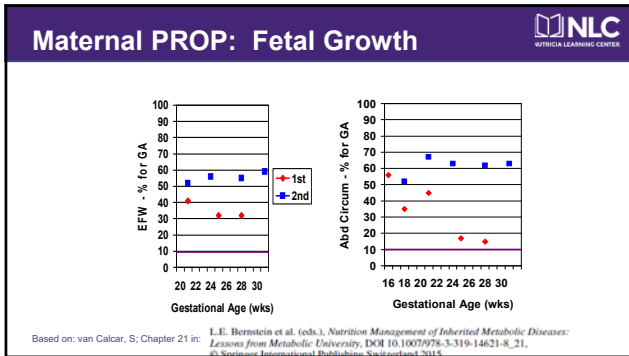
Propionic Acidemia: Case Study 

Pre-Pregnancy History

- Diagnosed at age 4 while in coma
- Self-restricts protein (0.6-0.8 g/kg)
 - ▣ No formula as adult
- Biotin & Carnitine
- Seizure x 1: anti-seizure med; cardiac: long-QT
- PCC-β mutations; 6% enzyme activity
- Two pregnancies: Induced b/c Preeclampsia

Maternal PROP: Pregnancy Comparison 

| | 1 st Pregnancy | 2 nd Pregnancy |
|--|---------------------------|---------------------------|
| Pre-Pregnancy Total Protein (gm/kg) | 0.7 | 1.0 |
| Total Protein @ 20 weeks (gm/kg) | 1.1 | 1.3 |
| Total Protein just prior to Delivery (gm/kg) | 1.4 | 1.6 |
| Week started formula | 14 | Pre-Pregnancy |
| Total Wt Gain | 15 kg (33 lbs) | 13 kg (28 lbs) |
| Carnitine dose at Delivery (mg/kg) | 151 | 100 |
| Gestational Age (wks) | 31 1/7 | 32 0/7 |
| Birth Weight (g) | 1170 | 1826 |




Goals for pregnancy

6. Anticipate protein catabolism during delivery and postpartum period


Delivery Plan

Provide IV energy source:

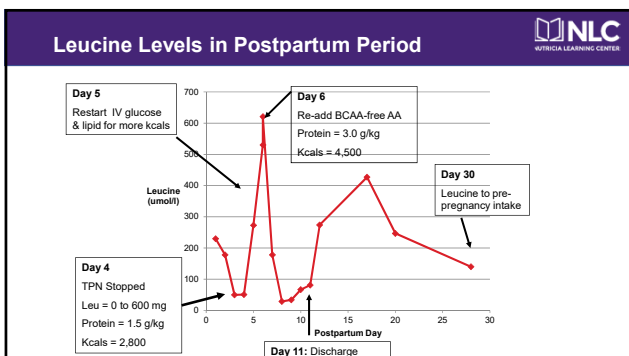
- Most deliveries include IV dextrose (10%)
- More aggressive options include protein equivalents

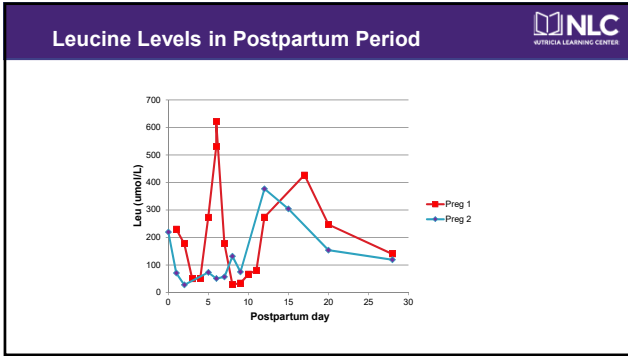
Postpartum Catabolism 

- MSUD: 7 of 16 pregnancies with increased LEU levels
- Decompensation: Day 3 to 14
- Why?
 - Metabolic stress with changes postpartum
 - Protein catabolism with involution of uterus
 - Begins day 2 after delivery, First week: 50% reduction
 - We're aggressive with calories first 48 hours, then back off.
- To return to pre-pregnancy metabolism: 6 to 8 weeks

Delivery and Postpartum Plan for MSUD pregnancy 

- C-section planned
- PICC line placed with maintenance fluids:
 - 7% BCAA-free AA soln, NS @ 50 ml/hr
 - 20% Dextrose @ 35 ml/hr
 - 20% Intralipid @ 15 ml/hr
 - 2300 kcals, 4.5 mg/kg/min glucose, 1 g/kg lipid
- Monitor electrolytes and glucose; insulin if needed
- Gradual decrease line with increased oral
- Breastfeeding planned





Benefits of Breastfeeding

- Can breastfeeding be “protective” against elevated leucine in postpartum period?
- Consider
 - 100 ml breastmilk = 95 mg leucine
 - 1.2 g protein
 - 70 kcals
- 3.5 kg infant @ 110 kcal/kg = 385 kcals = 580 ml = 550 mg leucine

Infant Outcomes

- No microcephaly, cardiac defects, abnormal facial features have been reported
 - Despite some cases of poor maternal metabolic control
- No overt developmental delays noted
 - Many report only neonatal outcomes
 - Some as adolescents and young adults are normal functioning
- Need systematic follow-up



Case report TYR
Maternal Tyrosinemia Type 1

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Disclosures

- Consultant and invited speaker for Nutricia (educational)
- Speaker at different symposium invited by Abbott Nutrition (2009), SOBI (2012), Nutricia (2013)

None pose any conflict of interest for this presentation

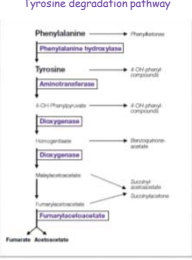
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Review

Tyrosinemia type 1 is an autosomal recessive disorder caused by a deficiency of the enzyme Fumarylacetoacetate hydrolase (FAH)

Tyrosinemia type 1 management

Phe + Tyr restricted diet
+
Nitisinone (NTBC)




The diagram illustrates the tyrosine degradation pathway. It begins with Phenylalanine, which is converted to Tyrosine by the enzyme Phenylalanine hydroxylase (requiring 4-OH-phenylpyruvate). Tyrosine is then converted to 4-OH-phenylpyruvate by Aminotransferase (requiring 4-OH-phenylpyruvate). This intermediate is further converted to 4-OH-phenylacetate by Chaperonase. 4-OH-phenylacetate is then converted to Fumarylacetoacetate by Chaperonase. Fumarylacetoacetate is cleaved into Fumarate and Acetoacetyl-CoA by Fumarylacetoacetate hydrolase. The diagram also shows the conversion of Tyrosine to Tyrosyl-CoA by Tyrosyl-CoA ligase, which is then converted to Tyrosyl-tRNA by Tyrosyl-tRNA synthetase. Tyrosyl-tRNA is used for protein synthesis, leading to Tyrosyl-protein. Additionally, Tyrosine can be converted to Tyrosine-3-O-sulfate by Tyrosine-3-O-sulfotransferase, which is then converted to Tyrosine-3-O-sulfate by Tyrosine-3-O-sulfate hydrolase.

Patient History


- Patient was born in 1988
- Homozygous for French Canadian mutation (IVS12 + 5G>A)
- Detected by neonatal screening
- Managed by a restricted phenylalanine + tyrosine diet
- Nitisinone (NTBC) was started at age 5
- Asymptomatic
- Pregnancy planning at age 28

Pregnancy in Nitisinone-treated patient


- What do we know ?
 - First reported human experience in 2011
 - Only a few reported cases in literature
- **BUT**
 - Phe + Tyr restricted diet must be strictly followed
 - Nitisinone must not be stopped

What do we know (cont'd) 


- High tyrosine plasma levels during pregnancy
 - Can affect fetal development
 - Mental deficiency
 - Microcephaly
 - Low birth weight
- Nitisinone
 - Crosses the placenta
 - No breastfeeding

Pregnancy course – Before pregnancy 


- Good metabolic control prior to pregnancy (except formula drinking)
 - Tyrosine levels : mostly between 200 and 400µmol/L
 - Normal phenylalanine levels
- Diet
 - 850 mg Phe +Tyr /day (34 equivalents)
 - Total protein intake of 35g/day (12g of natural protein) → Not optimal
 - Calories :1600 kcal/day
- BMI : 28

Pregnancy course – 3 months before pregnancy 

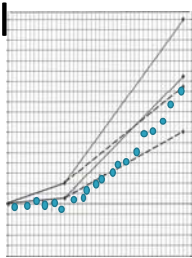
- Prenatal vitamins
 - Folic Acid and multivitamin
- Formula ↑
 - ≈70g of total protein , 50g from amino acid mixtures
- Monitoring
 - Amino acid profile each month
 - Adjust protein intake
 - Adjust formula
- Nitisinone
 - 0.5 mg/Kg/day


Pregnancy course – Pregnancy 

- Monitor amino acid profile each week
- Clinic visit every 2 weeks
 - Adjust protein intake
 - Adjust formulas (3 to 4 different types of formula each day)
 - Weight
 - Others (protein , albumin, iron,...)
- Regular pregnancy monitoring

Weight gain 


-- BMI : 25-29.9
 Total weight gain 7-11.5 kg (15-25lbs)
 BMI :<18.5
 Total weight gain 12.5-18 kg (28-40 lbs)
Patient total weight gain : 11.2 kg (24.6 lbs)




Phe + Tyr intake 

Phe + Tyr intake increased from 850 mg/day to 1550 mg/day (34 to 62 equivalents)
 Total protein : 65 g to 85 g/day (natural protein 12-20 g/day)
 Mean energy intake : 1800 kcal/day (1600-2700 kcal/day)

** At delivery, 1000 mg Phe+Tyr/day and 850 mg 48 hours post delivery*



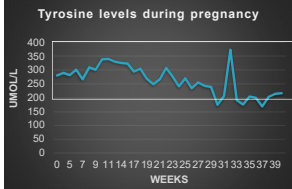
Tyrosine levels 


Tyr and Phe levels were monitored each week

Tyr levels in the normal range throughout the pregnancy


Mean Tyr level : 263µmol/L

Mean Phe level: 38 µmol/L



Other measured parameters 

- Maternal α-fetoprotein increase within the expected range
- Mean nitrosinone levels : 54.4 (normal range :40-60 µmol/L)
- Protein and albumin in normal range until 35 weeks of gestation
- Uneventful pregnancy

My baby boy ! 

- Born after 41 weeks of gestation
 - Weight: 4.250 Kg (97th percentile)
 - Height : 53 cm (97th percentile)
- Tyrosine in cord blood : 483µmol/L
- Tyrosine at day 5 (in plasma) : 791 µmol/L

} Normal within one month

- Phenylalanine levels in normal range from birth
- Nitrosinone was also elevated at birth → undetectable after 14 days
- No breastfeeding

He is now 11 months old with good development (85th percentile for weight and height)


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Maternal HCU Case Report

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Children's Hospital of Philadelphia


Disclosures 

No disclosures that would pose any conflict of interest for this presentation


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HCU Case Study: Pre-Pregnancy 


- History of non-compliance, picked up at 10 years of age
- No medical food
- 35-40 grams of protein daily (not tracking)
 - 0.7-0.8 g/kg

HCU Case Study: Pre Pregnancy 


- Diet recall:
 - Calories: 1450 (REE x 1.2)
 - Protein: 33 grams protein (0.67 g/kg)
- Anthropometrics:
 - Weight: 49.1 kg
 - Height: 163.8 cm
 - BMI: 18.3 (underweight)
- Labs:
 - Total Homocystine: 181.1 nmol/L
 - Free Homocystine: 13 (<2); Methionine: 64
 - Vitamin D, 25 OH: 6 ng/mL (>30)

HCU Case Study: Pre Pregnancy 


- Medications/Nutritional Supplements:
 - 500 mg Calcium 4 times daily
 - 2000 units Vitamin D
 - 3.5 gm Betaine BID (7 gm daily)
 - Vitamin B6, 500 mg BID
 - Hydroxocobalamin (B12) injections Q 3 months
 - 1 mg folic acid

1st Trimester (~11-12 wks) 

- Hyperemesis
- 24 hour diet recall:
 - 31.5 grams of protein (0.6 g/kg)
 - 650 kcal (REE x 0.5)
- Goal = maintain 40 grams of protein from food
- Start medical food
 - 40 gram protein equivalents

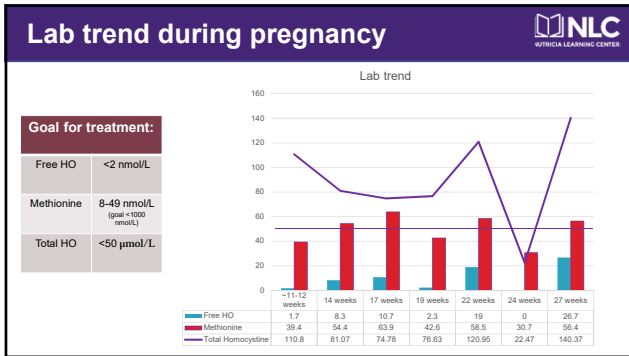
1st Trimester (~11-12wks) 

- Medications:
 - Vitamin B6: 500 mg, oral, twice daily.
 - Folic acid 2.5 mg, oral, daily.
 - Baby aspirin 81 mg daily, oral, daily.
 - Resume 1 mL B12 injections IM, every 3 months
 - Continue 3.5 gm Betaine BID

Nutrition Recommendations: 

- Weight gain goal: BMI < 19.8
 - 12.5 – 18 kg (28-40 lbs) (0.5 kg/~1lb every week after 12 weeks)
- Calorie goal:
 - 1 trimester = EER x PA + 0 (= 1459 kcal/day)
 - 2nd trimester = EER x PA + 340 kcal (=1800 kcal/day)
 - 3rd trimester = EER x PA + 452 kcal (=1911 kcal/day)
- Protein goal:
 - 1 trimester = 40 grams protein
 - 2nd trimester = 40 gm protein from food + 40 gm protein from medical formula + additional 20 gm protein from medical food near end of 2nd trimester
 - 3rd trimester = 40 gm protein from food + 60 gm protein from medical food

Source: Position of the American Dietetic Association: Nutrition and lifestyle for a healthy pregnancy outcome. J Am Diet Assoc. 2002;102(10):1479-1490.




Protein intake during pregnancy


| Weeks | Complete protein (g) | Calorie intake | Medical food (g) | Total Homocysteine (nmol/L) | Methionine | Free Homocysteine |
|--------------|-----------------------|----------------|------------------|-----------------------------|------------|-------------------|
| ~11-12 weeks | 31.5 | 650 | 0 | -- | -- | -- |
| 12-13 weeks | -- | -- | -- | 110.8 | 39.4 | 1.7 |
| 14 weeks | No diet record | -- | 0 | 81.07 | 54.4 | 8.3 |
| 17 weeks | 32 | 1305 | 40 | 74.78 | 63.9 | 10.7 |
| 19 weeks | 46 | 1758 | 0 | 76.63 | 42.6 | 2.3 |
| 22 weeks | Did not see in clinic | -- | -- | 120.95 | 58.5 | 19 |
| 23 weeks | 46 | 1376 | 12 | -- | -- | -- |
| 24 weeks | 40 | 1390 | 20 | 22.47 | 30.7 | 0 |
| 27 weeks | 46 | 1880 | 35 | 140.37 | 56.4 | 26.7 |

Weight gain throughout pregnancy


- Gain of 12.1 kg (26.6 lbs) x 107 days (15.3 weeks)
 - Gain from ~11-12 weeks till ~27 weeks
 - 0.79 kg/week (1.7 lbs/week)

Delivery Recommendations 

- Risk for clots, thromboembolic precautions were taken
- Administer Continuous IV Fluids of D5% with NS @ 1.5x maintenance
- Labs: PAA, Total Homocysteine (upon admission and 24 hours post partum)


Postpartum 

- No clinic/lab follow up between 27 weeks till 2 months postpartum
- Induced at 39 weeks
- Delivered a healthy baby girl with no reported complications despite overall poor control throughout pregnancy




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