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

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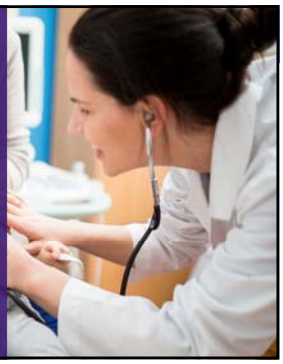
June 7, 2018



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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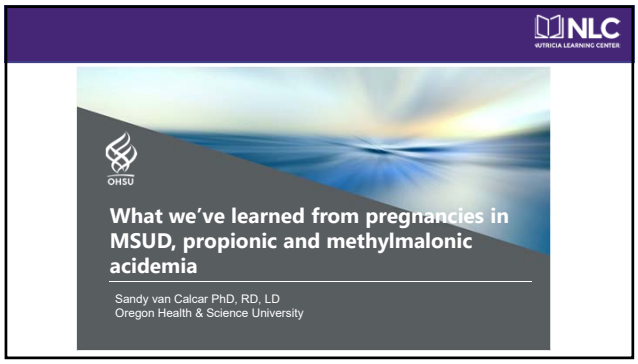

Disclosures

- Honoraria provided by Nutricia North America:
  - development of educational materials
  - speaker for presentations and webinars
- Honoraria provided by Met-Ed:
  - Metabolic University faculty
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- ***None pose any conflict of interest for this presentation***

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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%**	

Limited experience, but some trends

	Total #	Preeclampsia	Preterm < 37 wks	IUGR < 10%	Abnormal Infant Development
MSUD	16	1	1	2	0
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MMA					
TOTAL					
% of total		11 %	22 %	11 %	0 %
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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 2nd and 3rd 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

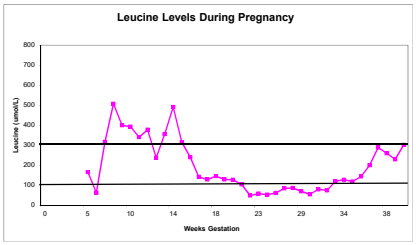
Example: MSUD Case Study

- 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



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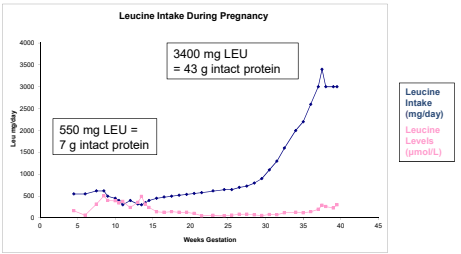
MSUD Case Study Cont'd



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Goals for pregnancy

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

Propionic Acidemia: Case Study

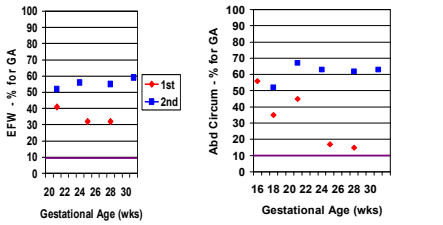
Pre-Pregnancy History

- 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

	1st Pregnancy	2nd 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

Maternal PROP: Fetal Growth



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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

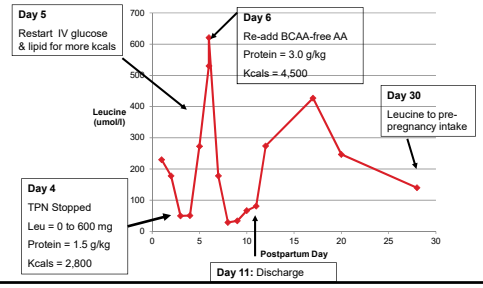
Postpartum Catabolism

- 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

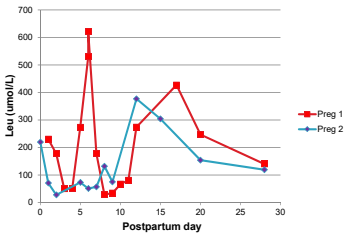
Delivery and Postpartum Plan for MSUD pregnancy

- 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

Leucine Levels in Postpartum Period



Leucine Levels in Postpartum Period



Benefits of Breastfeeding

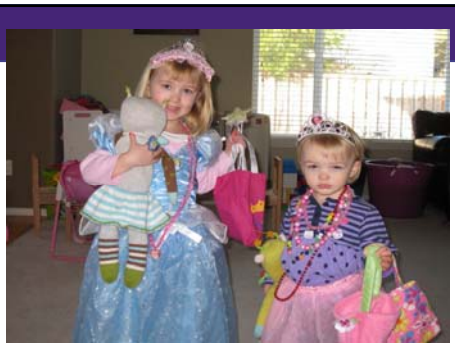
- Can breastfeeding be "protective" against elevated leucine in postpartum period?
- Consider

  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)

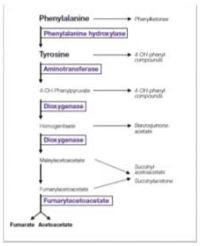
- **Tyrosinemia type 1 management**

  Phe + Tyr restricted diet

  \+

  Nitisinone (NTBC)

Tyrosine degradation pathway



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

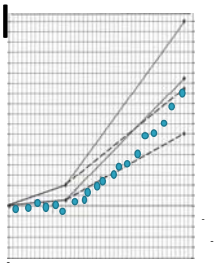
- Monitor amino acid profile each week
- Clinic visit every 2 weeks
  - Adjust protein intake
  - Adjust formulas (3 to 4 differents types of formula each day)
  - Weight
  - Others (protein , albumin, iron,…)
- Regular pregnancy monitoring

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*

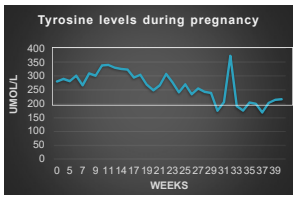
Tyrosine levels

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 nitisinone 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
- Nitisinone 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

Sarah Moran, MS, RD, CSP, LDN
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 nnmol/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

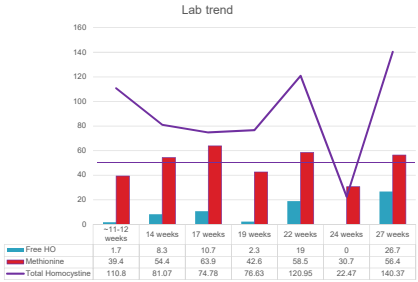
Nutrition Recommendations:

- 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.

Lab trend during pregnancy

Goal for treatment:	
Free HO	<2 nmol/L
Methionine	8-49 nmol/L (goal <1000 nmol/L)
Total HO	<50 µmol/L



	~11-12 weeks	14 weeks	17 weeks	19 weeks	22 weeks	24 weeks	27 weeks
Free HO	1.7	8.3	10.7	2.3	19	0	26.7
Methionine	39.4	54.4	63.9	42.6	58.5	30.7	56.4
Total Homocystine	110.8	81.07	74.78	76.63	120.95	22.47	140.37

Protein intake during pregnancy

	Complete protein (g)	Calorie intake	Medical food (g)	Total Homocystine (nnmol/L)	Methionine	Free Homocystine
~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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