BREASTFEEDING ON THE INSULIN DYSREGULATION SPECTRUM

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Learning Objectives:

1. Describe the pathway in which insulin regulates milk production through the stages of lactogenesis.
2. List 2 ways in which insulin resistance may negatively affect milk synthesis.
3. List at least two strategies for addressing low milk production related to insulin resistance.

I. Normal Insulin Dynamics

a. Metabolic

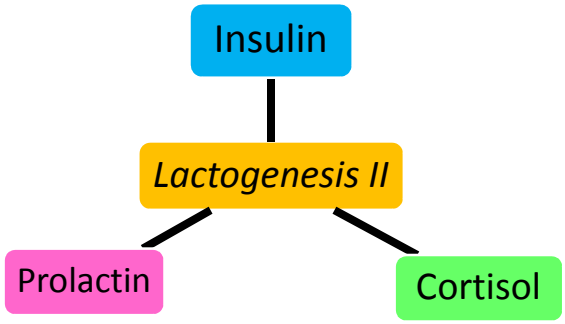
- Simple: Insulin binding affects glucose uptake
- Complex: Multiple pathways options triggered by insulin binding

b. Breast

- Insulin plays a supportive role in pubertal mammary development
- Breast is relatively insulin resistant during pregnancy
- During pregnancy, insulin regulates the switch from proliferation to differentiation *(Neville 2013)*

c. Lactation

- After delivery, breast becomes more insulin sensitive
- Lactogenic complex necessary for Lactogenesis II
- *Lemay 2013*- Insulin influences milk synthesis via PTPRF (protein tyrosine phosphatase, receptor type F)



Lactogenic Complex

RNA Sequencing of the Human Milk Fat Layer Transcriptome Reveals Distinct Gene Expression Profiles at Three Stages of Lactation. *Lemay 2013*

IDENTIFYING THE STAGES

	Colostrum →	Transitional Milk →	Mature Milk
Stages defined by Na/K ratio, (tight junction closure) not day PP	> 2.0	<2 - .6	< .6
Major expressed genes	FTL (ferritin) CTSD (cathepsin D)	LALBA (α-Lactalbumin) CSN2	CSN2 (β-casein) LALBA (α-Lactalbumin) = ~45%
Priority of gene expression	Immune defense	*Massive development of protein synthesis infrastructure *Inhibition of protein degradation	*Massive synthesis of lipids
Cell cycle genes	↑ regulated		↓ regulated
Immune response genes	↑↑↑	↑↑	↑
Lipid biosynthesis genes	↑	↑↑	↑↑↑

INSULIN NECESSARY FOR MILK PROTEIN SYNTHESIS

Colostrum → Transitional Milk	Transitional → Mature Milk
Strong modulation of insulin signaling *Breast becomes sensitized to insulin*	Insulin signaling maintains steady-state *Robust expression.*
Up-regulation of lipogenesis, protein synthesis	**Toning down** of initial steep up-regulation of metabolic signals via up-regulation of **PTPRF**, which suppresses insulin action
Inhibition of apoptosis, glycolysis and glycogenesis	
PTPRF ↑ Insulin action ↓	**PTPRF ↓ Insulin action ↑**

PTPRF = protein tyrosine phosphatase, receptor type F

MECHANISM FOR IMPACT OF IR ON MILK PRODUCTION

Markers	Mature Group 1	Mature Group 2
Median onset of notably fuller breasts	34 hrs	74 hrs
Insulin secretion	Above median	Below median
Insulin sensitivity	Above median	Below median
Expression of PTPRF	_baseline_	Significantly higher than Group 1 (over-expressed)
Milk Production	**Engorgement peaked day 4-5, then down regulated to demand**	All reported difficulty with milk supply at either day 4 or pp week 4-6 interviews

II. Type 1 Diabetes

a. Inadequate insulin production to support normal glucose metabolism

b. Poor control during pregnancy (*Neubauer 1990)*

- Lower prolactin levels
- Decreased thyroid hormones
- Decreased human placental Lactogen (HPL)→ mechanism to affect mammary growth?
- Onset of lactation ½-1 day longer than normal *(Hartmann 2001)*
- Breastfeed early and often to bring milk in sooner

c. Postpartum impact (*Neubauer 1990)*

- Diabetic infants may display immature sucking patterns, impacting milk removal and stimulation of lactation *(Bromiker 2006)*
- Poor glucose control can result in fluctuations of milk synthesis
- Insulin requirements can be 25-50% less during lactation
- Mastitis and yeast infections more common in diabetic mothers with poor control

Miyake 1989

Group	Suckled mls	Manually extracted mls	Total mls
Controls (40)	658 ± 87	446 ± 58	1105 ± 121
Ovulatory disturb (57)	510 ± 60	512 ± 52	1023 ± 103
Diabetes Mellitus (40)	**364 ± 40**	**490 ± 64**	**853 ± 98**
Hypo-thyroid (28)	435 ± 46	457 ± 61	892 ± 118
Hyper-thyroid (40)	578 ± 77	478 ± 71	1056 ± 170

III. Type 2 Diabetes / Gestational Diabetes

a. Insulin receptor resistance reduces insulin binding, affecting glucose uptake

- Body starts overproducing insulin to compensate—hyperinsulinemia
- Physical symptoms of insulin resistance (IR) include skin tags, acanthosis nigricans

b. Breast development

- Hyperinsulinemia prior to puberty acts like growth hormone, ***may*** fuel excessive growth
- Hyperinsulinemia soon after puberty ***may*** reduce breast size via fueling of excessive androgens, which may suppress growth
- Insulin resistance could affect differentiation of the mammary gland during pregnancy

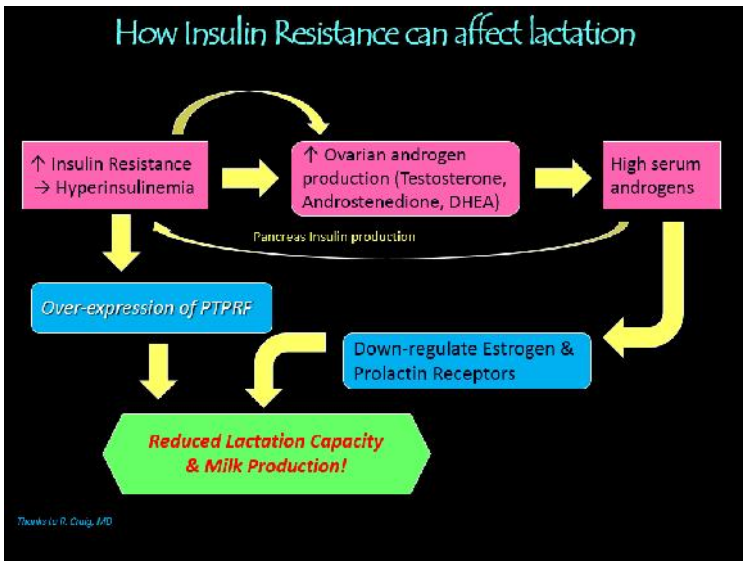
c. Lactation

- Higher risk of delayed onset of lactation *(Matias 2014; Chapman 2014)*
- GDM risk factors for problems: Obesity (AOR 1.56); insulin during pregnancy (AOR 3.11); Age increments of 5 yrs (AOR 1.05); LATCH score <7.5
- Excessive weight gain: High BMI + excessive weight gain = additive risk *(Hilson 2006)*

Hilson, 2006	IOM	<IOM OR	Within OR	>IOM OR
Overweight BMI 26-29	15-25 lbs	2.96	1.47	1.62
Obese BMI > 29	13-20 lbs	1.81	1.84	2.89

- Duration of lactation diminishes with increasing severity of diabetes *(Hummel 2008)*

	Any Bfg Rate	Duration: Full Bfg	Duration: Any Bfg
Healthy = 527	86%	17 wks	
GDM all = 257	75%	9 wks	
GDM-Diet		12 wks	20 wks
GDM Insulin		4 wks	10 wks
GDM + BMI <30	80%		17 wks
GDM + BMI >30	65%		12 wks



d. Long-term impact of breastfeeding on metabolic health

- Longer lactation associated with improved metabolic profiles *(Gunderson 2007, 2012; Ram 2008.)*
- Reverse causality? Metabolic profile affecting duration of lactation

IV. Treatment Strategies: Address the underlying issue: insulin resistance *(Nommsen-Rivers 2012)*

Level 1: Diet

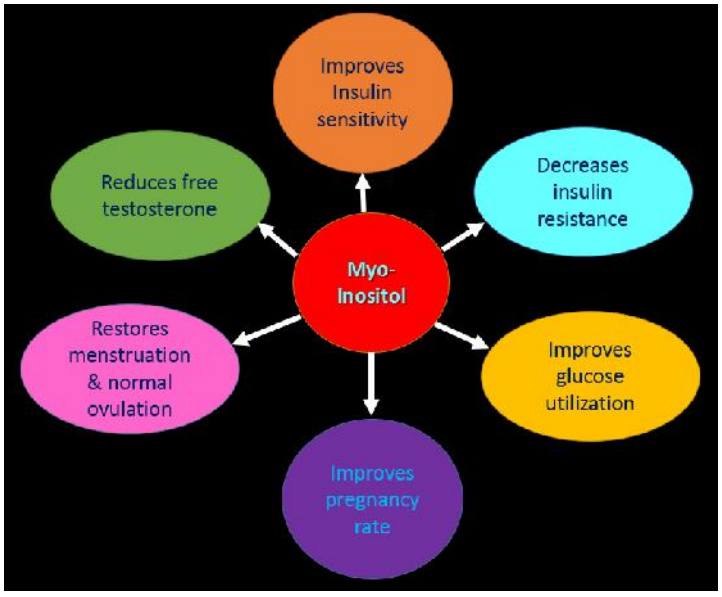
- Smart foods for insulin resistance: Legumes garbanzo & kidney beans, brown rice, carob, cinnamon
- Reversing calorie intake at meals *(Jakubowicz 2013)*
- Nutrients that help insulin resistance: Magnesium, Chromium, Gymnema *(Bindlish 2014)*

Level 2: Medications and Supplements

1. **Metformin** to improve insulin receptor sensitivity *(Bargiota 2012)*
   - Improved insulin dynamics may help with milk synthesis
   - Reduced insulin resistance slows androgen production, inhibition
   - Treatment during pregnancy may set up for better start-up of lactation; reduces miscarriages, GD, pre-eclampsia, premature births (Glueck 2002, 2004)
   - Impact on breast growth during pregnancy not yet validated *(Vanky 2012)*

   Note: Metformin can deplete B-12

2. **Myo-inosito**l: The Second M *(Larner 2010)*
   - Naturally occurring in foods *(Clements, 1980)*
   - Inositol is a secondary messenger for insulin
   - Myo- and D-chiro inositol signal different insulin pathways
   - Myo-inositol converts via epimerization to D-chiro-inositol
   - Insulin resistance frequently associated with imbalance of conversion
   - 40:1 ratio of Myo-inositol to D-chiro-inositol appears to give best results in PCOS *(Nordio 2012);* more effective in obese women *(Genazzani, 2012)*
   - Improves insulin sensitivity, glucose utilization; reduces free testosterone
   - Virtually no side-effects
   - No research on impact on lactation, but rationale same as for metformin



Inositol presentation: http://www.slideshare.net/LifecareCentre/what-is-40-1-in-management-of-dr-jyoti-agarwal-dr-sharda-jain-dr-jyoti-bhaskar

Level 3: Smart Galactogogue options (anti-diabetic properties)

- Goat's rue (precursor of metformin)
- Malunggay
- Blackseed
- Fenugreek
- Dandelion
- Nettle leaf
- Milk thistle
- Coriander seed

Natural progression of prediabetes into diabetes:

http://www.priorslegh.co.uk/Diabetes/index.php/what-is-prediabetes

Changing therapies to address diabetes progression:

http://www.medscape.org/viewarticle/418591_9

Proactive option for better start to breastfeeding: Antenatal Expression: early stimulation of lactation, provides colostrum for newborn if hypoglycemia treatment is necessary or lactation is delayed *(Forster 2011; Singh 2009)*

SMART FOODS, SUPPLEMENTS AND HERBS FOR INSULIN-RESISTANT MOTHERS WITH LACTATION PROBLEMS

Smart Foods for Insulin Resistance

- Legumes
- Garbanzo beans
- Kidney Beans
- Brown rice
- Cinnamon (½ tsp per day)
- Carob Powder

Dietary supplements to reduce diabetes

- Gymnema
- Magnesium
- Myo- and D-chiro-inositol 40:1

Foods high in inositol

- Cantaloupe ¼, (355mg)
- Orange (307mg)
- Grapefruit, ½ (199mg)
- Eggplant ½ c, (84mg)
- Kiwi, ½ c (136mg)
- Cabbage, ½ c (70mg)
- Brussel sprouts ½ c (80mg)
- Kidney beans, canned, ½ c (249mg)
- English peas, canned, ½ c (235mg)
- Green beans, ½ c (105mg)
- Wax beans, ½ c (144mg)
- Stone-ground wheat bread, 1 slice (287mg)
- Northern beans, canned, ½ c (440mg)
- Northern beans, dried, ½ c (327mg)
- Nectarine (118mg)

Foods high in chromium

- Orange
- Potatoes
- Broccoli
- Basil
- Garlic
- Red grapes

Foods rich in magnesium

- Bananas
- Broccoli
- Artichokes
- Watermelon
- Avocados
- Raspberries
- Salmon
- Blue berries
- Maple syrup

Smart herbal galactogogues for insulin resistance:

- Fenugreek
- Goat's Rue
- Dandelion leaf
- Nettle leaf
- Milk thistle
- Malunggay
- Coriander seed
- Black seed