Is it mom’s hormones?

**Hormonal Imbalances and Milk Insufficiency**

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**Hormonal Changes of Lactogenesis 2**

- Estrogen ↓
- Prolactin →
- Human Placental Lactogen ↓
- Progesterone ↓
- More insulin sensitive +

**The Pituitary**

- Hypophysis
- Anterior pituitary [Adenohypophysis]
- Posterior pituitary [Neurohypophysis]

Normally about the size of a
But doubles in size during pregnancy due to (↑ E→) hyperplasia and hypertrophy of prolactin-secreting cells (lactotrophs)

**Objectives**

- Describe the curve for prolactin from pre-pregnancy through lactation
- Explain the role of androgens in breast development
- Explain the role of the thyroid gland in lactation
- List at least 2 negative impacts of insulin resistance on lactation

No disclosures of financial or conflicting interests to make.

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**Normal human prolactin levels**

![Image of Normal human prolactin levels graph]

*Conversion factor: mU/l x 0.0472 = ng/ml; ng/ml x 21.2 = mU/l.

**Estrogen (E2) drives Prolactin in pregnancy**

![Image of Estrogen (E2) drives Prolactin in pregnancy graph]

*There is clearly a need to examine those changes that occur during normal pregnancy so that unusual or unexpected trends can be identified...*

**Pregnancy Prolactin range**

![Image of Pregnancy Prolactin range graph]

**What happens in pregnancy if prolactin is low/suppressed?**

![Image of What happens in pregnancy if prolactin is low/suppressed? graph]

**Prolactin through the reproductive cycle**

Driven by estrogen during pregnancy

Baseline a product of surges

Influenced by frequency & quality of stimulation

PRL clearance = 180 min; >8x sustains elevation (Cox 1996)

![Image of Prolactin through the reproductive cycle graph]

**Timing of initiation matters!**

Nedkova 1995 (Bulgarian)

Studied effect of early initiation on PRL in 90 women:
All newly delivered mothers had serum PRL level over 100ng/ml, author accepted as minimum threshold

<table>
<thead>
<tr>
<th>Initiation of breastfeeding</th>
<th>Prolactin on Day 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 hrs post-delivery</td>
<td>164</td>
</tr>
<tr>
<td>≥ 6-12 hrs post- delivery</td>
<td>124</td>
</tr>
<tr>
<td>≥ 72 hrs post-delivery (c-sections)</td>
<td>29</td>
</tr>
</tbody>
</table>

*Feeding frequency unknown, likely q4hrs

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“Good lactators gave a prolactin response 236% above baseline after nursing whereas poor lactators showed a blunted or flat response.” – Ostrom, 1990

What about Hyperprolactinemia?

Often treated w/ PRL inhibitors, radiation or surgery
Hx of galactorrhea is no guarantee of good lactation
Sporadic information


Case study of three women

Case I: Treated w/bromocriptine prior to pregnancy; levels rose normally then extra high (~600ng), headache @ 39 wks for 6 hrs.
Case 2: Treated with CRT (Cobalt Radiation Therapy); Twins
Case 3: Tumor removed surgically. Twin pregnancy.

Prolactin problem: risk factor

Family history of alcoholism
Smaller prolactin response to breast stimulation
Infants fed more often in late afternoon


Case study of three women

Iwama Case Study
Discovered auto-antibodies that specifically targeted prolactin-secreting cells


Prolactin Problems: A New Insight

Iwama Case Study
Discovered auto-antibodies that specifically targeted prolactin-secreting cells

Developed full supply for duration of recombinant hPRL study

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“big-big” or macroprolactin

Little or no biological activity

10-25% of serum prolactin in hyperprolactinemia

Frequently associated with anti-PRL autoantibodies!

Could some women have too much macro and not enough monomeric PRL?

http://www.infantrisk.com/content/presence-macroprolactinemia-mothers-insufficient-milk-syndrome

Measuring prolactin

Screening for prolactin problems

1. Did the milk ever come in?
2. Hx of pp hemorrhage, acute hypotension?
3. Hx of pituitary problems or tumors?
4. Hx of infertility, meds like cabergoline or bromocriptine
5. Personal or family hx of autoimmune problems? Alcoholism?

Prolactin Problems

Laboratory Measuring issues:
- Bound vs Unbound prolactin
- Receptors
- Labs have no reference ranges for lactation!
- Must factor in frequency of feeding/pumping when interpreting results
- Primip/multip status effect?

Treatment quandary for low prolactin

Pharmaceutical stimulation "Off-label"

Physical stimulation

N/A

Replacement therapy

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Prolactin Reference

Prolactin Pre-conception

- Too much >20ng
- Hyperprolactinemia: suppression of ovulation
- No known negative effects
- Normal: 0-20ng

Prolactin during Pregnancy

- Not enough
- Normal: rising→200-400ng
- High
- Poor mammary cell proliferation & differentiation
- Natural hyperprolactinemia: drives breast changes

Thyroid Hormones

- Influences breast tissue via prolactin & GH
- T3 = triiodothyronine
- T4 = thyroxine
- TSH = Thyroid-stimulating hormone: indicator of thyroid function

Thyroid Dysfunction

- Can be primary, secondary, overt, subclinical, autoimmune
- Onset can be prior to preg, during preg, post-delivery, or even later
- Can also occur in conjunction with other conditions such as PCOS
- Incidence much higher in women

Hypothyroidism

- High TSH verified by low T3/T4
- Sx may include weight gain, cold, fatigue, hair loss
- New suggested TSH range for fertility/early pregnancy: .5-2.5 → may flag more of those “borderline” cases
- Controversial— not yet settled

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Hypothyroidism in Pregnancy

- Uncontrolled hypothyroidism can cause
  - anemia
  - pregnancy induced hypertension
  - postpartum hemorrhage

Risk factors for delayed Lact 2

Rat studies: Hypothyroid

- Decreased GH, IGF-1, circulating Triglycerides, & milk-making tissue during pregnancy as well as a reduction in circulating oxytocin postpartum with impaired milk ejection & lactation (Hapon 2003, 2005)
- Hypothyroid rats have smaller litters and longer gestations

Impact on mammary development

Fig. 3. The effects of thyroid hormones and progesterone (P) on tertiary branching. Whole mounts of mammary glands from mice are presented. (A) 3-month-old C3H mouse; (B) 3-month-old hypothyroid C3H mouse, after treatment with propylthiouracil for 5 weeks; (C) 3-month-old hyperthyroid C3H mouse, treated with thyroxine for 5 weeks; (D) 39-day-old BALB/c mouse; (E) 39-day-old intact BALB/c mouse treated with P for 15 days (reproduced by permission of the Society for Endocrinology; 58).

What about subclinical hypothyroidism in pregnancy?

- Endocrine Society (2012)
  - Treat all pregnant women with subclinical hypoT
- American Thyroid Association (2011)
  - Treat subclinical hypoT only if TPO-Ab+ OR TSH >10.0mIU/liter
- ACOG 2007 & 2010 recommends against tx of subclinical hypoT & Most women are treated by OBs

Hyperthyroidism

- Low TSH verified by elevated T3/T4
  - Grave’s disease most common
  - Common sx include weight loss, fast heart beat, sleep problems, nervousness, frequent BMs
  - Previously thought not to affect lactation

Hyperthyroidism

- Sx often improve during pregnancy, but more severe HT can cause pregnancy complications such as fetal growth restriction, pre-eclampsia, preterm labor.
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**Rat studies** showed good mammary growth and evidence of milk production but poor or complete lactation failure depending on the degree of hyperT → poor oxytocin release & milk ejection (Varas 2002)

New rat studies show “advanced” prepartum surge in PRL and blunted PRL response to suckling (Pennacchio 2017)

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**Screening for thyroid problems**

1. Personal or fam hx of thyroid dysfunction?
2. Significant changes in energy, fatigue?
3. Sluggish or rapid preg breast changes?
4. Severe, unreleivable engorgement PP?
5. Fluctuations in milk output not attributable to meds, hormonal BC, changes in bfg patterns?
6. If on replacement therapy, when were levels last checked?

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**Strategy for Thyroid & Supply: the First Step**

Thyroid hormone replacement is first line of treatment for hypothyroidism-related supply problems... *The Armour debate*

Reducing thyroxine is the first line of defense for hyperthyroidism-related milk supply problems

Beware of over- or under-treatment postpartum

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**Secondary help for thyroid-related problems**

- **Oxytocin nasal spray?**

If MER a problem, may possibly provide the oxytocin needed for milk ejection exogenously while waiting for hormone correction to boost natural oxytocin

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**Be aware of thyroid affective herbs**

- Ashwagandha- stimulates T3
- Chickweed- supportive
- Dandelion- supportive
- Milk thistle- improves T4→T3
- Nettle- supportive/balancing
- Vervain- supportive
- Red clover- increased total & free T3 in ewes
- Fenugreek- Reduced T3 in mice & rats
- Lemonbalm (Melissa officinalis)- considered anti-hyperT
- Malunggay- tested for use with hyperthyroidism

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**Thyroid Hormones**

- **Hypo T (Low)**: Poor milk production, sluggish MER/OT
- **Just Right**: Good milk production
- **Hyper T (High)**: Onset preconception, antenatal or postpartum, hyper-production, inhibited OT/MEP

**Androgens... necessary for women in the right amount**

**Sources of Androgens in Women**

- **Adrenals**:
  - Dehydroepiandrosterone sulphate [DHEA-S] (90-100%)
  - Dehydroepiandrosterone [DHEA] (80%)
  - Androstenedione (50%)
  - Testosterone (25%)- most active form of androgen

- **Ovaries**:
  - DHEA (20%)
  - Androstenedione (50%)
  - Testosterone (50%)

- **Peripheral Tissues**: Convert DHEA into more Testosterone & Dihydrotestosterone for local use - not measurable in blood!

**Androgens vs estrogens in the breast**

- Estrogen stimulates development of mammary tissue
- **E↑ T↓**: Androgens slow growth of mammary tissue

**Androgens in pregnancy**

- **Carlsen 2010**
- **Negative breastfeeding association**

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>Androstenedione</th>
<th>Free T Index</th>
<th>DHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

- Controls: Random selection
  - Blood drawn @ 26 weeks gestation
- Experimental: Women at risk of SGA infant
  - 3 weeks & 6 months

“Mid-pregnancy androgen levels are negatively associated with breastfeeding”

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Clinical Sx of hyperandrogenism

Facial hair, acne

Androgens

Not enough
Delayed pubarche
Low sex drive

Just right
Good breast development, milk production

Too Much
Breast develop/growth, Prolactin receptors & Milk Production

Screening for androgen problems

Checklist
1. □ Laboratory history of hyperandrogenism?
2. □ History of pre-eclampsia or SGA infant?
3. □ Hirsutism? - ask!
4. □ Adult acne
5. □ Androgynous build?
6. □ Onset of above symptoms?

Insulin: Crucial member of the Lactogenic Complex

New findings about stages of lactation

New Study Reveals Important Role of Insulin in Making Breast Milk

Insulin dynamics change with stages

Calotestum → 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
Taming down of initial steep up-regulation of metabolic signals via up-regulation of PTPRF
Inhibition of apoptosis, glycolysis and glycogenesis

PTPRF\

PTPRF = protein tyrosine phosphatase, receptor type F
Insulin necessary for milk protein synthesis

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PTPRF as a limitor of insulin action and milk production

Insulin action & Milk Production ↑

PTPRF ↓ Insulin action & Milk Production ↓

PTPRF as a limitor of insulin action and milk production

Type 2 & Gestational Diabetes

Insulin resistance

Increased insulin ↓ SHBG production in liver; ↑ Ovarian androgens

More free androgens

Insulin resistance

Interference w/ removal of insulin by liver

Increased insulin

Vicious Cycle

Insulin resistance & breast development

Insufficient milk production associated w/ Central Obesity and Acanthosis Nigricans is likely caused by insulin resistance

Very large or small breasts in such women are likely associated with the pre- vs post-pubertal onset of insulin resistance

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RNA sequencing may explain how

<table>
<thead>
<tr>
<th>Markers</th>
<th>Mature Group 1</th>
<th>Mature Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median onset of notably fuller breasts</td>
<td>34 hrs</td>
<td>74 hrs</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Above median</td>
<td>Below median</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Above median</td>
<td>Below median</td>
</tr>
<tr>
<td>Expression of PTPRF</td>
<td>Significantly higher than Group 1 (over-expressed)</td>
<td></td>
</tr>
<tr>
<td>Milk Production</td>
<td>Engorgement peaked day 4-5, then down regulated to demand</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUDING HYPOTHESIS: “Women with decreased insulin sensitivity will experience a more sluggish increase in milk output in response to infant demand as a result of PTPRF over-expression in the mammary gland”

Another interesting study....

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Any bfg discharge</th>
<th>Full bfg discharge</th>
<th>Any bfg 4 mo</th>
<th>Full bfg 4 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>93%</td>
<td>72%</td>
<td>61%</td>
<td>49%</td>
</tr>
<tr>
<td>Type 2 (gestational)</td>
<td>86%</td>
<td>45%</td>
<td>34%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Standard practice:
- Insulin-controlled during pregnancy
- Infants automatically given mother’s milk or Nutramigen by cup or NG tube starting after first bfd/within 2 hrs & q3hrs first 24 hrs

Gestational diabetes

Breastfeeding in women with gestational diabetes (Hummel 2008).

<table>
<thead>
<tr>
<th>Any bfg Rate</th>
<th>Duration: Full bfg</th>
<th>Duration: Any bfg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy + F37</td>
<td>86%</td>
<td>17 wks</td>
</tr>
<tr>
<td>GDM all + 257</td>
<td>75%</td>
<td>9 wks</td>
</tr>
<tr>
<td>GDM-Diet</td>
<td>12 wks</td>
<td>20 wks</td>
</tr>
<tr>
<td>GDM Insulin</td>
<td>4 wks</td>
<td>10 wks</td>
</tr>
<tr>
<td>GDM + BMI &lt;30</td>
<td>80%</td>
<td>17 wks</td>
</tr>
<tr>
<td>GDM + BMI &gt;30</td>
<td>65%</td>
<td>12 wks</td>
</tr>
</tbody>
</table>

Conclusions: Mothers with gestational diabetes, especially mothers with insulin-dependent gestational diabetes, and obese mothers breastfed their children significantly less and for a shorter duration than healthy mothers.

GDM mothers start the same but supplement sooner

Glover (2017). Impact of metabolic dysfunction on breastfeeding outcomes in GDM

A1C, BMI, OGTT & subscapular were associated w/ shorter duration of lactation

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Confirmed by Verd 2016

Compared women with normal 1-hr glucose challenge tests (<7.8 mmol/L) with those who had elevated 1-hr test (≥ 7.8 mmol/L but <10.6 mmol/L) but clinical indices below threshold for GDM diagnosis

Results: Mildly impaired women abandoned exclusive breastfeeding sooner than non-impaired: OR 1.65

Insulin & Diabetes

Not enough I (T1) Can’t get glucose into cells

Normal Can’t get glucose into cells

IR/Too much I (T2) Feeds androgens & fat

Smart Foods for insulin resistance

Garbanzo beans

Kidney beans

Brown rice

Legumes

Metformin is FDA-approved to treat type 2 diabetes. While commonly used for PCOS and infertility, such usage is still considered off-label.

~Disclosure~

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The Next Level: insulin sensitizers

- Metformin
  - Insulin resistance
  - Glucose levels
  - Hypertriglyceridemia
  - Lipids

Metformin depletes B-12 (Larner 2010)

New Case Study

- Measured output via infant transfer = 52mls
- Did not respond to domperidone @ 30 or 60mg
- Clinical indications of insulin resistance
  - Metformin: Transfer increased 69% to 88mls

Metformin

- Milk production increases when insulin action is improved
- Need to be realistic
  - Improvement constrained by existing mammary tissue

The Second M

- Inositol Glycans
  - Naturally occurring nutrient, type of sugar

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Larner 2010

<table>
<thead>
<tr>
<th>Groups</th>
<th>Myo/chiro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.5</td>
</tr>
<tr>
<td>Type II diabetes patients</td>
<td>20.4</td>
</tr>
<tr>
<td>Nondiabetic relatives of type II diabetic patients</td>
<td>13.2</td>
</tr>
<tr>
<td>Type 1 diabetes patients</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Insulin resistance is frequently associated with imbalance of Myo-I to D-chiro-I

→ Caused by impaired conversion and/or increased urinary clearance of D-chiro-I

Myo-Insitol

- Improves insulin sensitivity
- Reduces free testosterone
- Restores menstruation & normal ovulation
- Improves glucose utilization
- Decreases insulin resistance
- Improves pregnancy rate

Myo - D-chiro

Virtually no side-effects

Promising Case study of Myo/D-chiro Inositol and T2DM  Pintaudi 2016

- 20 poorly-controlled T2DM, 75% women
- Took myo/d-chiro/folic acid supplement twice daily x 3 mos in addition to current meds
- Fasting blood glucose & HbA1C decreased

Level Two: Smart galactagogues

Screening for Insulin problems

Checklist

1. ☐ Personal or family history of diabetes?
2. ☐ Failed pregnancy glucose tolerance test?
3. ☐ Diagnosed with Gestational Diabetes Mellitus?
4. ☐ Visible acanthosis nigricans?
5. ☐ Visible skin tags? (When did they grow?)
6. ☐ Onset of above symptoms?

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Hypoplasia ↓ Prolactin Response

Hypertension

PCOS

Insulin Resistance/Diabetes


High BMI + excessive wt gain = additive risk

<table>
<thead>
<tr>
<th>Hilson, 2006</th>
<th>IOM</th>
<th>&lt;IOM OR</th>
<th>Within OR</th>
<th>&gt;IOM OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight BMI 26-29</td>
<td>15-25 lbs</td>
<td>2.96</td>
<td>1.47</td>
<td>1.62</td>
</tr>
<tr>
<td>Obese BMI &gt; 29</td>
<td>13-20 lbs</td>
<td>1.81</td>
<td>1.84</td>
<td>2.89</td>
</tr>
</tbody>
</table>

Please remember:
We Know Not Because We Ask Not

Is it really WNL?
Or did we just assume this?

DISORIENTED BEWILDERED

Hormone testing: The Next Step?

How do I know what is normal?

- Look at lab ranges
- Is this a hormone that is affected by pregnancy or lactation?
- Develop your expert contact network

Limitations of blood tests

Bound versus unbound hormone
Does not measure peripheral tissue hormones
May not account for receptor issues
Subclinical conditions may not show up with standard tests

Your Role in Interpreting the Results

Look for obvious abnormalities
Explain to mother the possible implications if significant
Discuss mother’s options based on what you know
Write summary of concerns to HCP
Possible phone call to explain or expedite action

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