Predicting and optimizing ‘coming to volume’

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Professor of Pediatrics
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Disclosures

- I have no real or apparent conflicts of interest related to the content of this presentation.

- The following terms are used throughout this presentation for simplicity: mother, woman/women, mother’s own milk, breast milk, and breastfeeding for anatomic clarity and brevity in this lecture.

- All concepts discussed here are applicable to transgender, nonbinary and non-birthing people who lactate and/or chest feed.

- The term “mother’s own milk” is intended to distinguish milk provided by a parent from donor human milk, knowing that not all human milk may come from a parent who identifies as a mother.

- We acknowledge that it is important to utilize a patient’s preferred pronoun and other preferred terminology when addressing patients directly regarding their lactation experience.

Outline

- Lactation physiology
- To review coming to volume and its association with later lactation outcomes
- To review lactation practices in the early postpartum period associated with coming to volume
- To identify milk biomarkers that may be associated with coming to volume
Example Case

- Ms. J is a 23 year old G1P0 with preeclampsia and obesity (BMI 32) who was admitted at 25 5/7 weeks gestation and started on magnesium and labetalol and received 2 doses of betamethasone.
- After 48 hours, due to rising BP she underwent urgent cesarean delivery and gave birth to a 26 0/7 week infant girl, weight 730g who was admitted to the NICU on CPAP.
- Ms. J received 24 hours of magnesium postpartum.
- She pumped for the first time 4 hours after delivery then again at 12 hours post delivery (DOL 1).
- On infant’s DOL 2, she pumped 3 times and produced drops of milk.
- On DOL 8 infant developed sepsis and was intubated.
- On DOL 22 infant was extubated and placed on CPAP
- Infant discharged home at DOL 92 at corrected age 39 1/7 weeks, weight 2900g

Socioecological Model

Lactation Physiology

Secretory Differentiation (Lactogenesis I)
- During pregnancy breast undergoes significant changes due to multiple hormones (estrogen, progesterone, prolactin, oxytocin, human growth hormone, glucocorticoids, insulin):
  - Increased blood flow
  - Mammary epithelial cells differentiate into lactocytes
  - Alveolar and ductal proliferation
- Breast development continues to occur until delivery (incomplete in preterm)
- Mid-pregnancy: starts to make colostrum – but secretory activity limited by high progesterone which inhibits prolactin

Secretory Activation (Lactogenesis II)
- Triggered by post-partum hormonal changes:
  - Progesterone falls
  - Inhibition of Prolactin ends – but secretory activity linked by high progesterone which inhibits prolactin
- Infant suckling increases secretion of prolactin and oxytocin
Tight junction closure prevents lactose from exiting the lumen via open paracellular pathways.

- Lactose = primary osmotic component draws water into lumen
- Secretory activation or milk “coming in” typically within 72 hours after term delivery

Failed lactogenesis

- **Preglandular**: hormonal causes, such as retained placenta or lack of pituitary prolactin
- **Glandular**: surgical procedures, such as reduction mammoplasty or insufficient mammary tissue
- **Postglandular**: ineffective or infrequent milk removal

Milk Synthesis and Removal in Mothers of Preterm Infants

- Secretory differentiation is incomplete at the time of preterm birth
- Disrupted secretory differentiation with inflammatory processes (obesity, pre-eclampsia, diabetes and other metabolic health problems)
- Mothers viewed as “too sick to pump” → not encouraged or assisted with pumping
- Breast pump dependency = the pump completely replaces the infant for MOM removal and the regulation of lactation processes
- Maternal pumping behaviors unrelated from infant feeding
- Insufficient MOM volume are often traced to the first 14 days postpartum
### Secretory differentiation in NICU mothers and maternal conditions

<table>
<thead>
<tr>
<th>Delayed Lactogenesis</th>
<th>Other Barriers</th>
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<tbody>
<tr>
<td>Premature delivery</td>
<td>Mother-infant separation</td>
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<td>Cesarean delivery</td>
<td>Stress associated with NICU</td>
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<td>Maternal blood loss</td>
<td>Lack of skin to skin (STS)</td>
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<tr>
<td>Overweight/Obesity</td>
<td>Breast pump dependence</td>
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<td>Diabetes mellitus</td>
<td>Cost or lack of equipment</td>
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<td>Maternal hypertension</td>
<td>Lack of lactation training/ availability</td>
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<td>Prolonged bedrest</td>
<td>Maternal health issues</td>
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<td>Duration and stress of labor</td>
<td>Limited maternity leave</td>
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<td>Competing responsibilities</td>
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<td>Lack of knowledge</td>
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<td>Lack of family support</td>
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</table>

*Hurst. J Midwifery and Women’s Health 2007*

*Hernandez et al., PLoS ONE 2012*

*Parker and Patel. Sem Perinatol 2017*

### Example Case

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### NICU Lactation Strategies

- Parent education – prenatally and postnatally
- Staff education
- Access to NICU-specific and culturally adapted lactation expertise
- Early milk expression
- Frequent pumping +/- hand expression
- Monitoring milk volumes during the first 14 days postpartum to achieve at least 500ml/day (coming to volume or CTV)
- Skin-to-skin (STS)
- Successful transition to direct breastfeeding

*Hagan, C. (2018). However, what is breastfeeding? The body of scientific evidence*
Outline

• Lactation physiology
• To review coming to volume and its association with later lactation outcomes
• To review lactation practices in the early postpartum period associated with coming to volume
• To identify milk biomarkers that may be associated with coming to volume

Coming to volume: MOM volume of 500 to 600 mL/day in first 14 days
• CTV occurs during transition from endocrine to autocrine control
• Suckling-induced prolactin surge
  • Feedback Inhibitor of Lactation (FIL)
    – Milk protein that downregulates sensitivity to prolactin and disrupts movement of milk constituents from endoplasmic reticulum to Golgi
    – FIL functions locally at each breast = MOM not removed from the same breast over time reduces MOM synthesis in that breast
    – Need to pump both breasts

CTV and Later Milk Volume

415 mother-VLBW infant dyads born 2008-12
Outline

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Pumping Influence on Breast Programming

Objective: To determine the impact of the pumping regimes of women with preterm infants on:
1. Daily milk production
2. Short-term rate of milk synthesis during early lactation

Subjects:
Mothers of preterm infants (n=25) recorded start time, finish time and expression volumes from every breast expression on days 10, 15–20 postpartum.

Results:
Expressing more often than five times per day did not result in a significant increase in daily milk production.
Milk volume per expression per breast increased for intervals between expressions of between 2 and 6 hours, then reached a plateau where the interval between expression was 7 hours or longer. The short-term rate of milk synthesis decreased as the interval between expressions increased until about 7.5 hours at which point it began to increase.

Pumping at least 5 times per day and at least once overnight by DOL 5 associated with coming to volume. Adjusted for maternal race, maternal insurance, method of delivery and infant’s birthweight.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Predictor Description</th>
<th>n</th>
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<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Cumulative MOM volume first 5 days postpartum</td>
<td>1278 mL cumulative MOM volume</td>
<td>1178.0</td>
<td>100.1</td>
<td>664.2-1489.7</td>
<td>0.019</td>
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</table>

- Mothers of preterm infants
- Each additional hour pumping in the first 5 days → additional 1278 mL cumulative MOM volume in first 7 days
### Example Case – Ms. J

#### Scenario 1
- Does not CTV
- Is not discharged on any MOM feedings

<table>
<thead>
<tr>
<th>DOL</th>
<th>Number of pumping sessions</th>
<th>MOM volume (mL)</th>
<th>Infant's ordered feeding volume</th>
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#### Scenario 2
- Does CTV
- Is discharged on MOM feedings

<table>
<thead>
<tr>
<th>DOL</th>
<th>Number of pumping sessions</th>
<th>MOM volume (mL)</th>
<th>Infant's ordered feeding volume</th>
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Potential Markers of Secretory Activation

- Four transcellular pathways involved in milk synthesis and secretion of milk components across the cellular membrane
  - A single paracellular pathway bypasses the epithelial cell \( \rightarrow \) direct communication between maternal blood and milk
  - The paracellular pathway is open at birth \( \rightarrow \) gradually closes during secretory activation \( \rightarrow \) continued milk secretion
  - The paracellular pathway reopens during inflammation (mastitis) and involution (weaning)
  - Over the first days postpartum:
    - lactose, citrate, and potassium (K) levels in MOM
    - total protein and sodium (Na) levels in MOM
Subjects: 196 first-time mothers of term, healthy singleton infants and exclusively breastfeeding at day 7

Primary objective:
Determine if elevated Na:K at day 7 is significantly more prevalent in mothers reporting a milk supply concern.

Secondary objective:
Determine whether elevated Na:K at day 7 is predictive of stopping breastfeeding before day 60.

Table 1. Logistic regression model predicting the odds of elevated breast milk Na:K according to presence of a milk supply concern among mothers exclusively breastfeeding on day 7.

<table>
<thead>
<tr>
<th>Milk supply concern at day 7</th>
<th>Number (%) with elevated breast milk Na:K</th>
<th>Model 1</th>
<th>Model 2</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>96 (33.3%)</td>
<td>1.448</td>
<td>1.448</td>
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<tr>
<td>Yes</td>
<td>50 (50.0%)</td>
<td>2.043</td>
<td>2.043</td>
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</table>

*Defined as maternal report of exclusive breastfeeding during the 24 hours before the day examined.

*Defined as breast milk Na:K > 70th percentile (0.83) on day 7 for the sample mean.

*P = .001, adjusted for ethnic group.

Objective: To explore associations between day 10 postpartum (D10) secretory activation biomarkers and breastfeeding outcome measures.
Are milk biomarkers affected by problems associated with preterm delivery

- preterm birth = interrupted secretory differentiation
- lactation risk factors
- inflammation
- maternal stress
- maternal health complications
- breast pump dependency

- 16 mothers of preterm infants
- Milk samples collected every 12hr for first 14 days
### Indicators of Secretory Activation in Mothers of Preterm Very Low Birth Weight Infants

**Subjects:** 69 mothers of VLBW infants (<=32 weeks of GA) during the first 7 days postpartum.

**Objective:** Compare timing of secretory activation compared using three separate indicators:
1. Maternal perceptions of milk coming in
2. Removal >=20mL of MOM per pump session for two consecutive sessions
3. Normal MOM biomarkers Na and lactose (collected when #2 was met)

Compared with normal values in healthy breastfeeding mothers, secretory activation was delayed.
1. Maternal perceptions of milk coming in at mean 130.6 – 170.3 hours (5±7 days)
2. Achievement of >=20 mL of pumped MOM volume/session at mean 123.4 – 91.9 hours (5±3 days)
3. Only 42% of mothers had normal Na and lactose at #2 time point
4. Mothers with normal biomarkers had significantly more pumping sessions during Days 3-5 (4.5-4.8 times/day vs. 3.0 times/day)

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### Objective
To determine associations between serial secretory activation MOM biomarker concentrations from breast pump-dependent mothers of preterm infants to and coming to volume (CTV)

**Variables:**
- Singleton infant born at gestational age <33 weeks
- Initiated lactation but MOM had not "come in" yet
- No hormonal contraception or breastfeeding for the first 14 days postpartum
- Access to hospital-grade double electric breast pumps in the NICU and at home
- Collected paired MOM volume and samples every 12hr for first 14 days
- 39 mothers (mean GA 28.8 weeks; 67% overweight/obese; 59% nonwhite)
- 33% achieved CTV between postpartum days 5 and 14
- Associated with CTV between days 6-14
  - Maternal prepregnancy BMI
- Maternal pre-pregnancy BMI (1 unit increase in BMI: OR, 0.88; 95% CI, 0.78-0.99; p= .04)

CTV was associated with expected directional changes in all biomarkers

Considerable within- and between-mother variability

Na and Na:K ratio were most consistent with respect to predicted directionality and CTV achievement.
A rapid decrease in Na = highly predictive of successful lactation

Prolonged elevation in Na or Na/K ratio = impaired secretory activation
Upcoming Studies using Milk BioMarkers

Early Pumping Behaviors Predict Pumped Milk Volume, Achievement of Secretory Activation and Coming to Volume in Breast Pump-Dependent Mothers of Preterm Infants

Rebecca Hoban, MD, MPH (University of Washington, Seattle Children’s Hospital)
Clarisa Medina-Poelinz, PhD, MN, ARNP, CPNP (Rush University Medical Center)
Maria Signorile, MMA TH (University Health Network, Toronto)
Judy Janes, BSN, IBCLC (Rush University Medical Center)
Chun-Po Steve Fan, PhD, P.Stat. (University Health Network, Toronto)
Paula P. Meier, PhD, RN (Rush University Medical Center)

Objective: To measure three pumping behaviors each day during postpartum days 1 to 14
– number of pumping sessions
– minutes spent pumping
– longest interval between pumping sessions
and to determine their relationships to
– achievement of secretory activation (MOM biomarkers: sodium [Na] and sodium-to-potassium ratios Na:K)
– coming to volume (CTV)
– daily and cumulative pumped MOM volume

• Non-randomized observational study of breast pump-dependent mothers of preterm infants
• October 2019-October 2020
• Rush University Medical Centre
• Inclusion criteria: singleton infant born at <34 weeks without major severe medical complications or anomalies, plan to provide MOM, no hormonal contraception or galactagogues
• Daily data (electronic pumping data with SMART pump, milk weights) and milk specimens for first 14 days postpartum
• Researchers measuring outcomes were blinded to pumping behaviors
• Outcome: achievement of secretory activation (defined as Na ≤16 mMol and/or Na:K ratio <0.8)

Unpublished data courtesy of Drs. Hoban and Meier
Early Pumping Behaviors Predict Pumped Milk Volume, Achievement of Secretory Activation and Coming to Volume in Breast Pump-Dependent Mothers of Preterm Infants

- 29 mothers with usable data
- Achievement of SA in 27 (93%) mothers, at median of 5.8 days [4.30, 8.23] postpartum
- None of the mothers achieved SA prior to postpartum day 4

Unpublished data courtesy of Drs. Hoban and Meier

Two pumping behavior clusters emerged

<table>
<thead>
<tr>
<th>High intensity (n=17)</th>
<th>Low intensity (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pumping sessions per day</td>
<td>5±2</td>
</tr>
<tr>
<td>Minutes spent pumping per day</td>
<td>105±53</td>
</tr>
<tr>
<td>Longest interval (hr) between pumping sessions</td>
<td>5.5±1.7</td>
</tr>
</tbody>
</table>

Unpublished data courtesy of Drs. Hoban and Meier
Early Pumping Behaviors Predict Pumped Milk Volume, Achievement of Secretory Activation and Coming to Volume in Breast Pump-Dependent Mothers of Preterm Infants

• Changes in pumping behaviors were confined to the first 5-6 postpartum days with little change in pumped MOM volume, Na and Na/K ratio and after postpartum day 8
• This study underscores the importance of early pumping behaviors for mothers of preterm NICU infants: a critical interval for achievement of SA and CTV may be within the first 6-8 days
• For clinicians, quality improvement initiatives should target the very early postpartum period with respect to the use of lactation experts, rapid access to high-quality breast pumps, and daily monitoring of achievement of SA and CTV

Upcoming Studies using Milk BioMarkers

• NOT YET RECRUITING
• Comparison of Breast Pump Suction Patterns
• ClinicalTrials.gov ID NCT06061913
• Sponsor University of Florida
• Information provided by University of Florida
• Last Update Posted 2024-02-14

Thank you