Lactogenesis I, II, and III

• Lactogenesis I – differentiation of alveolar epithelial cells into lactocytes that secrete colostrum, with ~100mL available to infant on day one postpartum
• Lactogenesis II – onset of copious milk secretion occurring between 32 and 96 hours postpartum
• Lactogenesis III – maintenance of milk production

Disclosure

• I have nothing to declare nor any conflicts of interest
Hormones of Lactation

- Lactogenesis I
  - ductal growth – estrogen, growth hormone
  - alveolar development – progesterone, prolactin, placental lactogen
  - mammary parenchyma – glucocorticoids
- Lactogenesis II – withdrawal of progesterone in the presence of high circulating levels of prolactin

Hormones of Lactation

- Metabolic hormones (coordinate metabolism)
  - Insulin – regulates nutrient delivery to the breast and a whole lot more!
  - Thyroid hormones – efficient milk production
- Lactogenesis III
  - Prolactin - required for milk synthesis to occur but does not regulate rate of short-term milk synthesis
  - Oxytocin – cause milk ejection, produces analgesic effects, reduces stress, causes uterine contractions, establishes caring and bonding behaviors

Lactogenesis II: Getting the show on the road

- Blood flow, oxygen, & glucose uptake ↑, citrate concentration increases sharply
- Increased milk citrate and lactose are considered reliable markers for the second stage of lactogenesis
- Progesterone receptors are lost in lactating mammary tissues, decreasing the inhibitory effect of circulating progesterone
- Maternal secretion of insulin, growth hormone (GH), cortisol, and parathyroid hormone (PTH) facilitates the mobilization of nutrients and minerals that are required for lactation
Importance of insulin—who knew?  
Lemay et al. (2013). PLoS ONE 8(7): e67531

- As breast transitions from colostrum to mature milk, dramatic switching on of the insulin receptor and its downstream signaling
- Strong pattern of modulation of insulin signaling between colostral and transition milk phases with up-regulation of fat and protein synthesis and down-regulation of apoptosis
- 20% of women between ages 20-44 are prediabetic affecting insulin in the breast
- Places up to 20% of new mothers at risk for delayed lactogenesis II and low milk supply

Indicators of Lactogenesis II

- Changes in colostrum/milk composition (biomarkers)
  - Decrease in sodium and chloride
  - Increase in citrate and lactose
  - These changes precede the onset of the large increase in milk volume by 24 hours
  - Maternal perception of onset of lactation is a valid proxy for lactogenesis II

Maternal indicators of onset of lactation

- Breast swelling
- Milk leakage
- Physical appearance of milk
- Infant cues
- Breast fullness
- Breast heaviness, hardness
- Breast tingling
- Wide range of when this occurs - usually 1-3 days post birth
Mean Milk Volume of Fully Breastfeeding US Women During the First Week Postpartum

Delayed onset of lactation

- ~25% of women experience delayed onset of lactation
- Defined as >72 hours postpartum & <9g/feeding at 60 hours
- Milk synthesis occurs during first 3 days post birth, even in the absence of suckling or milk expression
- On day 4, non-breastfeeding mother’s milk reverts to composition of colostrum
- Breastfeeding mother’s milk changes to more mature milk composition

Delayed onset of lactation is predictive of cessation of breastfeeding


- 2491 mothers in CDC Infant Feeding Practices II study
- 23.2% experienced delayed onset of lactation
- Can be predictive of any and exclusive breastfeeding
- Both are reduced when delayed onset of lactation is present
- May influence clinicians to supplement with formula which can shorten the duration and exclusivity of breastfeeding
Maternal Risk Factors

- Type I diabetes
- Parity
- Mode of delivery
- Maternal obesity
- Premature delivery
- Retained placenta
- Stress during labor and delivery
- Polycystic ovarian syndrome
- Sheehan’s syndrome
- Lower LATCH scores
- "Others"

Type I diabetes

- Can delay onset of lactation by 15-28 h
- This can result in a decrease in milk volume over the first 3 days
- Breast contains insulin-sensitive tissue
- Hypoglycemia may ↓ glucose availability to lactocytes ↓ lactose synthesis & ability to initiate lactation
- Less optimal breastfeeding management may result in delays in baby going to breast

Parity

- Postnatal increases in milk volume occur later in primiparous women
- 10-35 hours later in primips compared with multips
- Increases potential for formula supplementation if mothers are unaware of this

Bar plot for estimation of physiological breast engorgement (described by the mothers as "breast fullness/tension") during day 1–day 3 in all mothers (means and SE). The perception of breast engorgement was significantly higher in multiparous mothers (repeated measures ANOVA F1,145 = 4.10, p value = 0.0446). Bystrova et al. International Breastfeeding Journal 2007 2:9 doi:10.1186/1746-4358-2-9
Mode of delivery
- Unplanned cesarean section
- Emergency cesarean section
- Fewer pulses in oxytocin
- Lower prolactin concentration during feeding
- High levels of stress during labor and delivery
- Prolonged stage II of labor
- Duration of labor longer than 14 hours
- Maternal pain

Maternal obesity
- Less likely to have increased prolactin concentration after breastfeeding in first 2 days
- Low milk transfer at 60 hours post birth
- High leptin levels may inhibit milk ejection
- Mothers with later lactogenesis II had higher pre-pregnant BMI
- A one unit increase in BMI is associated with a .5 hour delay in lactogenesis

Maternal Obesity
- Breastfeeding durations decrease as maternal BMI increases
- Obesity alters the 24 hour spontaneous release of prolactin
- Prolactin response to sucking is blunted in obese mothers, decreasing by ~45ng/mL at 48 hours postpartum and 100ng/mL at 7 days, during the time period important for optimal milk production
Metabolic status/health

- Nommsen-Rivers (2012) discuss factors that contribute to delayed lactogenesis II relative to maternal metabolic status.
- 3 risk factors for delayed lactogenesis, higher body mass index (BMI-overweight/obesity), increased maternal age, and larger infant birth weight) as known correlates with carbohydrate intolerance and systemic inflammation.
- Primary predictors of onset of lactation in normal glycemic primiparous mothers was serum concentrations for insulin, glucose, and insulin to glucose ratio (I:G) - a measure of 1 hour insulin relative to 1 hour glucose concentration.
- A woman at the median for I:G ratio will experience the onset of lactation at ~ 66 hours. If I:G ratio is in the bottom 25% of this ratio, onset of lactation will be ~ 21-30 hours later, well beyond the 72 hour cutoff for normal onset of lactation.
- Concerning because among exclusively breastfeeding mothers who experience a delayed onset of lactation, 40% of their infants will lose more than 10% of their birth weight by the 4th day of life (Chantry et al, 2011; Nommsen-Rivers et al, 2008).

Key risk factors for delayed onset of lactation
- 33% of women with recent gestation diabetes experienced delayed onset of lactation (n=883)
- Key risk factors for delayed onset of lactation
  - Recent gestational diabetes
  - Maternal obesity
  - Insulin treatment
  - Suboptimal in-hospital breastfeeding
- We can’t change the first 3 risk factors but we can provide enhanced breastfeeding support when these risk factors are present

Delayed lactogenesis

- Delayed onset of lactation is associated with infants who are described as not breastfeeding well twice during the first 24 hours.
- Delayed onset of lactation more common with higher amounts (>60 mL) of formula supplementation during the first 48 hours.
- Because prolactin is necessary for the initiation of lactation, a new treatment using recombinant human prolactin may be helpful in those mothers with prolactin deficiency or blunted prolactin responses
Timing of first breast stimulation

- Parker and colleagues (2012) studied effects of early initiation of milk expression on the onset of lactogenesis stage II and milk volume in mothers of VLBW infants.
- 20 women were randomized to initiate milk expression within 60 minutes of birth (group 1) or 1 to 6 hours following delivery (group 2). Milk volume and timing of lactogenesis stage II was compared between the 2 groups.
- Group 1 produced significantly more milk than group 2 during the first 7 days and at week 3.
- Group 1 also demonstrated a significantly earlier lactogenesis stage II.
- Clinicians may wish to recommend that mothers of preterm or ill infants start milk expression within an hour of birth if possible when the infant cannot be put to breast during that time.

Delayed onset of lactation is common, but failed onset of lactation is not

- 44% of 431 mothers experienced delayed onset of lactation
- Associated factors
  - Greater BMI
  - Pitting edema
  - Lack of infant breastfeeding well ≥2x in first 24 hours
  - Older maternal age
- Adverse consequences
  - Excess neonatal weight loss
  - Suboptimal breastfeeding at day 7
  - Formula supplementation

Nomsen-Rivers et al, Am J Clin Nutr 2010; 92:574-584

Prematurity

- Chemical marker changes indicative of lactogenesis II are delayed in preterm mothers
- The volume of milk was reduced further when antenatal corticosteroids were administered between 28 and 34 weeks gestation and delivery occurred 3 to 9 days later
Retained placenta

- Viable placental fragments retained
- Continued secretion of progesterone by the retained fragments inhibits onset of lactation

Placental pathology

- Placenta Accreta - placenta attaches too deep in the uterine wall
- Placenta Increta - placenta attaches even deeper; penetrates into uterine muscle.
- Placenta Percreta - placenta penetrates through the entire uterine wall and attaches to another organ such as the bladder.
- Increased risk from previous cesarean deliveries

Stress in labor and delivery

Dewey J Nutr 2001; 131:3012S-3015S

- Duration of labor, time without sleep, maternal pain, urgent cesarean, excessive formula on day 2, prolonged stage II
Birth trauma

- Traumatic birth experience
- Disturbing flashbacks to birth or previous traumatic birth experiences
- Psychosocial stress
- Post traumatic stress symptoms
- High cortisol levels

Polycystic ovarian syndrome

- ↑ androgens downregulate estrogen & prolactin receptors
- Elevated estrogen
- Insulin resistance
- Low progesterone may impact ductile & lobuloalveolar development resulting in asymmetric or hypoplastic breasts
- Poor breast tissue development
- Low prolactin or decreased prolactin receptors may interfere with breast growth during pregnancy and lactogenesis

Assisted Reproductive Technology

- Mothers who utilized assisted reproductive technology (ART) were more likely to have delayed lactogenesis at >3 and ≥ 5 days
- They reported more breastfeeding problems
- They were less likely to be breastfeeding at 6, 9, & 12 months
- They were less likely to achieve exclusive breastfeeding at 3 and 6 months (Chalmers, 2006)
More risk factors
• Hypothyroidism
• Anatomic breast abnormalities
• Insufficient breast tissue
• Postpartum hemorrhage with Sheehan’s syndrome
• Theca-lutein cyst (elevate testosterone levels)
• Maternal medications such as birth control methods containing estrogen or progestin only

Prenatal SSRIs
• Serotonin acts as a neurotransmitter, a type of chemical that helps relay signals from one area of the brain to another
• Serotonin is a local regulator in the breasts for lactation
• SSRIs like Paxil inhibit serotonin reuptake in mammary epithelial cells and disrupt serotonin regulation in the breasts

Prenatal SSRIs
• 431 mothers
• Women taking SSRIs experienced lactogenesis II at 85.5h
• Control group at 69.1h
• Risk of delayed lactogenesis II was 2-fold greater in women taking SSRIs
Endocrine disrupting chemicals in animal studies

- Mammary gland differentiation during pregnancy may be disrupted by pollutants such as dioxins
- Timing of exposure during pregnancy may impact the breast’s ability to recover from cellular injury
- Reduced beta-casein protein induction in mouse mammary glands
- Organochlorine pesticides may disrupt functional breast tissue growth

Infant Risk Factors

- Absent suckling
- Inefficient suckling
- Dysfunctional suckling
- Incorrect latch

Effect of sucking on lactogenesis II

- Lactogenesis occurs in the absence of milk removal over the first 3 days
- Additional breast pumping prior to lactogenesis II has not been shown to hasten the event or result in increased milk intake at 72 hours
- Mothers who exclusively bottle-feed perceive lactogenesis II significantly later
Exclusive formula feeding prior to onset of lactation as a risk factor
• Frequent suckling promotes earlier onset of lactation
• Hospital practices that encourage frequent infant sucking such as rooming-in and avoidance of supplements are associated with earlier onset of lactation
• Tactile stimulation of frequent sucking causes secretion of lactogenic hormones
• Magnitude of hormonal response to sucking is greater during the onset of lactogenesis II than it is during established lactation

Importance of infant suckling
• Increased hormonal response to suckling during early postpartum days can account for the difference seen between women who exclusively breastfeed in hospital and those that don’t

Prenatal risk assessment
• History
  • diabetes
  • overweight/obesity,
  • PCOS
  • hypothyroid
  • hypopituitarism
  • endocrine
• History and exam
• breast surgery,
• growth during puberty and pregnancy
Prenatal risk assessment
• Breast symmetry, intramammary distance >1.5"
• Depression, stress, previous birth experience
• Previous slow infant growth, supplementation

Diagnosis--Mother
• The breast is the only organ in the body without a diagnostic test to measure its adequacy
• Biochemical markers can be measured to determine onset of lactation but is usually impractical
• Measurement of milk volume, especially if pumping for preterm infant
• <9g/feeding at 60 hours post birth
• No maternal perception of breast fullness, swelling, leaking >72 hours post birth

Diagnosis--Infant
Uric acid crystals in diaper at 4 days
Decreased diaper counts
  • <3 stools/day after day 4
  • <6 wet diapers/day after day 4
Minimal or no weight gain
  • Weight loss >7%
  • High bilirubin level
  • Fussy, unsettled infant
Interventions

- 2 or more risk factors present a high level of suspicion and should be used as signal for close surveillance following discharge
- Underlying cause drives the plan of care
- Maximize breast stimulation and assure adequate infant growth
- A wait and see approach may delay appropriate interventions and result in more serious sequelae
- Avoid use of Depo Provera prior to discharge

Breastfeeding management in hospital for at risk mothers

- Skin-to-skin, baby to breast within first hour post birth
- Breastfeed 12 times per 24 hours, especially if mother is diabetic or obese
- Hourly for 3-4 feedings until blood glucose is stable
- q 2-3 hours until 12 hours

Antenatal expression of colostrum

Diabetic mothers may wish to express colostrum, freeze it, and bring to hospital in case supplementation is needed for hypoglycemia

www.capitolvial.com

- Poorer sucking patterns seen among infants of insulin-managed mothers with diabetes
  - Insulin group averaged 5.2 fewer sucking bursts and 42 fewer sucks per 5 minute interval (on artificial nipple)
  - 42 x .14ml/swallow = 9ml decrease /5min sucking
  - 36ml decrease/20 minute feeding
  - 360ml/day decrease (10 feeds) = 13 oz deficit/day
Breastfeeding in the first hour

- SOFT Program from Loma Linda University Medical Center-Perinatal Services Network


- The First Hour after Birth: A Baby’s 9 Instinctive Stages
  http://www.healthychildren.org/skin2skin.htm

What if baby cannot transfer colostrum/milk?

- Early and frequent sucking helps assure maximum milk production and transition to mature milk composition following lactogenesis II
- Sleepy baby
- Late preterm infant
- Oral anomalies
- Birth trauma
Ineffective Latch

- Low tone
- Does not draw nipple/areola deep into mouth
  Younger infants exert lower vacuum
- Adequate vacuum is needed to remove milk from the breast

Alternate Massage/Breast Compressions

- Breast is massaged and compressed during pauses between sucking bursts
- Creates improved pressure gradient between breast and baby’s mouth
- Can increase volume and fat content of feeds

Adequate intake during prolonged colostral phase

- Increased number of feedings maximizes colostrum intake
- Prevents dehydration
- Prevents excessive weight loss
- Prevents hyperbilirubinemia especially important for late preterm infants
- More effective feedings
- Improve latch
- Alternate massage
- Assure mother knows when baby is swallowing
Improve flat nipples

Helping with Latch

- Nipple shield
  - 20mm size
  - 16mm may be too small and 24mm may be too large
  - Teat height should not exceed distance from infants lips to juncture of hard and soft palate
- Compensates for relatively weak suck
- Properly fitted
- Reverse pressure softening for edematous areola

Determine the need for supplementation

- Weight loss >10%
- continued weight loss after day 3
- Inadequate diaper count
- <6 wet diapers/day after day 4
- <3 stools/day after day 4
- Minimal breast changes by day 5 post birth
- Rising bilirubin levels
Determine the need for supplementation

- At-risk infant with poor feeding
- Difficult or no latch
- Lack of documented swallowing
- Uric acid crystals on day 4
- Swallowing absent for majority of feeding
- Milk transfer less than what is expected for day post birth
  - Pre and post feed weights

Fig 2. Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values

Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:307-316
What to supplement

Mother’s milk first
- Hand express colostrum into a spoon and spoon feed baby
  - Teaspoon is 5ml
- If using a pump, place the Ameda diaphragm between valve and collection bottle
- Banked human milk

What if we have to use formula?
- Cow’s milk based formula should not be used if additional milk is required
- If formula becomes temporarily necessary, a hydolyzed formula can be used
  - Drops bilirubin faster
- Sugar water should not be given by mouth due to its rapid absorption
- Cereal should not be given to an infant <3mo of age as it increases the risk for diabetes in susceptible families (Norris et al, 2003)
Examples of hydrolyzed protein and amino acid–based infant formulas available in the United States

Extensively hydrolyzed casein (cow milk protein)
- Nutramigen Lipil (Mead Johnson)
- Enfamil Pregestimil (Mead Johnson Nutritionals)
- Similac Alimentum Advance (Abbott Products)

Partially hydrolyzed whey (cow milk protein)
- Good Start Supreme (Nestlé USA)
- Enfamil Gentlease Lipil (Mead Johnson)
- Enfamil Alimentum Advance (Abbott Products)

Partially hydrolyzed whey/casein (cow milk protein)
- Good Start Supreme Soy (Nestlé USA)

Partially hydrolyzed Soy (Soy Protein)
- Neocate (and Neocate 1 for children 12 mo) (Nutricia)
- EleCare (Abbott Pediatrics)

Infant Stomach Capacity

Anatomic Capacity = stretched stomach capacity at autopsy
Physiologic Capacity = amount taken per feeding


How much?

Most infants well hydrated via placenta at birth
- Urine output exceeds intake days 1-3
- Small colostrum feedings (5-15 ml) physiologic
  - appropriate for size of infant’s stomach
  - sufficient to prevent hypoglycemia
  - easy to manage as infant learns to coordinate suck, swallow, breathing
- Some infants will need some supplementation
Quantities
• Calculate supplements by weight
  • 3-5ml/kg/feeding, or
  • 5-10ml per feeding on day 1
  • 10ml-20ml on day 2
  • 20ml-38ml on day 3
  • 58ml/feeding on day 4

How to supplement


Commercial tube feeding devices

Medela  Maternal Concepts
LactAid  Hazelbaker Finger Feeder