Physiology of Lactation in Preterm Mothers: Initiation and Maintenance

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The initiation of lactation in women, as in other mammals, depends on the growth of the glandular tissue of the breast (mammmogenesis) and the differentiation of the mammary secretory epithelial cells (lactocytes) during pregnancy (lactogenesis I). After birth the continuous nourishment of the fetus from the mother via the umbilical cord is replaced by the equally important but intermittent nourishment from the mother’s breast. Thus the onset of copious milk production (lactogenesis II) is closely coupled with factors controlling the birth process. In mothers who birth preterm infants, mammogenesis and lactogenesis I may be truncated, but the resilience of lactation is such that these women usually are able to eventually achieve successful lactation. Close consideration must be given to all physiological aspects of this complex process when assisting preterm mothers in establishing successful lactation so that they can provide mothers’ milk, the nutrition of choice, for their preterm infants.¹

PREGNANCY

For the breast, pregnancy is a time of preparation for lactation. The hormonal changes that occur during pregnancy are associated with breast development. There is an increase in the numbers of alveolar buds, differentiated alveoli become more evident, and there is cellular hypertrophy.² This leads to an increase in breast volume. Breast growth during pregnancy varies between women in both the amount and pattern of growth.³ Although Neifert⁴ found an association between minimal prenatal breast enlargement and insufficient lactation up to 21 days after birth, Cox et al.⁵ found no such relationship. Furthermore, by week 22 of pregnancy the increase in size of the breasts had stabilized in most women.

Lactogenesis I

Lactogenesis I is the development of the synthetic capability of the breast to produce milk-specific components, such as lactose, casein, and α-lactalbumin.⁶ At this stage the secretion is not discharged and these components are reab-

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EDUCATIONAL OBJECTIVES

1. Review the physiological processes involved in preparing the breast for lactation, milk synthesis, and milk expression.
2. Describe how preterm delivery may disturb these physiological processes.
3. Determine the best methods to assist women who have delivered preterm in establishing lactation.
sorbed via the paracellular pathway between the lactocytes into the bloodstream. During pregnancy, the luminae of the breast become distended with colostrum. Lactose is not metabolized in the blood and is cleared in the urine. Since the breast is the major source of lactose in the body, the concentration of lactose in the urine can be used as an indicator of lactogenesis I. Measurements of urinary lactose indicate that the onset of lactogenesis I is highly variable among women and occurs as early as week 10 of pregnancy and as late as week 22. The change in the rate of lactose excretion from preconception to birth was related to the increase in breast volume for the same period \( p = 0.023, r^2 = 0.36, n = 14 \). By week 22 of pregnancy, lactogenesis I has commenced in most women. Thus, it is apparent that even for the earliest preterm infants, the mothers likely have experienced significant mammmogenisis and the lactocytes have at least started to develop the capacity to produce the unique components that are present in breast milk.

**BIRTH**

Regardless of the length of gestation, little milk is produced immediately after birth. For the first 48 hours after term and occurs slightly earlier in multiparous than primiparous women. It has long been assumed that this was the marker of the initiation of lactation in mothers, but it is now clear that mothers can successfully initiate lactation without the sensation. This can be a very distressing time for some mothers whose breasts enlarge, becoming hard and very painful.

Lactogenesis II is the most critical stage of lactation, as it must be closely coupled with birth to provide the newborn with energy, nutrients, and protective factors as it begins to adapt to its independent life. Lactogenesis II requires adequate levels of prolactin, insulin, and adrenocorticoid hormones and is triggered as a result of withdrawal of circulating progesterone after birth following delivery of the placenta. In women the major fall in progesterone occurs after birth and lactogenesis II commences at 15 to 45 hours postpartum. This is in contrast to most other mammals in which progesterone falls before birth and lactogenesis II occurs at birth. Lactogenesis II can be determined objectively by test weighing the infant before and after each suckling. However, test weighing in the immediate postnatal period is a demanding procedure. Moreover, it is possible that the increase in milk production may not be matched by an increase in demand for milk by the infant and therefore the measurement of lactogenesis II may be masked.

Lactogenesis II is also a time when the concentration of milk components changes markedly. These changes occur within the first 5 days after birth because of the increased synthesis of milk components (particularly lactose, which induces water movement into the alveoli to maintain osmotic equilibrium) and the closure of the paracellular pathway between the lactocytes. Therefore, the high concentration of the pro-

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**TABLE**

Factors That May Inhibit or Delay Lactogenesis II in Term and Preterm Mothers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td><strong>Lactogenesis II inhibited</strong></td>
<td>Elevated progesterone</td>
</tr>
<tr>
<td>Retained placental fragments</td>
<td>Autocrine inhibition</td>
</tr>
<tr>
<td>Milk not removed</td>
<td></td>
</tr>
<tr>
<td><strong>Lactogenesis II delayed</strong></td>
<td>Unknown (possibly decreased glucose uptake)</td>
</tr>
<tr>
<td>Insulin-dependent diabetic mothers</td>
<td>Unknown (possibly progesterone from body fat)</td>
</tr>
<tr>
<td>Obese mothers</td>
<td>Progesterone switches on milk specific genes</td>
</tr>
<tr>
<td>Prolactin insufficiency</td>
<td>No labor - disturbed hormonal balance</td>
</tr>
<tr>
<td>Caesarian</td>
<td></td>
</tr>
<tr>
<td><strong>Preterm Mothers</strong></td>
<td>May prematurely initiate lactation</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>May cause progestagen inhibition</td>
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<tr>
<td>Depoprovera</td>
<td>Inadequate breast pump milk removal</td>
</tr>
<tr>
<td>Breasts not emptied</td>
<td>Milk ejection inhibited</td>
</tr>
<tr>
<td>Inadequate stimulation</td>
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tective proteins in colostrum (sIgA, lactoferrin, α-lactalbumin) are diluted by the synthesis of increasing volumes of milk as lactogenesis II proceeds. At first analysis it seems illogical that the infant consumes only a small volume of colostrum during the first day postpartum — a time of high demand for energy. However, because this small volume contains a high concentration of protective factors it may provide the ideal mechanism for protection of the gastrointestinal and respiratory tracts of the infant from pathogens at a time of rapid colonization by micro-organisms. From this reasoning, it is recommended that preterm infants receive their mothers’ milk in the same sequence that it was collected (ie, the first milk received by the infant should be the first colostrum produced by its mother).

Changes in the concentration of milk components have been investigated as an alternative to test weighing to assess the initiation of lactation. In mothers who have delivered at term, during the first 5 days after birth, the concentrations of lactose and citrate in milk increase, while those of protein and sodium decrease. Using these objective markers of lactogenesis II, it has been shown that lactogenesis II is either inhibited or delayed by a number of factors in term and preterm mothers (Table). There are differences in the changes in milk composition between mothers of term and preterm infants. The concentration levels of four markers of lactogenesis II — lactose, citrate, sodium, and total protein — in milk from preterm mothers (31-35 weeks) at day 5, postpartum had much greater variation about the mean than was observed in term breastfeeding mothers. Only 18% of the preterm mothers had all four markers within ±SD = 3, the mean range of the term mothers. The remaining preterm mothers had one or more of the markers outside the mean range for term mothers and had significantly lower milk production than preterm mothers who had all four markers within equal range of term mothers. It was therefore concluded that lactogenesis II had been compromised in 82% of the preterm mothers and that mothers with a greater number of markers outside the normal range were likely to have lower milk production. The reason for the compromised lactogenesis II is not clear but could relate to factors such as maternal medications during pregnancy and birth, as well as the frequency of expression. Furthermore, these problems may be accentuated in mothers of early preterm infants in whom it is possible that lactogenesis I has commenced but is not yet complete.

Of note, a study in the 1970s found that the timing of lactogenesis II was similar in vaginal and caesarean deliveries, whereas more recent research showed a delay in lactogenesis II following caesarean section. This may caused by anaesthetic agents used in emergency caesarean sections or because no labor takes place in elective caesarean sections.

Establishment of Lactation

Mothers who deliver term infants and breastfeed on demand produce 556 to 705 g of milk on day 6, postpartum. A further increase in milk production up to 1 month after birth depends on the demand of the infant. The normal range of milk production of 440 to 1220 g/d is maintained until 6 months of lactation.

In a study by Meier mothers of preterm infants produced only a few drops of colostrum at each expression for the first 24 to 48 hours after birth and showed a significant increase in milk production by 72 hours after birth. A wide range of milk production (20-550 g/d) was measured on day 5 after birth in mothers who delivered preterm, but their frequency of expression was not monitored. Although preterm infants do not initially require large volumes of breast milk, it is very important to establish a high level of milk production (> 440 g/d) during lactogenesis II. This will ensure that as the infant grows its mother’s milk supply will be adequate to meet its increasing nutritional needs.

Some mothers with good initiation of lactation and abundant milk early on can experience a drop in supply 10 to 14 days after birth. It is important to identify any faltering of the milk supply early. Immediate action is required to overcome the problem, eg, checking the efficiency of the breast pump, ensuring that the tunnel in the breast shield is an appropriate size for the mother’s nipple, increasing the frequency of breast expression, decreasing the mother’s level of stress, and assessing the possibility of improving the mother’s prolactin levels if they are deficient. Basal and stimulated levels of prolactin can be assessed in blood samples collected just prior to and 45 minutes after the beginning of the pumping session. The values can be compared to the normal range for breastfeeding mothers. The concentration of prolactin in the blood within the first 2 weeks after birth is expected to be higher than those reported for women at 1 month of lactation. Concentrations below this range would suggest the possibility of stimulating prolactin secretion with either domperidone or metoclopramide.

Breast Expression

Early initiation of either breastfeeding or breast expression have been shown to affect milk production positively later in lactation. Yet the correlation of the contribution of ineffective or infrequent milk removal to failed lactogenesis II has received insufficient attention. After term delivery it is rec-
ommended that the infant is breastfed within the first hour and frequently thereafter (8 to 12 feeds per day). A delay in breastfeeding of 4 to 6 hours after birth may lead to breastfeeding failure, and early initiation of breast expression in mothers of preterm infants is equally important.33 Hopkinson et al.34 demonstrated that later initiation of pumping (up to 6 days postpartum) was associated with decreased 24 hour milk production at 2 weeks postpartum in mothers who delivered at 28 to 30 weeks gestation. Meier13 recommends that mothers who are expressing their milk should use a hospital grade electric breast pump with a double collection kit and pump 8 to 10 times daily starting within 24 hours of birth.

It is also possible that poor milk production at this time, in a small percentage of expressing mothers, could be related to differences between the effectiveness of breast pumps in removing the available milk from some mothers' breasts.35 There are no routine tests to determine if a breast pump is effectively milking a mother’s breast. However, it is now possible to determine whether the breast pump is stimulating milk ejection by using ultrasound to observe changes in milk duct diameter (Figure). In addition, if a mother is synthesising milk but the breast pump in not removing it there will be an increase in lactose excretion in the mother’s urine. Our research has shown that the best outcome is obtained using breast pumps that provide both higher frequency stimulation and lower frequency expression vacuum curves.35,36

Once a mother’s milk supply is established, the ideal frequency of breast expression for providing milk for her preterm infant may not be absolute, but may depend on the storage capacity of the mother’s breasts. A mother with a large storage capacity (> 250 mL/breast) who can easily drain her breasts almost completely may need to express only three or four times daily for each breast. On the other hand, a mother who has a small storage capacity (< 100mL/breast) or who has difficulty draining her breasts with a breast pump may need to express as frequently as eight times a day. It is important that the expressions are spaced out over the entire 24 hour period so that no long intervals of time are present where the mothers can reach their storage capacity and down-regulate milk synthesis.

The possibility that milk production is inhibited by longer intervals between breast expressions can be assessed for an individual breast by comparing the hourly rates of milk production. The average hourly rate of milk production for the day can be calculated by dividing the total amount of milk produced over 24 hours by 24. This value is then compared to the hourly rate of production for the longest period between breast expressions. If the latter value is less than the former, introducing an additional pumping during the longest interval between breast expressions could increase milk production.

**Milk Expression Complications**

Ely and Petersen29 were first to describe the milk ejection reflex correctly. Their description for the cow was equated to lactating women through the work of Newton and Newton,30 who showed that stress in women, as in cows, inhibited the milk ejection reflex and reduced milk production and that this could be reversed by the administration of oxytocin. Their conclusion is applicable today, particularly for preterm mothers:

Our results support the idea that Petersen’s theory of the mechanism of let-down in animals holds for lactating women. It is interesting to speculate on the possible application of this knowledge to breast feeding in general. Many mothers are nervous about feeding their first baby; they are upset by the strange hospital surroundings; they are embarrassed by having to expose their breasts among strangers; their nipples are often sore and their breasts engorged. Emotional disturbances, embarrassment, and pain inhibit let-down to the sucking baby, and thus the baby gets little milk.

In stressful situations, all mothers may have difficulties with milk ejection when expressing, resulting in decreased milk production. Many preterm mothers have not breastfed previously, so they are not familiar with the sensation caused by the release of oxytocin. These sensations can vary from no sense of milk ejection, to a pins and needles sensation in the breast, to a painful squeezing in the breast prior to the increase in milk flow. It is possible that inadequate milk production in some stressed preterm mothers could be caused by failure of milk ejection.

An objective assessment of milk ejection can be obtained by using ultra-
sound to observe the diameter of the milk ducts just below the nipple area. A skilled ultrasonographer is required to visualize the milk ducts with ultrasound, as they are compressible with the application of even light pressure.) In term mothers, there is an acute increase in milk duct diameter in one breast as the infant feeds from the other (Figure). There is also an increase in duct diameter coincident with an increase in milk flow if the other breast is expressed with an electric breast pump. The visualization of the increase in the diameter of the ducts provides positive reinforcement, which is an important factor in establishing lactation in all mothers.

For the preterm mother who is generally under considerable stress because of concern for her infant, the provision of a calm environment for breast pumping, ideally within contact distance of her infant, provides the best opportunity for the stimulation of milk expression.

CONCLUSION

Mothers who deliver preterm can usually successfully establish lactation and provide the best source of nutrition for their infants. However, they may encounter difficulties that often can be overcome with adequate support. In this article, we have provided information on the physiology of milk synthesis and milk expression that can assist the pediatrician to give evidence-based advice to the mother and maximize her chances of success.

REFERENCES


