Journal of Midwifery & Women's Health www.jmwh.org
Review

Impaired Lactation: Review of Delayed Lactogenesis and Insufficient Lactation

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It is estimated that as many as 1 in 20 women worldwide are unable to successfully breastfeed or provide adequate nutrition for their infants through their breast milk alone. Compromised nutrition in the early stages of life places the infant at risk for insufficient growth as well as serious and potentially disabling or life-threatening complications. This review summarizes risk factors associated with impaired lactation that may result in either delayed lactogenesis or insufficient lactation. The risk factors for insufficient lactation are categorized into preglandular, glandular, and postglandular causes. Impaired lactation can occur despite maternal motivation, knowledge, support, and appropriate breastfeeding technique. Although there is no clear way to predict who will experience impaired lactation, knowledge about the risk factors can enable health care professionals to better identify at-risk mother-infant dyads. Early intervention may help prevent infant complications associated with inadequate nutritional intake.

J Midwifery Womens Health 2021;66:631–640

Keywords: failed lactogenesis II, lactation failure, delayed lactogenesis, low milk supply, breastfeeding

INTRODUCTION

The number of women in the United States who initiate breastfeeding following childbirth is at an all-time high of 84%.[1] The increase in breastfeeding initiation rates may be attributed to several factors including improvements in hospital policies and practices such as rooming-in, skin-to-skin contact immediately after birth, early initiation of breastfeeding, and the training of health care staff in basic breastfeeding management and support.[2] The American College of Nurse-Midwives, the American Academy of Pediatrics, and the World Health Organization recommend initiation of breastfeeding after birth and encourage exclusive breastfeeding for the first 6 months of life. These organizations recommend that after initiating nutritionally adequate and safe complementary feedings at 6 months of age, women should continue to breastfeed until one year of age and beyond as long as mutually desired by woman and child.[3–5]

Although breastfeeding has been promoted as a convenient and natural method of infant feeding, there are some women who cannot exclusively breastfeed. The literature suggests that despite maternal motivation, knowledge, support, and appropriate breastfeeding technique, as many as 1 in 20 women may experience impaired lactation.[6,7] This article reviews both delayed and insufficient lactation and their underlying causes.

LACTOGENESIS

Lactation is the process by which the mammary glands produce and secrete milk. The alveolar units within the female breast comprise a cluster of secretory cells surrounded by myoepithelial cells. The secretory cells are composed of a single layer of epithelial cells that produce and secrete milk into the alveolar lumina where the milk is stored. The milk is then released into the ductal system via contraction of the myoepithelial cells, which cause ejection of milk during breastfeeding or pumping.[8,9]

There are 2 stages of lactogenesis. *Secretory differentiation*, also known as lactogenesis I, begins around the 20th week of pregnancy when the mammary gland begins to secrete a small amount of milk. This stage lasts until approximately the second or third day after birth. *Secretory activation*, also known as lactogenesis II, is controlled by the endocrine system and begins with the onset of copious milk secretion. Secretory activation is triggered in response to the rapid decline in progesterone levels following birth of the placenta. Women often feel a sense of breast fullness during the first few days as secretory activation is initiated. Galactopoiesis, or the maintenance of lactation once it has been established, is controlled by the autocrine system, begins approximately 9 days after birth, and is maintained by the cyclic draining of milk from the breast. Therefore, milk synthesis will decline without suckling and milk removal by the infant or a breast pump.[8,9]

Hormonal Regulation of Human Lactation

The mechanisms controlling lactation are complex and regulated by hormones that develop the breast tissue, stimulate the

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Quick Points

- Not all women can breastfeed, and certain conditions place women at risk for impaired lactation.
- As breastfeeding rates rise, so will the incidence of impaired lactation. Health care professionals will undoubtedly encounter women seeking answers to their inability to make a full milk supply.
- Causes of insufficient lactation are categorized as preglandular, glandular, and/or postglandular. Understanding the cause and its etiology allows health care professionals to better care for the breastfeeding mother-infant dyad in the early postpartum period.

secretion of milk, assist in the ejection of milk from the alveolar cells, and maintain milk production. The withdrawal of progesterone that occurs with birth of the placenta is the initiating factor in the sequence of events that results in secretory activation. The anterior pituitary is then stimulated to secrete the hormone prolactin, which initiates milk secretion.[9]

Early erratic suckling by the neonate results in increased prolactin receptors on the lactiferous cells. If the woman then breastfeeds her newborn or the breast is stimulated by a breast pump, prolactin continues to be secreted in response to nipple stimulation and milk secretion is then maintained. Early removal of colostrum is important to lower sodium concentration in the milk, which can interfere with the increase of water and lactose into the lactiferous cells. This process, along with closure of the lactiferous cell gap junctions, results in increasing milk concentrations and volume within the cells, causing the sensation of breast fullness, a sign of lactogenesis. Cortisol also plays a key role in the balance of sodium and water. Milk is then ejected from the alveolar cells when the surrounding myoepithelial cells are stimulated by oxytocin, which is secreted by the posterior pituitary. The elevated levels of prolactin and oxytocin work in conjunction with glucocorticoids, insulin, growth hormone, and others to establish and maintain lactation.[9,10] Disruption in the interactions between these hormones may result in impaired lactation.

Delayed Lactogenesis and Insufficient Lactation

Impaired lactation may be due to either delayed lactogenesis or insufficient lactation. Delayed lactogenesis is diagnosed when the initiation of copious milk production is delayed beyond 72 hours after birth. Most women who experience delayed lactogenesis have the ability to achieve full lactation and exclusively breastfeed. Insufficient lactation is diagnosed when a woman is unable to achieve an adequate breast milk supply to exclusively breastfeed her infant, and it is identified when there is absence of postpartum breast engorgement and milk production despite sufficient stimulation and adequate drainage of the breasts.[11]

Insufficient lactation can be due to intrinsic or extrinsic factors. Some women with insufficient lactation may produce very small amounts of breast milk, whereas others produce more but not enough to sustain infant growth.[11] Various terms have been used to describe insufficient lactation, including failed lactogenesis II, low milk supply, insufficient milk syndrome, impaired lactogenesis, and lactation dysfunction. The term *insufficient lactation* is used in this article.

The prevalence of impaired lactation has not been determined. Rates of delayed lactogenesis from US studies range from 22% to 44%, with the higher rates found in studies limited to those who are primiparous.[12] Rates also vary by body mass index (BMI) with a California study reporting a rate of 31.4% for those with a BMI less than 25 and 53.8% for those with a BMI over 29.[13] The higher rate of obesity in the US population may explain why international rates of delayed lactation are lower.[13,14] Many studies quote the study by Neifert for estimates of lactation insufficiency secondary to anatomic abnormalities or health conditions as occurring in approximately 5% of lactating women.[6] Although multiple factors may contribute to insufficient lactation, the ability to predict insufficient lactation on the basis of the presence of risk factors is limited. There are both maternal and infant factors of insufficient lactation, which can be organized into 3 categories: preglandular, glandular, and postglandular (Table 1).[15]

PREGLANDULAR CAUSES OF IMPAIRED LACTATION

Preglandular causes of impaired lactation are considered intrinsic factors. These causes involve a disruption in the endocrine system that results in a hormonal imbalance that

Table 1. Categories and Related Causes of Impaired Lactation

Category of Impaired Lactation	Causes
Preglandular	Diabetes mellitus
	Maternal obesity
	PCOS
	Retained placental fragments
	Sheehan's syndrome
	Theca lutein cysts
	Thyroid dysfunction
Glandular	Breast surgery
	Insufficient glandular tissue
Postglandular	Infant factors, including cleft lip/palate, ineffective weak suck, ankyloglossia, lip tie
	Maternal medication
	Preterm birth
	Smoking

Abbreviation: PCOS, polycystic ovary syndrome.
Source: Morton.[15]

causes primarily delayed lactogenesis but also insufficient lactation.[16]

Diabetes

Diabetes is a metabolic disorder characterized by insulin resistance and/or impaired insulin production wherein the affected person has elevated blood levels of glucose. The role diabetes may play in impaired lactation is not fully understood, but it may result in both delayed lactogenesis and insufficient lactation. A recent study has shown that insulin is essential for both mammary acini secretory development and differentiation, and mammary gland functioning.[17] This study underpins the observation that higher insulin-to-glucose ratios and increased adiponectin levels are associated with earlier onset of lactogenesis in both animal and human studies.[18] Those with diabetes have the reverse, which can lead to impaired lactation through a decreased prolactin response by the lactiferous cells, alteration in sodium inhibiting water influx, and downregulating specific genes on the mammary gland.[13,16,19] Both pregestational diabetes and gestational diabetes mellitus (GDM) are risk factors for impaired lactation.[20,21]

De Bortoli and Amir conducted a systematic review of studies assessing the relationship between diabetes in pregnancy and delayed lactogenesis.[20] The studies were from 4 countries with the majority from the United States. They ranged from small case-control to larger cohort studies that compared persons without diabetes (controls) with those with type 1 diabetes and/or GDM. Over 1400 persons were included in the 10 identified studies. Of the 5 studies measuring breast milk biomarkers, all found either delayed onset or lower milk volume. One study showed decreased lactose levels among women with diabetes, supporting the hypothesized pathophysiology. Of the cohort studies, it appeared that lactogenesis among women with diabetes was delayed about 24 to 36 hours among the 33% to 58% who experienced it.[20] In a study of delayed lactogenesis in women with GDM (n = 883), Matias et al found higher abnormal glucose levels during testing or that the need for insulin in pregnancy was associated with 3 times increased odds of delayed lactogenesis (odds ratio [OR], 3.11; 95% CI, 1.37-7.05; $P = .0076$).[22]

Diabetes is also associated with insufficient lactation. A cross-sectional study of more than 700 Australian breastfeeding women with GDM found that 29% stopped breastfeeding by 3 months postpartum and that the most common reason given for early cessation was insufficient lactation (45%).[23] Additionally, a case-control study conducted among those seen at a lactation clinic with the first encounter at less than 90 days postpartum compared women with low milk supply but no nipple or latch problems (n = 176) with women without low milk supply but were seen for latch or nipple problems (n = 226).[24] More than twice the women with low milk supply but no nipple or latch problems had diabetes in pregnancy (15%) compared with the control group of women with latch or nipple problems who did not have a low milk supply (15% vs 6%, respectively; adjusted OR [aOR], 2.4; 95% CI, 1.3-5.1).[24]

Maternal Obesity

Similar to diabetes, the mechanism by which obesity may cause impaired lactation is not fully understood. There is evidence to support hormonal interference from obesity during puberty that may inhibit proper mammary gland development affecting future lactation,[25] decreased prolactin levels in response to a suckling newborn in the first 48 hours of life,[26] and/or increased insulin resistance and hyperinsulinemia with a mechanism similar to the effect of diabetes.

Maternal prepregnancy BMI classified as overweight or obese is a risk factor for delayed lactogenesis and shortened duration of lactation.[27] The previously mentioned California study among primiparous women found rates of delayed lactogenesis in 45% of overweight women and 54% of women with obesity.[13] The aOR for delayed lactogenesis for overweight women compared with women with a normal BMI was 1.84 (95% CI, 1.07-3.16). Women with obesity had 2.21 increased odds of delayed lactogenesis (95% CI, 1.24-3.94).[13] A cohort study of more than 200 breastfeeding women, conducted in Florida, also examined delayed lactogenesis by BMI. The researchers found a moderate correlation between prepregnancy BMI and delayed lactogenesis (r = 0.216) and an increased odds of delay of 7% for each unit increase in BMI (aOR, 1.07; 95% CI, 1.01-1.12).[21] A large study among women with GDM also found prepregnancy obesity associated with delayed lactogenesis, 43% with obesity versus 29% with BMI less than 25 (aOR, 1.56; 95% CI, 1.07-2.29).[22] An additional problem faced by women with obesity that may contribute to delayed lactogenesis is an increased incidence of cesarean birth.[28]

Stuebe et al conducted a longitudinal study of women from diverse settings in the United States that assessed breastfeeding intention in pregnancy and then breastfeeding practice postpartum.[29] The goal was to identify the proportion of women unable to meet their breastfeeding goals secondary to physiologic problems with lactation. The researchers defined disrupted lactation as early undesired weaning. In this study, 208 of 1721 women (12.1%) experienced disrupted lactation. After adjustment for sociodemographic confounders, the prevalence was 9% among women with a normal BMI, 13% among women who were overweight, and 14% among women who were obese (aOR, 1.6; 95% CI, 1.1-2.3 for overweight vs normal BMI; aOR, 1.7; 95% CI, 1.2-2.6 for obese vs normal BMI).[29] Several other studies have identified an association between increasing BMI and delayed lactation, including the study of women with GDM conducted in Australia, which found that early cessation of breastfeeding increased 8% for each 2-unit increase in BMI (OR, 1.08; 95% CI, 1.01-1.57).[23]

Thyroid Dysfunction

The thyroid gland is responsible for the production and secretion of the thyroid hormones thyroxine and triiodothyronine in response to thyroid-stimulating hormone, which is secreted by the anterior pituitary. The thyroid hormones act on multiple tissues throughout the body and are essential for normal development, growth, and metabolism. During the postpartum period the incidence of thyroid dysfunction is estimated to be approximately 5%.[30] The relationship between impaired lactation and thyroid dysfunction is not clear. It is believed thyroid dysfunction may adversely affect milk synthesis, the milk ejection reflex, and/or ongoing maintenance of lactation.[30–32] Additionally, it is hypothesized that effective

function of prolactin and oxytocin is dependent upon a normally functioning thyroid gland during lactation.[11,33]

Thyroid dysfunction may be associated with both delayed lactogenesis and insufficient lactation.[11,34] Although the literature regarding the relationship between thyroid dysfunction and impaired lactation is scant, a small study of 16 women that measured plasma levels of several hormones found thyroid hormone concentrations positively correlated with milk production.[35] Additionally, a single case study was found reporting a woman who experienced insufficient lactation thought to be associated with new-onset Graves' disease.[36] Overall, it is believed that hypothyroidism, rather than hyperthyroidism, is more frequently associated with impaired lactation.[31,32,36] Given that thyroid dysfunction is typically subclinical, it is recommended to evaluate thyroid function when a woman presents with either delayed lactogenesis or insufficient lactation.[30,31]

Retained Placental Fragments

Approximately 2% to 3.3% of women experience retained placenta immediately following birth.[37] If fragments of the placenta remain within the uterus after birth, the placental lactogenic hormones can continue to act as antagonists to mammary prolactin receptors and the preservation of elevated circulating levels of progesterone will interfere with secretory activation,[38] leading to either delayed lactation[38] or insufficient lactation.[11]

Theca Lutein Cysts

Theca lutein cysts may develop on the ovary in response to excessive levels of beta human chorionic gonadotropins in persons with gestational trophoblastic disease, fetal hydrops, diabetes, multiple gestation, or isoimmunization. These cysts produce high levels of testosterone, which can ultimately suppress secretory activation, leading to impaired lactation.[7,34] During the postpartum period, these cysts tend to resolve spontaneously, which causes circulating levels of testosterone to return to normal levels.[39] Given the rarity of this condition, the available literature documenting its influence on impaired lactation is limited to case studies. At this time there are no known guidelines for assessment of theca lutein cysts when impaired lactation occurs; however, it is important for health care professionals to recognize this differential diagnosis for women with impaired lactation.

Two case studies have documented impaired lactation in women with theca lutein cysts.[34,39] Betzold et al reported delayed lactogenesis in 4 women who were diagnosed with ovarian theca lutein cysts. Three of the women achieved secretory activation by postpartum days 20, 12, and 34, respectively; the fourth woman experienced insufficient lactation.[34] Hoover et al published a case report of 2 women who experienced delayed lactogenesis due to theca lutein cysts.[39] One of the women had testosterone levels 10 times higher than normal, and as the testosterone levels normalized, she was able to achieve secretory activation by postpartum day 21. In the second woman, it took 2 months before she no longer needed to supplement, and she continued to breastfeed for more than 15 months.[39]

Postpartum Pituitary Infarction (Sheehan's Syndrome)

Sheehan's syndrome occurs as a result of postpartum hemorrhage and accompanying hypovolemia, which causes infarction to the pituitary gland, resulting in inadequate production of adrenocorticotropic hormone and secretion of hormones including prolactin. Several publications have noted the negative effects Sheehan's syndrome has on secretory activation.[6,11,40]

Although much has been learned about management of postpartum hemorrhage, its incidence unfortunately has been increasing in the United States and is currently experienced by about 3% of people following birth.[41] Some authors suggest that Sheehan's syndrome is more common in developing countries that have limited resources to treat severe postpartum bleeding.

Among the most common early signs of Sheehan's syndrome are a failure to produce breast milk and failure to resume menses. Among 200 women with Sheehan's syndrome in 4 case studies, 71% were not able to lactate, and 87.5% failed to resume menses postpartum.[42–45] Additionally, women can have nonspecific symptoms such as fatigue, weight loss, anorexia, and loss of sexual hair. During the first year postpartum, some may attribute these symptoms to normal postpartum changes. Unfortunately, the hypopituitary state is frequently not diagnosed, and mean time to diagnosis ranges from 10 to 19 years.[43,44] Some experts suggest that any person who loses a large blood volume during or after birth, especially if transfusion is required, should have their adrenal hormones assessed early postpartum and other pituitary hormones (eg, growth hormone, thyroid-stimulating hormone, gonadotropins) later around 6 weeks.

Polycystic Ovary Syndrome

Polycysticovary syndrome (PCOS) is a hormonal disorder associated with insulin resistance and hyperandrogenism that affects women of reproductive age. Elevated levels of circulating androgens, especially testosterone, may interfere with prolactin receptors within the mammary tissue, thereby affecting normal breast tissue growth and milk synthesis. PCOS also can inhibit prolactin and oxytocin secretion from the pituitary gland, which impairs secretory activation. The literature suggests that impaired lactation has been observed in women with PCOS who otherwise have good breastfeeding technique.[7,11]

The published literature on the effects of PCOS on lactation is limited. Deknuydt et al published a case report that described the pregnancy course of 2 women diagnosed with PCOS. One, who had 4 births, ceased breastfeeding at approximately one week postpartum after her first 2 births because of delayed lactogenesis. Attempts to breastfeed were not made after her third or fourth pregnancies. Interestingly, her androgen levels, which included testosterone, were elevated during the first trimester, peaked at the end of pregnancy, and then spontaneously decreased by 2 weeks postpartum and returned to normal by one month postpartum.[46]

Conversely, Vanky et al performed a case-control study that included 36 women with PCOS and 99 women without PCOS who were matched for age, weeks' gestation at birth,

and parity.[47] The women with PCOS had androgen levels drawn at baseline (between 5 and 12 weeks' gestation) and at 19, 32, and 36 weeks' gestation. A questionnaire regarding breastfeeding practices was sent at 6 to 12 months postpartum and was returned by 97% of the participants in the PCOS group and 92% of the control group. Women with higher levels of dehydroepiandrosterone sulfate at 32 and 36 weeks' gestation had lower rates of breastfeeding at 1 and 3 months postpartum (correlation ranged from 0.35 to 0.44), although testosterone and androstenedione levels were not correlated with breastfeeding in the first 3 months postpartum.[47] A greater percentage of those with PCOS were not breastfeeding at 1 month (14% vs 2% controls), but there was no difference in rates at 3 and 6 months. This finding may imply a problem with lactation initiation but not maintenance once lactation is established. These authors highlight that those with PCOS also often have high BMI.[47]

GLANDULAR CAUSES OF INSUFFICIENT LACTATION

Glandular causes of impaired lactation are primarily due to an anatomic lack of the tissue necessary to create a milk supply that is sufficient for exclusive breastfeeding.[15] This lack of tissue can be the result of inadequate mammary gland development[48] or breast surgery.[49–51] However, genetic mutations and epigenetic changes beginning in utero and through puberty can alter critical receptors for prolactin and growth hormone, which can also affect milk production.[48]

Insufficient Glandular Tissue

Women may lack the glandular tissue within the breast for milk production and storage.[52,53] Currently the literature on insufficient glandular tissue is limited to documented case reports and one prospective descriptive study. The case reports provide documentation of women who have experienced insufficient lactation related to insufficient glandular tissue.[52] Huggins and colleagues prospectively identified 34 women with insufficient glandular tissue antenatally who planned to breastfeed and followed them until 6 weeks postpartum.[53] These women had a combination of noticeable breast asymmetry, large intramammary distance, stretch marks on one or both breasts, and minimal or absent breast changes in pregnancy. Of the 31 participants who completed the study, one woman experienced normal secretory activation, 11 women experienced delayed lactogenesis and had a full milk supply by week 6 postpartum, and 19 women were found to have insufficient lactation.[53]

Health care professionals may be able to identify those at high risk for impaired lactation prenatally when they identify signs of hypoplasia. Findings would include abnormal development of at least one breast, breast asymmetry, tubular breast shape, intramammary distance greater than 1.5 inches, high mammary fold, disproportionately large or bulbous areolae, or woman who report absence of typical breast changes that occur during pregnancy.[53] The majority of women diagnosed with impaired lactation related to insufficient glandular tissue will not be able to exclusively breastfeed their newborn despite efforts to increase milk supply and will need close follow-up during the early postpartum period.[53]

Breast Surgery

Breast surgery can cause destruction of breast tissue; interruption of the ducts, nerve supply, or blood supply to the glandular tissue; or damage to the nipple subsequently leading to impaired lactation.[54] Breast surgery includes excisional biopsy, augmentation, reduction, and/or chest surgery involving the breast.

For persons with breast implant surgery, Cheng and colleagues showed a somewhat higher incidence of impaired lactation in their meta-analysis of 5 studies.[55] The studies included 1165 women with implants and more than 40,000 women without implants who served as control subjects in the studies. Successful lactation was measured by studies assessing lactation at hospital discharge (the largest study), 2 weeks, 4 weeks, and 2 to 3 months postpartum. The summary results were dominated by the hospital discharge study by Roberts et al, which included 378,389 persons.[56] Those with implants had a 39% decreased risk of exclusive breastfeeding (relative risk [RR], 0.63; 95% CI, 0.46-0.86) and a 22% decrease in any breastfeeding (RR, 0.88; 95% CI, 0.81-0.95).[55] Jewell et al followed 4600 people who gave birth after a breast implant and found that 79% breastfed and 20% identified they had insufficient milk supply.[57] Roberts et al found that 79% of those with breast implants provided breast milk to their newborn at hospital discharge compared with 88.5% among those without implants (RR, 0.90; 95% CI, 0.87-0.93).[56] They also showed that people who had breastfed their first child and then had an implant between their first and second pregnancies had a significant decline in their breastfeeding rate from 87% to 72%.[56]

Breast reduction surgery requires the areola and nipple to be surgically removed and reattached symmetrically during the procedure. Evidence about impaired lactation following breast reduction surgery heavily depends on the surgical method used to preserve the column of parenchyma between the nipple areola complex and the chest wall. Kraut et al, in a meta-analysis of 51 studies, identified a median 4% (interquartile range [IQR], 0%-38%) breastfeeding success rate within persons who did not have preservation of the subareolar parenchyma, 75% (IQR, 37%-100%) in persons with partial preservation, and 100% (IQR, 75%-100%) in persons with full preservation.[58] This information has important implications for presurgery education regarding implications for lactation for those contemplating breast reduction. Health care professionals need to obtain detailed information from women who have had breast reduction concerning the surgical technique used in relation to the nipple areola complex because it has important implications for counseling about lactation.

Transgender persons who choose to breast/chestfeed may have had either breast augmentation or breast reduction surgeries. Trans women who are taking estrogens may produce milk, but to date reports on lactation success are anecdotal and limited to single case reports.[59] Trans men who choose to be gestational parents need to suspend any testosterone therapy during pregnancy and may choose to continue the suspension of therapy postpartum in order to chestfeed. If they have had breast surgery, their chances of successfully lactating are related to the surgical technique used and amount of preservation of the nipple areola complex.[59]

POSTGLANDULAR CAUSES OF IMPAIRED LACTATION

Postglandular causes of impaired lactation focus primarily on insufficient milk supply due to infant factors, including preterm birth that causes ineffective or inadequate emptying of the breast, and maternal factors, including maternal consumption of medications or substances that are known to inhibit milk synthesis[11] and maternal fatigue and stress.

Infant Factors Associated with Impaired Lactation

Sufficient milk production is dependent on regular adequate emptying of the breast. Any condition in which the infant is unable to adequately latch on to the breast and have a strong suck coordinated with swallowing will lead to inadequate breast emptying. Functional anomalies such as cleft lip/palate and ankyloglossia, or lip tie, can inhibit an adequate latch.[11] Prevalence of ankyloglossia in a meta-analysis of more than 24,000 infants is estimated at 8%, and slightly higher at 10% if a standardized assessment tool is used. Ankyloglossia is more common in male than in female infants.[60] Recognition of tongue-tied neonates in the hospital has increased dramatically in recent years.[61] In one study of 1041 newborns, 50 (5.8%) had ankyloglossia. The presence of ankyloglossia (without frenotomy) was associated with breastfeeding difficulties in 9 (25%) of the women whose newborns were affected compared with one (3%) of women whose newborns did not have ankyloglossia.[62]

Prematurity presents challenges to lactation for 2 reasons: adequacy of maternal mammary secretory differentiation and body system immaturity in the newborn that interferes with the latch-suck-swallow sequence. Preterm birth can interrupt the secretory differentiation stage of mammary development, which means the mammary epithelium may not be adequately prepared to produce milk proficiently, leading to impaired lactation.[63] Because of developmental immaturity, which will vary by the degree of prematurity, a preterm neonate may not have the neurologic maturity needed to coordinate sucking and swallowing, the muscle strength to sustain an adequate latch, or the energy stores required for the act of breastfeeding. Other health conditions associated with prematurity such as heart and metabolic disorders can add to the challenges. Literature on management strategies for effectively optimizing milk production in persons who give birth preterm stresses the importance of early initiation of milk removal and frequency of milk removal with a breast pump.[63–65]

Maternal Factors

Table 2 summarizes what is known about several medications that are known to interfere with human milk production. In addition to medications, substances such as nicotine and alcohol can have an adverse effect on breast milk production.

Maternal Medication

Drugs that affect endogenous production of dopamine have a significant effect on milk production. Two dopamine agonists among the ergot alkaloid drugs, bromocriptine (Parlodel) and cabergoline (Dostinex), are well studied as lactation suppressants.[66,67] Both of these are used in the treatment for hyperprolactinemia. Other classes of ergot alkaloids are thought to also have similar effects on milk production. However, there are limited data on these agents. For example, a few case reports of short-term decrease in milk volume associated with use of methylergonovine (Methergine) administered by injection to treat postpartum hemorrhage have been reported, but there is no evidence that typical short courses of this drug administered orally interfere with milk production.[66] Both methylergonovine and ergotamine are considered contraindicated once milk supply is established because of potential adverse effects on the infant.[67]

Hormones can affect either dopamine, which inhibits prolactin release (eg, estrogen), or interfere with prolactin binding on the alveolar receptors (eg, progesterone). Estrogen given early postpartum interferes with establishing an adequate milk supply, and the current recommendation from the Centers for Disease Control and Prevention is to delay use of estrogen-containing contraceptives until 4 weeks postpartum for those without risk factors for venous thrombosis and 6 weeks for those with risk factors.[68] Evidence about the effect of progesterone-containing intrauterine devices inserted immediately postpartum is conflicting, so caution may be indicated for persons with risk factors for lactation problems.[68] Similar caution applies to insertion of medroxyprogesterone acetate (Depo-Provera) and contraceptive implants at less than 21 days postpartum. A review of 4 studies estimated that the risk of lactation suppression with immediate postpartum implant insertion was low, at less than 1%.[66] There is no evidence of any breastfeeding problems associated with progestin-containing contraceptives initiated at 4 weeks postpartum or later.

Finally, higher serum testosterone levels in pregnancy are associated with lower breastfeeding success.[68] However, testosterone used in doses to treat depression once lactation is well established does not seem to have an adverse effect.[69]

H1-receptor antihistamines are thought to have potential to adversely affect milk supply via lowering prolactin secretion, but only first-generation drugs have been studied. High intravenous doses of diphenhydramine (Benadryl) significantly decreased serum prolactin levels, but whether it affects prolactin response to suckling is poorly studied.[70] It appears that single oral doses of diphenhydramine have little effect on breast milk supply. Sympathomimetics such as pseudoephedrine (Sudafed) can decrease breast milk supply through anticholinergic effects that cause decreased glandular secretions. Although pseudoephedrine has been replaced by phenylephrine (Neosynephrine) in combination over-the-counter cold medicines, this replacement has been shown to also decrease breast milk supply in animal studies.[70] Therefore, encouraging use of only single-ingredient medication for the indicated symptom is prudent. Other medications listed in Table 2 have either been poorly studied or are only an issue when given in higher intravenous doses.

Alcohol even in moderate amounts decreases breast milk supply. A study of women given intravenous alcohol showed dose-related effects on serum oxytocin levels.[71] Two hours after 22 women ingested alcohol (0.3 g/kg), the equivalent of 16 ounces of beer or 6.8 ounces of wine in a 140 pound person, they pumped 9% less breast milk and the first drops of milk were slightly slower to appear (less than 2 second

Table 2. Drugs and Substances that Impair Lactation

Drug, Generic (Brand)	Potential Effect	Guideline/Evidence
Alcohol	Lowers oxytocin, which leads to decreased milk ejection	Occasional 1 drink/day (0.5 g/kg) acceptable
Antihistamines, H1-receptor		Effects are potentiated with concomitant use of pseudoephedrine for all drugs in this class
Diphenhydramine (Benadryl)	Decreased prolactin secretion with IV doses	Single oral doses have little effect; case of daily oral dose with no effect
Chlorpheniramine (Chlor Trimeton)	Decreased prolactin secretion with IV doses	Oral doses not studied
Promethazine (Phenergan)	Decreased prolactin secretion	Delayed lactogenesis if given during labor
Atypical antipsychotics		
Aripiprazole (Abilify)	Decreases prolactin	Use once lactation established
Epinephrine	Decreased prolactin and oxytocin with IV dose	No evidence of effect on lactation with use of oral or eye drop doses
Ergot alkaloids		
Bromocriptine (Parlodel)[a]	Decreases prolactin	A proven lactation suppressant
Cabergoline (Dostinex)[a]	Decreases prolactin	A proven lactation suppressant
Ergotamine (Cafergot)	Decreased prolactin	Limited information; contraindicated secondary to potential adverse infant effects
Methylergonovine (Methergine)	Decreased prolactin following intramuscular dose but no change in prolactin following oral dosing	Short oral doses have no effect on milk production Isolated case reports of adverse effects on the infant (eg, elevated blood pressure, bradycardia, tachycardia, vomiting diarrhea) Product label recommends not breastfeeding for 12 h after administration of methylergonovine
Estrogen-receptor blockers		
Tamoxifen (Nolvadex)		Suppressed lactation in 2 studies; general advice against use because of accumulation of drug in breast milk but no data on adverse effects in the infant
Hormones		
Estrogen[b]	Estrogen can increase dopamine, which inhibits prolactin	Human data for adverse effect in immediate postpartum
Testosterone	Effect through dopamine	Human data for adverse effect in pregnancy or immediate postpartum
Progestins	Inhibits prolactin binding	Human data limited; small effect
Nicotine	Inhibits prolactin	Decrease or abstain if low milk volume
Steroids	Decrease supply with high IV doses	No effects with oral doses even if high doses used as for treatment for persons with transplants or Crohn's
Sympathomimetics		
Pseudoephedrine (Sudafed)	Vasoconstriction in breast vasculature causes decrease in oxytocin, growth hormone, and prolactin	Oral 60 mg dose acutely decreases milk supply by approximately 25%
Phenylephrine (NeoSynephrine)	Same as above	IV doses decrease milk supply in animals

Abbreviation: IV, intravenous.
[a] Proven effective lactation suppressant
[b] Estrogen-containing oral contraceptives should be avoided before 21 days postpartum.[68]

difference).[72] However, once alcohol is metabolized, no effects are seen on breast milk supply. Long-term use of more than 2 beers daily showed shorter breastfeeding duration between 1 and 6 months in one study.[71]

Nicotine consumption interferes with the secretion of prolactin, thereby decreasing the potential volume of milk that can be made in the lactating breast.[73,74] Additionally, nicotine can interfere with the let-down reflex and not allow milk to flow freely to the suckling infant.[55] A systematic review calculated persons who smoke had 100 mL per day less breast milk at 2 weeks postpartum compared with a similar group of women who did not smoke.[74] By 4 weeks postpartum, they showed no increase in supply compared with persons who did not smoke, who made more

than 100 mL per day milk compared with their amount at 2 weeks.[74]

CONSEQUENCES OF IMPAIRED LACTATION

The first week after birth is critical for the establishment of lactation, and it is important to remember that any person may encounter breastfeeding complications.[11] The consequences of impaired lactation include hyperbilirubinemia, infant hunger, slow weight gain, infant failure to thrive, hypernatremic dehydration, and life-threatening or even fatal dehydration and starvation.[6,75–77] Additional complications of hypernatremic dehydration include seizures, disseminated intravascular coagulopathy, vascular complications, renal failure, dural thromboses, massive intraventricular hemorrhage, brain damage, and death.[6,75]

Although the consequences of impaired lactation have been well documented for the infant, the maternal consequences are not known. The inability of a woman to breastfeed may lead to significant stress, a longing for an experience she had assumed would happen, and a disconnect between her goals and the realities of a difficult and insufficient lactation experience. Frequent health care visits for a newborn who is not gaining weight and who may be ill, coupled with the normal stressors of the early postpartum period, may adversely affect the physical and mental health of the woman and the overall health of the family. Research is needed to address this gap in knowledge and identify interventions that support women who have impaired lactation.

AREAS FOR FUTURE RESEARCH

A full understanding of the etiologies of impaired lactation is lacking. New research looking to better understand these biological processes is encouraging. Currently, delayed lactogenesis is mostly limited to self-report of subjective findings with very few studies incorporating biomarkers to evaluate the condition. More importantly, there is no standard method for determining milk volume, an important outcome measure.[78] Such a method is needed to compare results among studies. Adequacy of breast tissue has not been well studied at all. Huggins et al conducted a small study that attempted to categorize adequacy using basic anatomic descriptors, similar to those identified in the 1940s by Stein and Leventhal.[53,79] Use of current sophisticated imaging technology might elucidate both what adequate tissue consists of and its prevalence. Future research may reveal better intervention strategies, such as use of breast massage to prevent delayed lactation or possibly promote milk production, but to date the studies have been small and poorly designed.[80]

CONCLUSION

Certain conditions place women at risk for impaired lactation, in particular delayed lactogenesis and/or insufficient lactation. Health care professionals working with breastfeeding women need to be aware of these conditions so at-risk women can be identified in pregnancy or the early postpartum period and followed closely as they initiate breastfeeding. The framework of categorizing breastfeeding difficulties into preglandular, glandular, and postglandular causes of impaired lactation may be a helpful guide for health care professionals to facilitate a systematic diagnostic evaluation of those presenting with impaired lactation.

ACKNOWLEDGMENTS

Content from this review was presented at the American College of Nurse-Midwives Annual Meeting & Exhibition in 2019.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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