Induced Lactation

Ronald S Kensinger, Professor Emeritus, Department of Animal Science, Pennsylvania State University, University Park, PA, United States

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Introduction

There has been interest in inducing non-pregnant dairy animals into lactation for decades (Meites, 1961; Walker and Stanley, 1941). This interest was enhanced as the modern dairy enterprise became more commercial with the discovery, development and adoption of technologies like refrigeration, pasteurization, designed mating schemes, and advances in mechanical milking. The advanced dairy farm became more specialized with a great emphasis on milk sales, and the non-lactating animal was correctly perceived to be a profit-consuming resource. Dairy farms today are challenged with minimizing costs of production and maximizing volume of milk produced in order to remain profitable. Thus, profitability may be improved by reducing the number of non-lactating cows and heifers on the farm, increasing the percentage of days-in-milk relative to herd life, and by saving cows of high genetic merit (and high milk production) but reduced fertility. Each of those goals could be accomplished with an approved safe and reliable method to induce cows into lactation. The stated hormonal approaches to induce cows into lactation have not been approved for commercial use by the US Food and Drug Administration, or the cogent regulatory agencies in Canada and the European Community.

Fundamental Methodology

A variety of methods have been used in an attempt to induce cows, goats and sheep into lactation during the last century. These methods have included estrogen (or synthetic estrogen) alone, or in combination with progesterone and somatotropin; and administration of hormones orally, by injection or by implantation of hormone containing pellets. The dosage of steroid hormone tested, and the duration of administration varied from as brief as 7 days to over 100 days. The milk yield responses to these treatments were generally quite variable, with some animals not producing milk, and others at a low level of milk production.

A number of significant advances in approaches to hormonally induce lactation emerged during the last 50 years. One advance was the demonstration that open dairy cows could be induced into lactation with a simple 7-day treatment with estradiol-17 (50–100 μg/kg body weight) and progesterone (250 μg/kg bodyweight) injected subcutaneously (Smith and Schanbacher, 1973; 1974). This simplified treatment (referred to subsequently as 7-day estrogen progesterone treatment) but used higher daily doses of estrogen and progesterone than used previously. It was designed to mimic the high levels of these steroid hormones observed in plasma of cows during the last month of pregnancy, when very significant mammary parenchymal development occurs. This treatment was very significant in that it was simple, relatively brief and lead to higher milk production than previous reports; but the milk production remained variable, with cows producing only 50%–80% of their previous production from a postpartum lactation. A novel contribution during this period was the demonstration that an intravaginal sponge with high doses of oestrogen and progesterone could be used to administer these hormones over a 10 day period, with the sponge physically pulled from the cows after ten days (Davis et al., 1983). This approach was desirable in eliminating injections and the associated animal discomfort, but without adjunct treatments (dexamethasone or reserpine) did not attain the milk yield performance of the 7-day estrogen-progesterone treatment. The patterns of estradiol-17β, progesterone, and prolactin in plasma as a result of the 7-day high dose treatment have been described in several papers (Chakriyarat et al., 1978; Erb, 1977; Jordon et al., 1981). Cows and heifers typically had progesterone levels of less than 2 ng/mL at the start of the treatment (although this is dependent upon the stage of the estrous cycle). Progesterone concentrations in plasma increased to 2.5–5 ng/mL by day 5–8 of the treatment, and then decreased rapidly as no additional hormone treatment was provided. By day 15, progesterone decreased to 1–1.5 ng/mL and must decrease bibther to less than 1 ng/mL in order for lactogenesis and the initiation of milk secretion to occur between days 18–21. Estradiol-17β followed a similar pattern: starting at <30 pg/mL on day 0, increasing to >400 pg/mL by day 5–7, and declining to <100 pg/mL by day 18–21 relative to the start of treatment. The anterior pituitary gland in cows responds to the estrogen-progesterone treatment with an increase in endogenous prolactin secretion by day 10–15, and a bibther increase in prolactin concentration to 40–50 ng/mL at the initiation of lactation around 18–21 days from the start of the treatment. It is this response in plasma prolactin and the significant decrease in progesterone that is thought to promote mammary differentiation and appears to be one of the key factors in successfully inducing animals to produce milk (Collier et al., 1977; Kensinger et al., 1979). The milk yields of cows induced into lactation were dependent upon season of the year, as cows induced into lactation in very cold winter days, or cows induced in hot summers, depending upon latitude, had significantly reduced milk production (Kensinger et al., 1979). The observed relationship between prolactin and subsequent milk production encouraged investigators to add additional treatments including prolactin secretagogues, such as reserpine. In some cases, but not all, treatments that included drugs to increase prolactin secretion led to significant improvements in milk yield (Collier et al., 1977). Other investigators have added glucocorticoid treatments to the induction protocol, which were administered around the start of milking (typically days 18–21 with the 7-day protocol). Recent studies using glucocorticoid treatments have shown that there are improvements in milk production for a few days but that the effect is short-lived (Macrina et al., 2014). It may be that glucocorticoid or prolactin secretagogue supplementation to the treatment protocol was not beneficial to milk production in some studies because animals that did not have adequate mammary development to respond to these treatments.

Lactation-induced cows have lower somatotropin concentrations in blood than postpartum cows. Since bovine somatotropin (bST) has been approved for use in some countries, it is now possible to add bST to enhance metabolic processes in induced cows to support greater levels of milk production (Bauman, 1992). This has been tested in several recent studies and bST leads to a 15%, or more, increase in milk production with few significant changes in milk composition (Magliaro et al., 2004; Macrina et al., 2011a; 2011b; Mellado et al., 2011). The addition of glucocorticoid, bST and a significant increase in the dose of estrogen to the treatment protocol was used in a 1500 cow commercial study in Mexico and reported high milk yields and a 100% success rate (Mellado et al., 2011).

Physiological Responses

The purpose of the estrogen and progesterone treatment to induce lactation is two-fold, with the initial mammary response being the stimulation of mammary development and the second response the initiation of lactation. Estrogen and progesterone are the hormones of pregnancy that stimulate mammary ductal and lobulo-alveolar development. Successful induction of lactation also requires biochemical differentiation of mammary cells to initiate milk secretion. Failure of either mammary development or biochemical differentiation will result in poor milk production.

Changes in gross appearance of the mammary glands of cows hormonally induced into lactation are quite subtle in the first week after initiation of the treatment. During the second week of the 7-day protocol there is a small but observable increase in mammary gland size (**Fig. 1**). During the third week from the start of treatment, the teats increase in size and mammary glands become more turgid as they fill with milk. Many animals that will subsequently produce high volumes of milk will develop edema around the udder in the few days prior to milking, just as many cows do at the time of parturition.

Histological analyses of udders from hormonally induced cows show numerous small ducts and alveoli during the first two weeks from the start of treatment (Howe et al., 1974; Croom et al., 1976). Observations suggest that ducts grow into the mammary stromal areas, and that many small alveoli form. Magnetic resonance imaging analysis suggests that growth of the mammary parenchyma occurs after the period of oestrogen and progesterone treatment, and continues into early lactation (Fowler et al., 1991). Thus, at the initiation of milking in most induced lactation protocols, there is likely concomitant mammary cell proliferation as well as differentiation in the udder; as has been observed in rat and mouse mammary glands at the time of parturition. A two-dimensional image analysis of udders from cows that were induced into lactation demonstrates a modest 12% increase in udder area by 14 days of treatment when compared to pre-treatment area, and a bibther 30% increase in pre-milking udder volume on day 28 (**Fig. 1**). Some of the increased volume on day 28 is due to accumulation of milk over the previous 12 h, but the

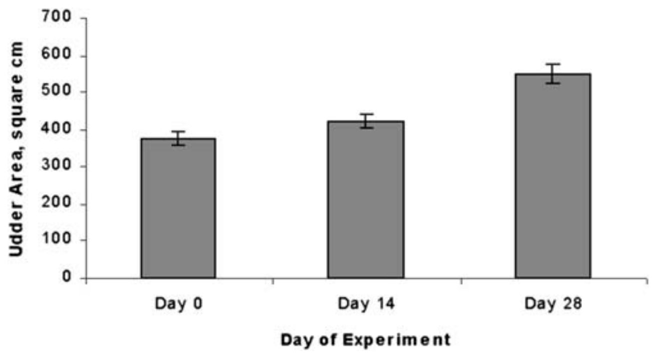

Fig. 1 Rear udder dimensions of cows from analysis of digital images captured on days 1, 14 and 28 of hormonally induced lactation. Cows (n = 28) were treated with estrogen and progesterone on days 1–7, and milking commenced on day 18 of the experiment.

remainder reflects increased mammary parenchymal tissue volume. Measurements of DNA, RNA and enzymatic activities generally reflect the developmental state of the tissue; with activities increasing around the initiation of milking, and with tissue from animals producing more milk having greater activity than tissue from lower producing animals.

A repeatable finding among researchers who have used the 7-day estrogen progesterone treatment to induce lactation is the consistent observation of behavioral estrus activity beginning the second week after the onset of estrogen treatment. This is expected given the normal proestrus effects of estrogen on the brain. It is potentially problematic in non-confined cows, however, because the duration of intense estrus-like activity including mounting behavior makes these animals prone to injury. The cause is known. The levels of estrogen in the circulation during the induction are designed to mimic the concentrations observed in late pregnancy and will cause the pelvic ligaments and tendons to remodel and loosen as occurs normally in preparation for parturition. However, since the induced cow has no corpus luteum (or adequate progesterone) to attenuate the estrus-behavior, the intense mounting activity in the face of the pelvic changes allows some unconfined-grouped cows to injure themselves. Many publications have indicated injuries to some animals that were allowed to run in groups. This problem can be avoided by simple management practices. Cows should be confined in a tie-stall facility for about 4 weeks after the initiation of the treatment to prevent them from injuring themselves. A goal of new induction protocols may be to refine the delivery of hormones in a manner to achieve the mammary growth effects without eliciting the behavioral estrus side effects.

Few data are available concerning voluntary appetites of animals hormonally induced into lactation, but casual observation suggests that appetites of animals are reduced when estrogen concentrations peak in the plasma, and it is clear that appetites increase significantly as milking commences. More data in this regard would be useful for verification, but it appears that the biological controls of appetite are working in the induced cow during lactation as they are in the postpartum cow.

Milk Production and Lactation Curve

The composition of colostrum and milk that results from methods to induce lactation is generally similar to normal colostrum and milk (see section below), but the shape of the lactation curve for the cow is somewhat different. Milk production commences very slowly (Fig. 2) and requires more time to reach peak milk yield than observed for cows in post partum lactations. Some studies report 60 to more than 100 days before peak milk yield is attained (Fig. 2). After peak milk production, the induced cows were very persistent (Fig. 2, data from Magliaro et al., 2004).

More recent studies show that the 7-day estrogen progesterone treatment when combined with bST leads to 100% success in bringing 15 month old heifers into milk (Macrina et al., 2011a and 2011b). Those heifers averaged over 17 kg milk/day for a full 305d lactation suggesting that opportunities exist to induce pubertal heifers into lactation and have them return income to the farm at a much earlier age. Several studies also show that these heifers grow well and conceive allowing them to remain in the herd (Macrina et al., 2011a).

Milk Composition and Value of Technology

The composition of the colostrum and milk from cows induced into lactation has been investigated in many studies. There is concurrence that the composition is normal given the level of milk production and the fact that the initiation of lactation is more gradual in the hormonally induced cows. Protein concentration in initial colostrum of induced cows can average as high as 20%, with the expected high somatic cell count, and low lactose and fat (Fig. 3). By day 7 of an induced lactation, most of the transition from colostrum to mature milk has taken place as milk protein has declined to about 5% and lactose and fat have increased to near the concentrations expected for mature Holstein milk (Fig. 3). There are small but continued decreases in protein and somatic cell count and increases in lactose and fat through 21 days in milk, reflecting the previously mentioned gradual

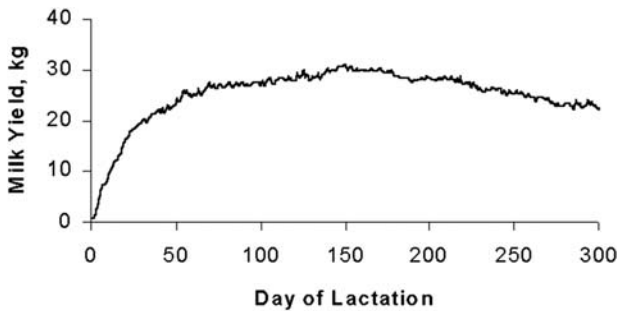

Fig. 2 Milk yields over 305 days for cows induced into lactation. Cows (n = 28) were treated with estrogen and progesterone for 7 days, milking commenced on day 18 of the experiment, and all cows were treated with bovine somatotropin during lactation.

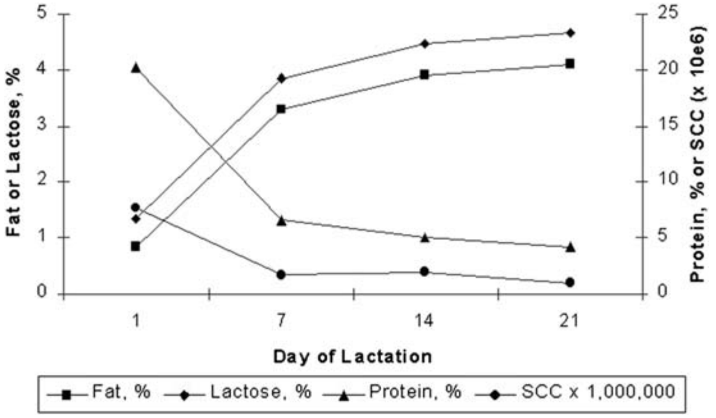

Fig. 3 Milk composition on days 1, 7, 14 and 21 of lactation from cows hormonally induced into lactation. Cows (n = 28) were treated with estrogen and progesterone on days 1–7, and milking commenced on day 18 of the experiment. SCC, somatic cell count.

increase in milk production. Thus, the only difference in major components between induced cow milk, and post partum cow milk is the more gradual transition from colostrum to mature milk.

The levels of immunoglobulin G (IgG) in the colostrum of induced cow milk are interesting given the desire to ensure adequate passive transfer of immunity to neonatal calves. The very viscous nature of day 1 colostrum from cows induced into lactation is reflected by IgG concentrations that averaged 200 mg/dL, and which decline precipitously to less than 20 mg/mL by day 7 of lactation, and even bibther by day 14 and 21 (Fig. 4). These data reinforce the conclusions above relative to the transition from normal colostrum to mature milk in induced cows and indicate that cows induced into lactation are an excellent model to study the mechanism of IgG transport into mammary secretions.

A number of studies have examined the concentrations of estrogen and progesterone in the colostrum and milk of cows induced into lactation, primarily due to concern for individuals consuming the milk. In general, the concentrations of these hormones in milk are not significantly greater than concentrations observed in the milk of postpartum cows. Some studies report concentrations that are actually lower in milk from induced cows. This is not surprising given the relatively short duration of elevated plasma hormone concentrations seen with modern approaches to induce lactation, such as the 7-day treatment. In contrast, a pregnant cow experiences significantly longer exposure to high concentrations of oestrogen and progesterone in plasma.

An analysis of the economic value of an open cow induced into lactation relative to replacing her with a replacement heifer indicate that the hormonally induced cow would have a 500 US dollar net present value advantage over the heifer (Magliaro et al., 2004). Thus, assuming that a commercially approved product was available, there is significant economic incentive for a farmer to retain a non-pregnant but otherwise healthy cow. Similarly, there should be significant economic incentive for private industry to develop this technology and attain the approval of the appropriate regulatory agencies.

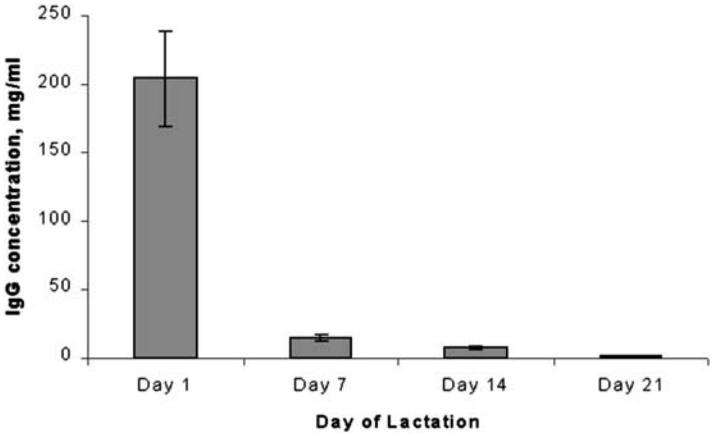

Fig. 4 Concentrations of immunoglobulin G as determined by enzyme-linked immunosorbent assay in mammary secretions on days 1, 7, 14 and 21 for cows hormonally induced into lactation. Cows (n = 28) were treated with estrogen and progesterone on days 1–7, and milking commenced on day 18 of the experiment.

Health Concerns

Some have suggested that treatments to hormonally induced lactation can lead to (1) abnormal structures on the ovaries, (2) should not be used to try to salvage problem breeders, and (3) will not result in very good subsequent reproductive performance. The reality is that most of those studies were performed with very limited numbers of animals, many of them were performed with cows that were problem breeders prior to the initiation of treatment, and few studies have allowed cows to complete full lactations and pregnancies to allow reporting actual calving data. One study (Magliaro et al., 2004) with 28 cows (mostly problem breeders) showed that 21 of 28 calved subsequent to the induced lactation and that was achieved with 1.6 services/conception. Thus, it appears that good reproductive success is possible, and that there should not be great concern about the subsequent reproductive health of these cows. Concerns previously stated about excessive and prolonged estrus behavior soon after the estrogen-progesterone treatment are real, as there are reports in the literature of cow injuries. However, simple confinement of animals for a few weeks can eliminate this problem, and there may be modified treatments in the future that attenuate these behaviors.

Concerns for long-term safety of cows and heifers are limited as few investigators have made the investment in long term studies to adequately evaluate health and survival data. The data available suggest that these animals can remain productive in the dairy herd for subsequent lactations. The heifers and cows that experience a nine month gestation are exposed to much more estrogen and progesterone than animals treated with estrogen and progesterone for 7–14 day as used in many experiments to induce lactation. An alternate view is worth consideration. Given that the majority of health problems experienced by dairy cattle occur within 14 days of parturition, including parturient paresis, ketosis, fatty liver, displaced abomasum, new intramammary infection, uterine infection and nerve damage, it is likely that hormonal induction of lactation (on a herd basis) could actually improve the general health of dairy cows, decrease herd culling rate, and make the entire enterprise more profitable. Given the complexity of regulation of mammary cell proliferation and lactogenesis, scientists may never develop techniques to hormonally induce lactation that will be superior to the stimulus of pregnancy and parturition. bibthermore, successful reproduction is required to make continued genetic progress in the herd. Consequently, induced lactations, assuming techniques are one day approved by regulatory agencies, should be viewed as a tool to use in selected situations to make the dairy enterprise more profitable.

Applications of Induced Lactation

Induced lactation on a dairy farm could increase income on commercial dairy farms by reducing the number of heifers raised on the farm. All dairy farms, at some time, experience good cows of high genetic merit that simply express low fertility during a given lactation. Healthy, multiparous open dairy cows could be induced back into lactation after a dry period, thereby reducing the number of replacement heifers needed. Profitability may be enhanced bibther by use of bST during the induced lactation. In addition, farmers could also induce pubertal age heifers into lactation if the practice proves to be safe, and a commercial product is available. This practice would significantly reduce heifer-rearing costs and make them profitable much sooner than current practice allows.

Hormonally induced lactation offers a useful scientific model for mammary gland biology, including the study of mammary development and tumorigenesis, biochemical differentiation of the mammary gland, and the regulation of IgG transport into mammary secretions. Many additional questions about regulation of gene expression, and the balance between cellular proliferation and apoptosis might be asked, as well.

Hormonal induction of lactation has additional value. There are a number of projects worldwide that endeavor to utilize transgenic dairy animals to produce commercially valuable proteins in milk; including clotting factors, human hemoglobin, growth factors, enzymes, and human lactoferrin (Houdebine, 2009). The great challenge in using dairy cattle for this purpose is their long generational interval (9 month prenatal period and about 24 months before a heifer has her first offspring and produces milk). Hormonally induced lactations could reduce this time (Ball et al., 2000). The use of techniques to hormonally induce young transgenic animals into lactation would allow much earlier identification of the females secreting the transgenic protein in milk, the level of expression, and whether it was expressed in a mammary-specific manner. All of these are important questions when one considers the cost of maintaining a herd or flock.

See Also: Galactopoiesis, Effects of Hormones and Growth Factors; Lactogenesis; Mammary Gland: Growth, Development and Involution

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