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Rewiev Article

Use of Bovine Somatotropin in the Management of Transition Dairy Cows

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Abstract: The major objectives of an efficient dairy farm operation include a successful lactation period, high milk yield relative to the feed costs, reproductive competence, and finally the returning of the cow to the body condition score (BCS) that existed before lactation so she will be prepared for another lactation. In cows a milk yield response to bovine somatotropin (bST) treatments at 60 d after parturition has been well studied and fully documented. Milk production response to bST occurs because of its known effects on partitioning of nutrients and because a greater proportion of the nutrient intake is used for milk synthesis. It increases liver glucose output, cardiac output, blood flow to the mammary gland and uptake of nutrients used for milk synthesis by the mammary gland among other effects. In addition, ST decreases the rate of oxidation of amino acid and glucose and therefore decreases glucose clearance. Treatment with bST results in coordinated changes of various organs and tissues that naturally occur during the transition from a nonlactating to lactating state when circulating concentration of ST is high. Because of the known effects of bST described above, use of bST during the transition period may cause positive and beneficial effects supporting milk synthesis prior to parturition. This review recaps the diverse physiological effects of ST on lactation, discusses the major mechanisms that mediate these effects, and summarizes the recent studies using bST during the transition period to increase milk production in cows.

Key Words: Somatotropin, lactation, transition period, metabolism, dairy cow.

Geçiş Dönemi İneklerde Bovine Somatotropin Kullanımı

Özet: Süt üreticilerinin en önemli amaçları başarılı bir laktasyon dönemi, yem maliyetine oranla daha yüksek süt üretimi, doğum sonrası hayvanların tekrar gebe bırakılması ve en son olarak da hayvanların doğum sonrası sahip oldukları kilolara tekrar ulaştırılmasıdır. Bovine smatotropin (bST) kullanıldığında süt verimindeki artışın nedeni, besinlerin vücut dağılımına olan etkisi ile alınan besinlerin büyük bir bölümünün süt sentezlenmesi için yönlendirmiş olmasıdır. bST bir çok etkisinin yanı sıra ayrıca karaciğerden glikoz salıverilmesini, toplam kalp hacmini, meme bezine gelen kan miktarını ve süt üretimi için gerekli olan besin alımını artırır. Bunlara ilaveten, bST amino asit ve glikozun oksidasyonunu ve böylece glikoz kullanımını da azaltır. bST kullanıldığında birçok doku ve organda koordineli olarak deıişikliğe sebep olur. Bu değişiklikler geçiş döneminde kandaki ST'nin yüksek olduğunda görülen değişiklikler ile benzerdir. bST'nin yukarıda da bahsedilen etkilerinden dolayı, geçiş döneminde kullanılması süt üretiminin artırılması açısından olumlu ve yararlı olabilir. Bu derleme kapsamında, ST'nin yararlı etkileri ve ana mekanizmaları tartışılarak geçiş döneminde bST kullanımı ile süt üretimine etkisi üzerine yapılan yeni araştırmalar hakkında bilgi verilmesi amaçlanmıştır.

Anahtar Sözcükler: Somatotropin, laktasyon, geçiş dönemi, metabolizma, süt ineği

Introduction

As early as the 1930s, the growth-promoting effects of somatotropin (ST) were characterized. Evans and Simpson (1) showed that crude extracts of bovine pituitary increased the growth rate of rats. In 1937, two Russian scientists, Asimov and Krouze (2), performed the first bST research, using 600 lactating dairy cows. These researchers found that injecting cows with extracts of the pituitaries of slaughtered cows resulted in increased milk production. Research continued during and after World War II as scientists sought an effective means of increasing food production. However, the amount of ST from each pituitary was so low that this source would not be practical for improving total milk production (3).

The arrival of modern technology enabled the development of recombinant bovine somatotrophin (rbST), which provided an unlimited source of ST for research and, potentially, for commercial application. This

allowed researchers to conduct many studies using recombinant bST. From these studies it was concluded that exogenous ST could increase milk production of dairy cows at least 10% to 15%. Obtaining a milk yield response to bST did not require special diets or different feed ingredients. However, treated cows did need adequate amounts of balanced diet that contains all nutrients necessary for supporting expected milk production (4).

Treatment of cows with bST during lactation was approved for use in the US in 1994. Since then it has been used extensively. In addition, more than 34 countries have reached similar conclusions with respect to food safety, and approved the use of bST, such as Algeria, Brazil, Bulgaria, Columbia, Costa Rica, Czech Republic, Honduras, Hungary, Jamaica, Kenya, Korea, Malaysia, Mexico, Namibia, Pakistan, Peru, Romania, Russia, Slovakia, South Africa, Turkey, United Arab Emirates, Ukraine and Zimbabwe.

Bovine somatotropin had been given to 335,000 cows in New York (45% of the state total), the major dairy state in the eastern US, after over a year period. About 55% of all sales of bST have been to farmers who have 100 or fewer cows (5). In 1998, of nearly 9 million dairy cows in the US, about 25% were in bST treated herds, and 300 additional dairy farmers were reported to be adopting use of bST per month. The average dairy farmer used the commercial bST product (POSILAC®) to supplement more than 50% of the herd depending upon individual herd management practices and stage of the adoption.

Responses to somatotropin supplementation

Somatotropin is a major regulator of growth in mammals. In the liver ST regulates the expression of a wide range of proteins including hormone receptors and growth factors, secretory products, and enzymes such as cytochrome P450 (6). Somatotropin also has a unique effect on stimulating mammary gland development (7) and lactation (8).

Typical milk yield (MY) response to bST is an increase of at least 10-15%. However, the response can be much greater with better care and management of the cows (9,10). After the first few days of bST treatment, MY increases gradually and reaches a peak and the increase is maintained with continuous injections of bST. Milk yield gradually returns to normal pre-injection levels after cessation of treatment (11).

Obtaining a MY response to bST does not require special diets or different feed ingredients. Substantial MY responses have been observed on diets ranging from pasture to the more typical total mixed ration (TMR) diets. However, dry matter intake (DMI) increases in bST treated cows after a few weeks of the supplementation and persists throughout the interval of bST use. Thus, treated cows require adequate amounts of a balanced diet rather than a special diet (10).

a) Effects of bST on the Mammary Gland

In early studies concerning the actions of ST, it was concluded that a direct effect of ST on mammary gland development was unlikely. Studies failed to detect an ST receptor on the mammary epithelial cell of the cow (12). Moreover, infusions of ST directly into mammary artery of sheep did not stimulate milk production (13). However, in rodents, a direct effect of ST on mammary development and function was established (14,15). Although most evidence suggested an indirect effect of ST on mammary gland development in ruminants, it was found that ruminants also expressed mRNA for the ST receptor in mammary gland (16). Furthermore, immunologic staining of ST receptors in mammary tissue of pregnant and lactating cows was also reported (17). Collier et al. (18) observed a significant effect of ST on mammary growth of pregnant heifers when it was administered through the teat canal. However, as indicated, unilateral close arterial infusion of ST into one-half of the mammary gland of sheep did not increase milk yield performance compared with the uninjected half (13). Furthermore, ST administration through the teat canal of lactating goats did not result in increased milk production response (19). This latter response would not be expected unless there was uptake of ST across the apical membrane of the epithelial cells or uptake into the general circulation and subsequent action in mammary gland.

The acute rise in MY in response to bST and rapid decline after stopping bST injection argues against cell proliferation being caused by ST in the short-term. Knight et al. (20) observed that ST treatment did not affect the amount of mammary parenchyma and BrdU-labeling of mammary epithelial cells in vivo during the first 6 wk of lactation. On the other hand, a large

increase in parenchymal volume was observed in mid-lactation goats treated over a 22 wk period with exogenous ST (21). Other studies with cows and goats reported trends and/or significant increases in key enzymes in the mammary gland (such as acetyl CoA carboxylase, acetyl CoA synthetase and fatty acid synthetase) due to bST supplementation. Thus, bST directly and/or indirectly causes an increase in the rates of milk synthesis per cell and improved maintenance of secretory cells (22,23).

Somatotropin shows one of its effects on mammary gland function indirectly via the action of insulin like growth factor-I (IGF-I) on the tissue (24). Concentrations and actions of IGF-I are likely the most important link to tissue response with higher concentrations of ST. Somatotropin has a major role in regulating the concentrations of IGFs that are in the circulation. Concentrations of IGF-I increase during bST treatments because of both induced release of IGF-I from a hepatic storage pool and greater biosynthesis of IGF-I. Biosynthesis is regulated by increased mRNA levels and mRNA stability (25). Increase in IGF-I concentration was maintained with continued injections of ST and the increase in MY was parallel to the increase in IGF-I. Cessation of ST supplementation caused a parallel decrease in both MY and blood concentrations of IGF-I (25).

Insulin like growth factor-I has both autocrine and paracrine actions in addition to its endocrine actions (26). At the cellular level, IGF-I locally stimulates amino acid transport, synthesis of RNA and DNA, and synthesis of cellular proteins (27). Receptors for IGF-I were demonstrated in mammary tissue and IGF-I is a local mediator of mammary epithelial growth and development (28). Intralobular stromal cells, small blood vessels, and capillaries contain IGF-I receptors in the mammary gland (29). During ST treatments, IGF-I binds in the cytoplasm and the stroma of epithelial cells. Insulin like growth factor-I stimulates the cellular activity of mammary gland, it increases synthesis of RNA and DNA, and the synthesis of cellular proteins. Therefore, it is a local mediator of mammary epithelial growth and development (27). Interestingly, close arterial infusions of IGF-I into mammary gland of goat, but not systemic infusions of IGF-I, increased MY dramatically (30). However, lactational response to close arterial infusion of IGF-I was much less than that of systematic bST treatments which suggests that the mechanism of action of bST with regard to stimulatory effects on MY cannot be limited only to the known effects of IGF-I.

b) Effects of Somatotropin on Other Tissues

Somatotropin exerts many different effects on protein metabolism in both mammary and non-mammary tissues. Bovine somatotropin increases MY with no change in milk composition, unless there is energy deficiency. It provokes MY increase by increasing overall blood supply to mammary gland (water uptake), altering glucose metabolism (lactose synthesis in the mammary gland), enhancing lipolysis and increasing lipogenesis in the mammary gland (supply of lipid precurcors), and also modifying protein metabolism (supply of amino acids). As a result, milk yield increases and the composition of milk does not change from normal (31).

Increased MY response due to ST results mainly from altered partitioning of nutrients in favor of mammary glands and from an increase in the synthesizing capacity and/or longevity of the milk synthesizing cells (22). Somatotropin is a primary homeorhetic regulator during pregnancy and lactation; it regulates partitioning of nutrients (carbohydrates, lipids, proteins, and minerals) and plays an important role in the coordination of various organs and tissues (4). To support milk synthesis, the metabolism of other tissues is stimulated to provide the necessary precursors.

Carbohydrate metabolism

During early lactation, glucose is used almost exclusively by the mammary glands (exceptions are nervous system and brain), and MY is heavily dependent upon increased glucose supply to the gland. If bST is to increase MY, then it must act in a way to direct more glucose to the mammary gland. This can occur through a variety of individual actions of bST. First, bST increases mammary blood flow so that more blood perfuses the mammary gland and increased uptake of glucose can occur (31). A decreased ability of insulin (INS) to inhibit gluconeogenesis is observed following bST treatments. Both in vivo (32) and in vitro (33) studies demonstrated that hepatic rates of gluconeogenesis were increased during treatment of dairy cows with bST. Furthermore, ST decreased sensitivity of INS receptors to INS in the peripheral tissues and this resulted in decreased overall uptake of glucose in peripheral tissues. This minimized the oxidation of glucose to CO_2, and as a consequence

more glucose was made available to the udder. Somatotropin also stimulated increased feed intake, and as a result, more propionate was produced in the reticulo-rumen and became available for gluconeogenesis (34). In vitro studies of liver tissue of ST treated cows showed a 60% increase in capacity to use propionate for glucose synthesis (33).

Pyruvate carboxylase (PC) and phosphoenolpyruvate carboxykinase (PEPCK) are potential rate-limiting enzymes for hepatic gluconeogenesis during the transition period (35). It was speculated that exogenous ST would increase mRNA synthesis in the liver that coded for these enzymes (11). On the other hand, Pershing et al. (36) concluded bST stimulation of milk production was not mediated through enhanced liver gluconeogensis in cows with 80 days in milk (DIM). Somatotropin also increased lipid mobilization and more glycerol then was available as a precursor for gluconeogenesis. To sum up, the total of these actions would be that higher blood glucose concentrations occurred and this glucose could be directed to the mammary gland to support lactation. In addition to increased glucose production in the liver, glucose usage by other lean body tissues decreased. Because glucose is used as a primary energy metabolite and as a substrate for synthesizing milk constituents, energy needed by other peripheral body tissues would be derived from products of lipolysis or metabolism of non-gluconeogenic compounds arising from the rumen and lower digestive tract.

Lipid metabolism

Nutritional status plays a major role in the regulation of lipid metabolism. Exogenous bST given to animals alters both lipogenesis and lipolysis in adipose tissue with the net effect being related to energy balance (EB) (11). When cows are in positive EB, synthesis and deposition of lipids in adipose tissue are reduced by ST, which, in turn, increases the availability of nutrients and their utilization for milk production (22). Insulin performs important homeostatic control in the regulation of lipid metabolism. Somatotropin reduces the ability of INS to stimulate lipogenesis in adipose tissue. Thus, ST reduces the action of INS, suppresses lipogenic enzyme activity, and reduces glucose uptake (22). These coordinated changes in INS actions would support production of glucose from available precursors and conservation of glucose for mammary use by shifting peripheral tissues to utilization of other substrates available, in large part, due to combined actions of ST and INS.

When cows are in negative EB, ST stimulates lipolysis; it alters the sensitivity of adipose tissue to β-adrenergic agents (22). Therefore, for cows that are in negative EB and are being treated with bST, increased lipid mobilization would be a major source of energy needed to support milk production (37). Lipolysis is regulated by a signal transduction system that includes cAMP, stimulatory G proteins (G_s) and inhibitory G proteins (G_i). Catecholamines act through the G_s system to stimulate lipolysis, whereas adenosine exerts its antilipolytic affects via the G_i system. When adenosine binds to its receptor it stimulates G_i which uncouples G_s protein activation of adenyl cyclase catalyzed by catecholamines. This leads to the inhibition of the lipolytic pathway that is stimulated by catecholamines. Somatotropin alters lipolysis through an increase in response to catecholamines with no change in sensitivity. Epinephrine challenge following ST treatment dramatically increased non-esterified fatty acid (NEFA) concentrations in plasma. Interestingly, ST treatment resulted in modest changes in β and α_2 adrenergic receptor numbers. However, the activity of G_i proteins was reduced significantly by ST treatments. As a result, it has been suggested that ST impaired the ability of G_i to interact with adenyl cyclase. This, in turn, would increase the effectiveness of G_s system stimulated by catecholamines (11).

The events described above would dramatically increase mobilization of lipids from the adipose tissue, and increase blood NEFA and glycerol. Thus, there would be greatly reduced fatty acid synthesis or no net synthesis, and hence, less acetate and glycerol use in the adipose tissue. Therefore, the net result would be a shift in the availability of these metabolites in the mammary gland where they can be used for synthesis of short and medium chain-fatty acids that are themselves used for TG synthesis and milk production. Therefore, lipolysis also must be an important pathway to provide needed precursors in the early postpartum period of cows especially to supply the energy needed for milk production (11).

Amino acid metabolism

Somatotropin treatment increases milk protein synthesis in lactating cows via improved efficiency of amino acid utilization. A reduction in circulating urea nitrogen and in urinary nitrogen loss were reported

following bST treatment (31). During negative energy balance ST will spare protein use as a source of energy in tissues because it increases lipid mobilization and enhances glucose metabolism. Proteins that are mobilized from the muscles can be used in the liver, in the gut, and in the blood and this will increase overall metabolism and efficiency of protein use. Amino acids mobilized have an important role in supporting growth of some organs (liver, heart, digestive tract) rather than to support milk synthesis (38). Amounts of amino acids that are oxidized to provide energy will be reduced and the protein mobilized can be used for growth of specific tissues and milk protein synthesis. As indicated, ST causes an increase in feed intake, which will make more nutrients and amino acids available to increase MY, and this will lessen the need for tissue mobilization processes.

Mammary blood flow

It has been established that nutrient supply to the mammary gland is one of the major limitations for the activity of secretory cells and milk synthesis. A lactating mammary gland places a heavy demand on the animal to provide substrates for milk synthesis (31). With bST injections, along with the increases that occur in MY, cardiac output also increases. Insulin like growth factor-I has a role in the increased blood flow to the mammary gland that appears to be mediated by production of nitric oxide (30). Somatotropin also increases conversion of T_4 to the tissue active thyroid hormone T_3 specifically in the mammary gland and the increase in T_3 alters local metabolism and helps mediating the galactopoietic response (39). Thus, both increased milk secretion and local metabolism drive more blood to mammary gland and this, in turn, supplies greater quantities of water and nutrients needed for milk synthesis.

bST during transition period

The approved time during the lactation cycle of cows to start use of bST is at about peak MY (~60 ± 3 d) and its use is continued throughout the remainder of the lactation (40). Milk yield gradually increased over the first few days following bST treatment and reached to maximum concentration during the first week. Despite large increases in milk production, feed intake did not increase immediately following bST treatment. Early production responses therefore, were due mostly to partitioning of nutrients away from body tissues to mammary gland use to support increased milk synthesis.

Although increased MY responses typically are found when cows are injected with bST beyond 60 d postpartum, no such increase in MY was observed when exogenous bST was injected during prepartum and early postpartum periods, which included the so-called transition period. Bines and Hart (41) speculated that because of delayed increase in DMI, treatment with bST during the transition period might lead to acute animal health problems such as ketosis, fatty livers, wasting, and increased susceptibility to other diseases, or it could result in lower than expected MY responses.

a) bST injections during prepartum period

Studies by Eppard et al. (42) failed to show an increase in MY when they injected Holstein and Jersey cows during the prepartum period with a full standard dose of bST (POSILAC®). Simpson et al. (43) administered growth hormone releasing factor (GRF) prepartum to beef heifers to increase secretion of ST before parturition and during early lactation. Treated heifers lost more body weights (BW) and had delayed ovarian activity, whereas no difference was observed in MY. In another trial, Holstein cows received 0, 5 or 14 mg bST/d during the last 46 d before parturition (44). Cows treated with 14 mg bST/d had increased yields of solids-corrected milk (SCM) only during wk 1. However, they found no differences in SCM among treatments. Except for the cows treated with 5 mg/d of bST during wk 10 of lactation, EB was negative for all cows during the first 70 d of lactation. Bachman et al. (45) evaluated whether a dose of 25 mg bST/ d administered prepartum affected postpartum MY of Holstein cows. After covariance adjustment for previous total lactation MY, 3.5% fat corrected milk (FCM) yields of treated and control cows did not differ. They concluded that bST treatments during prepartum period did not have either a positive or a negative effect on MY during the following lactation. None of the studies that used bST treatments during the transition period have reported acute animal health problems such as ketosis, fatty livers, wasting, and increased susceptibility to diseases in the treated cows.

Stelwagen et al. (46) administered 20 or 40 mg bST daily to Holstein heifers during the last trimester of the first pregnancy. They found a significant increase in FCM production of the heifers injected with 20 mg bST/d but only after 90 d of lactation. Putnam et al. (47) reported a significant effect of prepartum bST treatments on milk production during early lactation which appeared to

increase as lactation progressed. The exogenous bST injections (500 mg over 14 d period) were initiated 28 d prior to expected calving date and were continued until parturition. Cows treated with bST in their trial produced 3.3 kg/d more milk than uninjected controls during the first 42 d of lactation. However, cows in the bST treated group had significantly higher initial body condition score (BCS) than the controls when they were assigned to the trial. This allowed treated cows to mobilize more body reserves than controls and to lose more BCS without a negative effect due to bST. This is a very important factor because bST use likely increases negative energy balance and greater loss of body weight, which supports the greater milk production until the DMI increases.

b) bST injections during postpartum period

As reported for prepartum treatments, early postpartum injections of bST also showed inconsistent results. de Boer et al. (48) injected cows with 20.6 mg bST/d starting postpartum 4-9 d. No significant differences were detected for MY of control vs. bST treated cows. Unfortunately, the cows assigned to bST had lower MY potential based on the rate and extent of decline in MY after cessation of bST injection. Thus, bST injections enhanced MY to levels similar to those of controls (48). Moallem et al. (49) studied the mechanisms of how Ca soaps of fatty acids and bST affect production and reproduction of high producing cows. They injected 500 mg of bST every 14 d from 10 to 150 DIM. Milk yield during the first 60 d did not differ between treatments. However, bST treatment significantly enhanced MY beyond 60 d and the peak milk production increased for injected cows. On the other hand, the effect of treatment on BCS was severe. The BCS of injected cows decreased more and was considerably less for treated cows and postpartum conception rate was affected adversely compared to uninjected cows. Santos et al. (50) investigated effects of bST on the performance of early lactation cows fed diets differing in ruminally degradable starch. Holstein cows received biweekly injections of 500 mg bST for 90 d starting at 5 DIM. A positive MY response was observed during the first 45 d and for the total treatment period (90 d). Interestingly, MY response to bST was less between 7 and 13 wk than from 1 to 6 wk. Neither EB nor BCS were determined in this study. Authors concluded that the response to bST was less than usually observed for cows when bST injections began at peak MY. In another study, the same dose of bST was injected every 14 d from 10 to 150 DIM (51). They concluded that bST injected early in lactation increased MY. However, increase in MY occurred at the expense of an extensive period of NEB and decrease in BW and BCS despite an increase in DMI was observed due to bST treatment.

Richard et al. (52) reported a 6% increase in MY when cows were injected with 50 IU of bST starting postpartum 20th d; milk fat also was elevated by 25%. In the same trial, when cows were injected beginning on 0 d, MY response was greater (12%) with no change in milk fat. Chalupa et al. (53) treated cows fed a diet that contained 0% or 1.2% sodium bicarbonate with 50 IU bST starting at 4th wk of lactation. They reported that bST treatment increased MY by 4.7 kg over control cows and there also was a 1.05 point increase in milk fat percentage. Feed intake of injected cows tended to increase (17.6 kg vs. 16.1, $P < 0.11$). In one of the largest trials, Stanisiewski et al. (54) injected 5 mg or 14 mg bST/d from 14 d postpartum through 60 DIM. Cows that received either 5 or 14 mg of bST/d produced more FCM than controls, but FCM of the two bST treated groups did not differ. However, cows receiving the lower dose (5 mg/d) had higher pregnancy rate and higher conception rate than all other experimental cows. Cows receiving 5 mg bST/d also maintained BCS as uninjected controls.

Variable results within and among trials that evaluated use of bST either pre- or postpartum period may have been due, in part, to differences among the doses, diets the animals were fed, or due to differences in BW and BCS of the animals. Usually, a high dose of bST increased the length of time cows were in NEB; loss of BW and BCS occurred even though an increase in DMI might have occurred. Thus, adequate BCS (55) for cows injected with bST pre- and/or postpartum is required because the cows require good management and adequate nutrition to produce and reproduce well.

c) bST injections during both prepartum and postpartum periods

Treatment with a lower dose of bST during both prepartum and postpartum periods has a potential to cause metabolic changes after parturition that are beneficial to the health and performance of the cows (56). In one study, pre- and postpartum injections of

15.3 mg bST/d showed increased concentrations of ST, IGF-I and T_3 in plasma (57). Evidence suggests that changes in circulating concentrations of hormones, growth factor and glucose can be beneficial. In the same study, pre- and postpartum injections of bST increased DMI of cows after parturition, and there was a smaller decrease in BCS and BW. This allowed the cows to recover to satisfactory BW and BCS more rapidly during early lactation. Cows also produced quantitatively greater daily MY and 3.5% FCM. Thus, the changes in concentrations of metabolic hormones likely had a role in the positive effects on DMI, BCS, BW and MY of these cows.

Gulay et al. conducted two consecutive experiments with bST during the transition period. During the first experiment (58), injections of bST (10.2 mg bST/d) began approximately 21 ± 3 d before expected calving dates and biweekly injections of bST continued up to postpartum 42nd d. No injections of bST were given between postpartum 42nd d and d 100 ± 4 postpartum, but all cows received full dose of POSILAC® beginning at d 100 ± 4 postpartum. During the second experiment (59) injections began approximately 21 d (± 3 d) before expected calving dates and were continued up to d 42 (± 2 d) postpartum. After 60 d, all cows on experiment received the full dose of POSILAC® biweekly (500 mg/14 d). Data from both the first and second studies suggest that use of 10.2 mg bST/d during late prepartum and early postpartum periods caused no apparent negative effects on the treated cows. Although EB was measured only in the second study (59) during first 4 wk of postpartum, NEB was not greater in injected cows than in uninjected cows in either study (58,59). This was an indirect conclusion for the first study since the increase in MY and BW and the changes in BCS were equal or better in injected relative to in uninjected cows. Injection of bST resulted in better recovery of BW and BCS during early lactation, especially after injections were stopped around d 42 postpartum (58). During the second study, low dose of bST did not provoke a greater loss of BW or decrease in BCS compared to untreated cows. Cows in both groups appeared equally capable of replenishing their body reserves even though all cows started injection of a full dose bST around postpartum 60th d; a daily dose was three times greater than that injected before d 42. Bovine somatotropin treatments did not adversely or positively affect the rate of increase in DMI during the first 28 d of postpartum period; the increase in DMI was same for both treated and untreated cows (59). In both studies, bST treated cows produced more milk and 3.5% FCM during the injection period. In the first study, no carryover effects of bST were detected on MY as evidenced by the fact that the increase in MY did not persist after bST injections were stopped around d 42 postpartum (58). On the other hand, during the second study, treated cows also produced more milk when all cows (controls and treated) were injected with full dose of bST (>60 d of lactation). They also had higher concentrations of ST, INS and IGF-I prepartum and higher ST and IGF-I postpartum (59). The findings of these studies show that bST injection has general and likely more diverse effects, which results in greater MY and DMI without apparent negative effects. Indeed, results indicated the overall effects of prepartum and early postpartum bST were beneficial since BW and BCS were better maintained and concentrations of metabolic hormones were improved.

Summary and Conclusions

When injected during ongoing lactation, bST resulted in an exceptional increase in milk production of dairy cows. Because of its positive effects on blood glucose, lipids and amino acid concentrations and blood circulation, bST increases milk yield without affecting the overall composition of the milk. This increase would be equal to that normally achieved by AI and genetic selection over 10-20 y period. Somatotropin also has a pivotal role in homeorhetic control of metabolism and nutrient partitioning (carbohydrates, lipids, proteins, and minerals) of the cow during the transition period. The transition period and the early lactation period were considered as time periods that have the potential to enhance lactational performance. Increasing concentrations of ST has a potential to augment the metabolic changes that favor the mammary gland and have a positive effect on DMI. In a broad view, bST affects the system in a positive way and makes it possible for cows to respond better later in lactation without apparent negative effects on health. Changes in concentrations of metabolic hormones, likely coupled with effects on various organs, suggest strongly a beneficial effect of bST during the transition period. This can be interpreted that injections of bST may have a

potential use during the postpartum period and probably during the prepartum period, to improve metabolic status and improve overall milk yields during early lactation.

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References

1. Evans, H.M., Simpson, M.E.: Hormones of anterior hypophysis. Am. J. Physiol., 1931; 98: 511-546.
2. Asimov, G.J., Krouze, N.K.: The lactogenic preparations from the anterior pituitary and the increase in milk yield from cows. J. Dairy. Sci., 1937; 20: 289-306.
3. Young, F.G.: Experimental stimulation of lactation. Br. Med. Bull., 1947; 5: 155-160.
4. Bauman, D.E.: Bovine somatotropin: Review of an emerging animal technology. J. Dairy Sci., 1992; 75: 3432-3451.
5. Hartnell, G.F.: Bovine Somatotropin: Production, Management, and United States Experience. In Animal Science Research and Development; Moving Towards a New Century. Ivan, M. ed. Centre for Food and Animal Research, Agriculture and Agri-Food Canada. 1995. Ottawa ON K1A 0C6, Canada.
6. Norstedt, G., Enberg, B., Moller, C., Matthews, L.: Growth hormone regulation of gene expression. Acta. Paediatr. Scand. (Suppl.), 1990; 36679.
7. Feldman, M., Ruan, W, Cunningham, B.C., Wells, J.A., Kleinberg, D.L.: Evidence that the growth hormone receptor mediates differentiation and development of the mammary gland. Endocrinology, 1993; 133: 1602-1608.
8. Barber, M.C., Clegg, R.A., Finley, E., Vernon, R.G., Flint, D.J.: The role of growth hormone, prolactin and insulin-like growth factors in the regulation of rat mammary gland and adipose tissue metabolism during lactation. J. Endocrinol., 1992; 135: 195-202.
9. Bauman, D.E., Eppard, P.J., DeGeeter, M.J., Lanza, G.M.: Responses of high-producing dairy cows to long term treatment with pituitary somatotropin and recombinant somatotropin. J. Dairy. Sci., 1985; 68: 1352-1362.
10. National Research Council.: Metabolic modifiers: effects on the nutrient requirements of food producing animals. Natl. Acad. Press., 1994; Washington, DC.
11. Bauman, D.E.: Bovine somatotropin and lactation:from basic science to commercial application. Domest. Anim. Endocrinol., 1999; 17: 101-116.
12. Gertler, A., Ashkenazi, A., Madar, Z.: Binding sites of human growth hormone and ovine and bovine prolactins in the mammary gland and liver of lactating dairy cows. Mol. Cell. Endocrinol., 1984; 34: 51-57.
13. McDowell, G.H., Hart, I.J., Kirby, A.J.: Local intra-arterial infusion of growth hormone into the mammary glands of sheep and goats: effects on milk yield and composition, plasma hormones and metabolites. Aust. J. Biol. Sci., 1987; 40: 181-189.
14. Flint, D.J., Gardner, M.: Evidence that growth hormone stimulates milk synthesis by direct action on the mammary gland and that prolactin exerts effects on milk secretion by maintenance of mammary deoxyribonucleic acid content and tight junction status. Endocrinology, 1994; 135: 1119-1124.
15. Kleinberg, D.L.: Early mammary development: growth hormone and IGF-1. J. Mammary Gland. Biol. Neoplasia., 1997; 2: 49-56.
16. Glimm, D.R., Baracos, V.E., Kennelly, J.J.: Molecular evidence for the presence of growth hormone in the bovine mammary gland. J. Endocrinol., 1990; 126: R5-R8.
17. Plath-Gabler, A., Gabler, C., Sinowatz, F., Berisha, B., Schams, D.: The expression of the IGF family and GH receptor in the bovine mammary gland. J. Endocrinol., 2001; 168: 39-48.
18. Collier, R.J., McGraft, M.F., Byatt, J.C., Zurfluh, L.L.: Regulation of bovine mammary growth by peptide hormones: involvement of receptors, growth factors and binding proteins. Livest. Prod. Sci., 1993; 35: 21-33.
19. Sejrsen, K., Knight, C.H.: Unilateral infusion of growth hormone does not support a local galactopoietic action of growth hormone. Proc. Nutr. Soc., 1994; 52: 278A-285A.
20. Knight, C.H., Brown, J.R., Sejrsen, K.A.: A comparision of growth hormone induced mammogenesis in pregnant and lactating goats. Endocrinol. Metab., 1994; 1(suppl B): 52.
21. Knight, C.H., Fowler, P.A., Wilde, C.J.:. Galactopoetic and mammogenic effects of long term treatment with bovine growth hormone and thrice daily milking goats. J. Endocrinol., 1990; 127: 129-138.
22. Bauman, D.E., Vernon, R.G.: Effects of bovine somatotropin on lactation. Ann. Rev. Nutr., 1993; 13: 437-461.
23. Etherton, T.D., Bauman, D. E.: The biology of somatotropin on growth and lactation of domestic animals. Physiol. Rev., 1998; 78: 745-761.
24. Cohick, W.S.: Role of insulin like growth factors and their binding proteins in lactation. J. Dairy Sci., 1998; 81: 1769-1777.
25. Sharma, B.K., VandeHaar, M.J., Ames, N.K.: Expression of insulin like growth factor-I in cows at different stages of lactation and in late lactation cows treated with somatotropin. J. Dairy Sci., 1994; 77: 2232-2241.
26. McGuire, M.A., Vicini, J.L., Bauman, D.E., Veenhuizen, J.J.: Insulin like growth factors and binding proteins and their nutritional regulation. J. Anim. Sci., 1992; 70: 2901-2910.
27. Phillips, L.S., Harp, J.B., Godstein, S., Klein, J., Pao, C.I.: Regulation and action of insulin-like growth factor at the cellular level. Proc. Nutr. Soc., 1990; 49: 451-458.

28. Forsyth, I.A.: The insulin-like growth factor and epidermal growth factor families in mammary cell growth in ruminants: Action and interaction with hormones. J. Dairy Sci., 1996; 79: 1085-1096.

29. Glimm, D.R., Baracos, V.E., Kennelly, J.J.:. Northern and in situ hybridization analysis of the effects of somatotropin on bovine mammary gene expression. J. Dairy Sci., 1992; 75: 2687-2705.

30. Prosser, C.G., Davis, S.R., Farr, I., Lacasse, P.: Regulation of blood flow in the mammary microvasculature. J. Dairy Sci., 1996; 79: 1184-1197.

31. Davis, S.R., Collier, R.J.: Mammary blood flow and regulation of substrate supply for milk synthesis. J. Dairy Sci., 1985; 68: 1041-1058.

32. Cohick, W.S., Plaut, K., Sechen, S.C., Bauman, D.E.: Temporal pattern of IGF-I response to exogenous GH in lactating cows. Domest. Anim. Endocrinol., 1989; 6: 263-273.

33. Knapp, J.R., Freetly, H.C., Reis, B.L., Calvert, C.C., Baldwin, R.L.: Effects of somatotropin and substrates on patterns of liver metabolism in lactating dairy cattle. J. Dairy Sci., 1992; 75: 1025-1035.

34. Beauville, M., Harant, I., Crampes, F., Riviere, D., Tauber, M.T., Garrigues, M.: Effects of long term rhGH administration in GH deficient adults on fat cell epinephrine response. Am. J. Physiol., 1992; 263: E467-E472.

35. Greenfield,. R.B., Cecava, M.J., Donkin, S.S.: Changes in mRNA expression for gluconeogenic enzymes in liver of dairy cattle during the transition to lactation. J. Dairy Sci., 2000; 83: 1228-1236.

36. Pershing, R.A., Moore, S.D., Dinges, A.C., Thatcher, W.W., Badinga, L.: Hepatic gene expression for gluconeogenic enzymes in lactating dairy cows treated with bovine somatotropin. J. Dairy Sci., 2002; 85: 504-506.

37. Sechen, S.J., Dunshea, F.R., Bauman, D.E.: Somatotropin in lactating cows: effect on response to epinephrine and insulin. Am. J. Physiol., 1990; 258: E582-E588.

38. Erdman, R.A., Andrew, S. M.: Methods for estimates of body tissue mobilization in the lactating dairy cow. Proc. Pre. Symp. Monsanto. Cornell Nutr. Conf., 1989; 19.

39. Capuco, A.V., Keys, J.E., Smith, J.J.: Somatotropin increases thyroxine-5`-monodeiodinase activity in lactating mammary tissue of cow. J. Endocrinol., 1989; 121: 205-211.

40. Chalupa, W., Gilligan, D.T.: Nutritional implications of somatotropin for lactating cows. J. Dairy Sci., 1989; 72: 2510-2524.

41. Bines, J.A., Hart, I.C.: Metabolic limits to milk production, especially roles of growth hormone and insulin. J. Dairy Sci., 1982; 65: 1375-1389.

42. Eppard, P.J., Veenhuizen, J.J., Cole, W.J., Comens-Keller, P.G., Hartnell, G.F., Hintz, R.L., Munyakazi, L., Olsson, P.K., Sorbet, R.H., White, T.C., Baile, C.A., Collier, R.J., Goff, J.P., Horst, R.L.: Effect of bovine somatotropin administered to periparturient dairy cows on the incidence of metabolic disease. J. Dairy Sci., 1996; 79: 2170-2181.

43. Simpson, R.B., Armstrong, J.D., Harvey, R.W., Miller, D.C., Heimer, E.P, Campbell, R.M.: Effect of active immunization against growth hormone-releasing factor on growth and onset of puberty in beef heifers. J. Anim. Sci., 1991; 69: 4914-4924.

44. Simmons, C.R., Bergen, W.G., VandeHaar, M.J., Sprecher, D.J., Sniffen, C.J., Stanisiewski, E.P., Tucker, H.A.: Protein and fat metabolism in cows given somavubove before parturition. J. Dairy Sci., 1994; 77: 1835-1847.

45. Bachman, K.C., Wilfond, D.H., Head, H.H., Wilcox, C.J., Singh, M.: Milk yields and hormone concentrations of Holstein cows in response to Sometribove (Somatotropin) treatment during the dry period. J. Dairy Sci., 1992; 75: 1883-1890.

46. Stelwagen, K., Grieve, D.G., McBride, B.W.: Growth and subsequent lactation in primigravid Holstein heifers after prepartum bovine somatotropin treatment. J. Dairy Sci., 1991; 75: 463-471.

47. Putnam, D.E., Varga, G.A.,Dann, H.M.: Metabolic and production responses to dietary protein and exogenous somatotropin in late gestation dairy cows. J. Dairy Sci., 1999; 82: 982-995.

48. de Boer, G., Robinson, P.H., Kennelly, J.J.: Hormonal responses to bovine somatotropin and dietary protein in early lactation dairy cows. J. Dairy Sci., 1991; 74: 2623-2632.

49. Moallem, U., Kaim, M., Folman, Y., Sklan, D.: Effect of calcium soaps of fatty acids and administration of somatotropin in early lactation on productive and reproductive performance of high producing dairy cows. J. Dairy Sci., 1997; 80: 2127-2136.

50. Santos, J.E.P., Huber, J.T., Theurer,C.B., Nussio, L.G., Nussio, C.B., Tarazon, M., Lima-Filho, R.E.: Performance and nutrient digestibility by dairy cows treated with bovine somatotropin and fed diets with steam-flaked sorghum or steam-rolled corn during early lactation. J. Dairy Sci., 1999; 82: 404-411.

51. Moallem, U., Folman, Y., Sklan, D.J.: Effects of somatotropin and dietary calcium soaps of fatty acids in early lactation on milk production, dry matter intake, and energy balance of high yielding dairy cows. J. Dairy Sci., 2000; 83: 2085-2094.

52. Richard, A.L., McCutcheon, S.N., Bauman, D.E.: Responses of dairy cows to exogenous growth hormone administered during early lactation. J. Dairy Sci., 1985; 68: 2385-2389.

53. Chalupa, W., Gilligan, G., Kronfield, D.S.: Responses of cows in early lactation to exogenous growth hormone and dietary sodium bicarbonate. J. Dairy Sci. (Supp. I), 1985; 68: 143.

54. Stanisiewski, E.P., Krabill, L.F., Lauderdale, J.W.: Milk yield, health, and reproduction of dairy cows given somatotropin (somavubove) beginning early postpartum. J. Dairy Sci., 1992; 75: 2149-2164.

55. Nocek, J.E., English, J.E., Braund, D.G.: Effects of various forage feeding programs during dry period on body condition and subsequent lactation health, production, and reproduction. J. Dairy Sci., 1983; 66: 1108-1118.

56. Gulay, M.S., Garcia, A.G., Hayen, M.J., Wilcox, C.J., Head, H.H.: Physiological responses of Holstein cows to various bST treatments during the transition period. J. Dairy Sci. (Suppl.1), 2000; 83: 219.

57. Gülay, M.S., Garcia, A.G., Hayen, M.J., Wilcox, C.J., Head, H.H.: Responses of Holstein cows to different bovine somatotropin (bST) treatments during the transition period and early lactation. A. A. J. Anim. Sci., 2004; 17: 784-793.

58. Gülay, M.S., Hayen, M.J., Teixeira, L.C., Wilcox, C.J., Head, H.H.: Responses of Holstein cows to a low dose of somatotropin (bST) prepartum and postpartum. J. Dairy Sci., 2003; 86: 3195-3205.

59. Gülay, M.S., Hayen, M.J., Liboni, M., Belloso, T.I., Head, H.H.: Use of bST in transition dairy cows: effects on feed intake, milk yield and various physiological responses. J. Dairy Sci., 2004; 87: 948-960.