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# Influence of Prepubertal Feeding Level on Milk Yield Potential of Dairy Heifers: A Review<sup>1</sup>

K. Sejrsen<sup>2</sup> and S. Purup

Danish Institute of Animal Science, Foulum, DK-8830 Tjele, Denmark

**ABSTRACT:** In replacement heifers, high levels of feeding resulting in high growth rates in the prepubertal period can cause severe reduction of the milk production potential. This has been demonstrated in many experiments; however, there are a number of experiments where this effect is not seen. In many cases, the reason for the lack of effect seems fairly obvious (short treatment periods, high pretreatment growth rates, small growth rate differences between treatment groups, variation of growth rates within treatment groups, treatment periods outside the critical period, etc.). However, in a few experiments absence of treatment effect cannot be explained in this way. This demonstrates that our knowledge on the effect of nutrition during rearing on the future milk yield of heifers is incomplete and that it may be

possible to develop high growth rate feeding regimens for heifers. Experimental evidence suggests that the observed negative effects of feeding level on subsequent milk are due to impaired mammary development. Development of suitable high growth rate feeding regimens therefore requires understanding of the influence of nutrition on the physiological regulation of mammary development. Available data suggest that the growth hormone–insulin-like growth factor I axis is involved, but it is not clear how. It is likely that understanding of the role of insulin-like growth factor binding proteins is important. Alternative hypotheses involve possible effects of growth factors and modifications of mammary tissue sensitivity to hormones and growth factors.

Key Words: Heifers, Mammary Development, Milk Yield

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## Introduction

The main objective of feeding and management of replacement dairy heifers is to produce the best possible cows. Therefore the success of feeding and management of replacement heifers cannot be measured in terms of average daily gain or feed efficiency but has to be assessed by the milk yield potential of the heifer as a cow. The main limiting factor for the milk yield potential of cows is the number of milk-synthesizing cells in the mammary glands (Tucker, 1981; Knight and Wilde, 1994).

For the overall economy of the dairy industry, it is also important to minimize the costs of raising replacement heifers. The most effective way to reduce rearing costs is to lower the age at first calving. In most dairy cattle populations, the average age at first

calving is between 24 and 30 mo, but heifers can calve as early as 15 to 16 mo of age. Thus, the scope for a reduction of age at first calving is large. Age at onset of puberty is inversely related to growth rate. Therefore, heifers need to be raised on a high growth rate feeding regimen until puberty to obtain a substantial reduction of age at first calving. Unfortunately, high growth rates before puberty can have a negative influence on mammary growth and future milk production.

Thus, to develop the optimum feeding and management regimen for heifers, it is necessary to understand the relationship among onset of puberty, pubertal mammary development, and feeding level and to know the possible consequences for the milk yield potential. It is the objective of this article to give an overview of the existing knowledge on these topics.

## Onset of Puberty

In heifers of large dairy breeds, onset of puberty usually occurs at 9 to 11 mo of age and at an average body weight of 250 to 280 kg. However, both age and body weight at onset of puberty vary widely within as

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<sup>2</sup>To whom correspondence should be addressed: Department of Product Quality.

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well as between breeds. In our experiments with Friesian and Danish Red heifers, we have observed onset of puberty as early as 5 to 6 mo of age and as late as 18 to 20 mo of age (Foldager et al., 1988). The variation in body weight is also considerable (from 150 to 400 kg), but less than 5% of the heifers reached puberty before 200 kg body weight and less than 10% had first estrus after 300 kg body weight. In Jerseys, the average age at puberty is 9 to 11 mo and average body weight is 170 to 190 kg.

The main source of within-breed variation in age at onset of puberty is level of feeding (see reviews by Moran et al., 1989; Robinson, 1990; Schillo et al., 1992). The magnitude of the effect of feeding level on age at onset of puberty is illustrated in one of our experiments (Figure 1), in which wide variation in daily gain was achieved by varying the feeding level (Foldager et al., 1988). Average age at first estrus decreased from 16.6 to 8.4 mo as the growth rate increased from 450 to 850 g/d. Taking the normal conception rate into account, this means that an average daily gain of 900 g is needed to reduce the age at calving to 18 mo. Body weight at puberty, in contrast, was unaffected by feeding level. Puberty is the culmination of a gradual maturation process that is initiated before birth and continues throughout the pre- and peripubertal period (Kinder et al., 1987; Schillo et al., 1992). Most of the components of the endocrine system that are required to stimulate the onset of puberty are functional long before puberty occurs, but the onset is blocked by negative feedback of estradiol on the secretion of luteinizing hormone (Kinder et al., 1987; Schillo et al., 1992).

### Pubertal Mammary Development

Growth and development of mammary cells occur in distinct phases related to reproductive development during fetal life, puberty, pregnancy, and lactation. The extent of mammary development during puberty is, both qualitatively and quantitatively, less pronounced than during pregnancy, but impaired pubertal mammary development in relation to puberty may have great influence on the milk yield potential (Foldager and Sejrsen, 1987; Johnsson, 1988; Sejrsen, 1994).

The basic structures of the mammary glands are formed in fetal life, but the epithelial tissue is still rudimentary at birth. There are a few mammary duct cells present adjacent to the gland cistern, but there are no alveoli. In contrast, the non-epithelial tissues, i.e., the stroma and the circulatory system, are almost fully developed at birth, as is the outer shape of the glands. In the first few months after birth the glands grow at the same rate as the rest of the body. The growth is isometric. Only the non-epithelial tissue grows during this period.

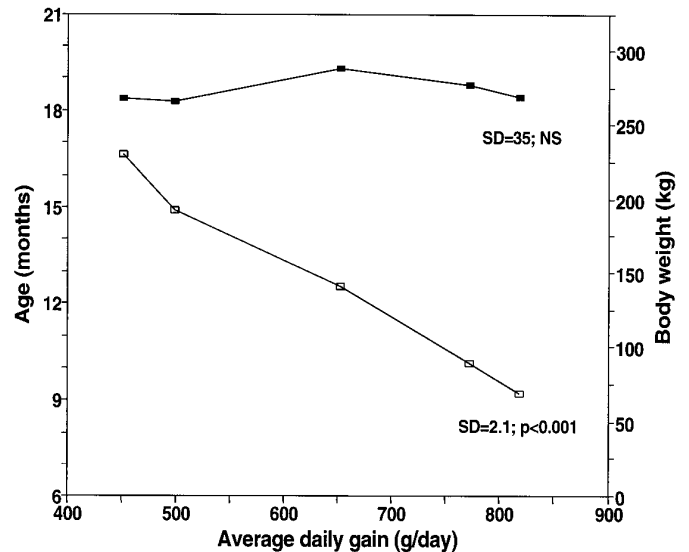


Figure 1. Effect of feeding level on age ( $\square$ ) and body weight ( $\blacksquare$ ) at first puberty (Foldager, Sejrsen and Sørensen, 1988).

At 2 to 3 mo of age, well in advance of the onset of puberty, the glands start to grow at a faster rate than the rest of the body. The growth becomes allometric (Sinha and Tucker, 1969). In this phase there is rapid growth of the fat pad and of the ducts that branch into it. There are still no alveoli formed. The ducts need the fat pad for their growth (Faulkin and DeOme, 1960), and in some species the size of the fat pad may limit the extent of ductular growth. This does not seem to be the case in heifers, because the tissue with the branching ducts, the parenchyma, constitutes only about one third of the total gland at this stage of development (Sejrsen and Foldager, 1992). In heifers, the ducts always seem to be surrounded by connective tissue (Woodward et al., 1993). In rodents, however, terminal end buds are in direct contact with the fat cells (see Akers, 1990).

Most studies suggest that the allometric growth phase ends at onset of puberty or shortly thereafter (Sinha and Tucker, 1969; Pritchard et al., 1972; Sejrsen et al., 1982). At this stage of development, the mammary glands of heifers weigh about 2 to 3 kg, of which only 0.5 to 1 kg is parenchyma. The parenchyma usually contains 10 to 20% epithelial cells, 40 to 50% connective tissue, and 30 to 40% fat cells (Sejrsen et al., 1982). In comparison, lactating mammary glands can weigh as much as 25 kg (Foldager and Sejrsen, 1991), and lactating parenchyma consists of 40 to 50% epithelial cells (ducts and alveoli), 15 to 20% lumen, about 40% connective tissue, and almost no fat cells (Harrison et al., 1983).

The allometric growth phase of the mammary glands is closely linked to the development of the reproductive organs. Ovariectomy in the first week of life abolishes mammary growth (Wallace, 1953), and

removal of the ovaries of heifers at 2.5 mo of age also inhibits mammary growth (Purup et al., 1993b). In two of eight heifers ovariectomized at 2.5 mo of age, mammary parenchyma was completely absent. In the remaining six heifers the amount of parenchyma was reduced to 10 to 15% of the amount in the intact control heifers.

It has traditionally been accepted that the dramatic effect of ovariectomy on mammary growth is due to a removal of estrogen secreted by the ovaries. In agreement, it has been shown that estrogen replacement can restore mammary growth in heifers and rodents (Cowie, 1949; Wallace, 1953). Furthermore, findings by Woodward et al. (1993) indicate that the growth of mammary duct cells is enhanced by treatment with estradiol *in vivo*, and we (Purup et al., 1993a) observed a dose-related effect of estradiol on mammary cell proliferation *in vitro*. However, circulating levels of estradiol were very low in both the intact and the ovariectomized heifers, and the difference between the groups was very small (.41 vs .31 pg/mL) (Purup et al., 1993b). It is difficult to imagine that the complete block of mammary development caused by ovariectomy was due to a .1 pg/mL reduction of the concentration of estradiol in serum. On the other hand, no other explanation is obvious (Sejrsen, 1994).

The physiological explanation for the return of the mammary gland to isometric growth at puberty is not known, but Tucker (1981) suggested that the asynchronous secretion of estrogen and progesterone starting at puberty could be the cause. However, recent observations suggest that the signal to end the allometric growth period is either independent of ovarian secretions or occurs before onset of puberty. Mammary growth was the same in control heifers as in heifers that had puberty permanently delayed by immunization against gonadotropin-releasing hormone at 8 mo of age (Sejrsen et al., 1994).

### Measurement of Pubertal Mammary Growth

Unfortunately it is very difficult, if not impossible, to get a reliable estimate of mammary growth in a live animal. Palpation scores and biopsies often give misleading results because the parenchyma constitutes a relatively small part of the total mammary gland and because the relative amount of parenchymal and extraparenchymal tissue is influenced by feeding level (Sorenson et al., 1964; Sejrsen et al., 1982; Stelwagen and Grieve, 1989). Therefore, to obtain a reliable estimate of mammary parenchyma it is necessary to kill the experimental animals and separate the parenchyma from the stroma by dissection or, alternatively, to subject the glands to computer tomography scanning (Sorensen et al., 1987). The reliability of these measurements is enhanced by estimation of total DNA (as an indirect measure of

cell number) and histological evaluation (to estimate the different cell types in the parenchyma) (Tucker, 1987).

It is important to take the close relationship between reproductive development and body growth into account in evaluation and interpretation of experimental data concerning the effect of feeding level on mammary development. Comparisons made at the same age will compare animals at different stages of mammary development. Therefore, such comparisons often include significant confounding effects caused by differing live weights. If the animals are no longer in the allometric growth period, the problem can be minimized by expressing the results on body weight basis. If the animals are still in the allometric period of mammary growth, there will be differences in the amount of "unused" potential for allometric mammary growth.

### Feeding Level and Pubertal Mammary Development

The effect of feeding level on mammary growth has been investigated in many experiments. The overall conclusion based on the available data is that a feeding level resulting in growth rates above 600 to 700 g/d can have a permanent negative impact on mammary growth. Furthermore, the data suggest that the negative effect of feeding level is limited to the prepubertal phase of mammary development and that the period when mammary growth is sensitive to a high feeding level starts as early as 3 mo of age (see reviews by Sejrsen, 1978; Foldager and Sejrsen, 1987; Johnsson, 1988; Troccon and Petit, 1989; Waldo et al., 1989).

In a recent experiment, Capuco et al. (1995) found that mammary DNA was reduced by feeding level, but the negative effect seemed to be most severe when heifers were fed a corn-based diet and very small when an alfalfa diet with a high protein content was consumed. This suggests that type of diet or protein level can modify the effect of feeding level on mammary development. Type of diet does not seem to be important, at least not at a low feeding level. We (Sejrsen and Foldager, 1992) investigated the effect on mammary parenchyma of diets containing maximal or minimal amounts of straw in heifers on a low feeding level. The amount of mammary parenchyma was not affected by treatment.

The specific effect of protein level on mammary development has not been investigated in heifers, but the data by Capuco et al. (1995) and from a recent abstract by Radcliff et al. (1995) suggest that high protein level may prevent the negative effect of feeding level. However, Mäntysaari et al. (1995) found that the negative effect of feeding level was not affected by the amount of bypass protein (Table 1). Specific effects of other nutrients cannot be ruled out.

Table 1. Effect of feeding level (low or high) and nitrogen source (urea or rapeseed meal) on prepubertal mammary growth<sup>a</sup>

Item	Treatment			
	Low/urea	Low/meal	High/urea	High/meal
No. of heifers	5	6	6	6
ADG, g/d	692	655	805	890
Parenchymal weight, g	134	146	107	109
Parenchymal DNA, mg	1,812	1,518	1,039	1,025

<sup>a</sup>Mäntysaari et al. (1995); high vs. low,  $P < .05$ ; urea vs. meal, not significant.

Polyunsaturated fat, for instance, has been shown to increase pubertal mammary growth in sheep (McFadden et al., 1990).

For the reduced pubertal mammary growth to be relevant for future milk yield potential, the reduction in mammary growth must be maintained during lactation. This long-term effect on mammary growth has been investigated in only a few experiments (Swanson, 1960; Harrison et al., 1983; Foldager and Sejrsen, 1991). The results indicate that the negative effect of high feeding level is maintained through both pregnancy and lactation. Similar observations have been made in experiments with sheep (Umberger et al., 1985; McCann et al., 1989). Furthermore, the mammary glands of cows raised on high feeding levels are clearly different in shape and size from glands of "normally reared heifers" (Herman and Ragsdale, 1946; Swanson, 1960; Little and Kay, 1979; personal observation). Together, these data support the conten-

tion that the negative effect of feeding level on milk yield potential involves long-term effects of reduced pubertal mammary development.

We have attempted to clarify the mechanism behind the negative effect of feeding level. A summary of our findings is illustrated in Table 2. Many of the investigations suggest that growth hormone (GH) is involved. Circulating levels of GH are reduced by high feeding level, GH is positively correlated with mammary growth (Sejrsen et al., 1983), and exogenous administration of GH enhances pubertal mammary growth (Sejrsen et al., 1986). However, the mammary gland does not bind GH, and GH does not stimulate mammary cell growth in vitro (Purup, 1995). Most evidence suggests that GH acts via increased secretion of IGF-I. Mammary tissue has IGF-I receptors, it binds IGF-I, and IGF-I stimulates mammary cell proliferation in vitro (Purup et al., 1993a, 1995). However, IGF-I is increased, not decreased, by a high

Table 2. Relationship between effects of feeding level and growth hormone on mammary growth<sup>a</sup>

	Feeding level (moderate vs high)	Growth hormone (GH vs placebo)
Milk yield potential	↑	— (↑)
Prepubertal mammary growth	↑	↑
Blood concentrations of:		
Growth hormone	↑	↑
IGF-I	↓	↑
IGFBP3	↓	↑
IGFBP2	↑	↓
IGFBP1	↓	↑
IGFBP4	↓	↑
Mitogenic activity <sup>b</sup>	↓	↑
Mammary tissue sensitivity:		
GH receptor mRNA	—	—
GH binding	none	none
IGF-receptors (Type 1)	?	— (↓)
Response to IGF-I <sup>c</sup>	↑	— (↓)

<sup>a</sup>Sejrsen et al. (1982, 1983, 1986, 1989), Foldager and Sejrsen (1991), Vestergaard et al. (1995), Purup et al. (1993a, 1995, 1996, unpublished data).

<sup>b</sup>Mitogenic activity measured as DNA synthesis in mammary explants cultured in medium containing serum from moderate vs high-fed heifers or GH-treated vs placebo-treated heifers.

<sup>c</sup>Measured as DNA synthesis in mammary explants cultured in medium containing IGF-I in different concentrations (0, 100, 300, and 600 ng/mL).

Table 3. Effect of prepubertal feeding level on milk production in different breeds<sup>a</sup>

Breed	n	ADG, g/d	At calving		FCM (250 days)	
			Age, mo	BW, kg	kg	(relative)
Danish Jersey	41	362	29	341	5,125	(100)
	44	487	26	353	4,750	(93)
	44	557	23	329	4,125	(80)
Danish Red	52	549	29	530	5,675	(100)
	52	718	26	525	4,900	(86)
	51	845	23	490	4,700	(82)
Danish Friesian	53	579	29	313	5,425	(100)
	53	731	26	500	5,400	(100)
	55	858	23	498	4,900	(90)

<sup>a</sup>Hohenboken et al. (1995).

feeding level, and on the basis of results from one of our recent experiments this paradoxical effect cannot be explained by changes in IGF binding proteins (Vestergaard et al., 1995). These data make it difficult to explain the reduced mammary growth by changes in IGF-I and IGF binding proteins. Preliminary data, however, suggest that the sensitivity of the tissue to IGF-I is reduced by high feeding level (Purup et al., 1996). Whether this reduction in sensitivity can explain the effect remains to be seen. An alternative hypothesis involves an inhibitory effect of transforming growth factor beta-1 (Plaut, 1993).

### Feeding Level and Milk Yield Potential

The relationship between feeding level during the rearing period and milk yield potential of the heifers as cows has been investigated in many experiments. It is the overall conclusion, that levels of feeding during the prepubertal period resulting in growth rates above 600 to 700 g/d in large dairy breeds cause a permanent reduction of the subsequent milk yield potential (see reviews by Sejrsen, 1978; Johnsson, 1988; Foldager and Sejrsen, 1987; Troccon and Petit, 1989; Waldo et al., 1989; Waldo and Capuco, 1992). This conclusion has recently been confirmed in a large experiment with the main Danish dairy breeds. The heifers of each breed were divided into three groups, fed diets of different energy concentration ad libitum to support three levels of daily gain from 6 wk of age to 300 kg live weight in Danish Friesians and Danish Reds and to 210 kg in Danish Jerseys. The heifers were bred at the same body weight. The average daily gains and milk yields are shown in Table 3.

The effects of feeding level and breed were statistically significant, but there was no interaction between breed and feeding level. Thus, the negative effect of feeding level exists and is similar in all breeds. Also, the feeding level that causes a reduction in milk yield potential is different in different breeds. A closer evaluation of the data revealed that the negative effect

of feeding level started when average daily gain was above 400 g in Jerseys, above 600 g in Danish Red, and above 700 g in Danish Friesians. Danish Friesians are almost identical to American Holstein Friesians.

The heifers entered the experiment over a period of several years. Each year the different energy density diets were composed of concentrates and various relative amounts of different roughages. The roughages were grass silage, corn silage, barley silage, and barley straw. The effect of type of roughage was confounded with year, but the negative effect of feeding level seemed to be independent of type of roughage in the diet. Thus, in agreement with our earlier results (Sejrsen and Foldager, 1992), the data indicate that the effect of feeding level is independent of type of diet. Waldo (1988) investigated the effect of feeding level on two types of diets (corn and alfalfa). In spite of an overall reduction of mammary development (Capuco et al., 1995), there was no significant effect of feeding level on milk yield of heifers on either diet (reported by Gaynor et al., 1995). However, numerically milk yield was reduced by 1.35 kg/d or 412 kg per lactation.

It has been suggested that the negative effect of high feeding level can be prevented by increasing the protein level of the diet (Kertz et al., 1987). However, this hypothesis has not been supported by experimental evidence. Van Amburgh et al. (1994) tested the effect of amount of bypass protein on the effect of feeding level. There was no effect of protein source. This agrees with the mammary gland data by Mäntysaari et al. (1995) mentioned above. Pirlo (unpublished data) has investigated the effect of feeding level (90% and 110% of NRC) on two levels of protein (90% and 110% of NRC). The results confirm that Holstein heifers raised to gain 600 to 700 g per day have higher milk yields than heifers gaining 800 g or above (24.5 vs 23.4 kg). The effect was independent of protein level. In fact, the milk yield was significantly reduced by protein level (23.1 vs 24.9 kg).

The exact period in which the development of the milk yield potential is impaired by high feeding level

is not known. It was originally suggested that the period coincides with the pubertal phase of mammary development (Sejrsen, 1978). Based on this, the so-called "critical period" lasts from 2 to 3 mo of age until about 2 mo after first estrus, corresponding to a live weight of approximately 300 kg in large dairy breeds. The age at the end of the critical period depends on the feeding level. The importance of this period (or a part of it) for the future yield capacity has since been supported by additional experimental evidence (Sejrsen et al., 1982; Ingvarsten et al., 1988; Foldager and Sejrsen, 1991). However, these experiments and those of others (Johnsson and Obst, 1984; Peri et al., 1993) suggest that the critical period may end earlier, even as early as at 200 kg body weight (well in advance of onset of puberty).

There are, however, a number of experiments in which the negative effect of feeding level on subsequent milk yield was not seen (Park et al., 1987; Gardner et al., 1988; Head et al., 1991; Troccon, 1993; Van Amburgh et al., 1994; Gaynor et al., 1995). In some cases this lack of effect may be explained by insufficient growth rate differences between treatment groups (Troccon, 1993) or treatment periods completely or partly outside the critical period (Park et al., 1987; Waldo, 1988; Head et al., 1991). Van Amburgh et al. (1994) found no significant reduction in milk yield after adjustment for body weight differences, although the yield was numerically reduced. Before adjustment the difference was significant (Van Amburgh, personal communication). It is questionable whether it is correct to adjust for body weight, because it is unlikely that a higher postpubertal feeding level would have increased milk yield (Foldager and Sejrsen, 1991; Lacasse et al., 1993; Foldager and Ingvarsten, 1995; Ingvarsten et al., 1995). Nevertheless, in a few experiments the reason for the absence of treatment effect is not obvious (i.e. Gardner et al., 1988), illustrating that our knowledge of the effect of nutrition on the future milk yield of heifers is incomplete.

### Implications

The available evidence concerning the relationship between prepubertal feeding level, age at puberty onset, mammary growth, and milk yield potential leads to the following conclusions: Increasing feeding levels above moderate feeding results in reduced age at onset of puberty and may lead to reduced mammary growth and reduced milk yield potential of the heifers as cows. The effect seems to be present in all breeds, but the level of feeding that results in reduced milk yield potential varies between breeds. The effect of feeding level seems to be independent of diet composition, and the suggestion that the effect can be prevented by high level of protein is not substantiated by experimental data. However, the fact that the

negative effect of feeding level is not seen in all experiments suggests that in the future, it may be possible to develop high-rate growth feeding regimens without a negative effect on the milk yield potential of heifers. A breakthrough is most likely to be a result of increased knowledge of the physiological relationship between nutrition and mammary development.

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