

## Relationships between nutrition, puberty and mammary development in cattle

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Production of colostrum and milk in sufficient amounts is essential for survival of the young in most mammals. Thus, lactation is an integral part of the reproductive cycle and, in line with its role in reproduction, mammary development occurs in distinct phases related to reproductive development during fetal life, puberty, pregnancy, and lactation. The main developments, quantitatively as well as qualitatively, occur during late pregnancy, when mammary ducts develop into lobulo-alveolar tissue with differentiated cells capable of producing milk with all its components. It is the number of mammary cells in the mammary glands that largely determines the lactation potential of the mother.

In cattle, lactation has an added significance in view of the important role of cow's milk in human nutrition. Mammary development in cattle largely follows the same pattern as in other mammals, but mammary cell growth is believed to end at parturition. Therefore the milk yield potential of cows is determined, to a large extent, by the growth of the mammary glands around puberty and during pregnancy. The extent of mammary gland development during puberty is much less pronounced than during pregnancy, but it has become clear that mammary development in this period is critical for the future milk yield potential of heifers (Sejrsen, 1978; Foldager & Sejrsen, 1987; Johnsson, 1988; Troccon & Petit, 1989; Waldo *et al.* 1989). One of the important factors influencing pubertal mammary growth is nutrition. Given this background it is the objective of the present paper to provide an overview of the relationships between nutrition, puberty and mammary development in heifers.

### PUBERTAL MAMMARY DEVELOPMENT

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; so is the outer shape of the glands. In the first few months after birth the glands grow isometrically at the same rate as the rest of the body; only the non-epithelial tissues grow in this period.

At 2–3 months 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 & Tucker, 1969). In this phase there is rapid growth of the fat pad, and of the ducts that branch into it. Alveoli are still unformed. The ducts need the fat pad for their growth (Faulkin & De Ome, 1960), and in some species ductular growth may be limited by the size of the fat pad. This is unlikely to be the case in heifers, since the tissue with the branching ducts, the parenchyma, only constitutes about one-third of the total gland at this stage of development (Sejrsen & Foldager, 1992). In contrast to the situation in rodents, the ducts in heifers always seem to be surrounded by connective tissue (see Akers, 1990).

At the end of the allometric growth phase the mammary glands of heifers weigh about 2–3 kg, of which only about 0.5–1 kg is parenchyma. The parenchyma usually contains between 10–20% epithelium, 40–50% connective tissue and 30–40% fat cells (Sejrsen *et al.* 1982). In comparison, lactating mammary glands can weigh as much as 25 kg (Foldager & Sejrsen, 1991), and lactating parenchyma consists of 40–50% epithelial cells (ducts and alveoli), 15–20% lumen, about 40% connective tissue and almost no fat cells (Harrison *et al.* 1983).

#### MEASUREMENT OF MAMMARY GROWTH

Since the parenchyma constitutes only a small part of the total mammary gland in heifers, it is very difficult, if not impossible, to get a reliable estimate of the amount of mammary parenchyma in the live animal. Palpation scores and biopsies often yield misleading results, because the relative amounts of parenchymal and extraparenchymal tissue can be changed by environmental factors, such as the level of feeding (Sorenson *et al.* 1964; Sejrsen *et al.* 1982; Stelwagen & Grieve, 1989). Reliable estimation of the amount of parenchyma therefore requires that the animals are slaughtered and the parenchyma separated from the stroma by dissection, or alternatively that the animals are subjected to computer tomography-scanning (Sørensen *et al.* 1987). These measures are more reliable if complemented by estimation of DNA content and/or histological evaluation to obtain a measure of the composition of the parenchyma (Tucker, 1987).

#### ONSET OF PUBERTY

Most studies suggest that the return to isometric mammary growth coincides with onset of puberty or occurs shortly thereafter (Sinha & Tucker, 1969; Pritchard *et al.* 1972; Sejrsen *et al.* 1982). Therefore variation in age and live weight at onset of puberty is an important factor for mammary growth.

Onset of puberty usually occurs at 9–11 months of age and at an average body weight of 250–280 kg in heifers of the large dairy breeds. However, both age and body weight at onset of puberty vary widely within as well as between breeds. In our experiments with Friesian and Red Danish heifers we have observed that heifers can reach puberty as early as 5–6 months and as late as 18–20 months of age (Foldager *et al.* 1988). The variation in live weight at onset of puberty was also large (from 150 to 400 kg), but fewer than 5% of the heifers reached puberty before 200 kg live weight, and fewer than 10% of the heifers had first oestrus after 300 kg live weight.

There is no doubt that nutrition is a major factor for the variation in age at onset of puberty (for reviews, see Moran *et al.* 1989; Robinson, 1990; Schillo *et al.* 1992). The impact of nutrition is illustrated by the results of one of our experiments, in which wide variation in daily growth rate was achieved by varying the feeding level (Foldager *et al.* 1988). Average age at first oestrus decreased from 16.6 to 8.4 months as the growth rate was increased from 400 to 850 g/d. In contrast, average live weight at first oestrus was unaffected by feeding level. These results clearly confirm that reproductive development in cattle, as in humans (Frisch, 1984), is more closely related to body development than to chronological age (see Moran *et al.* 1989 and Schillo *et al.* 1992). Consequently, it is very important to consider this relationship when interpreting data concerning the influence of nutrition on mammary growth. Comparison of mammary growth at the same

age will in many cases include a significant confounding effect of differences in mammary development due to differing live weights between nutritional treatment groups.

#### THE OVARIES AND PUBERTAL MAMMARY DEVELOPMENT

Puberty in females is the culmination of a long gradual maturation process, that is initiated before birth and continues throughout the prepubertal and peripubertal period (Kinder *et al.* 1987). Most components of the endocrine system required for stimulation of the onset of puberty are functional long before puberty occurs, but onset of puberty is inhibited by negative feedback of oestradiol on the secretion of luteinizing hormone (LH), resulting in release of LH in low-frequency pulses (Kinder *et al.* 1987; Schillo *et al.* 1992).

The allometric growth phase of the mammary glands in heifers is closely linked to gradual maturation of the ovaries. Ovariectomy within the first week of life abolishes mammary growth in heifers, but surprisingly not in lambs (Wallace, 1953; Johnsson, 1984). Ovariectomy of heifers at 2.5 months of age also reduces mammary growth. In two of eight heifers ovariectomized at 2.5 months of age, mammary parenchyma was completely absent (Purup *et al.* 1993c). In the remaining six heifers the amount of mammary parenchyma was reduced to 10–15% of that in intact control heifers. The two heifers with no mammary parenchyma weighed 60 kg at ovariectomy, while the others weighed 80 kg. The difference in weight could account for the difference in response, and support the idea that a relationship between 'physiological' stage of development (body weight) and mammary development exists.

Most evidence suggests that the effect of the ovaries on mammary development is mediated by oestrogen. First, oestrogen and stilboestrol replacement can restore the allometric growth of the mammary glands in ovariectomized rodents (Cowie, 1949) and in heifers (Wallace, 1953) respectively. Second, recent findings by Woodward *et al.* (1993) indicate that proliferation of mammary duct cells is significantly enhanced by oestradiol *in vivo*. Third, an effect of oestradiol on mammary cell growth *in vitro*, although difficult to demonstrate, has been observed (S. J. Winder & I. A. Forsyth, unpublished results) in sheep explants. Purup *et al.* (1993a) have also seen a dose-related stimulatory effect of oestradiol on *in vitro* thymidine incorporation in explants from prepubertal heifers. In heifers the plasma level of oestrogen was significantly reduced by ovariectomy (Purup *et al.* 1993c). However, the levels of oestradiol were very low, and the difference in circulating levels between intact and ovariectomized heifers was very small (0.41 *v.* 0.31 pg/ml;  $P < 0.05$ ). Therefore, it is difficult to imagine that the almost complete block of mammary growth can be due to this small difference in plasma oestradiol, unless somehow there is a significant difference in its biological activity. The biological activity of oestradiol is limited by its binding to a plasma globulin, and reproductive development seems to be related to the level of free circulating oestrogen (see Kirkwood *et al.* 1987). It is possible, therefore, that the difference in mammary growth is due to a lower proportion of free oestradiol in the ovariectomized animals. It is also possible that the difference in mammary growth following ovariectomy is due to changes in other ovarian secretions. Insulin-like growth factor 1 (IGF-1), for instance, is present in follicular fluid in large quantities (Spicer *et al.* 1991; S. Purup and K. Sejrsen, unpublished results). However, the plasma level of IGF-1 is not affected by ovariectomy (Purup *et al.* 1993c).

The effect of ovariectomy on mammary growth could also be indirect via changed secretion of hormones (or growth factors) from other tissues. Waksman *et al.* (1991) have demonstrated that extracts from the pituitary, the kidney and the uterus produce stimulatory effects on mammary cell proliferation. It is possible, therefore, that hormones secreted by the ovary might affect mammary growth indirectly by influencing the secretion of hormones (or growth factors) by other tissues. The secretion of LH, for instance, is elevated by ovariectomy (Kinder *et al.* 1987). On the basis of these findings we have conducted preliminary studies of the possible effect of LH on mammary cell proliferation (S. Purup & K. Sejrsen, unpublished results). Although no clear picture has emerged, it appears that the effect of LH is dependent on the level of IGF-1 in the incubation medium. Prolactin has previously been suggested as a possible mediator of oestrogen effects on mammary growth, because prolactin secretion is regulated by oestrogen. However, this hypothesis has not been confirmed (Akers, 1990).

Tucker (1981) suggested that the return of mammary tissue to isometric growth at puberty might be caused by the asynchronous secretion of oestrogen and progesterone that starts at this time. Recent observations (K. Sejrsen, D. Petitclerc, D. J. Prendeville and W. J. Enright, unpublished results) suggest that the signal to terminate the allometric growth phase is either independent of ovarian secretions or appears before onset of puberty. We found that the amount of mammary parenchyma at 20 months of age was the same in heifers reaching puberty at normal age, and in heifers that had puberty permanently delayed by immunization against gonadotrophin-releasing hormone at 8 months of age.

#### NUTRITION AND PUBERTAL MAMMARY DEVELOPMENT

The most important nutritional factor influencing mammary growth is, without doubt, daily energy intake (feeding level). The effect of feeding level on mammary growth in virgin heifers has been investigated in many experiments (Sejrsen *et al.* 1982; Harrison *et al.* 1983; Petitclerc *et al.* 1984; Valentine *et al.* 1987; Petitclerc & Bailey, 1991). The results demonstrate that feeding levels resulting in daily gains above 600–700 g by heifers of large dairy breeds have a negative influence on growth of the mammary parenchyma, and suggest that this negative effect is limited to the pubertal period of mammary growth. The mammary gland seems to be 'sensitive' to the negative effect of high feeding level as early as 3 months of age (P. E. Mantysaari, V. Toivonen, K. L. Ingvarsen & K. Sejrsen, unpublished results). The same conclusion is evident in experiments investigating the effect of feeding level during rearing on subsequent milk potential of heifers (Foldager & Sejrsen, 1991; Peri *et al.* 1993).

In several experiments, differences in feeding level were achieved by concentrating the energy composition of the diet. In this context, Little & Kay (1979) observed that the effect of feed energy concentration could be a contributing factor to the observed effects. However, results from several other experiments indicate that mammary growth is unaffected by the energy concentration of the feed (Capuco *et al.* 1986; Waldo *et al.* 1988; Sejrsen & Foldager, 1992).

In many experiments investigating the effect of feeding level it is not possible to separate the effects of energy and protein. While the specific effect of protein level alone has not been investigated, the effect of protein source has been studied. Results suggest that the effect of feeding level is independent of the protein source since there was no

difference between animals given protein supplement as rapeseed meal or urea (P. E. Mantysaari, V. Toivonen, K. L. Ingvarlsen & K. Sejrsen, unpublished results).

Recent results obtained by McFadden *et al.* (1990*a,b*) indicate that mammary growth can be affected by specific components of the diet. They showed that lambs given protected polyunsaturated fat had increased mammary growth. Addition of polyunsaturated fat resulted in an increased number of growth hormone (GH) and prolactin receptors in the liver tissue, indicating that the higher mammary growth could be due to increased level of IGF-1 in the blood.

#### ENDOCRINE BASIS FOR THE EFFECT OF FEEDING LEVEL

According to classical studies on regulation of mammary development, GH is required for normal growth of mammary ducts (Lyons *et al.* 1958; Cowie *et al.* 1966). Many investigations of the endocrine basis for the negative effect of high feeding level on mammary growth in heifers have focused on the possible role of GH. The results have shown that the circulating level of GH is reduced at high feeding level (Sejrsen *et al.* 1983; Johnsson, 1988). Consequently, the level of GH is positively correlated with mammary growth (Sejrsen *et al.* 1983; Johnsson *et al.* 1985; Sejrsen & Foldager, 1992). Furthermore, mammary growth is increased by exogenous growth hormone (Johnsson *et al.* 1986; Sejrsen *et al.* 1986; Sandles *et al.* 1987) indicating a cause and effect relationship between circulating level of GH and mammary growth. These results support the hypothesis that the effect of feeding level on pubertal mammary growth is mediated by reduced secretion of GH.

In spite of its documented effect on pubertal mammary growth, the mechanism of action of GH is not clear. Although GH-receptor mRNA is present in mammary tissue from pubertal heifers (S. Purup, H. Jammes, J. Djiane & K. Sejrsen, unpublished results), pregnant heifers (Hauser *et al.* 1990) and cows (Glimm *et al.* 1990), a direct effect of GH on the mammary gland of prepubertal heifers is questionable. First, it has not been possible to demonstrate GH binding to mammary tissue from prepubertal heifers (Purup *et al.* 1993*b*). Second, GH does not stimulate proliferation of mammary epithelial cells from prepubertal heifers *in vitro* (S. Purup & K. Sejrsen, unpublished results). Most evidence suggests that GH acts indirectly on the mammary gland of prepubertal heifers via IGF-1. Secretion of IGF-1 is increased by GH administration (Purup *et al.* 1993*c*), IGF-1 binding sites are present in the mammary tissue (Purup *et al.* 1993*b*) and IGF-1 stimulates proliferation of mammary cells *in vitro* (Shamay *et al.* 1988; Purup *et al.* 1993*a*).

The fact that GH seems to act on the mammary gland of prepubertal heifers via IGF-1 argues against the conclusion that the effect of feeding level on lactation potential is mediated by GH. This is because the level of IGF-1 is increased and not decreased, as is GH, by high feeding levels (Breier *et al.* 1988). This apparent paradox may be explained in different ways. The true cause and effect relationship between GH, IGF-1 and mammary growth may be modified by IGF-1 binding proteins and/or local IGF-1 production in the mammary gland. It is also possible that GH, despite the cited evidence to the contrary, acts directly on the mammary gland. Local action in the mammary gland was observed in the classical studies with rodents (Lyons *et al.* 1958). This observation was confirmed recently by Kleinberg *et al.* (1990). Collier *et al.* (1993) also observed a

stimulatory effect on mammary growth in cattle when GH was administered directly into the mammary gland via the streak canal during pregnancy.

We (S. Purup and K. Sejrsen, unpublished results) are attempting to ascertain the importance of IGF-1 for the biological effect of GH using *in vitro* techniques. In our initial experiments we found that the proliferation of pubertal mammary cells, as determined by thymidine incorporation in mammary explant DNA, was higher when explants were incubated with serum from GH-treated heifers than with serum from placebo-treated heifers. Our aim is to ascertain whether the effect of GH on mammary growth is mediated via IGF-1 or an unknown mediatory protein as suggested for lactation in rats (Flint *et al.* 1993).

A role for prolactin in the mediation of nutritional effects on mammary growth has been suggested, but no consistent relationship between prolactin and mammary growth has been demonstrated in several experiments with heifers and lambs (Sejrsen *et al.* 1983; Petitclerc *et al.* 1984; Johnsson *et al.* 1986; Sejrsen & Foldager, 1992). Johnsson *et al.* (1986) observed that mammary growth in lambs was unaffected by treatment with CB154, a synthetic compound that blocks prolactin secretion.

A role for oestrogen cannot be ruled out, since the proportion of free oestrogen, and oestrogen metabolism, are influenced by degree of fatness. The biological activity of oestrogen is modulated by its metabolism (Kirkwood *et al.* 1987). However, the relevance of these changes in biological activity to the effect of feeding level on mammary growth has not been investigated.

#### PUBERTAL MAMMARY DEVELOPMENT AND MILK PRODUCTION

The importance of the pubertal period as a determinant of the milk yield potential of heifers is evident in a large number of experiments. Results show that a feeding level resulting in gains of more than 600–700 g/d in heifers of large dairy breeds during growth between 100 and 300 kg live weight has a negative influence on the subsequent milk yield (see reviews by Foldager & Sejrsen, 1987; Johnsson, 1988; Troccon & Petit, 1989; Waldo *et al.* 1989). This period, which coincides with the pubertal phase of mammary development, therefore seems to be a critical period for the establishment of the milk yield potential of the heifers (Sejrsen, 1978). The critical importance of this period is clearly demonstrated in experiments published by Foldager & Sejrsen (1991), Ingvarlsen *et al.* (1988) and Peri *et al.* (1993) and in a large experiment involving about 300 heifers of three dairy breeds (J. Foldager, P. Madsen, J. Jensen & B. B. Andersen, unpublished results).

Although the negative influence of feeding level on subsequent milk yield has been observed in many experiments, there are exceptions (e.g. Gardner *et al.* 1988; Waldo *et al.* 1988). Although the reason for the variation in responses observed in different experiments is not clear, there are several possible explanations. For instance, in some experiments the differences in feeding level were fairly small and several experiments started at a fairly high body weight. In some experiments the heifers were only subjected to the different treatments shortly before the heifers at high feeding level reached puberty. Moreover, the discrepancies may have been caused by large individual variations in growth rate due to the feeding regimen used. It is our observation (Foldager & Sejrsen, 1991) that the negative influence of a high feeding level at one stage of the critical period cannot be compensated by lowering the feeding level in the

following stage. This is true even if the overall average growth rate is satisfactory. Finally, it is likely that heifers of different genetic backgrounds may tolerate different levels of nutrition. The optimal growth rate is clearly different in Jersey (Ingvartsen *et al.* 1988) and Holstein (Foldager & Sejrsen, 1991) heifers.

#### SUMMARY

The available studies concerning the relationships between nutrition, puberty and mammary development demonstrate the importance of pubertal mammary growth for the future development and ultimate milk-producing capacity of the mammary gland. A relationship between reproductive development and mammary development is also evident and mammary development at puberty is clearly influenced by the feeding level at that time. The role of specific nutrients has not been thoroughly investigated, but results suggest that specific fatty acids may be involved in the regulation of mammary growth. Mammary growth during puberty is affected by oestrogen and GH, but their respective roles and mechanisms of action have not yet been clarified.

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