Nutritional impact on mammary development in pigs: a review

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ABSTRACT: Milk yield is a crucial component of a sow operation because it is a limiting factor for piglet growth rate. Stimulating mammary development is one avenue that could be used to improve sow milk production. A number of studies have shown that nutrition of gilts or sows during the periods of rapid mammary accretion occurring during prepuberty, gestation, and lactation can affect mammary development. The present review provides an overview of all the information currently published on the subject. Various nutritional treatments can bring about increases in mammary tissue weight ranging from 27% to 52%. It was clearly established that feed restriction from 90 d of age (but not before 90 d) until puberty has detrimental effects on mammary development in pigs. Ad libitum feeding during that period increased mammary parenchymal weight by 36% to 52%. Body condition is also important because gilts that were obese (36-mm backfat) or too lean (12- to 15-mm backfat) in late gestation had less developed mammary tissue. Furthermore, overfeeding energy in late gestation seems to be detrimental. On the other hand, increasing energy and protein intakes of sows during lactation was beneficial for development of mammary tissue. Feeding certain plant extracts with estrogenic or hyperprolactinemic properties may also prove beneficial in stimulating mammary development at specific physiological periods. For example, feeding genistein to prepubertal gilts increased parenchymal DNA by 44%. Even though research was carried out on the nutritional control of mammogenesis in pigs, it is evident that much remains to be learned before the best nutritional strategy to enhance mammary development can be developed.

Key words: feed restriction, gestation, mammary development, nutrition, pig, prepuberty

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MAMMARY DEVELOPMENT IN PIGS: WHY IS IT IMPORTANT?

Pigs are a litter-bearing species, and as such, there is great pressure exerted on sows to provide enough milk to sustain maximal growth of all their piglets. Furthermore, hyperprolific sow lines were developed through genetic selection in the past decade so that sows can now easily have litters of up to 20 to 22 piglets. Managing sows so that they produce milk in adequate quantities is definitely a current problem in the pig industry. When looking at total sow milk yield on a per kilogram BW basis, their milk yield is comparable to that of dairy cows (National Research Council, 2001), and sow milk production has increased over the years. Early studies reported average daily milk yields of approximately 6 kg (Lewis and Speer, 1973; O'Grady et al., 1973) and in the late 1990s, values of 10 to 12 kg were observed (Auldist et al., 1998; Sauber et al., 1999). However, the early measures of milk yield (Lewis and Speer, 1973; O'Grady et al., 1973) were performed with the weigh-suckle-weigh method and a litter size of 9, whereas the latter studies used either the deuterium oxide technique and litter sizes of 6 to 14 (Auldist et al., 1998) or were estimated by dividing milk energy yield by milk energy content with a litter size of 13 (Sauber et al., 1999). Since the weigh-suckle-weigh method can underestimate milk yield and litter size is positively related to milk

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Table 1. Nutritional treatments that stimulated mammary development (in terms of mass of parenchymal tissue or amount of parenchymal DNA) in pigs

Treatment	Period[1]	Effect on parenchyma	References
10% flaxseed	In utero (day 63 gestation to end lactation)	31% ⬆ parenchymal weight	Farmer et al. (2007)
2.3 g/d of genistein	90 to 183 d	44% ⬆ total DNA	Farmer et al. (2010)
Ad libitum feeding vs. 25% feed restriction	90 d to puberty	46% ⬆ parenchymal weight	Sorensen et al. (2002b)
Ad libitum feeding vs. 20% feed restriction	90 d to puberty	36% ⬆ parenchymal weight	Farmer et al. (2004)
Ad libitum feeding vs. 33% feed restriction	90 d to 5.5 mo	52% ⬆ parenchymal weight 28% ⬆ total DNA	Sorensen et al. (2006)
24- vs. 36-mm BF[2] at the end of gestation via changes in energy and protein intakes	Gestation	Approximately 240%⬆DNA concentrations	Head and Williams (1991)
21- to 26- or 17- to 19-mm BF vs. 12- to 15-mm BF at the end of gestation via changes in feed intake	Gestation	Average of 33% ⬆ parenchymal weight	Farmer et al. (2016a)
5.76 vs. 10.5 Mcal ME/d	Day 75 to end of gestation	27% ⬆ parenchymal weight	Weldon et al. (1991)
Domperidone (0.4 mg /kg BW)	Days 90 to 110 of gestation[3]	80% ⬆ in lumen diameter of mammary epithelial cells	VanKlompenberg et al. (2013)
17.5 vs. 12 Mcal ME/d	Lactation	⬆ parenchymal weight[4]	Kim et al. (1999b)
65 vs. 32 g lysine/d	Lactation	⬆ parenchymal weight[4]	Kim et al. (1999b)

[1]Period where treatment was imposed.

[2]BF = backfat.

[3]Mammary development was not measured, but there was an increase in mammary epithelial cell differentiation.

[4]Percent increase could not be determined from the published data.

output (Auldist et al., 1998), it is likely that differences over time are less than reported. Nevertheless, the fact remains that the amount of milk ingested per piglet is inadequate and that piglet growth rate is limited by milk supply (Harrell et al., 1993). Improvements in sow milk yield through the years were mostly achieved via nutrition and management because a recent study demonstrated that 21 yr of genetic selection (between 1977 and 1998) increased piglet birth weight but had no effect on sow milk yield (Silalahi et al., 2017). It is therefore essential to devise management strategies that will optimize sow milk yield and one avenue that needs consideration is mammary development. This is most important because the number of mammary cells present at the onset of lactation has a major impact on potential sow milk yield (Head and Williams, 1991). Yet, any attempt to stimulate mammogenesis must be done during a period where there is already ongoing development of mammary tissue. Knowledge of ontogenesis of mammary development therefore becomes critical.

ONTOGENY OF PIG MAMMARY DEVELOPMENT

Even though there is embryogenic development of mammary buds that will eventually form mammary glands (Turner, 1952), the most extensive mammary development occurs postnatally. At birth, the duct system is poorly developed, and mammary glands consist mainly of subcutaneous stromal tissue (Hughes and Varley, 1980). Until 90 d of age, accumulation of mammary tissue and mammary DNA is slow. This is followed by 3 stages of rapid mammary accretion. The first stage is from 90 d of age until puberty, during which there is a 4- to 6-fold increase in mammary DNA (Sorensen et al., 2002a). Puberty in itself has a stimulatory effect on mammogenesis as parenchymal tissue mass increases by 51% in gilts that have reached puberty compared with gilts of a similar age that have not started cycling (Farmer et al., 2004). The second stage of rapid mammary development is during the last third of gestation. Quantitative development of mammary glands was shown to be slow in the first two-thirds of gestation, followed by a drastic accumulation of mammary DNA (King et al., 1996; Sorensen et al., 2002a). During that late gestation period, mammary glands undergo major histological changes as the adipose and stromal tissues are extensively replaced by lobuloalveolar tissue (Kensinger et al., 1982; Ji et al., 2006), which translates into a shift in mammary composition going from a high-lipid to a high-protein content (Ji et al., 2006). The third stage of rapid mammary development is during lactation. The average weight of suckled mammary glands increases linearly from 381 g on day 5 of lactation up to 593 g on day 21 (Kim et al., 1999a). Mammary growth in lactation is related to various factors, such as the

position of the gland on the udder (Kim et al., 2000), the intensity of the postejection massage (Thodberg and Sorensen, 2006), parity (Beyer et al., 1994), and nutrition (Kim et al., 1999b).

NUTRITIONAL EFFECTS ON MAMMOGENESIS

Feed Restriction

Growing gilts are generally fed ad libitum, yet, the very fast growing rate of current genetic lines and the high incidence of leg problems leading to lameness may entice producers to reduce feed intake in certain periods of growth. The impact of feed restriction in growing gilts on mammogenesis was studied. Restricting feed intake of growing gilts by 25% from 90 d of age until puberty reduced their mammary development (Sorensen et al., 2002b). This negative effect was corroborated in a later study where a 20% feed restriction was imposed during that same time period and mammary parenchymal mass was decreased by 26.3% (Farmer et al., 2004). Sorensen et al. (2006) then subjected gilts to a 33% feed restriction either from 28 d (weaning) to 90 d of age (period 1) or from 90 d until 5.5 mo of age (period 2). Feed restriction in the first period had no effect on mammary tissue mass or mammary DNA or RNA. However, when feed restriction was imposed in the second period, the amount of dissected mammary tissue as well as mammary DNA and RNA decreased. One possible mode of action for this effect is via alterations in the IGF-1 signaling pathway, which was shown to be important for growth of mammary tissue in rodents (Imagawa et al., 1986) and peripubertal cattle (review by Akers et al., 2000; Berry et al., 2003). In the study by Sorensen et al. (2006), no relation was found between circulating IGF-1 or IGFBPs and various measures of mammary development. However, as indicated by Flint et al. (2000), biological effects of IGFBPs may be independent of circulating IGF-1 concentrations. It can be concluded from these studies in pigs that a high feeding level from 3 mo of age until puberty, being a period of rapid mammary development, has a stimulatory effect on mammary development.

Compensatory Feeding

There were early indications that diet deprivation followed by overallowance during the growing, finishing, and gestation phases could be beneficial in terms of milk yield and mammary gene expression in pigs (Crenshaw et al., 1989). Yet, more recent studies could not show a direct effect on mammary development. Lyvers-Peffer and Rozeboom (2001) investigated the effects of a growth-altering feeding regimen before puberty on mammary development at the end of gestation. They used inclusion of dietary fiber (35% ground sunflower hulls) to achieve phases of moderate growth which alternated with phases of normal growth. They reported that gilts on the moderate feeding regimen from 9 to 12 wk and 15 to 20 wk of age had less mammary parenchyma on day 110 of gestation than control gilts. In a later experiment using a similar approach, specific periods of diet deprivation (providing 70% of the protein and DE contents from the control diet) followed by overallowance (providing 115% of the protein and DE contents from the control diet) in growing gilts did not have any beneficial effect on mammary development at puberty. In fact, this feeding regime led to a decrease in parenchymal tissue mass (Farmer et al., 2012a). This same nutritional treatment also did not affect parenchymal mass at the end of gestation but led to a tendency for reduced percent protein in mammary parenchyma (Farmer et al., 2012b). It is important to note that in those 2 studies by Farmer et al. (2012a,b), no compensatory growth was observed in gilts at the end of the finishing period. Even though formulation of the restriction diet decreased the DE content by 30% compared to that of the control diet in both Crenshaw and Farmer's studies, the composition of the fiber fraction differed, which may have led to the discrepancy in results. Sunflower hulls were used as fiber source by Crenshaw et al. (1989; J. D. Crenshaw, APC, Inc., Ankeny, IA, personal communication), whereas soybean hulls and wheat middlings were used by Farmer et al. (2012a,b). It is therefore still not known whether a compensatory feeding regime in the growing-finishing period could stimulate mammary development in gilts.

The impact of using a growth-altering feeding regimen during gestation was also studied. When a period of diet deprivation (providing 70% of the protein and DE contents from the control diet) for the first 10 wk of gestation was followed by a period of overallowance (providing 115% of the protein and DE contents from the control diet) until the end of gestation, gilts had less parenchymal tissue at the end of gestation with no changes in parenchymal tissue composition (Farmer et al., 2014b). However, even though growth rate was increased in the overfeeding period, this increase was not large enough to compensate for the BW loss incurred in the restriction period during early

gestation. It therefore appeared that the level of diet deprivation used was too severe to bring about the expected compensatory growth, and a further trial was carried out with a shorter period of diet deprivation. Similar treatment diets as in the previous study (Farmer et al., 2014b) were used. Dietary deprivation was imposed from days 28 to 74 of gestation and was followed by dietary overallowance from day 75 until farrowing (Farmer et al., 2018). Mammary glands were not collected because sows were allowed to farrow. Litter size was standardized and suckling piglets were not given access to creep feed so that their growth rate could be used as an indicator of milk yield. There was no effect of dietary treatment on piglet growth, but the level of compensatory growth of dams in gestation was not as expected. Even though the difference in BW between treated and control gilts on day 110 of gestation was much lower than previously seen (Farmer et al., 2014b), the increase in BW from days 75 to 110 of gestation was not as large as the reduction in BW from days 28 until 75, so that even though compensatory growth did take place in late gestation it was likely not important enough to stimulate mammary development. It is of interest to mention that maintaining an adequate BW at the end of pregnancy is also important to ensure optimal long-term reproductive performance of sows (Kim et al., 2016).

The potential in utero effect of diet deprivation and overallowance of the pregnant dam on mammary development of the female offspring at puberty was also studied (Farmer et al., 2015). A feeding regime during gestation similar to that described above (Farmer et al., 2014b) was used, and female offspring were grown under standard commercial conditions until puberty, to be slaughtered at 212 d of age. The maternal dietary regime did not affect mammary parenchymal tissue weight or composition of the gilts at puberty. This lack of effect could be due to too small a change in uterine environment for fetuses to be affected or to compensatory postnatal growth of mammary tissue.

Body Condition

The first demonstration that body condition can affect mammary development in pigs was provided by Head and Williams (1991). Body composition of gilts was altered by manipulating protein and energy intakes during gestation to create 2 groups of animals. Obese (36-mm backfat) and leaner gilts (24-mm backfat) had similar weights of mammary tissue at the end of gestation, but there was a drastic reduction (approximately 3-fold) in mammary DNA concentration in obese gilts. These findings are of importance, but the body conditions used do not reflect what is currently seen in pig herds. A study was therefore carried out to investigate the potential effect of more representative body conditions on mammary development in late gestation. Gilts of similar BW at mating were fed different amounts of feed throughout gestation (1.30, 1.58, or 1.82 times maintenance requirements) to achieve 3 levels of backfat thickness on day 109 of gestation, namely, 12 to 15 (lean), 17 to 19 (medium), and 21 to 26 (fat) mm. Parenchymal tissue mass was significantly reduced in lean gilts, being 1,059, 1,370, and 1,444 g for lean, medium, and fat gilts, respectively (Farmer et al., 2016a). Mammary parenchyma from lean gilts also tended to contain less dry matter, but it contained more protein and had greater RNA concentrations than parenchyma from fat gilts. These findings demonstrate that within this new range of body conditions, being too thin (12- to 15-mm backfat) at the end of gestation is detrimental for mammary development whereas showing medium (17 to 19 mm) or fat (21 to 26 mm) body conditions has no negative impact. Interestingly, this effect of body condition on mammary development was not linked to endogenous concentrations of IGF-1 or leptin so that, unlike ruminants (Silva et al., 2002), the negative impact of poor body condition was not mediated by increased leptin.

The question then arises as to what would happen if body conditions of late-pregnant gilts differed for another reason. Namely, what if backfat thickness already differed at mating and differences were maintained throughout gestation. Gilts of 3 ranges of backfat thicknesses at mating (lean: 12 to 15, medium: 17 to 19, and fat: 21 to 26 mm) were therefore used and fed varying feeding levels to maintain these backfat thicknesses until the end of gestation (Farmer et al., 2016b). Gilts were slaughtered at 110 d of gestation to collect mammary glands. Mammary parenchymal tissue mass was not affected by treatment; however, its composition was altered. Lean gilts had greater parenchymal concentrations of protein, DNA, and RNA compared with gilts from the 2 other groups. These studies emphasize the importance of nutrition during gestation for mammary development and demonstrate that underfeeding should be avoided to ensure maximal amount of parenchymal tissue mass. This was corroborated in a comparative study where relations between backfat thickness and mammary development were investigated in late-pregnant gilts (Farmer et al., 2017). Care into

avoiding thin gilts also has the added advantage of positively influencing sow longevity (Ocepek et al., 2016).

Energy and Protein Intakes

Only one experiment was carried out to study specifically the effect of protein intake during the growing-finishing period on mammary development in gilts. Contrary to what is seen with feed intake, reducing dietary CP from 18.7% to 14.4% from 90 d of age until puberty did not affect mammogenesis. Neither amount of parenchymal tissue nor composition of mammary parenchyma was altered (Farmer et al., 2004). This suggests that total feed intake is more important than protein intake per se to ensure proper mammary development of growing gilts.

A number of trials were carried out to study the potential effect of energy or protein intake on mammary development in pregnant pigs. Increasing dietary energy from 5.76 to 10.5 Mcal ME/d from day 75 of gestation until the end of gestation decreased mammary parenchymal weight, and total parenchymal DNA, RNA, and protein on day 105 of gestation (Weldon et al., 1991). On the other hand, increasing protein intake (330 vs. 216 g CP/d) had no effect on any of the measured variables of mammary development (Weldon et al., 1991). This absence of effect of protein intake was later corroborated by Kusina et al. (1999) who showed that lysine intakes of 4, 8, or 16 g/d from days 25 to 105 of gestation did not alter the amount of mammary parenchymal tissue or the concentrations or total amounts of DNA, RNA, or protein in mammary parenchyma at the end of gestation. Howard (1995) fed one of 2 energy levels (adequate: 6.1, or high: 10.5 Mcal ME/d) over 2 periods of gestation, namely, from days 0 to 74 or days 75 to 105. Total mammary parenchymal DNA, RNA, and protein on day 105 of gestation were not affected by energy intake regardless of the treatment period. However, total parenchymal lipid was greater when gilts were fed the high energy diet from days 0 to 74 of gestation irrespective of the level of energy fed from days 75 to 105. In another study conducted by Howard (1995), the same 2 levels of energy were fed from days 75 to 105 of gestation and, once again, there was no effect on mammogenesis. Taking all results into consideration, increasing the dietary energy feed level in late gestation should not be recommended when considering mammary development.

Nutrition during lactation can also affect mammary development, yet there is very little information on the subject. Kim et al. (1999b) fed lactating primiparous sows 4 diets that were a combination of 2 protein (32 or 65 g lysine/d) and energy (12 or 17.5 Mcal ME/d) levels. Wet and dry weights of suckled mammary glands were positively affected by both energy and protein intakes. Results suggested that mammary development was maximized when sows consumed an average of 16.5 Mcal of ME and 950 g of CP per day, the latter being equivalent to 52.3 g of lysine daily. Furthermore, sows with more than 6 piglets in a litter need an additional 0.96 g of lysine/d for each additional piglet in order to account for growth of the mammary glands (Kim et al., 1999c). Maximizing lactation feed intake was also shown to be a major effector of stayability of sows in the herd until the fourth parity (Knauer et al., 2010), further emphasizing its importance.

Energy Source

A diet rich in PUFA (containing 30% of a formaldehyde-protected sunflower seed supplement) was shown to stimulate mammary parenchymal growth in prepubertal lambs (McFadden et al., 1990). The impact of feeding flaxseed on mammary development of gilts was therefore investigated (Farmer et al., 2007), both because of its high PUFA content and because of its high concentration of secoisolariciresinol diglycoside. The latter being a precursor for lignin formation, which could be beneficial for mammary development due to its estrogenic activities (Adlercreutz et al., 1987). Dietary supplementation with 10% flaxseed from 88 until 212 d of age brought the expected changes in circulating fatty acid concentrations but had no beneficial effects on mammary development in pubertal gilts. Interestingly, when diets were supplemented with 10% flaxseed from day 63 of gestation until the end of lactation, it tended to increase mammary parenchymal mass of the offspring at puberty and increased parenchymal protein content (Farmer and Palin, 2008). This was a first demonstration of such an in utero effect in pigs. Howard (1995) also looked at the effect of providing supplemental PUFA using soybean oil in late pregnancy. Gilts were fed a corn-soybean diet that was supplemented or not with 5% soybean oil from days 75 to 105 of gestation. Animals were then slaughtered to collect mammary tissue. Neither parenchymal tissue weight nor composition was altered by treatment. The absence of effect of PUFA on mammogenesis in pigs could be linked with the source, amount, or duration of supplementation, but there could also be a species difference.

Plant Extracts

Estrogens are essential for mammary development, both at puberty (Farmer et al., 2004) and in late gestation (Kensinger et al., 1982). These last authors reported a positive correlation between circulating estrogen concentrations and DNA concentrations in mammary tissue of gilts on day 110 of gestation. An attempt was therefore made to stimulate mammary development in gilts by providing a dietary source of estrogen. When 2.3 g/d of the phytoestrogen genistein was added to a standard soya diet of growing gilts from 90 to 183 d of age, there was a 44% increase in mammary parenchymal cells at the end of the treatment period (Farmer et al., 2010). Supplementation of the diet of growing gilts with genistein therefore induces hyperplasia of mammary parenchymal tissue after puberty. During gestation, 2 daily i.m. injections of genistein led to similar increases in estrogen concentrations as seen when feeding 2.3 g/d of genistein to growing gilts (Farmer et al., 2013). Such a treatment was therefore used in late-pregnant gilts (days 89 to 110 of gestation) to determine its potential effect on milk yield. Mammary development was not measured, but the absence of treatment effect on growth of suckling piglets suggested that mammogenesis was not affected (Farmer et al., 2016c).

Prolactin is another hormone that was proven essential for mammary development in late gestation (Farmer and Petitclerc, 2003), so that increasing prolactin concentrations during that time period may be beneficial for sow lactation performance. The dopamine antagonist domperidone was used to create a state of hyperprolactinemia in late-pregnant gilts, leading to greater differentiation of mammary epithelial cells and to a 21% increase in milk yield the subsequent lactation (VanKlompenberg et al., 2013). However, mammary development per se was not measured. The use of feed additives to achieve late gestational hyperprolactinemia would be more practical and easily accepted in commercial pig operations. The plant extract silymarin (from *Silybum marianum*, generally known as milk thistle) was shown to significantly increase prolactin concentrations in female rats (Capasso et al., 2009) and to also increase milk yield in women (Di Pierro et al., 2008) and cows (Tedesco et al., 2004). In a recent study, 4 g of silymarin was fed twice daily to gilts from 90 until 110 d of gestation, at which time animals were slaughtered to collect their mammary glands. Even though feeding silymarin led to a 51.8% increase in circulating prolactin concentrations 4 d after the onset of treatment, this increase was transient and was not large enough to elicit beneficial effects on mammary development (Farmer et al., 2014a). It is possible that a larger dose of silymarin could have had a greater effect, yet, this may not to be economically feasible for producers.

Plant Toxins

Feed mycotoxins can impact mammary development, most likely through their estrogen-like activities. Marked epithelial changes, characterized by an increase in mammary glandular elements due to ductal hyperplasia, were observed in sows receiving 25, 50, or 100 ppm of purified zearalenone throughout gestation (Chang et al., 1979). Early mammary development was even observed in some of the 7-d-old female piglets suckling the zearalenone-treated sows (Chang et al., 1979). Yet, the potential impacts of this on sow milk yield and on future reproductive performance of these offspring were not investigated.

As early as 1945, there were indications that consumption of ergotized barley by late-pregnant sows had a detrimental effect on mammary development. Almost no mammary development was present in sows consuming barley ergot in late gestation, whereas all control sows had normal mammary development (Nordskog and Clark, 1945). Furthermore, sows fed ergotized barley showed agalactia. A negative impact of ergots on mammary development and milk yield was also reported more recently, when 1.5% sorghum ergot was fed to sows for the last 14 d of gestation (Kopinski et al., 2007). In that latter study, prolactin concentrations were measured, demonstrating and inhibitory effect of ergots on prolactin. Taking into account the essential role of prolactin for mammary development in late pregnancy (Farmer and Petitclerc, 2003) and for initiation of lactation in pigs (Farmer et al., 1998), it is therefore evident that any feeding regime with potential inhibitory effect on circulating prolactin should be avoided in late gestation.

SUMMARY AND CONCLUSIONS

It is clear that feeding management of gilts and sows can affect their mammary development, either positively or negatively. The 3 periods during which rapid mammary accretion takes place are those when nutrition can be effectively used to alter mammary development. A summary of the dietary treatments that can enhance mammary development in pigs is provided in Table 1. Feed restriction from 90

d of age (but not before 90 d) until puberty impairs mammary development. Feeding in gestation is also important because of its effect on body condition, and gilts that are either too fat (36-mm backfat) or too lean (12- to 15-mm backfat) at the end of gestation have less developed mammary tissue. During lactation, maximizing energy and protein intakes of sows will optimize their mammary development. Feeding certain plant extracts with estrogenic or hyperprolactinemic properties may also prove beneficial in stimulating mammary development at specific physiological periods. Even though advances were made in understanding the nutritional control of mammogenesis in pigs, much remains to be learned before the best nutritional strategy to enhance mammary development can be developed. The current review focuses on the effects of feeding on mammary development but other long-term factors, such as lameness and longevity, must obviously also be considered when developing such strategies.

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