Effect of intensive calf rearing on average daily gain in the pre-weaning period and first lactation milk yield

Effekt av intensivt kalveoppdrett på daglig tilvekst før avvenning og melkeytelse i første laktasjon

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I Abstract

Most studies on intensive rearing of dairy calves in the pre-weaning period have revealed a positive impact on early and later life performance, but have struggled to reveal statistically significant results. On this background, a literature search was performed on intensive calf rearing including recordings of later life performance from the last 15 years. The data was put into a spreadsheet for comparison of study design and selection of investigated variables. The variables reported most commonly was average daily gain in the pre-weaning period (ADG) and 1st lactation 305-d milk yield. Meta-analysis was used for synthesis of new information on these two variables, based on information from 7 studies on intensive rearing of calves of the Holstein or Holstein-Friesian breed/crossbreed. The feeding regimes varied between studies. Most studies used conventional milk replacers (MR) as the control group, and intensive MR or whole milk (WM) as the intensive group. To ensure that the results were not biased by publication, a funnel plot was created. The funnel plots revealed no presence of publication bias. The meta-analysis resulted in a significant positive effect on both ADG and milk yield in first lactation with mean effect sizes of 0.132 kg/day and 416 kg, respectively. The input data for the analysis was relatively heterogeneous in both variables measured, resulting in a relatively wide 95% confidence interval (CI) ranging from 0.061 to 0.203 kg/day for ADG and from 37 to 795 kg for 1st lactation milk yield. The heterogeneity was first and foremost thought to be due to differences in feeding regimes between studies, but immune status as a result of colostrum feeding may also have influenced the results. However, the analysis revealed a significant positive effect of intensive rearing in the pre-weaning period, both on ADG and milk yield, suggesting that the feeding in the pre-weaning period has effects on early and later life performance that might not be restored through compensatory growth in the post-weaning period.

II Sammendrag

De fleste studiene som har undersøkt intensivt kalveoppdrett for kvigekalver i melkekyrbesetninger har påvist en numerisk positiv effekt på produksjon både tidlig og senere i livet, men har ikke lyktes i å oppnå statistisk signifikante resultater. På denne bakgrunn ble det gjennomført et litteratursøk av studier på intensivt kalveoppdrett, som inkluderte data for produksjon senere i livet, gjennomført i løpet av de siste 15 år. Dataene ble satt inn i et regneark for sammenligning av studieoppsett og undersøkte variabler. Variablene som var mest sammenlignbare var gjennomsnittlig daglig tilvekst før avvenning og 305-dagers ytelse i første laktasjon. Meta-analyse ble brukt for syntese av ny informasjon på disse to variablene, basert på informasjon fra 7 studier på intensivt kalveoppdrett på Holstein eller Holstein/Frieser rasene. Fôringsstrategiene varierte mellom studier. De fleste studiene brukte konvensjonelle melkeerstatninger som kontrollgruppe, og intensive melkeerstatninger eller helmelk som den intensive gruppen. For å forsikre at det ikke var tilstedeværelse av en publikasjons skjevhet ble det laget et traktplott. Traktplottet viste ingen tilstedeværelse av dette. Meta-analysen resulterte i en signifikant effekt på både gjennomsnittlig daglig tilvekst og melkeytelse i første laktasjon, med sum effektstørrelser på 0,132 kg/dag og 416 kg/dag, henholdsvis. Datamaterialet analysen ble kjørt på var relativt heterogent for begge variablene og resulterte i et relativt bredt 95 % konfidensintervall på 0,061 to 0,203 kg/dag for gjennomsnittlig daglig tilvekst og fra 37 til 795 kg for melkeytelse i første laktasjon. Trolig ble heterogeniteten forårsaket av forskjellene mellom fôringsstrategier mellom studiene, men immunstatus som følge av råmelkstildeling påvirket muligens også resultatene. Uansett påviste analysene en signifikant positiv effekt av intensiv fôring før avvenning både på gjennomsnittlig daglig tilvekst i melkeperioden og melkeytelse senere i livet, noe som peker mot at fôringen før avvenning har en påvirkning på produksjon tidlig og senere i livet som kanskje ikke kan gjenopprettes gjennom kompensasjonsvekst etter avvenning.

III Preface

The background for this thesis was an increasing interest for distribution of milk replacers meant for intensive calf rearing in Norway. Also, a personal interest in calf feeding from practical work with dairy calves at the "*Senter for husdyrforsøk*" (SHF) influenced the choice of subject for the master thesis. I would therefore like to thank the staff there for an educational and inspiring workplace, valuable for the practical aspects of learning about animal husbandry.

The people I would like to thank for contributing to the master thesis is first and foremost my head advisor, Dr Egil Prestløkken at the Norwegian University of Life Sciences (UMB), and my second advisor, Dr Kari Ljøkjel at "*Felleskjøpet Fôrutvikling*" (FKF) who encouraged for this thesis to be written. You who have both been of incredible help, especially in the writing process.

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1.0 Introduction

The research on rearing of dairy calves and heifers for replacement has for the last decades increasingly focused on the effect of pre-weaning feeding regimes on post weaning performance. Preliminary results from studies at Cornell University indicate a positive effect of intensive pre-weaning feeding on milk yield during first and even second and third lactation (Van Amburgh et al., 2008). A meta-analysis by Zanton and Heinrichs (2005) support the findings of the researchers at Cornell University, concluding that increases in average daily gain (ADG) up to 799 g led to an increase in milk yield in the first lactation, while higher levels of ADG had a negative impact. However, studies investigating whether intensive feeding in the pre-weaning period is one of the factors influencing performance in later life are still limited in numbers and results are not consistent. Although most of them are numerically positive, several of the studies struggle to obtain significant results due to relatively small number of animals in the studies. As an example, Drackley et al. (2005) estimated that a herd size of 200 cows per treatment was needed to achieve significance in their study.

However, modern quantitative review techniques might be helpful in the search of reliable information based on the published studies (Borenstein et al., 2009). The objective of this thesis was to combine the results from studies performed during the past 15 years on intensified calf rearing in a combined qualitative and quantitative review using meta-analysis. It was expected to reveal a statistical positive effect of intensified calf rearing on post-weaning performance like milk production potential by applying the technique of meta-analysis on the available data created from these studies.

2.0 Literature study

2.1 The ruminant animal

2.1.1 The stomachs

2.1.1.1 Anatomy and physiology

The ruminant has several bulges in the digestive tract, hence considered a polygastric animal. The compartments are divided into the forestomachs, which are the rumen, the reticulum and the omasum, and the abomasum which is the "real" stomach (Figure 1).

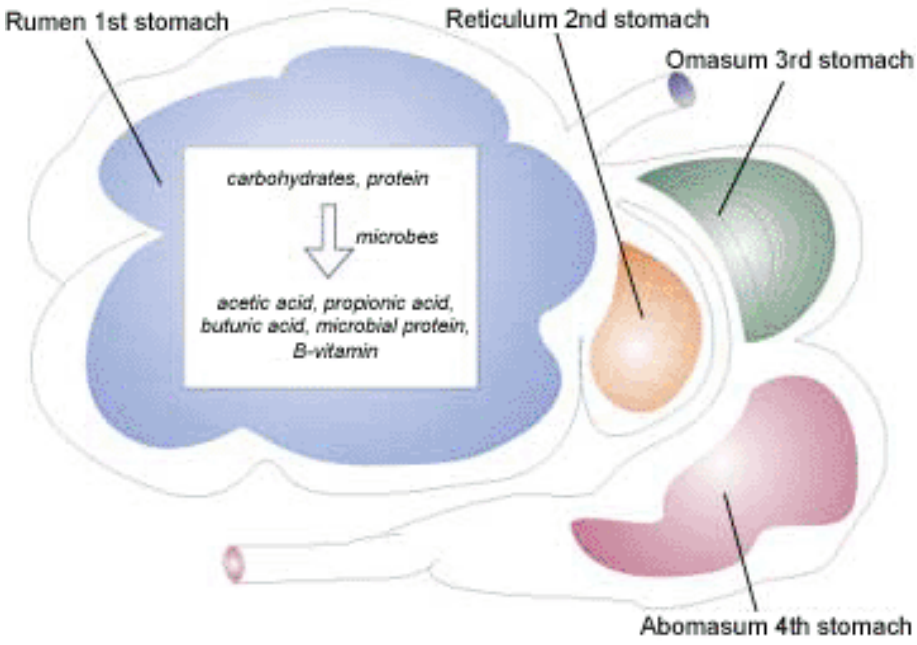


Figure1*.The ruminant stomachs and the most important end products from the rumen fermentation (DeLaval).*

In the forestomachs the adult ruminant has a unique ability to digest plant materials through microbial breakdown of the β-glycosidic bonds in structural carbohydrates and fermentation of these and other organic feed components (Sjaastad et al., 2003). The microbes are bacteria, protozoa and fungi (Kristensen et al., 2003). The bacteria can be classified in several ways, but are often classified after the main substrates they ferment, like cellulolytic and amylolytic bacteria (Yokoyama and Johnson, 1988). The end products from the ruminal fermentation are the volatile fatty acids (VFA), mainly acetic-, propionic- and butyric acid (Kristensen et al., 2003), which are absorbed and utilised as energy substrates. The amount of each acid depends on the type of feed, and is usually accounting for about 70% of the caloric requirements of the

animal (Bergman, 1990). Likewise, 75 % of the absorbed amino acids in the intestine is usually of microbial origin (Nørgaard and Hvelplund, 2003). The microbes have an optimal pH level, and the ratio within VFA change with the rumen pH (Kristensen et al., 2003). The rumen microbes use the feed energy released in the digestion of cellulose and hemicellulose and other rumen digestible nutrients to synthesise microbial protein. When digested in the small intestine the microbes supply the ruminant with microbial amino acids.

Fermentation takes place mainly in the rumen and the reticulum. Only a muscular folding divides the two compartments and they are often referred to as the reticulorumen (Tamate et al., 1962). The rumen and reticulum walls are covered with sandpaper textured epithelial foldings (papillaes) to increase the absorption area. In the reticulum the papillaes form a distinct criss-cross pattern (Sjaastad et al. 2003). The omasum is mainly absorbing water and minerals (Edrise et al., 1987) and the papillaes in this compartment are leaf-shaped and larger than in the reticulorumen. The abomasum is the "real" stomach where epithelial cells excrete gastric juices like in the stomach of monogastrics (Sjaastad et al., 2003). The rumen wall can be divided into a layer of connective tissue, a muscular layer, an epithelial layer, which is lined with a protecting keratin layer (Koehl, 2008) (Figure 3). Rumen motility is caused by the muscle layer and leads to mixing and moving of the content in the forestomachs (Sjaastad et al., 2003), while the inner epithelium (mucosa) absorbs VFA, water and ions from the fermentation process (Owens and Goetsch, 1988). There are no secretarial cells for production of digestive juices or enzymes in the forestomachs. All the feed is digested by microbes and their enzymes (Kristensen et al., 2003).

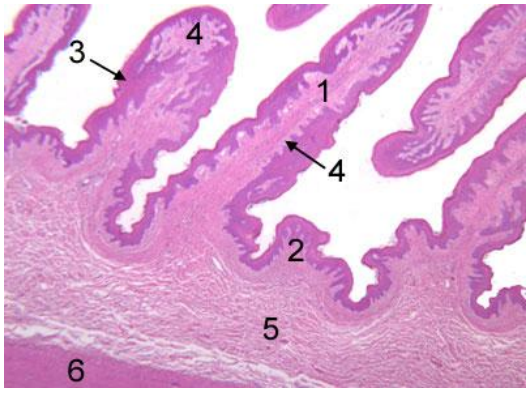


Figure 2. *The rumen wall layers. 1. Long papillae 2. Short papillae 3. Keratinized stratified squamous epithelium 4. Lamina propria 5. Submucosa 6. Muscularis externa (Koehl, 2008).*

In the pre-weaned calf, two muscular foldings in the rumen wall make up the "tube" which is called the reticular groove. The groove shunts milk into the abomasum through the abomasal orifice in the pre-weaning period (Hofmann, 1988), avoiding milk coming into the undeveloped forestomachs causing digestive disorders (Breukink et al., 1988). However, the volume of the abomasum is approximately 2 litres (Ljøkjel, personal communication), and larger amounts the milk in one meal may leak back to the forestomachs. It is recommended warm milk, close to body temperature, when fed to calves, as this leads to a higher secretion of digestive juices from the pancreas and abomasum than when milk is fed at lower temperatures (Ternouth and Roy, 1978). The closure of the tube is caused by a reflex initiated by suckling/drinking behaviour (Titchen and Newhook, 1975) and anticipation related to feeding (Ørskov, 1972). Sehested et al. (2003) found that it also is dependent on the presence of milk proteins. Water is normally differently distributed in the digestive tract than milk, allowing for water to enter the forestomachs (Welch and Hooper, 1988). Availability of fresh, clean water is important for the uptake of starter (Kertz et al., 1984).

2.1.1.2 Effect of feeding on rumen development

The newborn calf is born with a sterile tract and the inoculation of microbes is achieved by the cow licking the calf, microbes on feed particles and even microbes in water droplets in the environment (Mann, 1963). Depending on the feeding, especially the amounts of milk, the digestive tract might be fully developed at around 8 weeks of age, (Harrison et al., 1960; Tamate et al., 1962). In free grazing ruminants, Wardrop and Coombe (1961) suggested a dividing of the development of the digestive tract into three periods. The non-ruminant phase, where the young ruminant is mainly dependent on milk feeding from the mother, a transition phase at the age of 3-8 weeks, at which the young ruminant has started to consume vegetation, and the last stage from 8 weeks and onwards, where it is considered to be an adult ruminant.

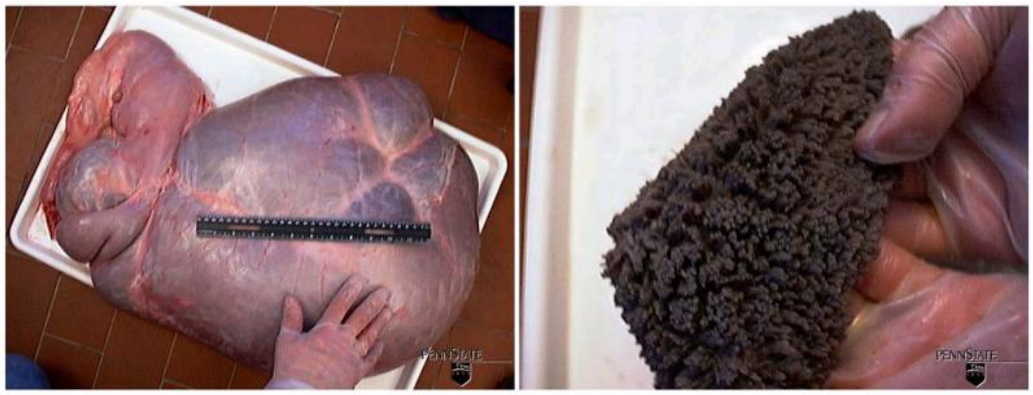
Butyric acid, and to some extent propionic acid, from the digestion of easily digested carbohydrates, are the main energy source for rumen epithelial growth and development (Britton and Krehbiel, 1993; Hodson et al., 1965; Tamate et al., 1962). Therefore, calves fed only milk have little papillae growth (Warner et al., 1956) as the milk bypasses the forestomachs through the reticular groove and into the abomasum. Harrison et al. (1960) found that in calves slaughtered at 16 weeks of age the papillae length of calves fed a ration consisting of 90 % concentrates was 7,5 mm long, while the calves fed 90% hay in the ration had papillaes that were only 4,1 mm long. They also found that the development of rumen

structures is reversible through replacing grain/concentrates with milk feeding in weaned calves. Intake of some bulky material, in form of concentrates with coarse texture or addition of other structure components like hay or other forages, is necessary to avoid un-normal papillae development. The absence of physical structure may lead to parakeratosis caused by too extensive keratinisation of the epithelial mucosa layer (Beharka et al., 1998). The branching ("clumping") of papillaes associated with parakeratosis is thought to have the function of compensating for the lost absorption area from keratinisation (Lyford, 1988).

In addition to preventing parakeratosis, the presence of bulky material is needed for rumination to take place and thereby development of the muscle layer in the rumen wall. Normally, such bulks are present in the feed through forages, hay or coarsely ground grain/concentrates (Beharka et al., 1998; Nocek et al., 1984b). However, inert bulks with no chemical feed value, like bedding (wood shavings) (Harrison et al., 1960) and plastic sponges (Tamate et al., 1962) also have a similar effect on the rumen development. Studies investigating the increase in volume of the forestomachs concluded that also in calves fed only milk the volume of the forestomachs increased in volume. However, this was thought to be due to stretching and not muscular growth according to data on weight of fat free tissue (Warner et al., 1956).

Figure 3 compares the stomachs of a 12 week old calf offered milk, hay and grain to the stomachs of a calf, at the same age, fed only milk and hay. The size is almost the same but the appearance of the rumen epithelium differs greatly between the two calves.

a



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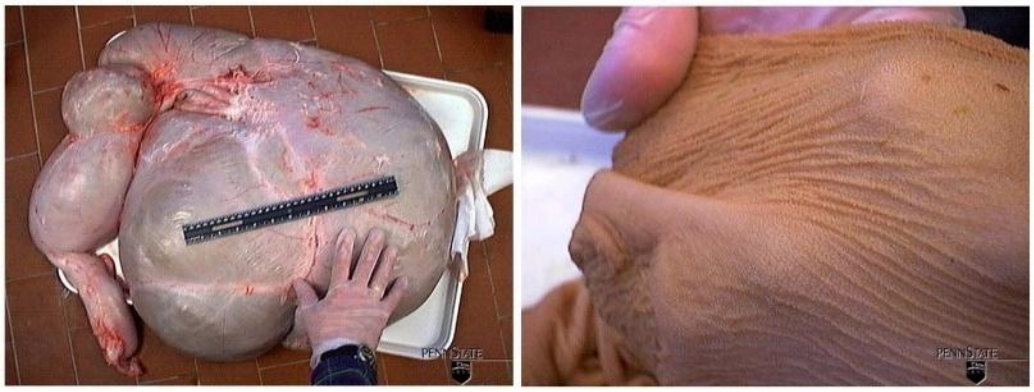
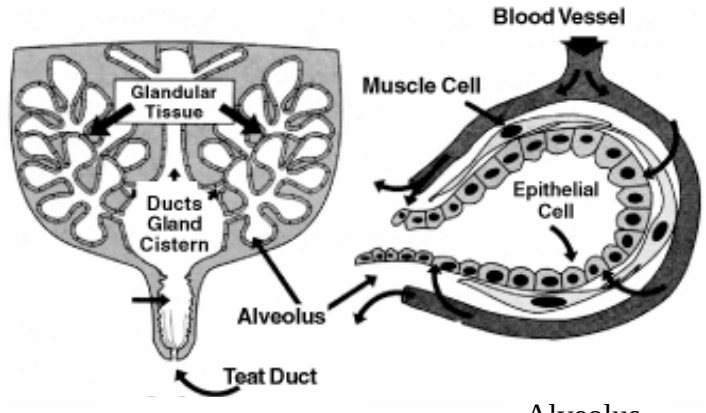


Figure 3. *The stomachs of a 12 weeks old calf fed milk, hay and grain to the left, the rumen papillae to the right (**a**). The stomachs of a 12 weeks old calf fed milk and hay to the left. The rumen papillaes are still in a rudimentary state. Also, notice the pale* colour of the rumen eptihelium*(**b**) (Penn State University, 2003).*

2.1.2 The mammary gland

2.1.2.1 Overview

The mammary gland consists of the mammary parenchyma (PAR) and the connective tissue often referred to as the mammary fat pad (MFP) (Figure 4). The PAR is the glandular tissue, with milk producing epithelial cells organised in alveoli and lumen, forming milk ducts. The milk is ejected by means of the neuroendocrine milk ejection reflex (Sjaastad et al., 2003).



Mammary gland Alveolus

Figure 4*. The bovine mammary gland with the milk producing parenchyma (glandular) tissue with the epithelial cells organized in alveoli (Modified after Schroeder, 1997).*

2.1.2.2 Development of the mammary gland

A fully developed mammary gland can weigh more than 30 kg (Capuco et al., 2001), consisting of about 40-50 % parenchyma, 40% connective tissue, 15% lumen and almost no fat cells (Harrison et al., 1983). Mammogenesis, or the development of the mammary gland, undergoes five periods; fetal-, pre- and post-pubertal periods, and the period of pregnancy and lactation (Sejrsen et al., 2003) (Table 1).

Table 1. *Growth and development of the bovine mammary gland (Sejrsen et al., 2003).*

Period	Tissue
Fetal	-outer structure -mammary fat pad -blood circulation -ducts
Pre-pubertal **0 - 3 months***	- mammary fat pad - duct network
Pre-pubertal ¤ **3-9 months ***	-mammary fat pad -milk ducts
Postpubertal **-pregnancy**	Little development
Pregnancy	-mammary fat pad -duct network -alveolis developing from the duct network towards end of pregnancy
Lactation	Initiation of milk synthesis

*depending on body weight, ¤ allometric growth

The growth is clearly allometric, growing at higher rates than the rest of the body, from approximately 3 months up to 9 months. In the other periods, apart from the pregnancy period where the growth of the udder is exponential, mammary growth is more or less isometric, growing at the same rate as the rest of the body (Swanson and Poffenbarger, 1979). Pre-pubertal growth is characterized by growing and stretching of the PAR into the MFP, but there is no formation of the milk secreting alveoli before the period of pregnancy. This means that the framework of the milk yield capacity is made up in the pre-pubertal period, and thus influenced by the feeding in this period (Sejrsen et al., 2003).

2.1.2.3. Effect of feeding in the pre-pubertal period on development of the mammary gland.

The heifers ability to produce milk depends on the capacity of the udder to synthesize milk and the ability to utilize the nutrients (Sejrsen et al., 2003). There seems to be a broad acceptance for that the feeding greatly influences the MFP (Meyer et al., 2006; Daniels et al., 2009). However, the effect of feeding in the pre-pubertal period on the milk producing tissue, the PAR, is not clear. Sejrsen et al. (1982) and Capuco et al. (1995) concluded that an accelerated heifer growth in the post-weaning period before puberty lead to a decrease in PAR

and Sejrsen et al. (1982) introduced the concept "critical period" as the period when the mammary development is sensitive to plane of nutrition. This period coincided with the allometric growth period of the mammary gland, from 3 months up to puberty at around 12 months (Foldager and Sejrsen, 1991). However, this might have been misinterpreted because of the study design, as suggested by Daniels et al. (2009). Comparing heifers at same slaughter age caused heifers to be at different ages due to differences in ADG, as the heifers with highest nutrient intake reached slaughter weight at an earlier age. Therefore, the difference in mammary development might have been due to the shorter time period for growth of the PAR tissue, rather than a direct effect of feeding. Several studies found no effect of feeding on development of the PAR when the heifers were compared at the same age (Meyer et al., 2006b; Daniels et al. (2009). Daniels et al., (2009) did not show any significant effect of increasing nutrient intake in the pre-weaning period on the PAR when comparing heifers at same age (65 days) with group means ranging from 470 to 850 g/day during this lifetime. However, there was a numerical increase in the telomerase abundance in the PAR. Telomerase is an enzyme that protects chromosomes from shortening by adding protective six-base deoxy ribonucleic acid (DNA) to the end of the DNA strand after transcription (Fu et al., 1999). The increased abundance therefore indicated an increased activity in the cell proliferation (growth characterized by increasing cell numbers) in the mammary stem cells. It was therefore concluded that although the study did not show any positive effects; neither did it show any negative effects on the mammary development.

Preliminary results of Van Amburgh et al. (2008), investigating data from the Cornell University herd, revealed that increasing ADG with 0.1 kg in the pre-pubertal period led to an increase in milk yield in first lactation of 107 kg milk. This positive correlation remained throughout 2nd and 3rd lactation but with decreasing effect with increasing lactation number. A meta-analysis performed on experiments studying intensive calf rearing (Zanton and Heinrichs, 2005) revealed that first lactation milk yield increased linearly with increase in ADG up to around 800 g. Higher ADG led to a decrease in first lactation milk, indicating an optimum level of ADG in the pre-weaning period. This is somewhat higher than the optimum level reported by Sejrsen (1994), who recommended levels of ADG at 600-700 g in the pre-pubertal period.

Recent research has suggested that also feeding in periods other than the "critical" period has effect on mammary development. Brown et al. (2005) revealed a positive effect of increased

nutrient intake in the pre-weaning period on PAR development from 2-8 weeks. Studies investigating the effect of intensified MR (high protein, low fat) revealed a numerical positive effect on milk yield in first lactation (Bar-Peled et al., 1997; Drackley et al., 2007; Raeth-Knight et al., 200; Terré et al., 2009), indicating an effect of feeding in this period on mammary development. However, in spite of this numerical positive effect, most of them struggled to obtain statistical significance. Also, feeding with 2% more protein in the post-weaning period in two of these studies also seemed to be critical to further enhance the positive effects of the increased protein intake in the pre-weaning period (Moallem et al., 2006; Shamay et al., 2005). Morrison et al. (2009) stood apart from these studies as there was a negative effect on ADG and no effect on milk yield from feeding a high-protein MR compared to a conventional MR. The authors pointed out that lack of energy in the ration and problems with the feed consumption in the milk feeding period, resulted in a ADG of only 400 g and therefore might biased the results. However, this effect of feeding, also in the pre-weaning period, supports the studies that found a correlation between ADG in pre-pubertal period and later life performance (Van Amburgh et al., 2008; Zanton and Heinrichs, 2005).

2.2 Feed for calves

2.2.1 Liquid feed

In the pre-weaning period, the digestive tract of the calf is not fully developed and most of the feed is fed as liquid. Apart from drinking water, the three types of liquids used are colostrums, whole milk and milk replacers. An overview of typical content of protein, fat and lactose in these three liquids is given in Table 2. In addition, the National Research Council (NRC) (2001) requirement of protein and fat for calves in the pre-weaning period is given in the table.

Table 2. *Content of protein, fat and lactose (% of dry matter) in colostrum, whole milk and milk replacers compared to requirement of protein and fat of calves in the pre-weaning period.*

	Dry matter	Protein	Fat	Lactose
Colostrum	28[a]	54[a]	24[a]	9[a]
Whole milk	13[b]	25-27[b]	25-36[b]	38[b]
Milk replacers (as powder)	~ 95	18-30[c]	18-28[c]	0-70[b]*
NRC (2001) Requirement	-	20-26[e]	16-18[e]	-

[a] Kehoe et al., 2007, [b] Tanan, 2005, [c] Byers et al., 2002, [d] National Research Council, 2001, *depending on source for milk replacer

2.2.1.1 Colostrums

The first few days after parturition the milk is called colostrum. The composition of colostrum differs from whole milk, especially with a higher content of protein (Table 2). The high protein content of colostrum is mainly due to immunoglobulins (Ig) (Nocek et al., 1984a) that are crucial for the passive immune system of the newborn calf. Because of limited (or no) transfer of Ig over the placenta, the calf is born with a very low immune status and fully dependent on a passive transfer of Ig from the colostrum (Smith and Little, 1922). The first hours after birth are critical because the intestine of the calf gradually becomes less permeable for the large Ig molecules (Quigley et al., 2005). In practice, the content of Ig in the milk decreases dramatically already after the first milking (Stott et al., 1981).

There are three types of Ig's; Ig-G (80-90%), Ig-A (5%) and Ig-E (7%) (Larson et al., 1980). Although the Ig-G is the quantitatively most important in ruminants, all the types need to be present to obtain an optimal immunity (Logan et al., 1974). A blood serum level of Ig-G of less than 10 mg/l at 48 h age is defined by the Bovine Alliance of Management and Nutrition (BAMN) (1995) to be an indication of failure of passive transfer (FPT). Therefore, to insure an optimal immune status, modern recommendations are to give the calf *ad-libitum*, or a minimum of 6 l colostrum the first 24 hours after birth. At least 2 of these litres should be given within 6 hours to ensure proper immunity effect. If the calf cannot suckle itself, colostrum should be force fed ("oesophageal feeder") to ensure absorption of Ig before the intestine becomes less permeable. The mortality of calves increases from 5% to as much as 20% if colostrum is offered later than 24 hours post-parturition compared to within the 6

hours limit (Margerison and Downey, 2005). In practice, the immune status of the calf can be determined from the serum level of immunoglobulins.

The quality of colostrum varies between individual cows with factors like time after parturition, breed, feeding in the dry-period, extent of feeding, lactation number and infection pressure from the environment as reviewed by Godden (2008). The quality (concentration of Ig) is indirectly measured through the colostral specific gravity of the milk, using a colostrometer (Fleenor and Stott, 1980). Alternatives to raw colostrums are commercial colostrum replacers, or colostrum pasteurized for 60 minutes at 60º C. This tends to reduce pathogens transmitted from the cow to the calf by colostrum, for example subclinical cases of Johne's disease (Manning and Collins, 2010) caused by the bacteria *Mycobacterium paratuberculosis* (Manning and Collins, 2001).

2.2.1.2 Whole milk

Whole milk (WM) is highly digestible and considered an ideal feed for the newborn calf as it matches the required levels and types of nutrients in early life growth and development (National Research Council, 2001). WM consists on average of 26% protein, 30% fat and 38% lactose on dry matter (DM) basis (Table 1). Excess WM is considered a cheap feed compared to milk replacers. However, the price or cost of WM as feed is highly dependent on external factors like quota fill. High performance farms in Norway use excess WM and unsaleable milk, like milk with elevated cell count and transition milk, in their calf rearing when available (Bekkevoll and Helberg, 2009). In general, the use of such milk have not caused any elevated scouring or long term negative effects in first lactation heifers (Kesler, 1981, Keys et al., 1980). However, use of discarded milk from cows on antibiotic treatment is not recommended due to the possible resistance to certain bacteria.

2.2.1.3 Milk replacers

Milk replacers (MR) have been commercially available for the last 60 years (Crane, 1991) and in 2006 as much as 70% in USA used MR (Bridges, 2009). In Norway, the ratio seems to be opposite (Ljøkjel, personal communication). MR is considered by many farmers as less ideal because of sediment accumulating in feeding equipment, and for some farmers also by lower performance compared to WM. However, the research and development of MR the last ten years has led to MR equal to or even better than WM, provided correct use of replacer. Three such examples are use of correct MR for the particular production; correct mixing at the correct water temperature and optimal feeding rate of MR as advised by the manufacturer.

The use of MR represents an opportunity to control the ratio between nutrients like protein and fat. The chemical composition of modern MR varies depending on intending use (BAMN, 2002). MR protein levels in European conventional MR normally range between 20-23%, whereas fat levels normally range from 16-18% (Ljøkjel, personal commnication). MR for intensive calf rearing typically has protein levels above 25% of DM and fat levels similar to the conventional MR (Raeth-Knight et al., 2009).

Protein

MR are often based on skimmed milk (milk with fat removed) or whey. Whey is the liquid left over from cheese making and it is rich in carbohydrates (lactose). The main protein source is lactalbumin (BAMN, 2002). To achieve an acceptable protein level, MR is added external protein feeds. When choosing source of protein feed for the MR, anti nutrients and bioavailability are important factors to consider in addition to amino acid profile and total crude protein (CP) content. This especially holds for MR intended for the very young calf as the digestive tract is not fully developed. Table 3 classifies protein feeds for MR by their suitability (BAMN, 2002).

Table 3. *Protein sources for milkreplacers categorised according to suitability for the young ruminants digestive tract (BAMN, 2002).*

Acceptable (all-milk protein sources)	**Acceptable (alternative protein sources)**	**Marginal**	**Not Acceptable**
Dried Whey Protein Concentrate	Soy Protein Isolate	Soy Flour	Meat Solubles
Dried Skim Milk	Protein Modified Soy Flour		Fish Protein Concentrate
Casein	Soy Protein Concentrate		Wheat Flour
Dried Whey	Animal Plasma		
Dried Whey Product	Wheat gluten or isolate		

Fat

The main fat sources in MR are milk fat. Alternative fat sources are vegetable fat as ruminant fat was banned from 2001 and other animal fats were also banned. Among vegetable fat sources, coconut oil and palm oil have a digestibility greater than 95% (Toullec and Matthieu, 1969). Most fat sources incorporated in MR contain coconut oil and palm oil in the ratio 20% and 80%, respectively (Tanan, 2005). Lecithin extracted from soya is used as an emulsifier in milk replacers to enhance the mixing of MR powder with water (BAMN, 2002). In addition, it enhances fat digestion and functions as an antioxidant. Homogenization, agglomerating and spray drying are other techniques that enhance emulsification and mixing of MR (Tanan, 2005).

Carbohydrate

There are only a few possible carbohydrate sources available for the young calf as the digestive tract is not fully developed at birth. Lactose is the main carbohydrate source the first few weeks after birth as amylase is only present in the pancreas at very low levels and so is maltase and isomaltase found in the small intestine (Le Huerou-Luron et al., 1992). Lactase activity follows a different pattern, having highest activity at birth and decreasing with age, especially after weaning (Le Huerou et al., 1992). Lactose is a disaccharide made up of one galactose and one glucose molecule and hydrolyzed by lactase in the small intestine, mainly in the jejunum part of the small intestine (Le Huerou et al., 1992). Other possible carbohydrate sources are therefore galactose and glucose.

Minerals and vitamins

The levels of minerals in the MR varies between types of MR, but on average a total ash content of 76 g/kg DM was found in skim milk powder MR (diluted at 125 g/kg liquid feed) and 75 g/kg DM for sweet whey powder. The lowest values where found for soluble wheat gluten (11 g/kg DM) and the highest for delactose whey powder (198 g/kg DM) (Tanan, 2005). Total ash content in WM is in the range of 5-7% of DM (Tanan, 2005). In MR the ash content varies with the source. Values for vitamins and minerals are not given as they vary with the feeding of the cows (Ljøkjel, 2010). However, it is important to have in mind that high total ash content can lead to diarrhoea due to the osmotic pressure in the intestine, making too much water diffuse into the faeces. In particular sulphate, sodium, potassium and chloride are important when it comes to osmolality (Tanan, 2005). According to Tanan et al.

(2005) the skim milk based MR had values closer to WM than whey based and soy based MR. Too much calcium when given as calcium formiate reduce fat digestibility by combining with bile acids important for the fat digestion and cause diarrhoea (Xu et al., 2002), depending on the form the calcium is given. However, calcium and phosphorus are important for the formation and maintenance of the skeleton and teeth and also in making nerves, muscles and heart function normally, as well as blodclotting (Davis and Drackley, 1998). Phosphorus is associated with several organic and inorganic compounds in the body, including the body's "energy currency"; adenosine triphosphate (ATP). Magnesium is important in the skeleton (Davis and Drackley, 1998) and in the cellular metabolism of organic compounds (McDowell, 1992). The most critical micro minerals are iron, zink, copper and selenium important for haemoglobin and enzymes required for normal growth and development. Vitamins and trace elements should be supplemented to MR as the levels in WM are usually below requirements (Davis and Drackley, 1998). This is due to for example destruction of thermo sensitive vitamins in the processing of the MR.

Medical additives/growth hormones

In some countries the MR contains medication like growth promoters and medication to treat different kinds of infections. Examples of such medicaments are chlortetracycline and oxytetracycline (BAMN, 2002). However, this is not allowed in Norway (Ljøkjel, 2010).

2.2.1.4 Acidified milk/milkreplacers

Acidifying the WM/MR is done for two main reasons; conservation of the milk,- killing pathogens and destruction of some antibiotics (Keys et al., 1976; Keys et al., 1979), but also as a way of reducing the pH in the calves digestive tract and thereby prevent diarrhoea caused by bacteria like *E. coli* (Jaster et al., 1990). Fallon and Harte, (1980), as cited in Davis and Drackley, (1998), reported an improvement in the calf performance, but other studies show no advantage when it came to calf growth (Jaster et al., 1990; Raeth-Knight et al., 2009). The acidified milk should ideally have a pH of >5.0 in order to impair the growth of *E.Coli* (Cherrington et al., 2008; Constable, 2009) and for stable preservation (Tomkins and Jaster, 1991). The pH is easily measured on farm with a pH meter or pH paper. A too low pH might impair palatability. The acidification can be caused by adding organic acids like formic acid, propionic acid or citric acid (Davis and Drackley, 1998) but can also be achieved by adding of *Lactobacillus* bacteria (natural fermentation). The fermentation of milk from treated cows seems to be affected by the antibiotic residues in the first two milkings after administration of

the treatment, but not thereafter (Keys et al., 1976). Temperature is important in natural fermentation of the milk and should be between 20-30° C (Keys et al., 1979). When adding organic acids, however, the milk should be cold, under approximately 10° C, and the acid should be added carefully and mixed properly in order to achieve a homogenous liquid.

2.2.2 Solid feeds

2.2.2.1 Calf starters

In order to trigger early intake of the starter there is a considerable focus on factors influencing the intake, like palatability and texture. However, nutritional value and digestibility are, of course, also important. When it comes to chemical composition, the calf starters differ from other concentrates first and foremost in the protein content (Davis and Drackley, 1998).

Physical form

In a study from 2007 by Bach et al. the effect of physical form on intake and performance was investigated. They concluded that the intake seemed to increase when the calves were given multi particle starters (textured feed) compared to pelleted feed. However, the feed efficiency was higher for calves receiving pellets due to technological treatment of the feed making the nutrients more available. This resulted in same weight gain in the two groups. However, the pelleted feed turned out to be economically favourable as it increased the feed efficiency. The physical form of the calf starter also affects the rumen development, described in section 2.1.1.2

Chemical composition

Optimal level of crude protein in calf starters was set at 200 g/kg DM (180g/kg on an as-fed basis) according to the National Research Council (NRC) (2001). At this level energy is the limiting factor in live weight gain, although some studies suggests that higher levels might improve feed efficiency (Drackley et al., 2002). The fat content should not be above 5%, as a higher percentage will depress DM intake. The content of neutral detergent fibre (NDF) was recommended to be 15 and 25% (Davis and Drackley, 1998), depending on the digestibility of the feed source.

Ingredients

The most common grains in starters are corn and barley for digestion and palatability reasons. Maiga et al. (1994) found that corn gave the best live weight gains. Oats have been reported to be highly palatable and a good fibre source (Davis and Drackley, 1998). It also adds bulk to the starter and is therefore suitable for use in starters. Several fibre sources like beet pulp, cottonseed hulls, whole fuzzy cottonseed and soyabean hulls fed to calves less than two months have reported to depress ADG and feed efficiency (Hill, 2005). Soybean meal is one of the most commonly used protein sources in calf starters (Davis and Drackley, 1998). Other protein sources like rapeseed meal, ground or extruded heat-treated soy beans, canola meal and cottonseed meal have also been successfully used for calf starters (Davis and Drackley, 1998). Non-protein nitrogen sources in starters are not recommended as it depresses ADG and feed efficiency in young calves (Fiems et al., 1987). Supplemental fat ingredients in order to increase the energy content are mostly free fats, like hydrolyzed animal fat (Luchini et al., 1993). Molasses is a source of carbohydrates in calf starters but is mostly added for palatable reasons and it also functions as a dust binder. However, levels above 50 g/kg feed of molasses appeared to cause osmotic scour and to be detrimental to DM intake and ADG (Lesmeister and Heinrichs, 2005).

Additives

Flavouring the calf starter with additives like ethyl butyrate, maple, saccharin and butterscotch (Morrill and Dayton, 1978) have been studied. The conclusion so far has been that it is the consistency, not the specific flavour, that is important (Hill, 2005) as flavouring a calf starter make the flavour more consistent and thereby increase the intake of starter. The additives of herbs, botanicals, plant extracts and essential oils have been very little investigated and the data from such trials are therefore limited, however some herbal mixtures have shown to have some positive effect (Hill et al., 2007) but the mechanism is not understood yet.

Adding coccidiostats to the feed have a preventive merit when it comes to reducing the shedding of coccidian (Conlogue et al., 1984; Heinrichs and Bush, 1991). However, intake of concentrates in young calves varies considerably and therefore might be more effective when administrated separate from the feed. In Norway the addition of coccidiostats into the feed for dairy cattle is not allowed (Ljøkjel, 2010). Likewise, addition of microbial additives, pre-

biotics and pro-biotics has shown some effect but the results are quite variable, and therefore might be more effective when added to products that are directly administrated to young calves (Hill, 2005).

2.2.2.2 Forages

Hay is often preferred to straw or silage as a mean of bulk in the diet (Hill, 2005). High intakes of hay could be detrimental to development as it fills up the stomach and reduces the intake of grain/concentrates (Penn State University, 2003). However Hill et al. (2005) fond that young calves wasted 3 times more than they consumed when offered straw or hay (Hill, 2005). Silage is also widely used, but silage can cause lesions in the abomasum when combined with high levels of milk feeding (Wensing et al., 1986). When feeding silage to very young calves there is a risk for silage to become mouldy and contain mycotoxins. If fed, fresh silage should be offered often and fed in small amounts as the forage intake of young calves is relatively low, thereby not allowing for the silage to become mouldy and contain mycotoxins. Intake of mould and mycotoxins have negative influence on performance like feed intake, live weight gain and fertility and also reduce immune status (Adams et al., 1993; Diekman and Green, 1992). Other alternatives to forages are coarsely ground grain or other fibrous feed like coarsely ground starters/grains (Beharka et al., 1998) and soybean hulls (Shain et al., 1993).

2.3 Rearing system

2.3.1 Conventional rearing

Until recently, little attention has been on the nutrition in the pre-weaning period. The live weight gain in the pre weaning period has thought to be of less importance as the calves have been thought to be able to compensate for this growth through compensatory growth (Owens et al., 1993; Brameld, 2005) post-weaning. Therefore, the calves have been given restricted amounts of milk/MR at rates of 8-10% of body weight, aiming at growth rates far less than the genetic potential. In contrast, intakes of 16-24% of body weight were measured in calves fed WM/MR *ad libitum* (Davis and Drackley, 1998). Restricted amounts of liquid feed normally leads to increased intake of dry feed like grain/concentrates at earlier age (Hopkins, 1997; Huber et al., 1984), which again leads to earlier weaning. Other arguments for early weaning is improved calf health and less labour required for the calf rearing (Davis and Drackley, 1998) and reduced feed costs in the heifer rearing, as liquid feed normally is more expensive than dry feed (Brameld, 2005).

2.3.2 Intensive rearing

The view on calf and heifer rearing for replacement is changing. More focus is now on feed quality and amounts of nutrient intake in the pre-weaning period, as several studies have concluded that an elevated nutrient intake in the pre-weaning period is a good investment in the replacer herd as positive effects both in early and later life was revealed (Drackley et al., 2007; Foldager et al., 1997; Raeth-Knight et al., 2009; Shamay et al., 2005; Terré et al., 2009).

The term "intensive rearing" is here defined as an elevated nutrient intake during the pre-weaning period of the calves through WM or MR with protein levels like in WM, fed at feeding levels close to *ad libitum*, aiming at levels of ADG of 800 g in the pre-weaning period. The growth curve would look like Figure 5 below (CVB, 2001).

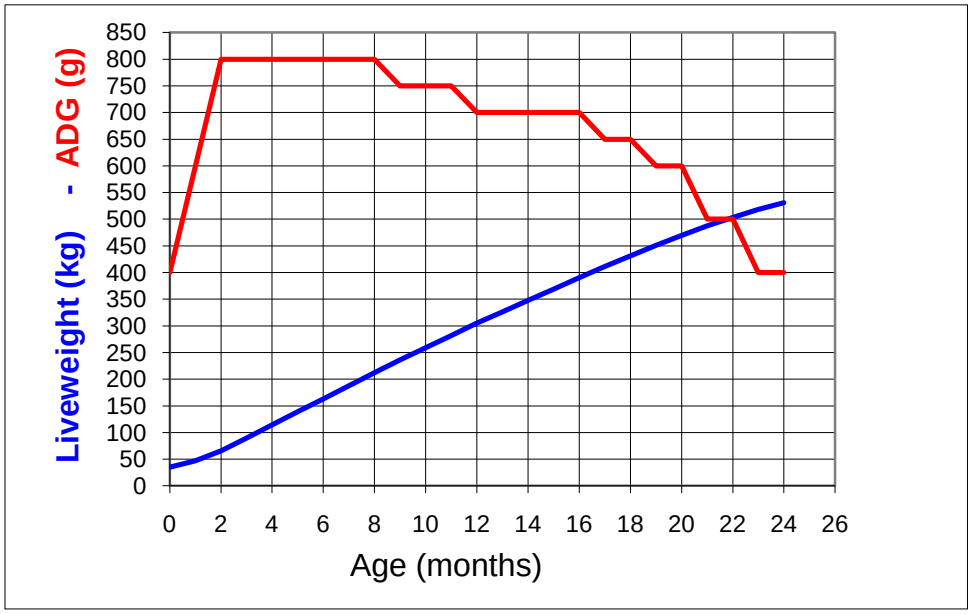


***Figure 5**. Recommended growth rates of heifers, aiming at 1st service a 360 kg (14,5 months age) modified after Verkorte table (CVB, 2001).*

This is in line with what Zanton and Heinrichs (2005) found in their meta-analysis when investigating the optimal growth rate in the pre-pubertal period for maximum milk yield in 1st lactation. This level of growth rate in early life is only possible through liquid feed like milk or milk replacers (Davis and Drackley, 1998).

2.4 Meta-analysis

2.4.1 General/history

The phrase meta-analysis was first used by Glass in 1976. He defined a meta- analysis as *"..the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings."* This differs from traditional or narrative reviews, where results are discussed on basis of published literature. In practice, meta-analysis is used instead of, or complementary to, narrative reviews. Meta-analysis generally addresses broader questions than what single studies do. Borenstein et al. (2009) stated that "…*the goal of a synthesis is not simply to compute a summary effect, but rather to make sense of the pattern of effects.*" In a meta-analysis there is a considerable focus on effect sizes, rather then p-values. An effect size is the amount of response of a treatment, calculated as the difference between a treatment group and a control group. Although meta-analysis first started in agriculture studies, they have been most frequently used in disciplines like medicine and public policy (Rafoss, 2010). However, progresses in development of powerful statistical software have made meta-analysis more convenient and meta-analysis is today frequently used also in agro-science studies.

Meta-analysis can be divided in analysis without access to raw data, only literature, (MAL) and analysis with access to raw data (MAD). Irrespective of that, the process of a meta-analysis can be summed up in seven steps (Hamer and Simpson, 2002). The steps are; (1) decide on a topic, (2) decide what hypothesis to test, (3) perform literature search/review, (4) evaluate literature studies, (5) create data set from selected studies, (6) perform the meta-analysis, and (7) interpret the results. Of these, step 3, 4 and 5 and 6 is of particular interest and is discussed more in detail.

Step 3

When searching for studies for a meta-analysis both published and unpublished results should be included if possible. Studies with larger effect sizes, achieving statistical significance, usually have a higher probability of getting published (Borenstein et al., 2009). A bias like this is called publication bias or also the "file drawer problem". In order to address such a bias a funnel plot is useful. A funnel plot is a plot of the effect size on the x-axis and the inverse of the standard error (SE) on the Y-axis. Asymmetric patterns in the plot then indicates a publication bias (Borenstain et al., 2009).

Step 4

Awareness of the quality of the study, for example study design, should be considered as it influences the quality of the output of the meta-analysis. Therefore, knowledge of both what the studies are investigating in addition to knowledge of the statistics is important when conducting a meta-analysis.

Step 5

A spreadsheet could be created as a way of getting an overview of available data and to pick the variables that are reported similar enough, both when it comes to study design and the reported index of the variable. If the raw data is not available, the group means with their standard error or variance and number of observations (n) is required input-information for the meta-analysis.

Step 6

Statistical software makes it possible to easily include the random effect of study. The reason study is considered as a random effect is that even though the studies are alike, there is no reason to assume that they are identical. This introduces a component of variance between the true effects across studies in addition to the variance within study. The phenomenon is called heterogeneity and is further explained in section 2.4.2.1. The total variance is the sum of heterogeneity and variance within studies. In a meta-analysis the studies are weighted according to their total variance, thereby accounting for the study effect. Also, by regarding studies as random effects, it makes the outcome of the analysis relevant not only for the included studies, but also the whole "population" in general (Borenstein et al., 2009).

2.4.2 Criticism of meta-analysis

Some have claimed that meta-analysis is a comparison of "oranges and apples" (Borenstein et al., 2009). If a meta-analysis would mean combining studies without weighting them according to their informativeness, this criticism would have been justified. In a meta-analysis it is important to be aware of the possible variance components that influence the results and this is accounted for by including the variance within studies and also the variance between studies when calculating the mean effect size.

2.4.2.1 Heterogeneity

To understand the term heterogeneity, it is important to be aware that there is a difference in true effects and observed effects. The observed effect contains both the true effect and a random error. Whilst the term variance might be used for dispersion in both observed effects and true effects, heterogeneity is a term exclusively used for the variance in true effects. The real heterogeneity in a random effect model is given as the parameter τ^2 in a meta-analysis and is estimated by the parameter tau-squared (T^2). The absolute value of the square root of T^2 gives the standard deviation of the true effects, tau (T). Both values are on the same index as the variable studied, but as T is not a squared value, this makes it easier to interpret (Borenstein et al., 2009).

The value for T should ideally be as low as possible to avoid being criticized for ”comparing oranges and apples.” If T is small, this suggests consistency between studies and the focus should be on finding the mean effect size of the variable studied. However, the presence of single studies with wide confidence intervals (CI) might mask the presence of real heterogeneity and should therefore not be used for deciding if the analysis should use a random or a fixed model. The choice of model should be based on the assumptions of whether the studies are identical or not. If the T is of a moderate size, this indicates more variation between studies and the focus should be on what is causing the heterogeneity, in addition to the effect studied. However, if T is high, this implies great variation in true effects between studies and the focus should be on finding the cause of heterogeneity rather than the variables mean effect size. A bombastic focus on an effect size in a meta-analysis with a large T could in worst case be an artefact (Borenstein et al., 2009). Heterogeneity is not dependent on number of studies, (Borenstein et al., 2009) but as with any random selection of observations from a population, the probability for a representative selection for the rest of the population increases with increasing number of studies.

3.0 Materials and methods

3.1 Study material

3.1.1 Selection criteria

Studies from the past fifteen years on intensive calf rearing were gathered for a meta-analysis. Most of the studies were gathered by ordinary literature search. In the case of unpublished data, only found as preliminary results in abstracts, the required information was gathered by personal request to the authors. For some studies the required data was calculated based on information available in the publications. To be accepted, the studies had to include data on average daily gain (ADG) in pre-weaning period and 305 days milk yield from first lactation measured as kg milk.

3.1.2 Input information in the analysis

All together, 7 publications/studies with intensive calf rearing including the requested data were found. Information about the studies and feeding in the pre-weaning period is given in Table 4, whereas the input data for the meta-analysis are given in Table 5 and 6. Most studies had more individuals in the start, measuring early life performance, than in the end of the experiment when later life performance like milk yield was measured. This was due to culling or failure in obtaining a 305-days lactation.

3.1.2.1 Detail information on designs in the included studies.

The studies all investigated the effect of increasing total nutrient intake in the pre-weaning period on early life and later life performance of Holstein heifers (one study used Holstein-Friesian heifers). However, the study design regarding feeding regimes varied between studies. Enhanced liquid feeding programmes were accomplished by using either an intensified milk replacer (MR) or whole milk (WM) (Table 4). Not all control groups were fed conventional MR and not all intensive groups were given intensive MR. In one of the studies the same type of liquid feed was used for both the control group and the intensified group, however, the treatment of the groups then differed in dilution rate of the MR. Common for all studies was an increase in total nutrients in the feed given in the intensive treatment, and most treatments had an increase in the protein/fat ratio in the liquid feed given.

Table 4. *The liquid feeding regimes in the studies comparing conventional to intensified heifer rearing.*

Study	Study No.	Feed control group	Feed intensive group
Terre et al., 2009	1	MR (25% CP, 19% fat)[a]	MR (25% CP, 19% fat)[b]
Raeth-Knight et al., 2009	2	MR (20% CP, 20% fat)	MR (27%, 17% fat)
Morrison et al., 2009	3	MR (21% CP 18 % fat)	MR (27% CP 17% fat)[c]
Drackley et al., 2007*	4	MR (20% CP, 20% fat)	MR (28% CP, 20% fat)
Moallem et al., 2006*	5	MR (23% CP, 12% fat)[d]	WM (26% CP, 29% fat)[d]
Shamay et al., 2005	6	MR (23% CP, 12% fat)[d]	WM (27% CP 29% fat)[d]
Bar-Peled et al., 1997	7	MR (23% CP, 15% fat)	WM (3.28% CP, 3.12% fat)[e,f]

[a] 12% dilutionrate,[b] 18% dilutionrate, [c] 3 different intensive treatment groups, [d] one control group and one intensive group were also fed additional 2% protein pre-pubertal post-weaning period, [e] as fed, [f] suckled from dam 3x daily, * needed data for the meta-analysis not published in the abstract was gathered by personal communication.

In all of the studies calves had free access to water and they were given calf starters with an average CP content of 18-20 %, but varied from 16% to 25%. In some of the studies the calves were also offered forages, like wetched hay in Bar-Peled et al. (1997). Two studies also included the effect of increasing CP level with 2% (DM basis) in the post-weaning period before puberty (Shamay et al., 2005; Moallem et al., 2006). When computing effect sizes in these studies, only groups with the same feeding regime post-weaning were compared. The weaning age varied between 6 and 8 weeks, one exception being the conventional calves in Drackley et al. (2007) that were weaned at 5 weeks.

3.2 Preparation of input data

The observed mean in each treatment group (Y_i) was defined according to (Borenstein et al., 2009) as "*the grand mean* (μ)*, the deviation from the study's grand mean* (ζ_i) *and the deviation of the study's observed effect from the study's true effect(* ε_i)."

$$Y_i = \mu + \zeta_i + \varepsilon_i$$

Required input data on ADG in the pre-weaning period and data on milk yield in first lactation was modified according to Borenstein et al. (2009). As the data in all the studies were reported on a common, well-known scale, the effect sizes were simply computed as the raw mean difference (MD) between two independent groups, $\bar{Y}_1$ *and* $\bar{Y}_2$, with sample sizes n_1 *and* n_2, respectively;

$$MD = \bar{Y}_1 - \bar{Y}_2$$

It was assumed that the standard deviations of the two populations were the same so

$\sigma_1 = \sigma_2 = \sigma$.

The pooled *SE* for the *MD (*SE_{MD}*)* was given in some studies. In some studies the SE_{MD} was calculated based on information on variance and sample size of each group. The variance of the *MD* was computed as

$$V_{MD} = \frac{n_1+n_2}{n_1 n_2} S^2_{\text{pooled}},$$

where S^2 is the pooled variance for population $n_1 + n_2$. Likewise S_{pooled} is the pooled standard deviation calculated as

$$S_{pooled} = \sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}},$$

where S_i^2 was the estimator for the variance of population *i*.

Taking the square root of this variance gave the SE_{MD} needed for weighting the studies in the analysis

$$SE_{MD} = \sqrt{V_{MD}}$$

***Table 5**. Studies included in the meta-analysis on effect of intensified calf rearing on average daily gain (ADG) in the pre-weaning period.*

Study No.	Group No.[a]	Total n I[b]	Total n C[c]	Total n study[d]	Effect size ADG[e]	SE_{MD}[f]
1	1	29	31	60	0.100	0.030
2	2a	26	54	133	0.115	0.020
	2b	29			0.085	
	2c	24			0.245	
3	3	75	78	153	-0.040	0.020
4	4a	11	12	23	0.228	*0.110
	4b	21	21	42	0.109	*0.102
5	5	23	23	46	0.074	0.020
6	6	20	20	40	0.291	0.034
7	7	20	20	40	0.290	*0.207
Tot = 7	**Tot = 10**			**Tot = 537**		

[a] different letters within study indicates multiple intensified groups [b] I; intensive group, [c] C; control group, [d] total n (calves) at the end of pre-weaning period, [e] effect size of average daily gain (ADG) calculated as difference between control group and intensified group (kg/day) * standard error for the raw mean difference calculated from information given for each treatment group, [f] SE_{MD}; standard error of the mean differences.

Table 6. *Studies included in the meta-analysis of effect of intensified calf rearing on milk yield in first lactation (kg/day).*

Study No.	Group No.[a]	Total n I[b]	Total n C[c]	Total n study[d]	Effect size milk yield[e]	SE_{MD}[f] (kg)
1	1	14	14	28	624	1046
2[***]	2a	18	34	95	161	393
	2b	21			-193	
	2c	22			718	
3	3	40	41	81	0	183
4	4a	10	10	20	1329	*857
	4b	14	18	32	342	*384
5	5a	8	10	36	92	171
	5b[**]	8	10		1373	
6	6a	7	8	34	132	365
	6b[**]	9			546	
7	7	15	14	29	¤453	*487
Tot =7	**Tot =12**			**Tot = 365**		

[a] different letters within study indicates multiple intensified groups [b] I; intensive group, [c] C;control group, [d] total n (calves) at the end of study, [e] effect size calculated as difference between control group and intensified group (kg), [f] SE_{MD}; standard error of the mean differences, *standard error for the raw mean difference calculated from information given for each treatment group, **groups fed additional 2% protein in post-weaning period, *** acidified and fresh milk replacer in the control group was pooled when the results were presented, ¤300 d in milk instead of 305 days

3.3 The meta-analysis

From the input data, a mean effect size (M), its 95% confidence interval (CI), Z-value and P-value was calculated by the means of the statistical software MIX 1.7 (Bax et al., 2006, Bax et al., 2008) using Microsoft Excel as the background program.

The weighting of each study was based on the inverse of the within-study variance, given as the SE_{MD} and the amount of variance between studies, a measure of the heterogeneity, given as T^2. The weighting method is called DerSimonian and Laird-method and is a mean of minimizing both sources of variance in the analysis (Borenstein et al., 2009) when computing the *M*.

The main formulas used in the analysis were according to Borenstein et al. (2009) as follows:

Estimating the variance between studies, tau-squared:

$T^2 = \frac{Q - df}{C}$

where

$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i}$,

$df = k - 1$

where k was the number of observations (studies/independent study groups), and

$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$

Each effect size was assigned with the weight

$W_i^* = \frac{1}{V_{Y_i}^*}$,

The asterix indicates a random effects model.

The variance, $V_{Y_i}^*$, in the random model contained both the variance within study (V_{Y_i}) and the variance between studies (T^2);

$V_{Y_i}^* = V_{Y_i} + T^2$

The mean effect size *M* was then calculated as

$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*}$,

The variance for the summary effect was then given by

$V_{M^*} = \frac{1}{\sum_{i=1}^{k} W_i^*}$,

Taking the square root gave the standard error of the mean effect size

$SE_M = \sqrt{V_M}$

The mean effect size and its standard error is then used for computing a 95% confidence interval with a lower and upper limit

$LL_M = M^* - 1.96 \; x \; SE_{M^*}$

$UL_M = M^* - 1.96\ x\ SE_{M^*}$

The Z value in the outcome from the meta-analyses is a test of the null hypothesis that the mean effect is zero, computed as

$Z^* = \frac{M^*}{SE_{M^*}}$.

The p value for a two tailed test was given by

$p^* = 2[1 - (\boldsymbol{\Phi}(|Z^*|))]$

$\boldsymbol{\Phi}(Z^*)$ is the standard normal cumulative distribution (table value).

In order to investigate the presence of any publication biases, a funnel plot was created with the effect size on the X-axis and the inverse of the standard error on the Y-axis (Borenstein et al., 2009).

The results of the meta-analysis outcome were presented in a standard forest plot in addition to a table of the numerical output for a visual pattern of effects (Borenstein et al., 2009).

4.0 Results

4.1 Average daily gain in the pre-weaning period

The outcome of the funnel plot for the dataset used on ADG is shown in Figure 6. The plot indicated no presence of a publication bias in the dataset constructed.

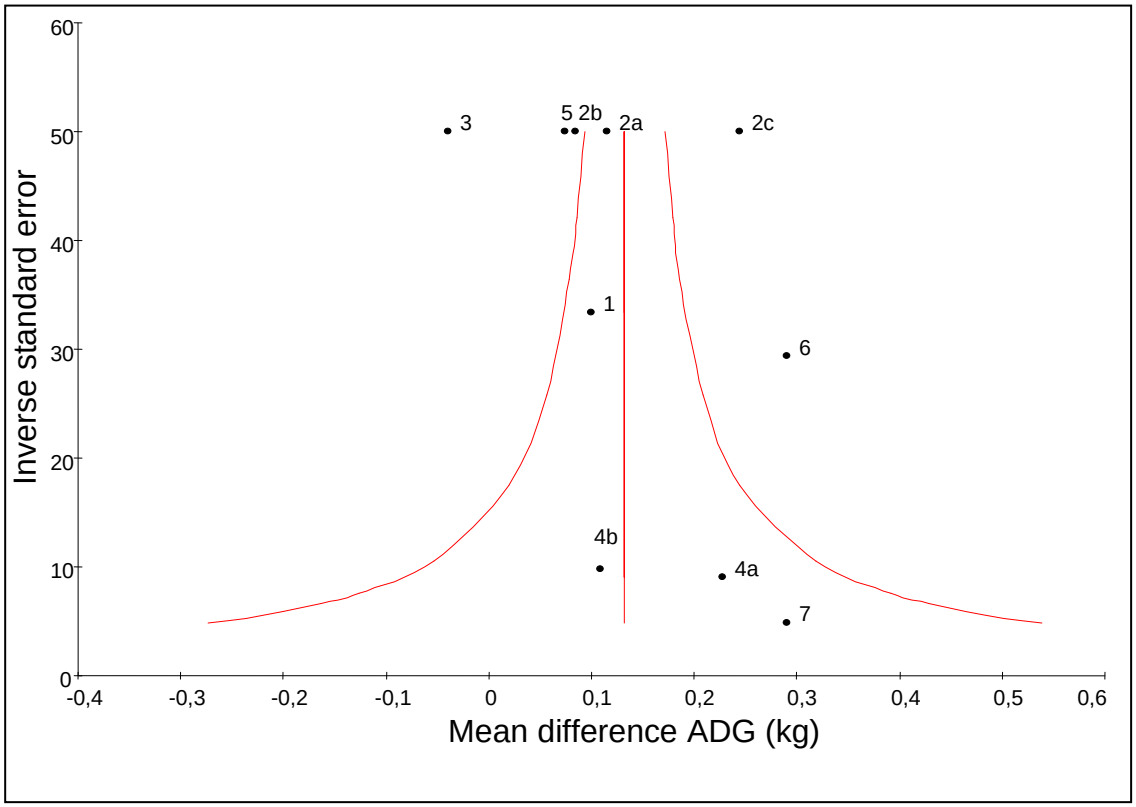


Figure 6. *A plot of mean difference (MD) on the x-axis and inverse of the standard error (SE) on the y-axis. The numbers 1-7 indicate study numbers.*

Publication bias would have accumulated studies in the top of the plot, clustering around the vertical red line (the mean effect size). Studies missing in the middle and few or no studies present towards the bottom of the plot, as well as asymmetry around the vertical red line would have indicated the same. Thus, the data set was well suited for meta-analysis.

The result of the meta-analysis on ADG is given in Table 7 and 8. The outcome of the analysis revealed an overall increase in ADG of 0.132 kg (p=0.0003) for calves on an intensified feeding program.

***Table 7**. Numerical output in the meta-analysis on effect of intensive feeding on average daily gain (ADG) (kg) in the pre-weaning period.*

Study No.	Total No. animals*	MD[a]	SE_{MD}[b]	Weight (%)	95% CI[c]	
					LL[d]	UL[e]
1	60	0.100	0.030	11.82	0.041	0.158
2a	133	0.115	0.020	12.37	0.075	0.154
2b		0.085	0.020	12.37	0.045	0.124
2c		0.245	0.020	12.37	0.205	0.284
3	153	-0.040	0.020	12.37	-0.079	0.000
4a	23	0.228	0.110	5.91	0.012	0.443
4b	42	0.109	0.102	6.40	0.090	0.308
5	46	0.074	0.020	12.37	0.034	0.113
6	40	0.291	0.034	11.55	0.224	0.357
7	40	0.290	0.207	2.49	-0.115	0.695
Mean effect size		**0.132**		**100**	**0.061**	**0.203**

* in the calf period of the studies, [a] MD = mean difference in average daily gain [b] SE_{MD}=standard error of the mean differences, [c] CI = confidence interval, [d] LL = lower limit, [e] UL = upper limit

***Table 8.** Level of statistical significance and heterogeneity in the meta-analysis of effect of intensive feeding on average daily gain (ADG) in the pre-weaning period.*

Random effect model	
z	**3.636**
p-value (two-tailed)	**0.0003**
Heterogeneity	
T^2	**0.0103**
T (kg/d)	**0.101**

The pattern of effects of intensive feeding in the pre-weaning period is visualized in Figure 7.

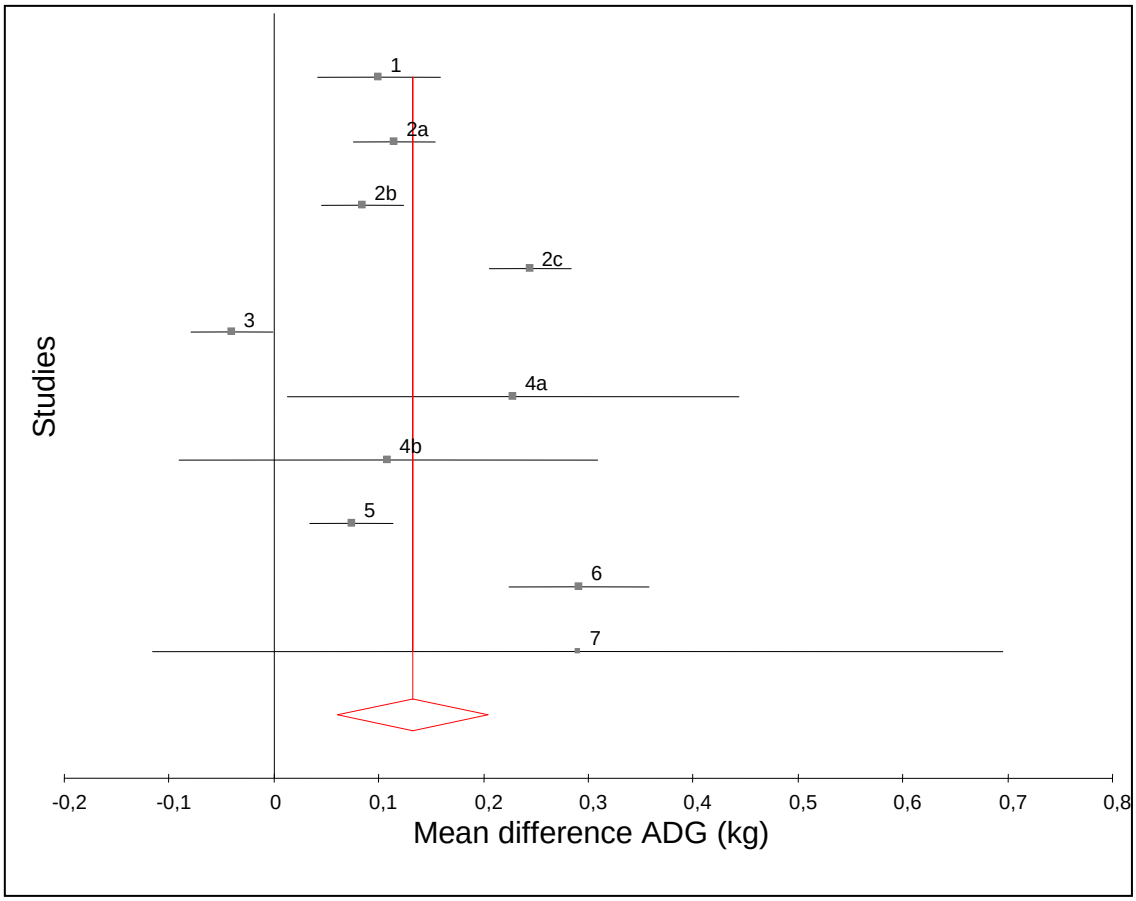


***Figure 7**. Forest plot of effect of intensive feeding regime in the pre-weaning on ADG (kg). The numbers 1-7 indicate study numbers.*

The horizontal lines give the 95% confidence interval (CI) within study. The lines indicate a considerably difference in variation within study. However, except for study 3(Morris et al., 2009), all studies have a positive effect size. The red line and the diamond box show the overall mean effect size for ADG on 0.132 kg and an estimated 95 % CI between approximately 0.05 and 0.2 kg.

4.2 Milk yield in first lactation

The outcome of the funnel plot for the dataset used on milk yield is shown in Figure 8. The plot indicated no presence of a publication bias in the dataset constructed.

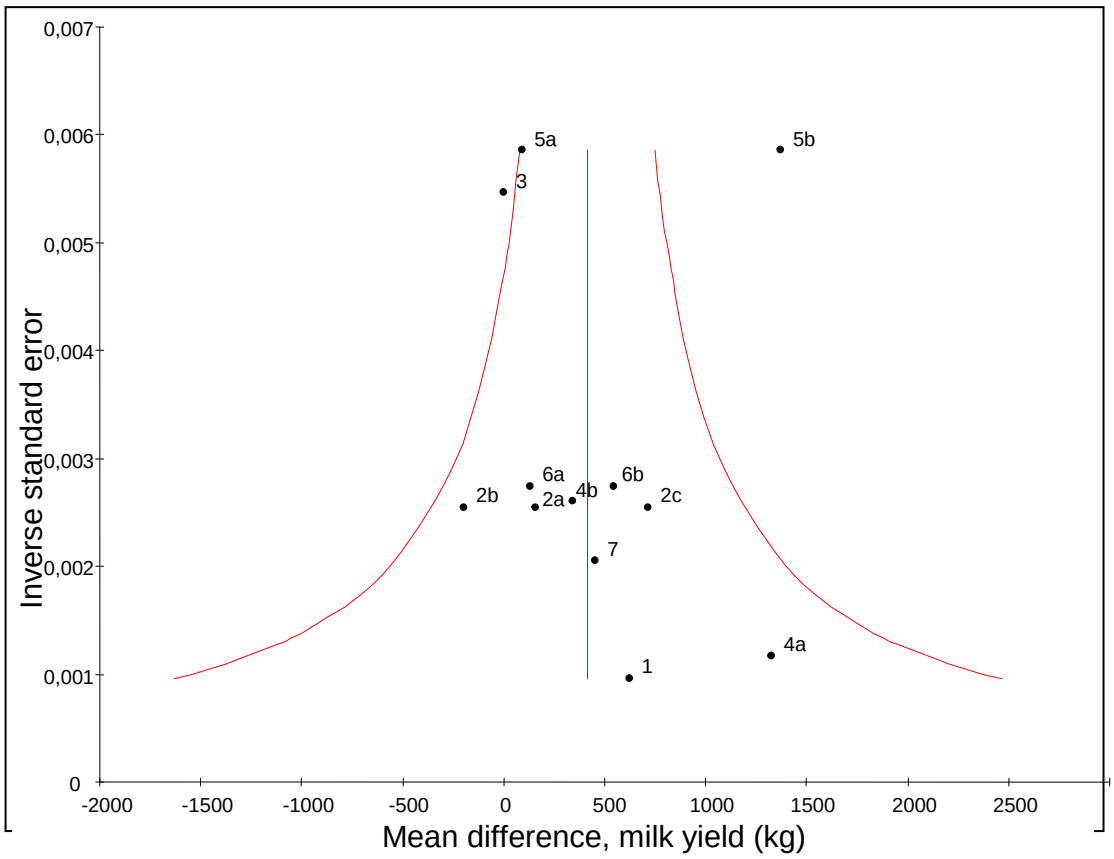


Figure 8. *A plot of mean difference (MD) on the x-axis and inverse of the standard error (SE) on the x-axis. The numbers 1-7 indicate study numbers.*

Publication bias would have accumulated studies in the top of the plot, clustering around the vertical red line (the mean effect size). Studies missing in the middle and few or no studies present towards the bottom, as well as asymmetry around the vertical red line would have indicated the same. Thus, the data set for milk yield was also well suited for meta-analysis.

The result of the meta-analysis on milk yield in first lactation is given in Table 9 and 10. The outcome of the analysis revealed an overall significant increase in first lactation milk yield ($p=0.0313$) for calves on an intensive feeding program. The mean effect size was 416 kg with a 95 % CI between 37 and 795 kg.

***Table 9**. Numerical output in the meta-analysis of effect of intensive feeding in the pre-weaning period on milk yield (kg) in first lactation.*

Study No.	Total No. animals*	MD[a]	SE_{MD} [b]	Weight (%)	95% CI[c]	
					LL[d]	UL[e]
1	28	624	1045	2.70	-1425	2673
2a	95	161	393	8.42	-609	931
2b		-193	393	8.42	-963	577
2c		718	393	8.42	-52	1488
3	81	0	183	11.57	-358	358
4a	20	1329	857	3.65	-350	3008
4b	32	342	384	8.56	-410	1094
5a	36	91	170	11.73	-243	426
5b		1372	170	11.73	1037	1707
6a	34	132	365	8.84	-583	847
6b		546	365	8.84	-169	1261
7	29	453	487	7.10	-501	1407
Mean effect size		**416**		**100**	**37**	**795**

* heifers who completed 305-d in milk in first lactation, with study 7 as an exception, where milk yield was measured as 300-d in milk. [a] MD = mean difference in milk yield [b] SE_{MD}=standard error of the mean differences, [c] CI = confidence interval, [d] LL = lower limit, [e] UL = upper limit

***Table 10.** Level of statistical significance and heterogeneity in the meta-analysis of effect of intensive feeding in the pre-weaning period on milk yield in the first lactation.*

Random effect model	
z	**2.1527**
p-value (two-tailed)	**0.0313**
Heterogeneity	
T^2	**289621**
T(kg)	**538**

Figure 9 shows the pattern of effect sizes from each study in a standard forest plot.

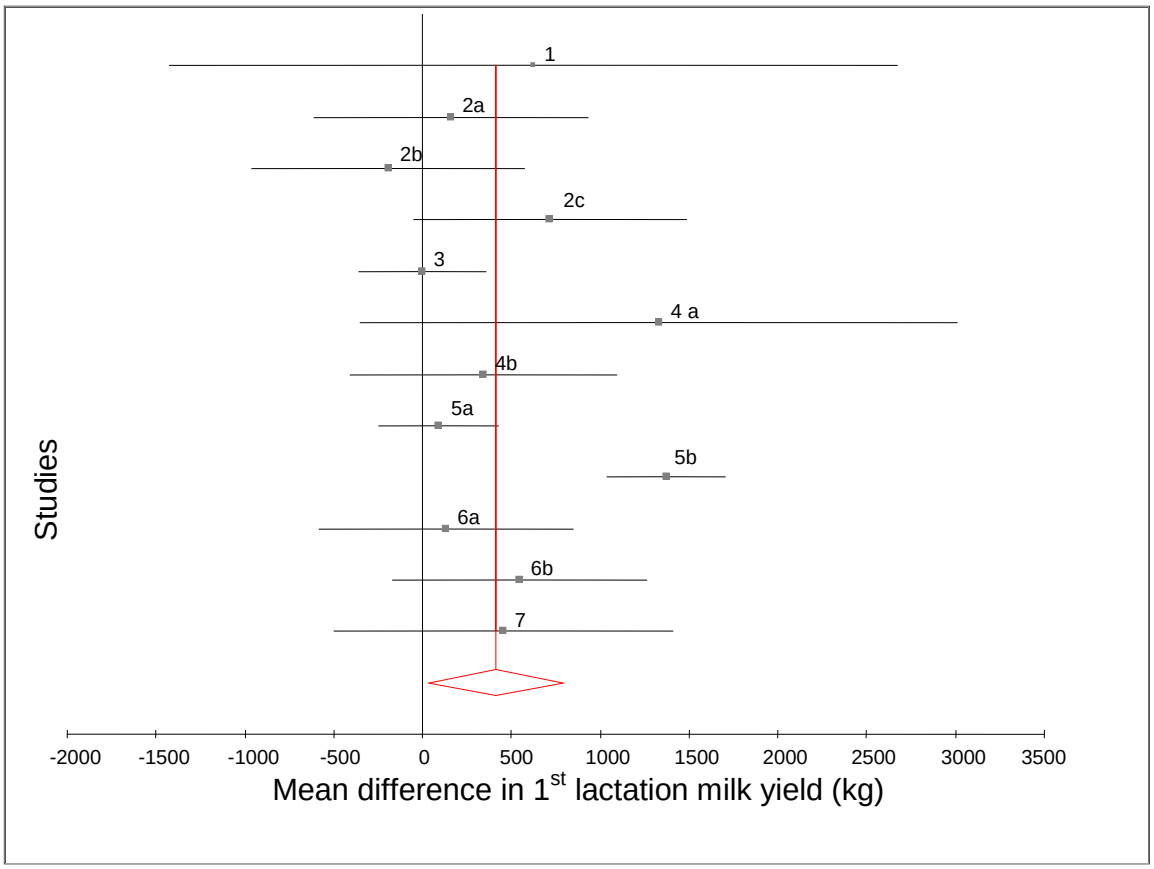


Figure 9*. Forest plot of effect of enhanced feeding regime pre-weaning on milk yield (kg) in first lactation. The numbers 1-7 indicate study numbers.*

The horizontal lines give the 95% CI within study. The lines indicate a considerably difference in variation within study. The red line and the diamond box show the overall mean effect size for milk yield on 416 kg and an estimated 95 % CI between approximately 40 and 800 kg.

5.0 Discussion

5.1 Methodological considerations

Meta-analysis combine statistical data from several small and confounding studies to create a dataset with more statistical robustness to address broader questions than single studies can do (Borenstein et al., 2009). Ideally the meta-analysis should include as many studies as possible from as many different sources as possible to make a fully randomized selection of studies. Also, the studies should be independent and effects and variation should be calculated on comparable basis and represent comparable units (Hamer and Simpson, 2002).

The funnel plots revealed no presence of a publication bias. The dataset therefore represents a random selection of studies. The meta-analysis was based on 7 randomly selected studies including 10 and 12 independent observations for ADG and 1st lactation milk yield, respectively. Some of the observations were independent groups within a study, for example differing in solid content of the intensive MR. However, their independence might be argued, as some of them were reported with a pooled variance (study 2 in analysis for ADG and study 2, 4 and 6 for analysis of milk yield). Ideally, they should have been reported with variance for each treatment, not just a pooled variance, so that each group could be weighted accordingly (Leon Bax, personal communication). Since the statistical software make the assumption that all studies are independent this probably introduced a minor error when weighting the studies.

Heterogeneity reflects the in-between variance of true effects across studies, and is estimated by T^2. The square root of this value yields the standard deviation, T, of the distribution of true effects and is used for deciding the consistency of effects across studies. The level of T in the meta-analysis decides where focus should be when interpreting the results. In case of a high T, the focus should be on finding the under laying factors causing the heterogeneity, if the T is moderate, the focus should be on both the mean effect size, and also on the causes of heterogeneity. In the case of a small T the focus would be on the resultant mean effect size in the analysis. A high focus on the mean effect size in a dataset with a high T would in worst case lead to a conclusion based on artefacts (Borenstein et al., 2009). In the present study, heterogeneity was relatively high both for ADG and milk yield. The actual effect size itself is therefore of moderate importance. This was reflected in the relatively large CI, ranging from 0.061 to 0.203 kg/day for ADG and from 37 to 795 kg for milk yield. The reason for the heterogeneity was most likely due to some differences in feeding regimes between studies.

For example, study 6 used WM as the intensive feed and study 7 used suckling calves, whereas most of the other studies used intensive MR. This would imply a difference in chemical composition of the feed and amount of intake. Nevertheless, they all represented intensive feeding and the overall effect was significantly positive. Other factors like immune status and post-weaning feeding regime were also likely to differ between studies and contribute to the relatively high *T*. Despite this heterogeneity, the meta-analysis revealed a significantly positive effect of intensive calf rearing. However, more studies with a more standardized study design for comparing conventional and intensive milk feeding would make it possible to predict a more accurate effect on performance in early and later life. Therefore, a meta-analysis like this ought to be continuously updated as results from new comparable studies are published. This would also improve robustness and might reveal possible under laying factors explaining the results.

5.2 Physiological mechanisms

Diseases in early age are known to negatively affect both early growth and later life performance like calving age (Correa et al., 1988). The hypothesis is that the immune status to some extent is affected by nutrition, especially in the early pre-weaning period when the calf is dependent on passive immune transfer through the milk (Quigley et al., 2005). An increase in nutrient intake, especially of protein, is thought to be of particular importance as certain amino acids like glutamine is widely used for growth of cells (lymphocytes, macrophages and cytokines) in the immune system (Calder and Yaqoob, 1999). Likewise, lysine seems to be an important fuel for the immune system in chickens. Klasing and Calvert, (1999) as cited in Drackley, (2005), showed a demand of 7% of total lysine intake for immune response when challenged with a bacterial lipopolysaccharide. A positive effect on immune status may explain the observed increase in ADG and feed efficiency when protein content was increased to calves fed iso-caloric MR, energy was not limiting and no starters were offered (Bartlett et al., 2006; Blome et al., 2003). The same was also found in trials were starters were offered (Hill et al., 2009). The trial of Hill et al. (2009) kept lysine (2.44%), methionin (0.75%) and threonin (1.56%) constant when lowering total CP content. This, however, led to a decrease in ADG and feed efficiency, indicating that other amino acids might be limiting factors. In addition to immune cells, glutamine is an important fuel for rapidly proliferating gut cells (Newsholme et al., 1985), and thus might enhances the absorption of nutrients in the digestive tract and thereby improve feed efficiency. Another element in this discussion is that protein digestibility for calves probably are closer to 0.7 than 0.8 as given by NRC (2001) (Van

Amburgh et al., 2008). Thus, calves might have been underfed on amino acids. As a consequence Van Amburgh and Drackley (2005) revised the protein requirements for calves, ensuring better supply of amino acids to young calves. Also, calves are sensitive to the effect of nutrition during temperature stress as this leads to higher feeding level for maintenance and growth. A feeding level of less than 12% of BW in Drackley et al.(1996) led to unhealthy Jersey calves with poor ADG when kept in hutches outside during winter.

The outcome of the present meta-analysis was positive for intensive reared calves. However, it is possible that colostrum administration before the start of the studies included in the meta-analysis affected the results. Denise et al. (1989) found that every milligram increase of Ig in the calf at 24 h age led to an increase of 8,5 kg milk in 1st lactation (adjusted 305-d lactation of energy corrected milk). This study is supported by Faber et al. (2005) who found a positive effect on ADG in the pre-weaning period when force feeding 4 litres compared to 2 litres of colostrums during the first hour after birth. The effect of force feeding was positive also on survival through 2nd lactation and milk yield in 1st lactation. The referred studies suggest that intensive rearing is important already from the very first meal. Unfortunately, feeding of colostrums after birth was not given in most of the studies used in the meta-analysis, and therefore could not be studied.

Calves on intensive feeding program have been reported to have higher feed efficiency, and higher ADG. The increased stature, BW, lean tissue deposition and increased whole body protein deposition might be due to signals from insulin and amino acid status that activate protein synthesis (Drackley, 2005). Studies with other animals like rats (Winick and Noble, 1966), pigs (Campbell and Dunkin, 1983) and lambs (Greenwood et al., 2000, Greenwood et al., 1998) demonstrated that when animals were protein malnourished in early life, this lost growth failed to be restored later in life. The same might be the case in cattle as suggested by Drackley (2005). The muscle mass is the main site for utilization of none esterified fatty acids (NEFA) and ketone bodies from the liver when energy is obtained from adipose tissue. Based on studies of this metabolism, combined with the fact that cows become leaner when selecting for milk yield (Murphy et al., 1991 as cited in Drackley, 2005), Drackley, (2005) suggested that the muscle mass might be important for health and metabolism during the lactation and when challenged with metabolic adaptations.

When the heifers were fed an additional 2% protein in the feed in the post-weaning period before puberty this enhanced the effect of the intensive feeding in the pre-weaning period in

the studies of Moallem et al. (2006) and Shamay et al. (2005). This might have been due to mechanisms like increased protein supply for mammary development in the allometric growth of the mammary gland, indicating that the protein supply in the whole rearing period seems to affect the mammary development and that the critical period seems to be the whole period of heifer rearing and not only the allometric growth period.

Growth and development in the young calf is largely regulated by growth hormone (GH) from the pituitary gland and insulin-like growth factor (IGF-1) produced in the liver but also locally in several tissues, like the mammary fat pad (MFP) (Berry et al., 2001). Mammary growth and development is thought to be regulated through the GH/ insulin like growth factor (IGF-1) axis (Akers et al., 2005). Components in this axis are GH, IGF-1, binding receptors and IGF binding proteins (IGFBP) (Akers, 2006). Increasing level of IGF-1 has thought to lead to an increase in proliferation in mammary stem cells (Akers et al., 2005, Meyer et al., 2006a).

Studies have revealed that IGF-1 increases with greater feeding rates and linearly with increasing dietary CP (Bartlett et al., 2006) and is also highly correlated with patterns of ADG (R=0,72) (Drackley, 2005). High feeding levels were implicated to have negative effects on the mammary development through this axis in Sejrsen, (1983) and Berry et al., (2003). The detrimental effect on milk yield observed at too high feeding levels before puberty was explained by decreased sensitivity to IGF-1, presumably because of elevated production of IGFBP-3 impairing the effect of IGF-1 (Sejrsen, 2005). Also Quigley et al. (2006) found effect of nutrition on level of IGF-1. However, Meyer et al. (2007) found no effect on level of IGF-1 from intensive rearing, and neither did Daniels et al. (2009). These conflicting results suggest that there might also be other hormones and growth factors (Sejrsen, 2005) controlling the growth and development of the mammary gland. Therefore more research seems to be needed to fully understand the physiological regulation.

6.0 Conclusion

- The meta-analysis based on the literature on effect of intensive calf rearing from the past 15 years reveals that there is a significant merit in pre-weaning ADG and first lactation milk yield. These results lead to the suggestion that the terms “compensatory growth” and “critical period” might be questioned as the results indicate an effect of early life nutrition that appears not to be restored later in life.

- The relatively large heterogeneity in the analysis implies that more studies, with more comparable feeding regimes is needed for a meta-analysis to state an accurate size of this positive effect of intensive feeding in the pre-weaning period.

- The large heterogeneity in the studies is thought to be caused by factors like feeding regimes and immune status. The protein supply after weaning seems to have effect on the performance when all other managing factors are the same.

7.0 Literature

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