Italian Journal of Animal Science

ISSN: (Print) 1828-051X (Online) Journal homepage: http://www.tandfonline.com/loi/tjas20

Some new aspects of nutrition, health conditions and fertility of intensively reared dairy cows

Giuseppe Bertoni, Erminio Trevisi & Rosanna Lombardelli

To cite this article: Giuseppe Bertoni, Erminio Trevisi & Rosanna Lombardelli (2009) Some new aspects of nutrition, health conditions and fertility of intensively reared dairy cows, Italian Journal of Animal Science, 8:4, 491-518, DOI: 10.4081/ijas.2009.491

To link to this article: http://dx.doi.org/10.4081/ijas.2009.491

Published online: 01 Mar 2016.

Review article

Some new aspects of nutrition, health conditions and fertility of intensively reared dairy cows

Giuseppe Bertoni, Erminio Trevisi, Rosanna Lombardelli

Istituto di Zootecnica. Università Cattolica del Sacro Cuore, Piacenza, Italy

Corresponding author: Prof. Giuseppe Bertoni. Istituto di Zootecnica. Facoltà di Agraria, Università Cattolica del Sacro Cuore. Via Emilia Parmense 84, 29122 Piacenza, Italy – Tel. +39 0523 599277 – Fax: +39 0523 599276 - Email: giuseppe.bertoni@unicatt.it

Received November 21, 2008; accepted April 12, 2009

ABSTRACT

Speaking in terms of the general relationship between nutrition and reproduction, many different aspects are more or less involved depending on geographical areas, species, production systems, technological levels etc. There are deficiency conditions: energy, proteins, vitamins and minerals; but also some excesses (namely protein and few minerals) or toxic substances such as micotoxins or plant compounds (i.e. phyto-oestrogens). Their relevance is different in the intensive systems for better feeds and relative easiness to create appropriate diets. Nevertheless, intensification does not reduce the nutritional risks for livestock reproduction for several reasons: namely, a suspected higher susceptibility of high genetic merit cows to the usual stresses. There is also a new risk: metabolic stress (e.g. negative energy balance). The latter is particularly relevant when early lactation and new pregnancy are close (as in dairy cows), however, of great importance are also oxidative stress and disease stress (pro-inflammatory cytokines). In dairy cows, inflammatory phenomena around calving - when an immune response occurs in spite of clinical symptoms are missing - are significantly related to a lower pregnancy rate. A possible explanation can be seen in the pro-inflammatory cytokines, which modify liver synthesis and seem to impair energy balance thereby reducing feed intake and increasing energy expenditure. This suggests that in order to improve fertility not only better feeding mecahnisms, but any husbandry tool that can reduce diseases and health disorders are needed.

Key words: Fertility, Dairy cows, Nutrition, Health, Inflammations.

RIASSUNTO

TALUNI ASPETTI RECENTI DELLA NUTRIZIONE, DELLO STATO DI SALUTE E DELLA FERTILITÀ NEGLI ALLEVAMENTI INTENSIVI DI LATTIFERE

In termini generali, molti fattori sono coinvolti nel rapporto alimentazione e riproduzione, ma in modo differente in relazione all'area geografica, alla specie, al sistema produttivo, al livello tecnologico ecc.. Tali fattori alimentari includono: carenze di energia, proteine, vitamine e minerali, ma talora anche eccessi *(specie proteine ed alcuni minerali) o la presenza di sostanze tossiche come micotossine o composti vegetali (es. estrogeno-simili). Per molti di essi l'incidenza è ridotta nei sistemi intensivi, per una maggior facilità nel disporre di alimenti sani e nel formulare diete appropriate. Cionondimeno i sistemi intensivi non riducono i rischi nutrizionali per la riproduzione delle vacche da latte anzitutto per gli elevati livelli produttivi che accrescono la suscettibilità delle bovine agli stress usuali di allevamento, ma soprattutto a quello metabolico (frutto del bilancio energetico negativo). Quest'ultimo è rilevante quando le fasi iniziali della lattazione e l'avvio di una nuova gravidanza sono vicine (come avviene nella vacca da latte), mentre di grande rilievo per questi animali sono anche lo stress ossidativo e lo stress da malattia (con rilascio di citochine pro-infiammatorie). Nelle vacche da latte, i fenomeni infiammatori nel periparto - frutto di una risposta immunitaria, talora in assenza di sintomi clinici - sono significativamente correlati ad un più basso tasso di concepimento. Una possibile spiegazione può essere vista nelle citochine pro-infiammatorie che modificano le sintesi epatiche, ma soprattutto aggravano il bilancio energetico: riducendo l'ingestione ed aumentando la spesa energetica. Ne consegue che, per aumentare la fertilità, non basta una migliore alimentazione, nel periodo di transizione, ma è utile anche qualsivoglia accorgimento gestionale, purchè utile a ridurre malattie ed anomalie nello stato di salute delle bovine.*

Parole chiave*: Fertilità, Bovina da latte, Nutrizione, Salute, Infiammazioni.*

Introduction

Fertility is the result of so many factors that the definition of Fromageot (1978) is not surprising: reproduction can be considered a "luxury" function. In fact, several experiments have demonstrated how numerous and different are the causes of reduced fertility. Among them, nutrition has a relevant role (Wolter, 1973; Bertoni, 1990; Ferguson, 1991) related to the deficiency (and sometimes excess) of either energy, protein, fiber, macro and trace elements, and vitamins, as well as toxic effects from natural compounds (e.g. phytoestrogens, nitrates), from conservation spoilage of feeds (e.g. mycotoxins), and from environment or farming pollution (e.g. heavy metals, pesticides). The real risks from each potential cause can be different depending on many factors of which the breeding system is of major importance. In fact, from a nutritional point of view, the intensive breeding systems tend to reduce many of the above causes for the better conservation technologies of feeds and for a more accurate selection of the diet ingredients which offer a better satisfaction of the nutritional requirements.

This is particularly true as respects the supplementation of minerals and vitamins, better achieved in the intensive farms (Schaver and Howard, 1993), and it could explain why trace elements and vitamin supplements do not always improve the reproductive efficiency of intensively bred dairy cows (Jukola *et al.*, 1996). Therefore, the levels of vitamins and minerals, as well as toxic factors will not be considered here. For similar reasons many other causes of low fertility will not be considered: e.g. general management (Ouweltjes *et al.*, 1996; De Vries and Risco, 2005), climatic conditions and, in particular, heat stress (Jordan, 2003) and any other stress factor (Bono, 2003). Nevertheless, we acknowledge the importance of these last aspects with a quote from Lucy (2001): […] *declining fertility is probably a combination of a variety of physiological and management factors that have an additive effect* […].

At the same time, the intensive dairy systems can be the cause of reproductive impairments: high risk of large ratio of cows to labourers, unsuitable buildings and equipment and, primarily, continuous genetic improvements for milk yield level which create difficulties for energy-protein nutrition and for health conditions. For these reasons greater attention will be paid to the effects on reproduction efficiency, on milk yield level, on energy and protein intakes, but also on health status and inflammatory conditions.

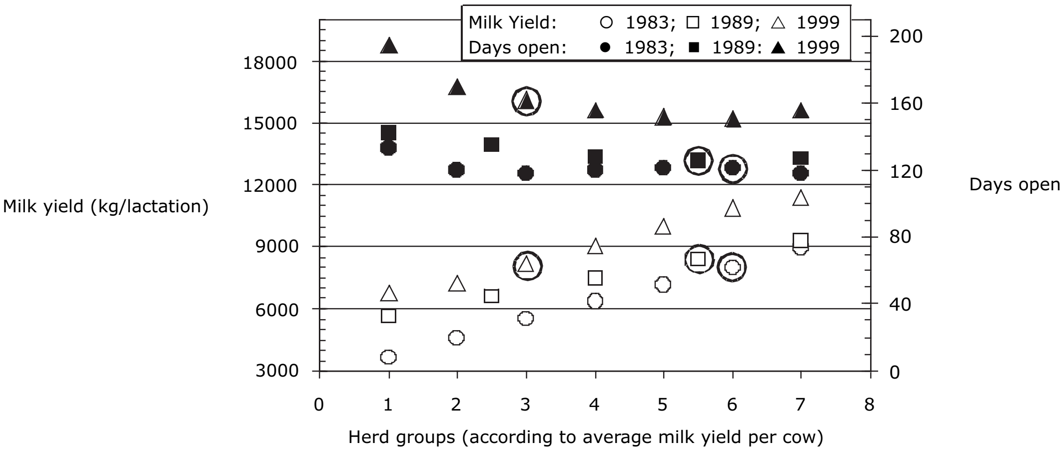
Fertility and milk yield level

According to the most recent reviews regarding dairy cow fertility, the close negative relationship between genetic merit increase for milk yield and fertility reduction have been underscored (Butler, 1998; Webb *et al.*, 1999; Lucy, 2001, 2003; Santos, 2001; Webb *et al.*, 2004; Oltenacu and Algers, 2005). A possible explanation could be a genetic antagonism between milk yield and fertility, more likely due to a pleiotropic gene effect (Veerkamp *et al.*, 2003) which modifies the level of some hormones (e.g. insulin and GH/IGF-1 axis) and induces changes in energy partitioning with a consequent reduction in metabolic fuel availability for reproductive organs. Nevertheless, Hansen (2000) suggests that direct genetic control of fertility is low, while environmental factors are so numerous and important. A confirmation of the low direct genetic importance can be seen in the good level of fertility in heifers with a very high genetic merit for milk yield (Hansen *et al.*, 1983; Lucy, 2003). The low genetic control does not exclude the possibility of a profitable, yet slow, improvement in fertility by a proper selection scheme (Gonzales-Recio and Alenda, 2005). Furthermore, the low direct relationship does not exclude a reduction in fertility in case of high milk yield; in fact, the great importance of management suggests that, according to Ouweltjes *et al.* (1996), Webb *et al.* (1999), Santos (2001), and Inskeep (2004), it can be inappropriate for this kind of cow, leading more often to the inverse relationship between milk yield and fertility.

The strong negative relationship has been suggested by Butler (1998) and Royal *et al.* (2000): a similar and dramatic reduction in fertility occurred in the USA and UK in the last quarter of the 20th century, but milk yield rose (3000 *vs* 1500 kg/cow) and final levels (9000 *vs* 6000 kg/cow) were extremely different and higher in the USA. A worsening of fertility at the end of last century was also observed in the DHI tested Holstein herds (Raleigh Dairy Records Processing Center) and evaluated by Call and Stevenson (1985) and by Stevenson (1999). As shown in Figure 1, the lower yielding farms had higher days open in all the 3 surveys. Nevertheless, the days open appeared markedly increased in the 1999 one, but also in low yielding herds; when the comparison was done within the same average yield of 8000 kg of three surveys (circled), the difference for 1999 survey is confirmed.

Both previous comparisons (USA *vs* UK and within USA herds different for milk yield) seem to suggest - in our view - that reproductive success is not only affected by milk yield (direct genetic effect), but other factors could be important, such as the management. In other words, the existing negative relationship between milk yield and fertility, particularly in farms that are not well managed, could be due to the difficulty to satisfy the energy (and maybe protein) requirements of high genetic merit cows that genetically direct nutrients toward the mammary glands (Verkaamp *et al.*, 2003). Furthermore, these kinds of cows could become more susceptible to metabolic stress and, consequently, to metabolic and/or to infectious diseases, as well as to reproductive problems (Garnsworthy and Webb, 1999; Knight *et al.*, 1999; Ward and Parker, 1999). Namely, the higher frequency of infectious problems regarding the reproductive apparatus (Heuer *et al.*, 1999), as well as other apparatus of the above cows, could be the consequence of an unsatisfactory nutrition supply which impairs the immune system

Figure 1. Ranking according to individual milk yield of DHI tested herds (Holstein) in the last two decades of the 20th century (Raleigh Dairy Records Processing Center): 5480 herds in 1983 (Call and Stevenson, 1985), 2138 herds in 1989 and 9684 herds in 1999 (Stevenson, 1999). In addition to the average milk yield per lactation of every group, the corresponding average data of days open in the same herds have been indicated. For a better comparison, groups of the three surveys with milk yield close to 8000 kg/lactation have been circled, both for milk yield and days open.



(Ferguson, 1991; Schukken *et al.*, 1999). Further greater difficulties for high yielding cows could occur for the higher susceptibility to negative environmental factors (Drackley, 2006).

As previously suggested, it can therefore be inferred that high milk yield is an indirect predisposing factor for the reduction in fertility as suggested by Oltenacu and Algers (2005); however, the high variability among dairy farms (Stevenson, 1999), as well as within the cows of the same farm (Bertoni *et al.*, 2008), suggests the possibility of improvement by addressing the general management (Drackley, 2006). Notwithstanding this, the long term genetic selection for better fitness and tolerance to metabolic stress (Oltenacu and Algers, 2005) appears essential to maintain, particularly in the future, acceptable levels of fertility in high yielding cows.

The conclusions of Ingvartsen *et al.* (2003) appear noteworthy to us: *there is not an inevitable association between increased milk production and poorer health.* Higher yield and unsuitable life conditions increase the risks*; nevertheless, a proper feeding strategy, can help to alleviate these risks*. Similar conclusions were previously given by Distl *et al.* (1989) who studied double purpose cows. More recently, quite similar suggestions have been proposed by Aeberhard *et al.* (2001): *cows yielding ≥45 kg ECM/day could be maintained with no more serious problems than the cows with yields of around 35 kg ECM/day, if husbandry, management and feeding were adequate*.

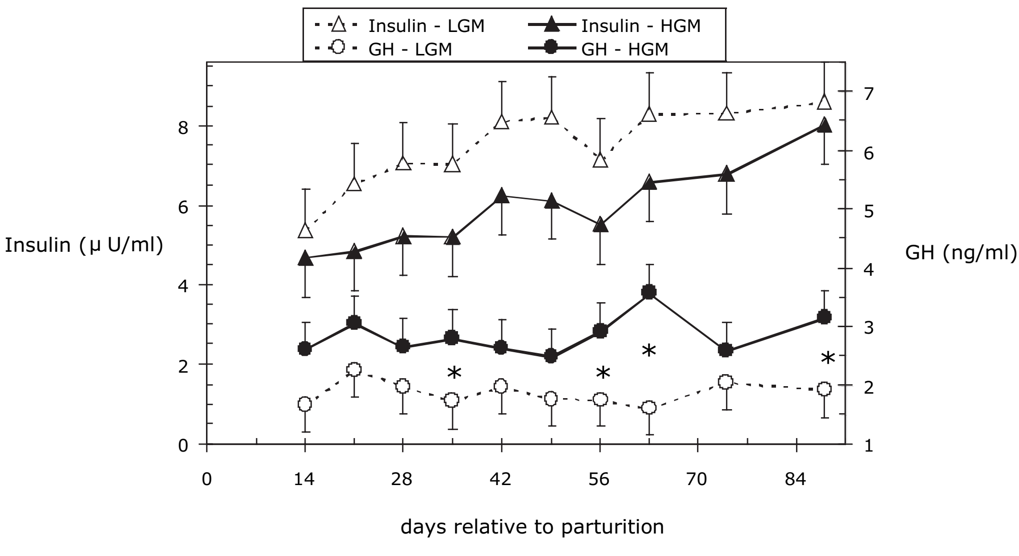
In short, it appears essential - as respects high yielding cows - to use special care in general management and nutrition, particularly during the dry (and transition) periods. Our interest is mainly directed toward the nutritional management and within it we shall discuss the main aspect of energy and protein imbalances, along with the metabolic consequences of "diseases" (inflammatory phenomena), sometimes linked to nutrition as well.

Fertility and energy balance

It is generally well accepted that a shortage of energy, mainly occurring before calving in beef cows (Hess *et al.*, 2005) and after calving in the dairy cows (Butler, 1998), impairs reproduction efficiency. For dairy cows, the major interest for a long time has been devoted to the early oestrus resumption which appears to have a strong relationship with the following pregnancy (Butler, 2003). In other words, prolonged anestrus after calving seems justified by the negative effect of lower insulin levels which affect both follicle development and ovulation (Bean and Butler, 1997; Landau *et al.*, 2000; Gong *et al.*, 2002). The importance of insulin on reproduction has been confirmed by Opsomer *et al.* (1999) who suggested an increase in cystic ovarian diseases in cows affected by insulin resistance (i.e. a peripheric insensitivity to the hormone, which, however, is often associated with inflammatory conditions, as shown by Grimble, 2002).

Nevertheless, it is important to bear in mind that a low insulin level is closley linked to negative energy balance (NEB), but also to the high genetic merit of cows (Bonczek, 1986) at least in the first 2-3 months of lactation (Figure 2). Furthermore, NEB would

Figure 2. Pattern of changes of basal blood insulin and GH (mean values ± pooled SEM) in dairy cows with different genetic merit: low (LGM; 4 cows) or high (HGM; 4 cows). Blood samples were taken before morning meal during the first 3 months of lactation (Lombardelli *et al.*, 2002).



*Overall difference between the two groups is statistically significant (P<0.05) for GH; *=P<0.05 between groups at the same days.*

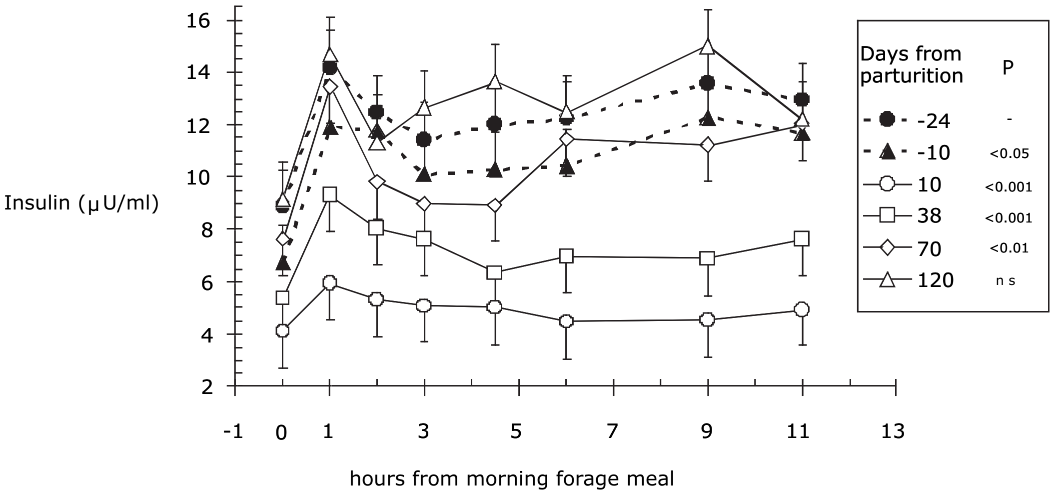
also compromise the blood levels of IGF-1, which is reduced, despite higher GH, due to the lower presence of GH receptors in the liver (Lucy *et al.*, 2001; Veerkamp *et al.*, 2003). The IGF-1 seems important for the growth of small follicles and for granulosa cell proliferation. Low energy availability also seems to compromise LH surge through the reduction of GnRH pulse frequency and ovarian responsiveness to LH (Butler, 2005). Protracted intervals to first oestrus are also associated with delays in the recovery of leptin concentrations after calving (Kadokawa *et al.*, 2000) and low concentrations of leptin have been observed in cows with abnormal post-partum reproductive cycles (Mann and Blache, 2002). This hormone is produced primarily by adipose cells; therefore, its blood concentration is positively correlated to the size of the fat deposits and then to the nutritional status (BCS). The receptors of leptin have been identified in the hypothalamus and bovine ovarian granulosa cells, suggesting a permissive threshold of its blood level for pubertal or postpartum reproductive activity (Barash *et al.*, 1996; Chilliard *et al.*, 2005).

Finally, the NEB is obviously characterised by a shortage of some metabolic fuels (e.g. glucose and aminoacids), mainly because they are drained by the mammary glands for syntheses, and by an increase in others (e.g. NEFA, BHBA). Therefore, besides the above hormone changes, the glucose shortage could be a primary cause of lower reproduction activity as suggested by Wade *et al.* (1996), Schneider and Wade (2000), Veerkamp *et al.* (2003) and partly confirmed by Francisco *et al.* (2003) as well as Butler *et al.* (2006). Moreover, the rise of NEFA and ketone bodies could exert a negative (toxic) effect on follicles and oocytes (Kruip *et al.*, 1999; Jorritsma *et al.*, 2004).

This last finding suggests that the issue of energy deficiency and reproduction cannot be limited to post-calving NEB and anestrus, also because in literature some contradictory results are available. The negative effects of NEB on the prolonged anestrus are important according to Call and Stevenson (1985), Butler and Smith (1989), Butler *et al*. (2006), but NEB is not considered so important according to Villa-Godoy *et al.* (1988), Harrison *et al.* (1990) and Spicer *et al.* (1990). Our experience (Bertoni *et al.*, 1999) suggests that cows retrospectively grouped according to genetic merit for milk yield had a different reproductive behaviour: high yielding cows showed a shorter anaestrus post-partum, but lower pregnancy rate. From the metabolic and endocrine point of view, the high yielding cows had, however, the expected features according to Bonczek (1986) and Veerkamp *et al.* (2003): lower glucose, higher NEFA and BHBA (then higher BCS loss), while insulin was lower and GH higher (Figure 2). It is interesting that the slight rise in insulin level starts during early lactation, but it rapidly becomes greater in the 2nd and 3rd month and at the end the difference is very small. The increase during lactation can be better evaluated from Figure 3 with the post-meal changes in different stages (but all cows have high genetic merit). Going back to the data of Bertoni *et al.* (1999): earlier resumption of oestrus, lower fertility and quick rise of insulin in the first three months of lactation of high yielding cows suggest again that the role of insulin is perhaps important, but not crucial.

A further mechanism of NEB to impair reproductive efficiency could be the quality of oocytes; it has been recently recognised - although indirectly - by Garnsworthy *et al.* (2008) that a diet which ensures good insulin values (high starch) has a favourable effect on follicle growth and early resumption of oestrus cycle, but not on oocyte quality and progesterone level. Similar results - dif-

Figure 3. Daily pattern of changes of blood insulin (mean values ± pooled SEM), after morning forage meal, in late pregnancy (-24 and -10 days relative to parturition) and in different stages of lactation (10, 38, 78 and 120 days of lactation) of 8 high genetic merit dairy cows (Bertoni *et al.*, 2002).



Statistical difference between overall daily means at -24 days from calving and each other day is shown by P value.

ferent pattern of change of ovarian activity re-establishment and conception rate - have been obtained by Horan *et al.* (2005). In an earlier study Britt (1994) suggested that different quality of oocytes could justify a good conception rate if insemination occurs very early (around 50 DIM), but a lower one if insemination is delayed to 80-90 DIM, despite the fact an early oestrus resumption occurred in this second case. The quality of oocytes seems mainly affected by the chronic energy deficiency. In fact, according to Britt (1992), the exposure to adverse conditions, such as NEB during the initial growing and developing phases of oocytes (60-80 d before full maturation of follicles), results in altered or impaired development of mature oocytes and embryos. Some experiments have confirmed Britt's hypothesis, among them Kruip *et al.* (1996), Walters *et al.* (2002), and Sakaguchi *et al.* (2004). The latter experiment reported greater pregnancy rates at the first detected oestrus after calving, possibly because the released oocytes matured early during dry period. The possibility that the nutritional status occurring during last pregnancy could have an effect on oocyte quality has also been suggested by Hess *et al.* (2005) who have pointed out an effect - in beef cows - of pre-calving nutrition both on follicle development and oocyte quality in the subsequent breeding season. Similarly, Markusfeld *et al.* (1997) showed that dairy cows that lost more BCS during the dry period (with too low BCS at calving) had reduced fertility, mainly through the delay in the onset of ovaries activity. The negative effect of NEB occurring long before the evaluation of oocyte quality has been shown by Snijders *et al.* (2000). They slaughtered 98 cows in late lactation (23-24 kg/d of milk) to evaluate oocyte quality by counting them and assessing blastocyst formation after *in vitro* maturation and fertilization. The number of oocytes was similar, but cleavage and blastocyst formation rates were lower for oocytes from cows with a lower BCS. The same finding has been confirmed by Walters *et al.* (2002) who observed that oocyte quality was reduced in the 3rd month of lactation - after a maximum level between 30 and 70 days post-partum – in cows that immediately after calving showed higher NEFA and greater BCS losses (worse NEB).

The following general hypothesis seems therefore to arise: the regular (or not excessively delayed) resumption of oestrus is important for fertility, but not more important than the good quality of oocytes. Both aspects are affected by energy availability, in an acute way for oestrus resumption and in a more chronic way for oocyte quality. Furthermore, the reduced metabolic fuel availability, rather than the direct effects of hormone concentrations on reproduction, seems to cause poorer level of fertility, i.e. poorer oestrus behaviour and poorer oocyte quality (Veerkamp *et al.*, 2003).

Causes of NEB and BCS loss

As shown above, the NEB in the first month of lactation appears as a major cause of low fertility, at least in high yielding dairy farms, because it is almost unavoidable (or, better, rather difficult to be matched). Now a first question is whether the high yield and the obvious limits of the digestive apparatus capacity are the only causes of NEB. The following response was suggested by Lucy (2003): *Cows selected for high milk production, partition nutrients toward lactation. The partitioning of nutrients leads to cows with less adipose tissue mass (lower body condition) and greater infertility*. It is definitely true, but it appears to us an over simplification - at least at farm level - because it does not explain the results of Stevenson (1999) which showed that herds with higher milk yield had slightly better reproductive performance (Figures 1). Interesting are on the contrary the results of Lopez *et al.* (2005), showing that high incidence of prolonged anovulatory period is not associated with the high milk production but with the lower BCS. These results suggest, in fact, that milk yield and BCS changes can be decoupled as shown in our recently published results (Bertoni *et al.*, 2008). However, BCS reduction seems important per se as suggested by Santos *et al.* (2001): *cows that lose BCS during the breeding period, or have a low BCS (<2.75 vs >2.75) during insemination have reduced conception rate (32 vs 46%) and are less likely to respond to oestrus synchronization*.

The second question is whether the reduction of BCS can be, at least in part, independent from the level of milk yield. A partial response has been given above, nevertheless, we must bear in mind the generally accepted reasons for serious NEB in the transition period: the quick rise of milk yield and the usually slower rise of Dry Matter Intake (DMI) because the digestive apparatus needs to adapt to the energy requirements imposed by high milk yield. Nevertheless, two additional causes appear to impair the NEB: 1) the delayed increase of DMI - during early lactation - imputable to the impaired health status (negative effect that could overtake the opposite effect due to milk yield reduction); 2) the possibility that such health status could increase the maintenance cost. These last two possibilities are only rarely considered, but are not new; Villa-Godoy *et al.* (1988) showed clearly that the variations in NEB were largely explained by intake of energy (appetite) and to a lesser extent by milk yield. Similarly, Staples *et al.* (1990) have showed that anestrus cows, with similar genetic merit and receiving the same standardized husbandry ate less feed, produced less milk and lost more body weight, resulting in a more negative energy status than cycling cows. Therefore, the recent observation of Butler *et al.* (2006) appears to be of great interest: a voluntary reduction in appetite was the main cause of either lower energy balance or longer anestrus after calving of certain cows, while milk yield was similar in the ovulating and late ovulating cows (interestingly, the lower DMI began before calving). Also Drackley (2006) has not found a statistical correlation between milk yield and energy balance (r=0.238, P=0.90), but the same author has found a good correlation between energy balance and DMI in the first weeks of lactation: r=0.80, P<0.0001. These last data support a more crucial role of DMI which, particularly in the transition period, is not strictly affected by milk yield and/or diet features (e.g., fibre content, protein level, fermentability etc.), as suggested by Ingvartsen *et al.* (1999).

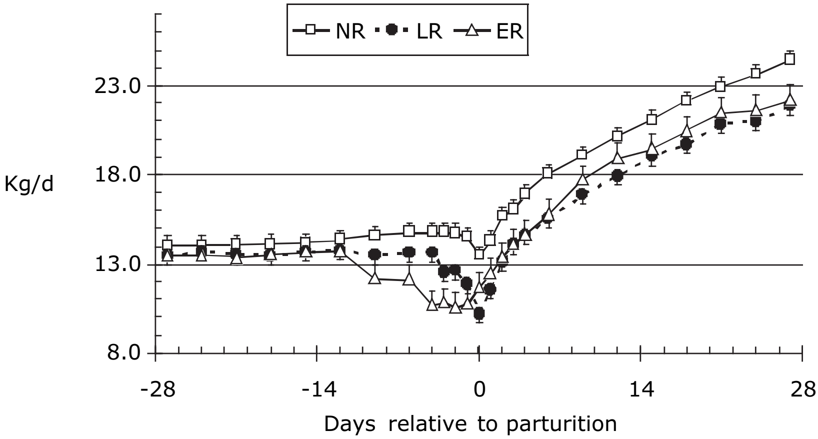
Consequently, the last question asks which other significant factors can substantially modify DMI (and perhaps the maintenance cost). Until now any confirmed answer was available, but a hypothesis can be derived from the available literature. According to Grummer (1995), the periparturient metabolic disorders occurring at calving time can be justified by the reduced DMI in late pregnancy, but the disorders themselves could be in turn the origin of the abnormally lower DMI - only partly related to milk yield level - occurring in early lactation. The attempt to increase DMI in late pregnancy by higher energy concentration was, in fact, unsuccessful the same author (Grummer *et al.*, 2007) has recently recognised it was an error, suggesting that a quite low energy diet is preferable at the end of pregnancy. Similarly, Drackley his coworkers (Douglas *et al.*, 2006) have observed that a low energy diet (80-100% of NRC requirements) during dry period reduces liver lipid content at calving time and allows a higher DMI in early lactation. Our partly published results (Janovick-Guretzky *et al.,* 2007) have suggested that this pre-calving feeding condition (low energy) seems to reduce the inflammatory phenomena and fatty liver after calving.

In short, it appears reasonable that inflammatory conditions could contribute to lower DMI before and after calving. This has been shown by Trevisi *et al.* (2002) because the reduction of DMI observed at the end of pregnancy (last 10 days) was responsible for a lower intake after calving. Moreover, the DMI reduction (Figure 4) occurred contemporarily with a subclinical acute phase response (inflammation) as measured by plasma haptoglobin and shown in Figure 5. Therefore, the worsening of NEB can be partly independent from milk yield and can be caused by any factor of pro-inflammatory cytokine release. Besides DMI reduction, they are furthermore responsible for an increased energy expenditure (higher maintenance cost), as suggested by Trevisi *et al.* (2007). In any case, the final consequence of pro-inflammatory cytokines can be an accentuation of BCS loss (Klasing, 2000).

Fertility and diet proteins

The second major nutritional cause of lower fertility - at least for intensive dairy farms that are not well managed - has been considered the protein excess (less often the deficiency), or the consequent level of urea nitrogen in milk above 19.0 mg/100 ml (Butler *et al.*, 1996; Butler, 1998). Nevertheless, in our previous review on nutrition and fertility in dairy cows (Bertoni, 1990), has been shown that in literature there were papers suggesting that fertility can be either negatively affected (Jordan and Swanson, 1979)

Figure 4. Pattern of changes of daily dry matter intake (mean values ± pooled SEM) during one month prior and one month after calving of dairy cows retrospectively divided according to dry matter intake reduction before calving: no (NR; 13 cows), late (LR; 11 cows) or early (ER, 5 cows) reduction. Animals were kept tied in a well climatized barn and fed well controlled amounts of corn silage and hays two times a day and of concentrate according to milk yield. Statistical differences (P<0.05) were reached between NR and LR, from -3 to +27 days relative to parturition, and between NR and ER, from -9 to +6 days relative to parturition (Trevisi *et al.*, 2002).



or without consequences (Howard *et al.*, 1987) by a very high protein intake (19-20% of dry matter).

The link between the potential reproductive impairment from excessive protein was suggested to be the high blood NH_3 (Visek, 1984). If this is the case, the real cause might be the excess of rumen degradable protein. This hypothesis has been also suggested by the results of Folman *et al.* (1981) in which the same protein content (16%) gave much better fertility results when soybean was treated to reduce rumen degradability by formaldehyde. Nevertheless, many successive papers agree for a reduction of fertility in dairy cows fed excesses of any proteins, particularly in the case of high blood urea level (Butler *et al.*, 1996; Garcia-Bojolil *et al.*, 1998; Rajala-Schultz *et al.*, 2001). Other papers have, on the contrary, excluded a significant negative effect of urea on fertility (Gustafsson and Carlsson, 1993; Godden *et al.*, 2001). According to Godden *et al.* (2001), there are many possible explanations to this disagreement:

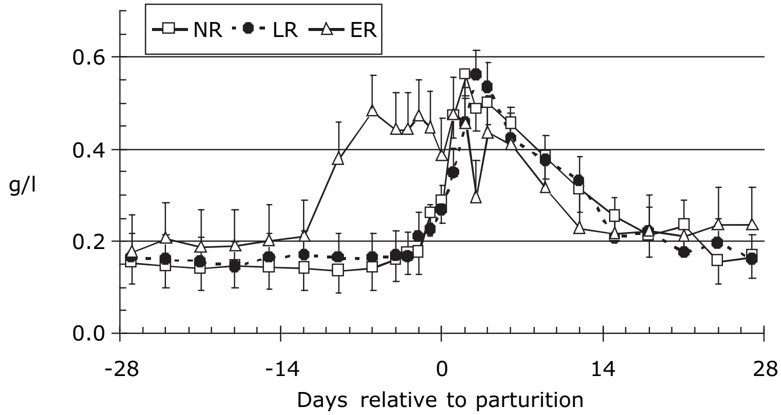
only extremely high values of urea could be a cause of reduced fertility;

high urea values could impair reproduction performance only when associated with some diseases (Ferguson *et al.*, 1993; Barton *et al.*, 1996);

the negative effect of high urea levels could occur only in case of a concurrent incorrect protein: energy ratio.

According to our experience, the first two points cannot be excluded; however, we suggest that the last one could be the most likely; particularly important however, could be

Figure 5. Pattern of changes of plasma haptoglobin (mean values ± pooled SEM) during one month prior and one month after calving of dairy cows retrospectively divided according to dry matter intake reduction before calving: no (NR; 13 cows), late (LR; 11 cows) or early (ER, 5 cows) reduction. Animals were kept tied in a well climatized barn and fed corn silage and hays two times a day and of concentrate according to milk yield. Blood samples were taken in the morning before forage meal. Statistical differences (P<0.05) were reached between NR and ER, from -9 to -1 days relative to parturition (Trevisi *et al.*, 2002).



the high degradability of proteins (in addition to the low availability of fermentable energy). In fact, both contribute to a higher release of NH_3 into the rumen as shown by Ferguson and Chalupa (1989) and by Gustafsson and Carlsson (1993). According to this hypothesis, the mechanism would not be urea and its negative effect at the uterine level, as suggested by Butler (1998) (and still possible), but once again the increase of NH_3 in blood which depresses insulin (Sinclair *et al.*, 2000b), impairs the quality of oocytes and their capacity to develop (Sinclair *et al.*, 2000a). The negative effect of excessive dietary protein on oocytes, and not on the uterus environment, has been demonstrated by Gath e*t al.* (1999) because good embryos transferred in heifers with low or high urea levels allowed a similar pregnancy rate.

To conclude this topic, we agree with the following statemennt by Santos (2001): *although there is no clear relationship between protein intake and reproduction, cows fed diets that result in high urea nitrogen concentrations in blood might have reduced conception or pregnancy rates*. Furthermore, if high urea is not always clearly followed by a reduction in fertility, acceptable values generally occur when crude proteins are within requirements and the ratio between degradable proteins and fermentable energy is appropriate. The well managed intensive dairy farms have all the required tools -such as NRC (2001) or other protein systems- to cover protein needs for good milk yield and quality as well as satisfactory fertility. In any case, any excess of nitrogen intake or bad metabolic utilisation (as suggested by high urea) must be avoided as they contribute, moreover, to lower efficiency as well as to environmental pollution.

Fertility and health conditions

It is well known that nutrient deficiencies (and sometimes also excesses) are responsible for metabolic diseases, as well as the impairment of the immune system, hence the higher frequency of infectious diseases. For instance, it has been quite recently observed (van Knegsel *et al.*, 2007) that NEB is the cause of a reduction in natural antibodies in the blood and milk of periparturient cows. Perhaps less known is the strong negative relationship between the above diseases and fertility and how this relationship occurs, particularly with respect to the energy balance. However, in the last few years, increasing attention has been paid to the diseases as potential causes of a reduced pregnancy rate. This is not only for the obvious lower fertility observed in animals with reproductive disorders (Ouweltjes *et al.*, 1996; Rajala and Grohn, 1998; Labernia *et al.*, 1999), but also for the negative effects on reproduction of both peripartum metabolic diseases (Markusfeld *et al.*, 1997; Beaudeau *et al.*, 2000; Fleisher *et al.*, 2001; Sogstad *et al.*, 2006) and infectious diseases such as mastitis (Barker *et al.*, 1998; Schrick *et al.*, 2001), as well as any other kind of health problems around calving (Opsomer *et al.*, 2000; Walsh *et al.*, 2007). Thus, the statement reported by Roche *et al.* (2000) that… *high reproductive efficiency in the dairy cow requires a disease free transition period* …, must be called to mind again and carefully accomplished as suggested by Lucy (2001).

This appears interesting because, particularly in the last few decades, the incidence of diseases in dairy herds has increased, almost concurrent with the reduction in fertility (Oltenacu and Algers, 2005). In fact, according to Müller *et al.* (1999), from 1970 to 1996 the percentage of culling as a result of disease was more than doubled: from 13.4% to 27.4%. These data have been obtained from German Black Pied cattle that in the same period had an increase in milk yield from 4,670 to 7,020 kg/lactation. The same authors have highlighted the relationship between milk yield increase and physiological changes in fitness-related traits which can justify more diseases and less fertility in cows. Thus they have suggested selecting cows not only for performance, but rather for a balance of performance and non productive traits (longevity, resistance to specific diseases, fertility etc.) as also reported by Oltenacu and Algers (2005).

The above mentioned data confirm that high yielding cows are more susceptible to both infectious diseases - namely mastitis - and to metabolic stress; moreover, they are less tolerant to small management mistakes (Garnsworthy and Webb, 1999; Heuer *et al.*, 1999; Knight *et al.*, 1999; Ward and Parker, 1999). This susceptibility is further increased in a period of reduced immunological capacity as the transition period seems to be (Mallard *et al.*, 1998; Hammon *et al.*, 2006; Lacetera *et al.*, 2007). In fact, it has been demonstrated that periparturient cows experience more rapid bacterial growth, a higher peak of bacterial concentration, higher fever, and equal or greater pro-inflammatory cytokine concentration in foremilk, than mid-lactation cows (Shuster *et al.*, 1996).

While it is quite clear that high yield can be responsible for higher disease susceptibility, it is well known that the majority of health disorders occurs in the transition period. It appears, therefore, problematic to explain how they can affect reproduction (at least fertilization which occurs 2-3 months later). Obviously, some infectious diseases, particularly mastitis, can occur during the insemination period and can directly impair the reproductive performance, but the indirect effects appear to be of greater relevance. Our recently published paper (Bertoni *et al.*, 2008) appears, therefore, of great interest as it involves 120 multiparous cows belonging to 3 high yielding dairy herds with an acceptable management, which were monitored (blood sampling, milk yield, health conditions, BCS, reproduction events, etc.) from the end of pregnancy and until the subsequent pregnancy. The non pregnant cows or those with serious problems in the 2nd-3rd month of lactation (insemination period) have been excluded, while the remaining 77 cows have been retrospectively divided into 4 equal groups (within each herd) according to LAI (Liver Activity Index), which is an indicator - based on the reduction of negative acute phase proteins (Bertoni *et al.*, 2008) - of inflammatory phenomena occurring in the 1st month of lactation. The main data of milk and reproductive indices are shown in Figure 6 and Table 1 while the plasma level of haptoglobin is shown in Figure 6. They appear to demonstrate the following:

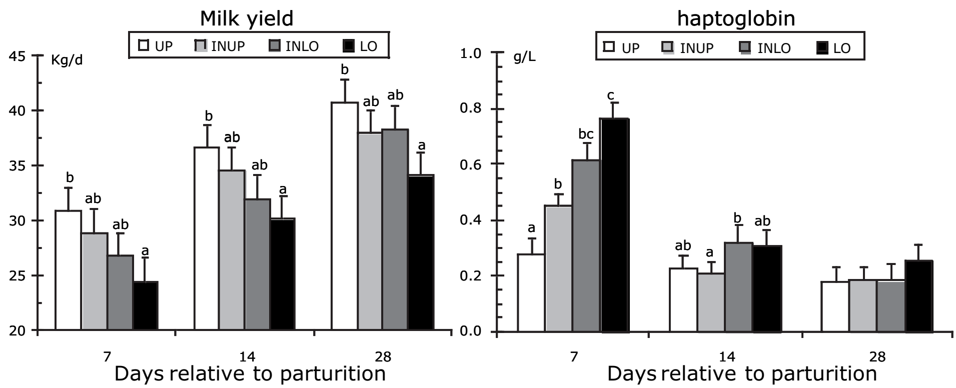
the cows in the upper quartile of LAI (UP, with best liver functions due to lower inflammatory phenomena, i.e. lower haptoglobin at 7 DIM) had both higher milk yield and better fertility (93 days open, 53% pregnant at 1st insemination and 1.6 services per pregnancy);

the cows in the lower quartile of LAI (LO, with the worst liver functions due to higher inflammatory phenomena) had both lowest milk yield and less satisfactory fertility compared to UP (111 days open, 37% pregnant at 1st insemination and 2.0 services per pregnancy);

the intermediate groups (INUP and INLO) had quite good milk yield, but they presented the worst fertility.

In the light of these results, of special

Figure 6. Average milk yield and blood haptoglobin (mean values ± pooled SEM) in the first month of lactation of 77 pregnant cows of three different dairy farms, retrospectively grouped according to quartiles of LAI (Liver Activity Index): upper (UP), intermediate upper (INUP), intermediate lower (INLO) and lower (LO) quartile. LAI is a composite index obtained from the blood levels of three negative acute phase proteins: albumin, lipoproteins and retinol binding protein (Bertoni *et al.*, 2008).



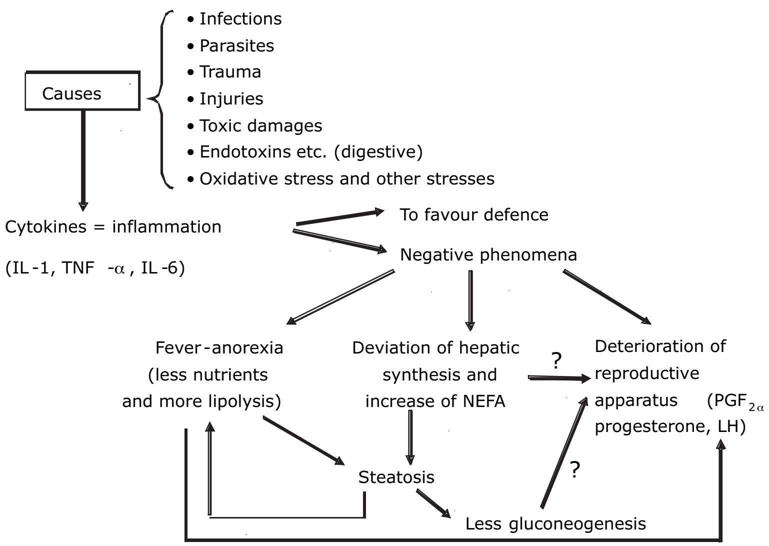
Significant differences between groups are shown by different letters: (a,b,c) P<0.05.

Table 1. Average values of main fertility indices observed in cows within upper (UP), intermediate upper (INUP), intermediate lower (INLO) and lower (LO) quartiles of LAI (Liver Activity Index) (Bertoni *et al.*, 2008).

Item		UP n = 19	INUP n = 20	INLO n = 19	LO n = 19
Services per pregnancy*	no.	1.65 ± 1.3[a]	2.04 ± 1.6[ab]	2.68 ± 1.5[b]	2.01 ± 1.5[ab]
Days open*	DMI	92.9 ± 48[a]	132.5 ± 89b	138.8 ± 89[b]	110.5 ± 55[ab]
Conception rate at 1st service	%	52.6	45.0	21.0	36.8
Repeat breeders (at least 3 services)	"	21.0	45.0	57.9	31.6

**after logarithmic transformation.*
Letters [(a,b,c)] show significant differences between groups (P<0.05).

Figure 7. Recognized causes of pro-inflammatory cytokine release and possible mechanisms that compromise performance of cows (production and fertility) (Bertoni, 2003).



interest appears the high frequency of inflammations in the transition period shown by Cappa *et al.* (1989) and Sordillo *et al.*, (1995). These inflammations could be justified by clinical diseases which could be more or less serious (followed by lower milk yield and other problems), but they could be due to some subclinical situations that are not easily revealed by milk yield reduction or by other clear negative consequences. Their identification is mainly based on blood parameters which are an indicator (acute phase proteins of liver origin) of the pro-inflammatory release of cytokines (Bionaz *et al.*, 2007; Bertoni *et al.*, 2008).

Cytokines and inflammation

According to Calder (2002), inflammation is the body's immediate response to infection or tissue injury. It begins the immunological processes to eliminate invading pathogens and toxins, and to repair damaged tissue. The process occurring after any tissue damage is also termed as acute-phase response (Richard and Gauldie, 1995) and comprises immediate events localized at sites of inflammation as well as an activation of systemic phenomena mediated by cytokines. Cytokines are part of a counter regulatory system that plays a critical role during immune system activation in preventing the host from mounting an excessive defence response (Kapcala, 1999), which would be dangerous. There are pro-inflammatory cytokines (IL-1, IL-6 and TNFα) which promote a local and a systemic response to help the defence system (Cousins, 1985; Dinarello, 1997; Elsasser *et al.*, 1997; Gruys *et al.*, 1999), but also anti-inflammatory cytokines such as IL-4 and IL-10, which depress the activity of the former to avoid unneeded and dangerous effects (Grimble, 2001b). The pro-inflammatory cytokines are responsible for a sequence of events that involve several organs and tissues such as the hypothalamus, liver, and reproductive apparatus (Elsasser *et al.*, 1997). In addition, these cytokines increase body temperature, induce anorexia, and promote lipolysis in adipose tissue and muscle break down, and determine several endocrine and metabolic changes (Elsasser *et al.*, 1995). Some of these effects can be particularly pernicious in the peripartum period: anorexia, catabolic conditions, fever - with an increase in energy wastage (Klasing, 2000) - adipose mobilization and significant disturbance of liver synthesis activity. All together, these effects can increase the risk of metabolic diseases, such as ketosis and liver lipidosis, but also of infectious ones (Goff and Horst, 1997).

The reduction of DMI (Johnson and Finck, 2001) appears to be of great interest as respects the effects of cytokines, previously hypothesized by Ingvartsen and Andersen (2000) to explain the lower DMI of periparturient cows and it has been strongly suggested by our results (Trevisi *et al.*, 2002) in the last part of dry period, as previously shown (Figure 4 and 5). This could, in fact, be connected to the previously suggested peculiar causes of NEB worsening in the early part of lactation such as unexpected lower DMI and higher maintenance costs. This last aspect has been demonstrated in our lab (Trevisi *et al.*, 2007) because the energy efficency was 12-15% lower in cows showing inflammatory conditions in the 1st month of lactation. Other effects of cytokines are on adipose tissue and liver but they can be discussed together for their well known interactions (Drackley, 1999; Drackley *et al.*, 2005). Cytokines promote the liver synthesis of several plasma proteins (Powanda, 1980; Cousins, 1985; Elsasser *et al.*, 1997; Gruys *et al.*, 1999; Peterson *et al.*, 2004; Gruys *et al.*, 2005) including the positive acute phase proteins (+APP: i.e. haptoglobin, SAA, ceruloplasmin, C-reactive protein, α1-antitrypsin). Unfortunately, this increased synthesis partly competes with the production of the usual liver proteins, which are more or less reduced (Fleck, 1989; Wan *et al*., 1989). Several proteins are thus affected (i.e. albumins, some enzymes, "carriers" of vitamins and hormones, lipoproteins) and are hence called negative acute phase proteins (-APP). The functions of the latter proteins are essential to the metabolic integrity of the animal; their synthesis is therefore highly maintained, even under conditions of nutritional deprivation, including low protein intake and fasting in sheep and humans, as well as in dairy cows (Raggio *et al.*, 2007). Otherwise, such synthesis priority does not occur when cytokines induce the inflammatory response; thus, -APP are reduced and consequently many liver functions can be impaired for short or longer periods. This apparent paradox of liver - active to produce +APP and less active to produce -APP - becomes particularly important in the transition period when it is engaged for gluconeogenesis from amminoacids and for metabolization of fatty acids (Drackley, 1999; Drackley *et al.*, 2005). Noteworthy among other effects of cytokines at liver level, is the decrease in fatty acid oxidation by reducing the expression/activity of several nuclear receptors involved in lipid metabolism, at least in human and rodents (Kim *et al.*, 2007). In addition, cytokines can also lower the synthesis of apolipoproteins which can contribute to a worsening of liver lipidosis (Bertoni, 1990; Murthy *et al.*, 1997; Lippi *et al.*, 1998; Katoh, 2002; Ametaj *et al.*, 2005; Bertoni *et al.*, 2006).

Finally, the pro-inflammatory cytokines can also interfere directly with reproductive function in different ways as summarized in Figure 7. In particular, we are referring to the negative effects of an inopportune release of LH (Braden *et al.*, 1998), an inopportune release of progesterone from adrenals (Trevisi *et al.*, 1996) or a large release of $PGF_{2\alpha}$ (Fredriksson *et al.*, 1985). Nevertheless, many of these effects - if occurring in the transition period as suggested in this case - are unlikely to be effective on the reproductive cycle.

In short, the contemporary increase in health problems and the reduction in fertility observed in recent decades in high yielding cows, suggest a possible direct relationship. Nevertheless, in case of health disorders in the transition period, the pro-inflammatory cytokines – and their effects – could represent an important linkage between any kind of inflammatory conditions occurring at calving time and the impairment of reproduction efficiency. These cytokines can, in fact, cause a worsening of NEB - reducing both DMI and energy efficiency - and perhaps disturbing liver functions with many long lasting consequences.

How to improve NEB

NEB appears to be the most notable nutritional cause of impaired reproductive performance because it is often unavoidable. In addition to high milk yield, other causes include digestive limits, “diseases” or other inflammatory situations. It appears, therefore, a priority to find ways to reduce its seriousness and extension after calving. Proper feeding management of far-off dry, close-up dry and early lactation cows is essential; moreover, good health and general management, avoiding any cause of inflammation or reducing the response (and consequences) to inflammations itself, can also reduce the risks of NEB.

Proper feeding to maximize DMI

Before calving this means the correct satisfaction of needs, the proper function of digestive apparatus, and metabolic disease prevention. After calving, the main aim of the feeding schedule is the quickest achievement of maximum DMI without any digestive upset. In practice we suggest (Bertoni and Trevisi, 1997) the following for the dry period: low energy concentration (1.20-1.25 Mcal/kg NEl DM); acceptable crude protein concentration (11-12% DM), high fibre (hay and perhaps straw), low Ca and P (as well as Na and K), good trace elements and vitamin supply. For the last pregnancy period, known as the close-up, we suggest a slightly richer diet (1.4-1.5 Mcal/kg NEl and 12-13% crude protein on DM), but for no longer than 8-10 days. These rules agree with Drackley *et al.* (2007) and Grummer *et al.* (2007) who have recently suggested feeding low energy diets during the dry period to maximize DMI after calving. They also agree with Kruip *et al*. (2001), but particularly with Van den Top *et al.* (1996) who observed that cows fed *ad libitum* in the dry period were more susceptible to fatty liver after calving (in non obese cows as well).

Afterwards, in the early lactation, we think that NRC (2001) suggestions for high yielding cows can be appropriate to cover the higher energy and protein requirements, being safe either for rumen and intestine micro-population. However, it can sometimes be helpful to feed cows with an intermediate diet in the first 10-20 days of lactation.

Avoiding inflammation occurrence

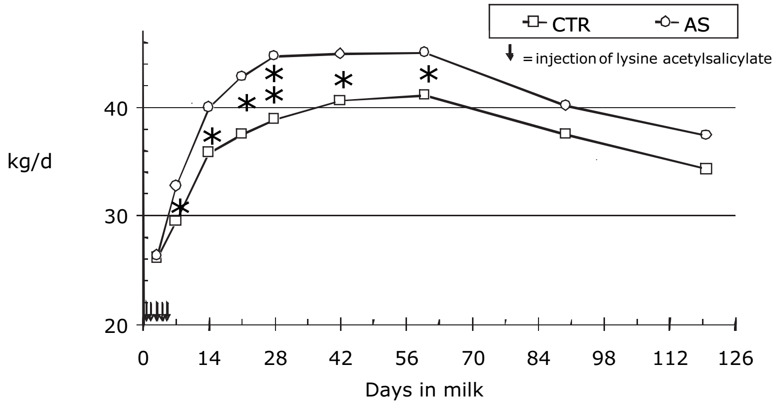
To prevent inflammatory phenomena, simultaneous attention must be payed to indirect and direct factors of health problems. Several are the indirect factors that cause stress, injuries, immunodepression etc.; namely they are related to the comfort of the rest area, proper feeding strategy from dry-off till calving, avoidance of heat and other stress, hygienic conditions, sire selection to avoid distocia, etc. Of major importance, however, are the direct factors which include mastitis prevention, vaccinations (e.g., against viruses, leptospirosis), treatments against parasites, foot trimming and treatments for lameness and, finally, proper feeding to avoid digestive issues.

Feeding can be part of an indirect strategy to reduce inflammations when utilised to prevent such post-partum health problems as milk fever, retained placenta and ketosis (Bertoni and Trevisi, 1997), as well as infections, by optimizing the immune system. Feeding strategy can also be a direct tool in the reduction of health problems (e.g. avoiding rumen and/or intestinal troubles), especially during the transition period. These troubles, and particularly rumen acidosis, can be a source of endotoxins which are a cause of laminitis (Nocek, 1997). In line with this we have observed an increase in inflammatory blood indices in sheep after abrupt changes from hay to corn silage (Calamari *et al*., 1980). Furthermore, the results of 24h intra-venous infusion of E. coli endotoxin or histamine have allowed us to conclude: that"…it is reliable to suppose that histamine and endotoxins (or indirectly LEM, *now known as interleukin-1*), could be involved in the *inflammatory-like* effects of digestive upsets …" (Bertoni *et al.*, 1989). The digestive tract as source of inflammations has been recently confirmed by Pié *et al.* (2007) in young pigs and by Gozho *et al.* (2006) in steers. Both have found that high fermentable diets cause a higher release of cytokines or an increase in rumen endotoxins, often the cause of the release of cytokines, and, consequently, of systemic inflammation.

Modulation of the inflammatory response

Avoiding diseases and health disorders is henceforth possible, although not an easy task. Unfortunately, other less obvious causes of cytokine release can occur in addition to those previously described and summarized in Figure 7 (Bertoni, 2003). This means that the absence of infectious and metabolic diseases and proper feeding may not be enough to avoid quite serious inflammations at calving time; a first trigger of pro-inflammatory cytokine release can be the labour itself (hard physical activity) (Simpson *et al.*, 1998) or the placenta, as observed in pregnant women (Hauguel-de Mouzon and Guerre-Millo, 2005). Further causes of cytokine release can be linked to

Figure 8. Pattern of changes of daily milk yield (kg/d) during the first 4 months of lactation in cows of two different farms, treated (AS, 24 cows) or not (CTR, 24 cows) with lysine acetylsalicylate during the first 5 days after calving (*P<0.05; **P<0.01) (Trevisi and Bertoni, 2008).



uterus re-absorption with possible growth of opportunistic microbes.

This suggests that any attempt to reduce the degree of inflammation and its effects could be useful. In fact, the treatment with lysine acetylsalycilate in dairy cows for 5 days immediately after calving (Trevisi and Bertoni, 2008) has shown an increase in milk yield (Figure 8) and fertility (Table 2). In the future we can forsee that both genetic (Howell *et al.*, 2002) and nutritional tools (Grimble, 2001a) will be utilised to modulate (reduce) the inflammatory response. To date some good information regarding immune-nutrition science (O'Flaherty and Bouchier-Hayes, 1999; Suchner *et al.*, 2000) has been made available. In addition to anti-oxidants and omega-3 fatty acids (Grimble, 2001a; Calder 2002), there is also interest in the use of some other fats (e.g., conjugates linoleic acids) as shown by Roche *et al.* (2001), and in such aminoacids as glutamine, arginine, cysteine, taurine (Calder and Jackson, 2000; Grimble, 2001a), as well as trace elements including Se (Spears, 2000; Mc Kenzie *et al.*, 2002). Future studies, however, will likely add many other "nutrients" (Calder and Kew, 2002).

Conclusions

Reproduction could be considered a "luxury" function and the female appears able to "sense" whether the environment is too harsh and risky for a successful reproductive cycle (Friggens, 2003). Therefore, almost all the environmental, managerial (above all nutrition), and sanitary aspects interfere with fertility and can impair it if they are not suitable to satisfy the genetic potentiality for milk yield. Nevertheless, from our experience and the overview of the available literature, it appears unlikely - at least in high yielding dairy farms - that a deficiency of proteins, minerals and vitamins or the presence of toxic factors could seriously impair fertility. Slightly more likely, in these kinds of farms, are the negative effects on reproduction of some excesses, with particular regard to proteins.

On the contrary, the farms with high genetic merit cows present two peculiar dif-

Table 2. Main fertility indices observed in breeded cows treated (AS) or not (CTR) with lysine acetylsalicylate in the 5 days after calving (Trevisi and Bertoni, 2008).

Group		CTR	AS
cows[1]	no.	22.0	23.0
culled cows	% of total	15.8	9.5
pregnant cows	"	86.4	91.3
pregnant at 1st insemination	% of pregnant	21.1	52.4
repeat breeders	%	36.8	28.6
services per pregnancy (§)	no.	2.68	2.38
days open (§)	"	131.8	106.3
Fertility Status Index (FSI) (@)	"	12.6	61.8

(§) after logarithmic transformation; (@) Esslmont and Eddy (1977), optimal value = 80.
[1] two cows of CTR group and one of AS group were culled before breeding.

ficulties which can seriously impair the fertility level, particularly during the early post-partum:

for cows, to partition nutrients to the mammary glands without incurring in serious NEB and the consequent metabolic stress;

for herdsmen, to guarantee optimal conditions (environmental, managerial and sanitary) aimed to reduce risks, for health and fertility of such demanding animals.

These peculiar problems can be faced by genetics and husbandry. It is widely recognised that genetic selection can be effective but requires a long period of time before obtaining cows with specific resistance or able to better overcome the aforementioned problems. The management, instead, has an immediate effect and can face short-term problems, mostly because the problems discussed herein are not necessarily associated with milk yield. Nevertheless, it has to be emphasised the 1st rule of husbandry is the choice of animals with genetic traits which make them suitable to the available farm conditions (i.e., high genetic merit cows only for good dairy farms).

As respects the nutritional aspect, the proper energy balance appears of major importance. In fact, the energy requirements after calving rise quickly (≥ 4 times the energy for maintenance), but DMI increases slowly, while feed energy concentration cannot be freely increased. The consequent dramatic NEB appears, therefore, to be the main cause of a great mobilisation of reserves, with a marked loss of BCS. This energy defect, both deep and prolonged, is obviously well correlated to lower BCS values and associated with a prolonged anestrus, in addition to a lower quality of oocytes and embryos later on (therefore to lower fertility).

Nevertheless, if NEB is widely recognised as the major cause of lower fertility, the negative effects of high genetic merit for milk yield are less obvious. In fact, despite a substantial homogeneity of genetic traits in cows, several studies have shown significant variability in reproductive performance among the herds and within each herd. Very interesting in this regard are the data showing that fertility is more related to BCS changes than to milk yield levels thus suggesting the crucial role of DMI variations as a major cause of a worse NEB in the transition period. It appears, however, unlikely that digestive tract volume and diet bulkiness could represent the main factors of the inadequate DMI. On the contrary, there is much evidence that "disease stress" conditions - which are due to the pro-inflammatory cytokine release - could slow down the increase in DMI. These cytokines are also responsible for increased energy waste (lower efficiency) with further impairment of energy balance.

To conclude, the results presented in this review seem to suggest that low fertility is not exclusively linked to milk yield; therefore, low reproductive performance should not be ineluctable in the farms with high genetic merit cows. At the same time they suggest that the improvement in management conditions cannot be limited to feeding improvements aimed to achieve better energy balance in close-up dry period and early lactation. On the contrary, the overall management of dairy cows (including nutrition) must guarantee optimal physiological and health conditions at calving time, which in turn accelerate the rate of DMI increment. In particular, attention should be paid to the following:

improve nutrition status before and after calving, and particularly to avoid any disease or health disorder which could trigger the release of pro-inflammatory cytokines. In general, this means to modulate energy and proteins in order to have good BCS at dry-off, but also to maintain this proper BCS by means of a relatively low energy diet followed by a proper close-up (light and short). Finally, the early lactation diets would provide the needed nutrients, but also maintain optimal digestive tract function. Besides energy and protein, a proper supplementation of major minerals, trace elements and vitamins can be helpful in reducing the risks of metabolic diseases and digestive troubles (e.g. use of buffers in lactation), but also in enhancing the immune system;

the prevention of inflammatory conditions as much as possible and, in addition to proper feeding, this means vaccinations, foot care, reduced injuries and trauma (e.g. distocia), avoidance of heat stress or any other stressful situation (overcrowding, improper rest area etc.);

the modulation of inflammation response, because it is almost impossible to avoid the phenomenon itself. This means a rapid therapy of "diseases" and, perhaps even better, a prompt association of anti-inflammatory drugs (besides antibiotics if needed). Furthermore, it means reducing the cytokine and eicosanoid release, particularly avoiding the self-perpetuation of inflammations after any cause of their appearance. Some immune-nutrition tools, mainly based on nutrients able to reduce the above pro-inflammatory cytokines and metabolites, appear very promising (e.g. omega-3 and CLA fatty acids, some aminoacids, any antioxidant etc.).

REFERENCES

Aeberhard, K., Bruckmaier, R.M., Kuepfer, U., Blum, J.W., 2001. Milk yield and composition, nutrition, body conformation traits, body condition score, fertility and diseases in high-yielding dairy cows – Part 1. J. Vet. Med. A 48:97-110.

Ametaj, B.N., Bradford, B.J., Bobe, G., Nafikov, R.A., Lu, Y., Young, J.W., Beitz, D.C., 2005. Strong relationships between mediators of the acute phase response and fatty liver in dairy cows. Can. J. Anim. Sci. 85:165-175.

Barash, I.A., Cheung, C.C., Weigle, D.S., Ren, H., Kabigting, E.B., Kuijper, J.L., Clifton, D.K., Steiner, R.A., 1996. Leptin is a metabolic signal to the reproductive system. Endocrinology 137:3144-3147.

Barker, A.R., Schrick, F.N., Lewis, M.J., Dowlen, H.H., Oliver, S.P., 1998. Influence of clinical mastitis during early lactation on reproductive performance of Jersey cows. J. Dairy Sci. 81:1285-1290.

Barton, B.A., Rosario, H.A., Anderson, G.W., Grindle, B.P., Carroll, D.J., 1996. Effects of dietary crude protein, breed, parity and health status on the fertility of dairy cows. J. Dairy Sci. 79:2225-2236.

Bean, S.W., Butler, W.R., 1997. Energy balance and ovarian follicle development prior to the first ovulation post-partum in dairy cows receiving three levels of dietary fat. Biol. Reprod. 56:133-142.

Beaudeau, F., Seegers, H., Ducrocq, V., Fourichon, C., Bareille, N., 2000. Effect of health disorders on culling in dairy cows: a review and a critical discussion. Ann. Zootech. 49:293-311.

Bertoni, G., 1990. Recenti acquisizioni sulla ipofertilità della bovina da latte. Inform. Agr. 46(4):35-39; 46(6):89-94; 46(8):73-84.

Bertoni, G., 2003. Dismetabolie puerperali e rapporti con il sistema immunitario, l'attività epatica e la riproduzione. In: G. Bertoni (ed.) La ipofertilità nella bovina da latte. Fondaz. Iniziative Zooprof. Zoot. ed., Brescia, Italy, pp 67-91.

Bertoni, G., Lombardelli, R., Orioli, F., 1999. Postpartum reproductive and metabolic behaviour of fertile and infertile dairy cows with different genetic merit. pp 413-415 in Proc. 13th Nat. Congr. ASPA, Piacenza, Italy.

Bertoni, G., Piccioli Cappelli, F., Calamari, L., Trevisi, E., 1989. Digestive upsets of ruminants: possible role of endotoxins and/or histamine. pp 370-373 in Proc. 7th Int. Conf. on Production Disease in Farm Animals, New York, NY, USA.

Bertoni, G., Trevisi, E., 1997. Le principali malattie della produzione delle lattifere. Inform. Agr. 53(Suppl. 47):1-34.

Bertoni, G., Trevisi, E., Calamari, L., Bionaz, M., 2006. The inflammation could have a role in the liver lipidosis occurrence in dairy cows. In: N. Joshi and T.H Herdt (eds.) Production diseases in farm animals. Wageningen Academic Publ., Wageningen, The Netherlands, pp 157-158.

Bertoni, G., Trevisi, E., Han, X., Bionaz, M., 2008. Effects of Inflammatory Conditions on Liver Activity in the Puerperium and Consequences for Performance in Dairy Cows. J. Dairy Sci. 91:3300-3310.

Bertoni, G., Trevisi, E., Lombardelli, R., Piccioli-Cappelli, F., 2002. Factors affecting level and postfeeding behaviour of insulin in dairy cows. Proc. ADSA/ASAS/CSAS Joint Meeting, Quebec City, Canada. J. Dairy Sci. 85(Suppl.1):7(abstr.).

Bionaz, M., Trevisi, E., Calamari, L., Librandi, F., Ferrari, A., Bertoni, G., 2007. Plasma Paraoxonase, Health, Inflammatory Conditions and Liver Function in Transition Dairy Cows. J. Dairy Sci. 90:1740-1750.

Bonczek, R.R., 1986. Correlated response to selection for high milk yield in Holstein dairy cattle: average daily concentrations of plasma prolactin, thyroxine, insulin and growth hormone at two stages of lactation. Ph.D. Diss., University of Minnesota, USA.

Bono, G., 2003. Subfertility in postpartum dairy cow as a stress symptom: analysis of the involved mechanisms. In: G. Bertoni (ed.) La ipofertilità nella bovina da latte. Fondaz. Iniziative Zooprof. Zoot. ed., Brescia, Italy, pp 31-48.

Braden, T.D., Fry, C., Sartin, J.L., 1998. Effects of interleukins on secretion on luteinizing hormone from ovine pituitary cells. Am. J. Vet. Res. 59:1488-1493.

Britt, J.H., 1992. Impacts of early postpartum metabolism on follicular development and fertility. Bov. Proc. 24:39-43.

Britt, J.H., 1994. Follicular development and fertility: potential impacts of negative energy balance. pp 103-112 in Proc. Nat. Reprod. Symp., Texas Agric. Ext. Serv., College Station, Pittsburgh, PA, USA.

Butler, W.R., 1998. Review: effect of protein nutrition on ovarian and uterine physiology in dairy cattle. J. Dairy Sci. 81:2533-2539.

Butler, W.R., 2003. Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows. Livest. Prod. Sci. 83:211-218.

Butler, W.R., 2005. Inhibition of ovulation in the postpartum cow and the lactating sow. Livest. Prod. Sci. 98:5-12.

Butler, W.R., Calaman, J.J., Beam, S.W., 1996. Plasma and milk urea nitrogen in relation to pregnancy rate in lactating dairy cattle. J. Anim. Sci. 74:858-865.

Butler, S.T., Pelton, S.H., Butler, W.R., 2006. Energy balance, metabolic status and the first postpartum ovarian follicle wave in cows administered propylene glycol. J. Dairy Sci 89:2938-2951.

Butler, W.R., Smith, R.D., 1989. Interrelationship between energy balance and postpartum reproductive function in cattle. J. Dairy Sci. 72:767-783.

Calamari, L., Maianti, M.G., Bertoni, G., 1980. L'influenza della totale e repentina sostituzione del fieno con mais-silo su alcuni parametri ematochimici. Proc. 34th Nat. Congr. SISVet, Sorrento (NA), Italy, 34:254.

Calder, P.C., 2002. Dietary modification of inflammation with lipids. P. Nutr. Soc. 61:345-358.

Calder, P.C., Jackson, A.A., 2000. Undernutrition, infection and immune function. Nutr. Res. Rev. 13:3-29.

Calder, P.C., Kew, S., 2002. The immune system: a target for functional foods? Brit. J. Nutr. 88:165-176.

Call, E.O., Stevenson, J.S., 1985. Current challenges in reproductive management. J. Dairy Sci. 68:2799-2805.

Cappa, V., Trevisi, E., Bertoni, G., 1989. Variazioni ematiche nel primo mese di lattazione in bovine di allevamenti con o senza problemi "post-partum". Zoot. Nutr. Anim. 15:645-660.

Chilliard, Y., Delavaud, C., Bonnet, M., 2005. Leptin expression in ruminants: nutritional and physiological regulations in relation with energy metabolism. Domest. Anim. Endocrin. 29:3-22.

Cousins, R.J., 1985. Absorption, transport and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. Physiol. Rev. 65:238-309.

De Vries, A., Risco, C.A., 2005. Trends and seasonality of reproductive performance in Florida and Georgia dairy herds from 1976 to 2002. J. Dairy Sci. 88:3155-3165.

Dinarello, C.A., 1997. Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. Chest 112:321S-329S.

Distl, O., Wurm, A., Glibotic, A., Brem, G., Kräußlich, H., 1989. Analysis of relationships between veterinary recorded production diseases and milk production in dairy cows. Livest. Prod. Sci. 23:67-78.

Douglas, G.N., Overton, T.R., Bateman II, H.G., Dann, H.M., Drackely. J.K., 2006. Prepartal plane of nutrition, regardless of dietary energy source, affects periparturient metabolism and dry matter intake in Holstein cows. J. Dairy Sci. 89:2141-2157.

Drackley, J.K., 1999. Biology of dairy cows during the transition period: the final frontier?. J. Dairy Sci. 82:2259-2273.

Drackley, J.K., 2006. Advances in transition cow biology: new frontiers in production diseases. In: N. Joshi and T.H. Herdt (eds.) Production disease in farms animals, Wageningen Academic Publ., Wageningen, The Netherlands, pp 24-34.

Drackley, J.K., Dann, H.M., Douglas, G.N., Janovick-Guretzky, N.A., Litherland, N.B., 2005. Physiological and pathological adaptations in dairy cows that may increase susceptibility to periparturient diseases and disorders. Ital. J. Anim. Sci. 4:323-344.

Drackley, J.K., Janovick-Guretzky, N.A., Loor, J.J., 2007. Linkage between metabolism and the immune system. pp 214-227 in Proc. 13th Int. Conf. on Production Diseases in Farm Animals, Leipzig, Germany.

Elsasser, T.H., Kahl, S., Steele, C., Rusmey, T.S., 1997. Nutritional modulation of somatotropic axis-cytokine relationships in cattle: a brief review. Comp. Biochem. Physiol. 116:209-221.

Elsasser, T.H., Steele, N.C., Fayer, R., 1995. Cytokines, stress and growth modulation. In: M.J Myers and M.P. Murtaugh (eds.) Cytokines in animal health and disease. Marcel Dekker Inc., New York, NY, USA.

Ferguson, J.D., 1991. Nutrition and reproduction in dairy cows. Vet. Clin. North Am. Food Anim. Pract. 7:483-507.

Ferguson, J.D., Chalupa, W., 1989. Impact of protein nutrition on reproduction in dairy cows. J. Dairy Sci. 72:746-766.

Ferguson, J.D., Galligan, D.T., Blanchard, T., Reeves, M., 1993. Serum urea nitrogen and conception rate: the usefulness of test information. J. Dairy Sci. 76:3742-3746.

Fleck, A. 1989. Clinical and nutritional aspects of changes in acute phase proteins during inflammation. P. Nutr. Soc. 48:347-354.

Fleisher, P., Metzner, M., Beyerbach, M., Hoedemaker, M., Klee, W., 2001. The relationship between milk yield and the incidence of some diseases in dairy cows. J. Dairy Sci. 84:2025-2035.

Folman, Y., Neumark, H., Kaim, M., Kaufmann, W., 1981. Performance, rumen and blood metabolites in high-yielding cows fed varying protein percents and protected soybean. J. Dairy Sci. 64:759-768.

Francisco, C.C., Spicer, L.J., Payton, M.E., 2003. Predicting cholesterol, progesterone and days to ovulation using postpartum metabolic and endocrine measures. J. Dairy Sci. 86:2852-2863.

Fredriksson, G., Kindahl, H., Edqvist, L.E., 1985. Endotoxins-induced prostaglandin release and corpus luteum function in goats. Anim. Reprod. Sci. 8:109-121.

Friggens, N.C., 2003. Body lipid reserves and the reproductive cycle: towards a better understanding. Livest. Prod. Sci. 83:219-236.

Fromageot, D., 1978. Animal husbandry approach to infertility in dairy cattle. 2a. Nutritional factors. Recl. Med. Vet. 154:207-213.

Garcia-Bojolil, C.M., Staples, C.R., Risco, C.A., Savio, J.D., Thatcher, W.W., 1998. Protein degradability and calcium salts of long chain fatty acids in the diets of lactating dairy cows: reproductive responses. J. Dairy Sci. 81:1384-1395.

Garnsworthy, P.C., Lock, A., Mann, G.E., Sinclair, K.D., Webb, R., 2008. Nutrition, metabolism and fertility in dairy cows: 1. dietary energy source and ovarian function. J. Dairy Sci. 91:3814-3823.

Garnsworthy, P.C., Webb, R., 1999. The influence of nutrition on fertility in dairy cows. In: P.C. Garnsworthy and J. Wiseman (eds.) Recent advances in animal nutrition. Nottingham Univ. Press, UK, pp 39-57.

Gath, V.P., Lonergan, P., Boland, M.P., O'Callaghan, D., 1999. Effect of diet type on establishment of pregnancy and embryo development in heifers. Theriogenology 51:224 (abstr.).

Godden, S.M., Lissemore, K.D., Kelton, D.F., Leslie, K.E., Walton, J.S., Lumsden, J.H., 2001. Relationship between milk urea concentrations and nutritional management, production and economic variables in Ontario dairy herds. J. Dairy Sci. 84:1128-1139.

Goff, J.P., Horst, R.L., 1997. Physiological changes at parturition and their relationship to metabolic disorders. J. Dairy Sci. 80:1260-1268.

Gong, J.G., Lee, W.J., Garnsworthy, P.C., Webb, R., 2002. Effect of dietary-induced increases in circulating insulin concentrations during the early postpartum period on reproductive function in dairy cows. Reproduction 123:419-427.

Gonzales-Recio, O., Alenda, R., 2005. Genetic parameters for female fertility traits and fertility index in spanish dairy cattle. J. Dairy Sci. 88:3282-3289.

Gozho, G.N., Krause, D.O., Plaizier, J.C., 2006. Rumen lipopolysaccharide and inflammation during grain adaptation and subacute ruminal acidosis in steers. J. Dairy Sci. 89:4404-4413.

Grimble, R.F., 2001a. Nutritional modulation of immune function. P. Nutr. Soc. 60:389-397.

Grimble, R.F., 2001b. Stress proteins in disease: metabolism on a knife edge. Clin. Nutr. 20:469-476.

Grimble, R.F., 2002. Inflammatory status and insulin resistance. Curr. Opin. Clin. Nutr. 5:551-559.

Grummer, R.R., 1995. Impact of changes in organic nutrient metabolism of feeding the transition dairy cow. J. Anim. Sci. 73:2820.

Grummer, R.R., Brickner, A., Silva-del-Rio, N., 2007. High forage or high grain for dry cows: what is best for animal health and production? pp 187-195 in Proc. 13th Int. Conf. on Production Diseases in Farm Animals, Leipzig, Germany.

Gruys, E., Toussaint, M.J., Landman, W.J., Tivapasi, M., Chamanza, R., VanVeen, L., 1999. Infection, inflammation and stress inhibit growth. Mechanisms and non-specific assessment of the processes by acute phase proteins. In: Th. Wensing (ed.) Production diseases in farm animals. Wageningen Pers, Wageningen, The Netherlands, pp 72-87.

Gruys, E., Toussaint, M.J., Niewold, T.A., Koopmans, S.J., 2005. Acute phase reaction and acute phase proteins. J. Zhejiang Univ. Sci. B. 6:1045-1056.

Gustafsson, A.H., Carlsson, J., 1993. Effects of silage quality, protein evaluation systems and milk urea content on milk yield and reproduction in dairy cows. Livest. Prod. Sci. 37:91-105.

Hammon, D.S., Evjen, I.M., Dhiman, T.R., Goff, J.P., Walters, J.L., 2006. Neutrophil function and energy status in Holstein cows with uterine health disorders. Vet. Immunol. Immunop. 113:21-29.

Hansen, L.B., 2000. Consequences of selection for milk yield from a geneticist's viewpoint. J. Dairy Sci. 83:1145-1150.

Hansen, L.B., Freeman, A.E., Berger, P.J., 1983. Association of heifer fertility with cow fertility and yield in dairy cattle. J. Dairy Sci. 66:306-314.

Harrison, R.O., Ford, S.P., Young, J.W., Conley, A.J., Freeman, A.E., 1990. Increased milk production versus reproductive and energy status of high producing dairy cows. J. Dairy Sci. 73:2749-2758.

Hauguel-de Mouzon, S., Guerre-Millo, M., 2005. The placenta cytokine network and inflammatory signals. Placenta 27:794-798.

Hess, B.W., Lake, S.L., Scholljegerdes, E.J., Weston, T.R., Nayigihugu, V., Molle, J.D., Moss, G.E., 2005. Nutritional controls of beef cow reproduction. J. Anim. Sci. 83(Suppl. E):90-106.

Heuer, C., Schukken, Y.H., Dobbelaar, P., 1999. Postpartum body condition score and results from the first test day milk as predictors of disease, fertility, yield and culling in commercial dairy herds. J. Dairy Sci. 82:295-304.

Horan, B., Mee, J.F., O'Connor, P., Rath, M., Dillon, P., 2005. The effect of strain of Holstein-Friesian cow and feeding system on postpartum ovarian function, animal production and conception rate to first service. Theriogenology 63:950-971.

Howard, H.J., Aalseth, E.P., Adams, C.D., Bush, L.J., McNew, R.W., Dawson, L.J., 1987. Influence of dietary protein on reproductive performance of dairy cows. J. Dairy Sci. 70:1563-1571.

Howell, W.M., Calder, P.C., Grimble, R.F., 2002. Gene polymorphisms, inflammatory diseases and cancer. P. Nutr. Soc. 61:447-456.

Ingvartsen, K.L., Andersen, J.B., 2000. Integration of metabolism and intake regulation: a review focusing on periparturient animals. J. Dairy Sci. 83:1573-1597.

Ingvartsen, K.L., Dwhurst, R.J., Friggens, N.C., 2003. On the relationship between lactational performance and health: is it yield or metabolic imbalance that cause production diseases in dairy cattle? A position paper. Livest. Prod. Sci. 83:277-308.

Ingvartsen, K.L., Friggens, N.C., Faverdin, P., 1999. Food intake regulation in late pregnancy and early lactation. In: J.D. Oldham, G. Sim, A.F. Groen, B.L. Nielsen, J.E. Pryce and T.L.J. Lawrence (eds.) Metabolic stress in dairy cows. Occasional Publ. No. 24, BSAS ed., Edinburgh, Scotland, UK, pp 37-54.

Inskeep, E.K., 2004. Preovulatory, postovulatory and postmaternal recognition effects of concentrations of progesterone on embryonic survival in the cow. J. Anim. Sci. 82:E24-E39.

Janovick Guretzky, N.A., Dann, H.M., Bionaz, M., Trevisi, E., Bertoni, G., Drackley, J.K., 2007. Evaluation of acute phase reactants and indices of liver function in serum from dairy cows fed different levels on energy prepartum. J. Dairy Sci. 90(Suppl. 1):408 (abstr.).

Johnson, R.W., Finck, B.N., 2001. Tumor necrosis factor α and leptin: two players in an animal's metabolic and immunologic responses to infection. J. Anim. Sci. 79:E118-E127.

Jordan, E.R., 2003. Effects of heat stress on reproduction. J. Dairy Sci. 86(Suppl. E.):104-114.

Jordan, E.R., Swanson, L.V., 1979. Effect of crude protein on reproductive efficiency, serum total protein, and albumin in the high-producing dairy cow. J. Dairy Sci. 62:58-63.

Jorritsma, R., César, M.L., Hermans, J.T., Krintwagen, C.L.J.J., Vos, P.L.A.M., Kruip, T.A.M., 2004. Effects of non-esterified fatty acids on bovine granulosa cells and developmental potential of oocytes *in vitro*. Anim. Reprod. Sci. 81:225-235.

Jukola, E., Hakkarainen, J., Saloniemi, H., Sankari, S., 1996. Blood selenium, vitamin E, vitamin A and β-carotene concentrations and udder health, fertility treatments and fertility. J. Dairy Sci. 79:838-845.

Kadokawa, H., Blache, D., Yamada, Y., Martin, G.B., 2000. Relationships between changes in plasma concentration of leptin before and after parturition and the timing of first post-partum ovulation in high producing Holstein dairy cows. Reprod. Fert. Develop. 12:405-411.

Kapcala, P.L., 1999. Inflammatory stress and the immune system. Nutrition and Immune Function. National Academy Press, Washington, DC, USA.

Katoh, N., Oikawa, T., Oohaahi, T., Takahashi, Y., Itoh, F., 2002. Decreases of apolipoprotein B-100 and A-I concentrations and induction of haptoglobin and serum amyloid A in nonfed calves. J. Vet. Med. Sci. 64:51-55.

Kim, M.S., Sweeney, T.R., Shigenaga, J.K., Chui, L.G., Moser, A., Grunfeld, C., Feingold, K.R., 2007. Tumor necrosis factor and interleukin 1 decrease RXRalpha, PPARalpha, PPARgamma, LXRalpha, and the coactivators SRC-1, PGC-1alpha, and PGC-1beta in liver cells. Metabolism 56:267-279.

Klasing, K.C., 2000. Dietary approaches to protecting animal health. In: Agenda 2000: the food revolution. Alltech's European ed., Nicholasville, KY, USA, pp 9-19.

Knight, C.H., Beever, D.E., Sorensen, A., 1999. Metabolic loads to be expected from different genotypes under different systems. In: J.D. Oldham, G. Sim, A.F. Groen, B.L. Nielsen, J.E. Pryce and T.L.J. Lawrence (eds.) Metabolic stress in dairy cows. Occasional Publ. No. 24., BSAS ed., Edinburgh, Scotland, UK, pp 21-26.

Kruip, T.A.M., Meijer, G.A., Rukkwamsuk, T., Wensing, T., 1999. Investigation into the mechanisms of reduction in fertility of high yielding cows. In: Th. Wensing (ed.) Production diseases in farm animals. Wageningen Pers, Wageningen, The Netherlands, pp 183-190.

Kruip, T.A.M., Van Beek, H., De Wit, A., Postma, A., 1995. Influence of food intake ante partum on the quality of oocytes post partum in dairy cows. In: G. Enne, G.F. Greppi and A. Lauria (eds.) Proc. Symp. Reproduction and Animal Breeding, Advances and Strategy. Elsevier Italia, Milano, Italy, pp 327-331.

Kruip, T.A.M., Wensing, T., Vos, P.L.A.M., 2001. Characteristics of abnormal puerperium in dairy cattle and the rationale for common treatment. In: M.G. Diskin (ed.) Fertility in the high producing dairy cow. Occasional Publ. No. 26., BSAS ed, Edinburgh, Scotland, UK, pp 63-79.

Labernia, J., Lopez-Gautius, F., Santolaria, P., Hanzen, C., Laurent, Y., Houtain, J.Y., 1999. Influence of calving season on the interactions among reproductive disorders of dairy cows. Anim. Sci. 67:387-393.

Lacetera, N., Scalia, D., Mashek, D.G., Bernabucci, U., Grummer, R.R., 2007. Effects of intravenous triacylglycerol emulsions on lymphocyte responses to mitogens in fasted dairy cows undergoing intense lipomobilization. J. Dairy Res. 74:323-328.

Landau, S., Braw-Tal, R., Kaim, M., Bor, A., Bruckental, I., 2000. Preovulatory follicular status and diet affect the insulin and glucose content of follicles in high-yielding dairy cows. Anim. Reprod. Sci. 64:181-197.

Lippi, G., Braga, V., Adami, S., Giudi, G., 1998. Modification of serum apolipoprotein A-I, apolipoprotein B and lipoprotein(a) levels after biphosphonates-induced acute phase response. Clin. Chim. Acta 271:79-87.

Lombardelli, L., Bani, P., Delavaud, C., Chilliard, Y., Bertoni, G., 2002. Leptin variations in dry and lactating periods of dairy cows with different genetic merit. ADSA/ASAS/CSAS Joint Meeting, Quebec City, Canada. J. Dairy Sci. 85(Suppl.1):6 (abstr.).

Lopez, H., Caraviello, D.Z., Satter, L.D., Fricke, P.M., Wiltbank, M.C., 2005. Relationship between level of milk production and multiple ovulations in lactating dairy cows. J. Dairy Sci. 88:2783-2793.

Lucy, M.C., 2001. Reproductive loss in high-producing dairy cattle: where will it end? J. Dairy Sci. 84:1277-1293.

Lucy, M.C., 2003. Physiological mechanisms linking reproduction to nutrition in high-producing dairy cows. pp 39-48 in Proc. Mid-South Rum. Nutr. Conf., Arlington, TX, USA.

Mallard, B.A., Dekkers, J.C., Ireland, M.J., Leslie, K.E., Sharif, S., Lacery, V., Wagter, L., Wilkie, B.N., 1998. Alteration in immune responsiveness during the periparturient period and its ramification on dairy cow and calf health. J. Dairy Sci. 81:585-595.

Mann, G.E., Blache, D., 2002. Relationship between plasma leptin concentration and reproductive function in dairy cows. BSAS ed., Edinburgh, Scotland, UK.

Markusfeld, O., Galon, N., Ezra, E., 1997. Body condition score, health, yield and fertility in dairy cows.

Vet. Rec. 141:67-72.

McKenzie, R., Arthur, J.R., Miller, S.M., Rafferty, T.S., Becket, G.J., 2002. Selenium and the immune system. In: P.C. Calder, C.J. Field and H.S. Gill (eds.) Nutrition and immune function. CAB International, Wallingford, UK, pp 229-250.

Müller, U., Leucht, W., Reinecke, P., Dalle, T., 1999. Breeding and biological evaluation of yield selection in dairy cattle. Anim. Res. 49:51-62.

Murthy, S., Mathur, S., Bishop, W.P., Field, E.J., 1997. Inhibition of apolipoprotein B secretion by IL-6 is mediated by EGF or an EGF-like molecule in CaCo-2 cells. J. Lipid Res. 38:206-216.

National Research Council, 2001. Nutrient requirement of dairy cattle. 7th rev. ed. National Academy Press, Washington, DC, USA.

Nocek, J.E., 1997. Bovine acidosis: implications on laminitis. J. Dairy Sci. 80:1005-1028.

O'Flaherty, L., Bouchier-Hayes, D.J., 1999. Immunonutrition and surgical practice. P. Nutr. Soc. 58:831-837.

Oltenacu, P.A., Algers, B., 2005. Selection for increased production and the welfare of dairy cows: are new breeding goals needed? Ambio 34:311-315.

Opsomer, G., Gröhn, Y.T., Hertl, J., Coryn, M., Deluyker, H., de Kruif, A., 2000. Risk factors for post partum ovarian dysfunction in high producing dairy cows in Belgum: field study. Theriogenology 53:841-857.

Opsomer, G., Wensing, Th., Laevens, H., Coryn, M., De Kruif, A., 1999. Insulin resistance: the link between metabolic disorders and cystic ovarian disease in high yielding dairy cows? Anim. Reprod. Sci. 56:211-222.

Ouweltjes, W., Smolders, E.A., Van Eldik, P., Elving, L., Schukken, Y.H., 1996. Herd fertility parameters in relation to milk production in dairy cattle. Livest. Prod. Sci. 46:221-227.

Petersen, H.H., Nielsen, J.P., Heegaard, P.M., 2004. Application of acute phase protein measurements in veterinary clinical chemistry. Vet. Res. 35:163-187.

Pié, S., Awati, A., Vida, S., Falluel, I., Williams, B.A., Oswald, I.P., 2007. Effects of added fermentable carbohydrates in the diet on intestinal proinflammatory cytokine-specific mRNA content in weaning piglets. J. Anim. Sci. 85:673-683.

Powanda, M.C., 1980. Host metabolic alterations during inflammatory stress as related to nutritional status. Am. J. Vet. Res. 41:1905-1911.

Raggio, G., Lobley, G.E., Berthiaume, R., Pellerin, D., Allard, G., Dubreuil, P., Lapierre, H., 2007. Effect of protein supply on hepatic synthesis of plasma and constitutive proteins in lactating dairy cows. J. Dairy Sci. 90:352-359.

Rajala, P.J., Gröhn, Y.T., 1998. Effects of dystocia, retained placenta, and metritis on milk yield in dairy cows. J. Dairy Sci. 81:3172-3181.

Rajala-Schultz, P.J., Saville, W.A., Frazer, G.S., Wittum, T.E., 2001. Association between milk urea nitrogen and fertility in Ohio dairy cows. J. Dairy Sci. 84:482-489.

Richards, C.D., Gauldie, J., 1995. Role of cytokines in acute-phase response. In: B.B. Aggarwal and K.R. Puri (eds.) Human cytokines: their role in disease and therapy. Blackwell Science, Cambridge,USA, pp 253-263.

Roche, H.M., Noone, E., Nugent A., Gibney, M.J., 2001. Conjugated linoleic acid: a novel therapeutic nutrient? Nutr. Res. Rev. 14:173-187.

Roche, J.F., Mackey, D., Diskin, M.D., 2000. Reproductive management of postpartum cows. Anim. Reprod. Sci. 60/61:703-712.

Royal, M., Mann, G.E., Flint, A.P., 2000. Strategies for reversing the trend towards subfertility in dairy cattle. Vet. J. 160:53-60.

Sakaguchi, M., Sasamoto, Y., Suzuki, T., Takahashi, Y., Yamada, Y., 2004. Postpartum ovarian follicular dynamics and estrous activity in lactating dairy cows. J. Dairy Sci. 87:2114-2121.

Santos, J.E., 2001. Dietary ingredients and nutritional management impact fertility in dairy cattle. pp 189-220 in Proc. 36th Annual Pacific Northwest Animal Nutrition Conf., Boise, ID, USA.

Santos, J.E., Thatcher, W.W., Pool, L., Overton, M.W., 2001. Effect of human chorionic gonadotropin on luteal function and reproductive performance of high producing lactating Holstein dairy cows. J. Anim. Sci. 79:2881-2894.

Schaver, RD., Howard, W.T., 1993. Feeding dairy cows for efficient reproductive performance. University

of Wisconsin-Madison ed., Madison, UW, USA.
Schneider, J.E., Wade, G.N., 2000. Inhibition of reproduction in service of energy balance. In: K. Wallen and J.E. Schneider (eds.) Reproduction in context: social and environmental influences on reproductive physiology and behaviour. Massachussets Institute of Technology, Cambridge, MA, USA, pp 35-82.
Schrick, F.N., Hockert, M.E., Saxton, A.M., Lewis, M.J., Dowlen, H.H., 2001. Influence of subclinical mastitis during early lactation on reproductive parameters. J. Dairy Sci. 84:1407-1412.
Schukken, Y.H., Zadoks, R.N., Kornalijnslijper, Jorritsma, R., Heuer, C., Suriyasathaporn, W., Wensing, T., Rukkwamsuk, T., Döpfer, D., 1999. Production diseases in farm animals epidemiology and a holistic approach. In: Th. Wensing (ed.) Production diseases in the farm animals. Wageningen Pers, Wageningen, The Netherlands, pp 241-253.
Shuster, D.E., Lee, E.K., Kehrli, M.E., 1996. Bacterial growth, inflammatory cytokines production and neutrophil recruitment during coliform mastitis in cows within ten days after calving, compared with cows at midlactation. Am. J. Vet. Res. 57:1569-1575.
Simpson, K.L., Keelan, J.A., Mitchell, M.D., 1998. Labor-associated changes in intelreukin-10 production and its regulation by immunomodulators in human choriodecidua. J. Clin. Endocr. Metab. 83:4332-4337.
Sinclair, K.D., Kuran, M., Gebbie, F.E., Webb, R., McEvoy, T.G., 2000a. Nitrogen metabolism and fertility in cattle: II. Development of oocytes recovered from heifers offered diets differing in their rate of nitrogen release in the rumen. J. Anim. Sci. 78:2670-2680.
Sinclair, K.D., Sinclair, L.A., Robinson, J.J., 2000b. Nitrogen metabolism and fertility in cattle: I. Adaptive changes in intake and metabolism to diets differing in their rate of energy and nitrogen release in the rumen. J. Anim. Sci. 78:2659-2669.
Snijders, S.E., Dillon, P., O'Callaghan, D., Boland, M.P., 2000. Effect of genetic merit, milk yield, body condition and lactation number on in vitro oocyte development in dairy cows. Theriogenology 53:981-989.
Sogstad, A.M., Osteras, O., Fjeldaas, 2006. Bovine claw and limb disorders related to reproductive performance and production diseases. J. Dairy Sci. 89:2519-2528.
Sordillo, L.M., Pighetti, G.M., Davis, M.R., 1995. Enhanced production of bovine tumor necrosis factor-alpha during the periparturient period. Vet. Immunol. Immunop. 49:263-270.
Spears, J.W., 2000. Micronutrients and immune function in cattle. P. Nutr. Soc. 59:587-594.
Spicer, L.J., Tucker, R.K., Adams, G.D., 1990. Insulin-like growth factor-I in dairy cows: relationship among energy balance, body condition score, ovarian activity and oestrus behaviour. J. Dairy Sci. 73:929-937.
Staples, C.R., Thatcher, W.W., Clark, J.K., 1990. Relationship between ovarian activity and energy status during the early postpartum period of high producing dairy cows. J. Dairy Sci. 73:938-947.
Stevenson, J.S., 1999. Can you have good reproduction and high milk yield? Hoard's Dairyman 13:536.
Suchner, U., Kuhn, K.S., Fürst, P., 2000. The scientific basis of immunonutrition. P. Nutr. Soc. 59:553-563.
Trevisi, E., Bertoni, G., 2008. Attenuation with acetylsalicylate treatments of inflammatory conditions in periparturient dairy cows. In: P.I. Quinn (ed.) Aspirin and health research progress. Nova Science Publ., Hauppauge, NY, USA, pp 23-37.
Trevisi, E., Gubbiotti, A., Bertoni, G., 2007. Effects of inflammation in peripartum dairy cows on milk yield, energy balance and efficiency. pp 395-396 in Proc. 2nd Int. Symp. on Energy and Protein Metabolism and Nutrition, Vichy, France.
Trevisi, E., Han, X.-T., Piccioli-Cappelli, F., Bertoni, G., 2002. Dry matter intake reduction before calving in dairy cows: relationship with immune system and metabolism conditions. Page 54 (abstr.) in Proc. 53rd Annual Meet. EAAP, Cairo, Egypt.
Trevisi, E., Lombardelli, R., Calamari, L., Bertoni, G., 1996. Variazioni ematiche del progesterone in bovine trattate con endotossine in fasi riproduttive e con modalità diverse. pp 47-51 in Proc. 8th Nat. Meet. of Istituto Sperimentale Italiano Lazzaro Spallanzani, Milano, on Study of reproductive efficency in farm animals, Bergamo, Italy.

Van Den Top, A.M., Geelen, M.J., Wensing, T., Wentink, G.H., Van't Klooster, A.T., Beynen, A.C., 1996. Higher postpartum hepatic triacylglycerol concentrations in dairy cows with free rather than restricted access to feed during the dry period are associated with lower activities of hepatic glycerolphosphate acyltransferase. J. Nutr. 126:76-85.

Van Knegsel, A.T.M., de Vries Reilingh, G., Meulenberg, S., van den Brand, H., 2007. Natural antibodies related to energy balance in early lactation dairy cows. J. Dairy Sci. 90:5940-5948.

Veerkamp, R.F., Beerda, B., van der Lende, T., 2003. Effects of genetic selection for milk yield on energy balance, levels of hormones and metabolites in lactating cattle and possible links to reduced fertility. Livest. Prod. Sci. 83:257-275.

Villa-Godoy, A., Hughes, T.L., Emery, R.S., Chapin, L., Fogwell, R.L., 1988. Association between energy balance and luteal function in lactating dairy cows. J. Dairy Sci. 71:1063-1072.

Visek, W.J., 1984. Ammonia: its effects on biological systems, metabolic hormones and reproduction. J. Dairy Sci. 67:481-498.

Wade, G.N., Schneider, J.E., Li, H.Y., 1996. Control of fertility by metabolic cues. Am. J. Physiol. 270:1-19.

Walsh, R.B., Kelton, D.F., Duffield, T.F., Leslie, K.E., Walton, J.S., LeBlanc, S.J., 2007. Prevalence and risk factors for postpartum anovulatory condition in dairy cows. J. Dairy Sci. 90:315-324.

Walters, A.H., Bailey, T.L., Pearson, R.E., Gwazdauskas, F.C., 2002. Parity-Related changes in bovine follicle and oocyte populations, oocyte quality and hormones to 90 days postpartum. J. Dairy Sci. 85:824-832.

Wan, J.M., Haw, M.P., Blackburn, G.L., 1989. Nutrition, immune function and inflammation: an overview. P. Nutr.Soc. 48:315-335.

Ward, W.R., Parker, C.S., 1999. Field evidence of metabolic stress in dairy cows? In: J.D. Oldham, G. Sim, A.F. Groen, B.L. Nielsen, J.E. Pryce and T.L.J. Lawrence (eds.) Metabolic stress in dairy cows. Occasional Publ. No. 4, BSAS ed., Edinburgh, Scotland, UK, pp 21-26.

Webb, R., Garnsworthy, P.C., Gong, J.G., Armstrong, D.G., 2004. Control of follicular growth: local interactions and nutritional influences. J. Anim. Sci. 82: E63-E74.

Webb, R., Garnsworthy, P.C., Gong, J.G., Robinson, R.S., Wathes, D.C., 1999. Consequences for reproductive function of metabolic adaption to load. In: J.D. Oldham, G. Sim, A.F. Groen, B.L. Nielsen, J.E. Pryce and T.L.J. Lawrence (eds.) Metabolic stress in dairy cows. Occasional Publ. No. 24, BSAS ed., Edinburgh, Scotland, UK, pp. 99-110.

Wolter, R., 1973. Alimentation et fecondité de la vache. Recl. Med. Vet. 124:297-325.