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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
Review Article

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

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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 mechanisms, 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...
BertonI et al.

(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 anziuttro 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’ingestion 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.
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) peri-

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.
ods. 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 peripheral 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 closely 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

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**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).

![Graph showing changes of basal blood insulin and GH](image)

*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 anestrus 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 - diff-
different 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 Kruij 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

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.
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 ated 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)
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...
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 et 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 statement 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

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).
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 nonproductive 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 interest is the finding that cows with better liver functions (UP) had both higher milk yield and better fertility compared to those with lower liver functions (LO). This suggests that liver health is a critical factor in both milk production and reproductive performance in dairy cows.
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     | INUP   | INLO   | 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 efficiency 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; Petersen 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 integ-
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Importance 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 NEI 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 NEI 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...
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 acetylsalicylate 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 foresee 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-
difficulties 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 \( \geq 4 \) 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 vari-

**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                          | 22.0| 23.0|
| culled cows                   | 15.8| 9.5 |
| pregnant cows                 | 86.4| 91.3|
| pregnant at 1st insemination  | 21.1| 52.4|
| repeat breeders               | 36.8| 28.6|
| services per pregnancy ($)     | 2.68| 2.38|
| days open ($)                 | 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.
ations 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.).

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