INTRODUCTION
Milk production level has increased substantially in dairy cattle over the past decades. Its major drive has been an on-going genetic improvement of sires coupled to high merit selection of dams. Furthermore, new farm technologies were developed (e.g. feed mixer wagons, computerised feeding, milking robots) as well as housing systems (e.g. loose housing, under glass housing, deep straw yard). Farm sizes continue to increase, not least to deal with increasing production costs in relation to staggering or falling farm income. Unfortunately, farm management has not always kept pace with the new developments and/or the demands of high yielding cows and/or the new production environment (Noordhuizen 2012). The term of the “10 minutes a day cow” speaks for itself. This means that, given the many processes and functions a farmer with or without coworkers has to deal with, some of these functions/processes will be neglected or omitted – most often unwillingly – because time is lacking or the on-farm organisation is deficient. The latter reflects in the fact that the farmer spends on average 10 minutes per cow per day on respective activities, milking and feeding mainly. As a consequence, several cow-bound activities do not or hardly take place. Among the latter are: cow observation for heat, for detecting lameness or for other disease at an early stage. At the same time a large amount of farm data has become available which are not (always) utilised in the best manner for an in-depth analysis of performance and performance disorders. Furthermore, cows are confronted with various stressors during the dry period, at parturition and in the early postpartum period. These stressors have a certain negative impact on their immune responsiveness and metabolic regulatory processes. Health and reproductive processes are under (co-)control of the immune system in cows. Moreover, there are functional bonds between immune cells and reproductive hormones.

All the above-mentioned phenomena and factors have contributed to an increase of the incidence and prevalence of a more or less severe negative energy balance (NEB) as well as of subsequent disorders like ketosis and rumen acidosis. The latter on their turn impact on the occurrence of various other health and fertility disorders (Cardoso and others 2013). In this paper the occurrence of negative energy balance (NEB) and ketosis is highlighted, their effect on fertility discussed, and possible ways to prevent and control disorders addressed.

OCCURRENCE OF NEB AND KETOSIS
The energy balance (EB) in dairy cows represents the outcome of outputs (e.g. growth, maintenance, milk production) and inputs (energy from forages and concentrates). During the dry period this EB is usually positive, while around and after parturition the EB is commonly more or less severely negative (NEB). This NEB is gross modo due to the fact that feed intake frequently drops 7 to 10 days ante-partum, and that the energy intake after parturition is insufficient to meet the energy demands set by the increasing milk production postpartum, next to maintenance and growth in first lactation heifers.

The cow has several ways to counteract the NEB: adaptation processes (Dantzer 2002), which comprise different domains, such as lipolysis, liver function, immune responsiveness (Chelmonska-Soyta 2013) and neuro-endocrinology (Dantzer 2002) being among the most relevant ones (Figure 1). The phenomenon of ketosis development is schematically represented in Figure 2 and is -in general- physiological in nature, except when different negatively impacting conditions prevail. In Table 1 examples of such conditions are given.

The role of the immune system in the transition period has lately gained much more research attention than previously. It has been established...
that severe NEB, or NEB of long duration, is associated with a more severe and prolonged uterine inflammation (LeBlanc 2012a). Mononuclear blood cells and their interferon-gamma production decrease with an increasing non-esterified fatty acid (NEFA) serum concentration. The oxidative burst of polymorphonuclear cells (PMN) is also decreased in cows with high NEFA levels. PMN are key uterine effector cells. In periparturient cows the functional capacity of PMN is downregulated. In fatty liver cows they show less and slower phagocytosis (Zerbe 2013). Immune cells produce cytokines; the latter influence oestrogen and progesterone, as well as prolactin and glucocorticoids. Oestrogen and progesterone on their turn affect immune cells (e.g. T-helper cells 1 and 2; natural killer cells NK; macrophages; dendritic cells). Prostaglandin E and – to a lesser extent - prostaglandin F2α as secreted by the endometrium cells represent an anti-inflammatory response. It currently is the question whether a pro-inflammatory response (from T-helper 1 cells) would be more beneficial for the transition cow than an anti-inflammatory response (from T-helper 2 cells). For example, the increase in Interleukine-2 and Interferon-gamma postpartum highlights embryonic death and abortion. Adipose tissue contributes to various pro-inflammatory signals (IL-6 and tumor necrosis factor, TNFα) and contains many tissue-specific macrophages. It seems likely that the metabolic and reproductive problems in cows with (severe) NEB are not only due to the NEB, but also (and maybe more even so) to a specific metabolic and immune regulation or downregulation in the transition period. The pleiotropy, affinity and duration of signals from bacteria present or from immune cells and metabolism (including the somatotropic axis – IGF-1) are probably the major risk factors of reproductive problems after parturition (Chelmonska-Soyta 2013, Zerbe 2013).

Recently Bradford (2011) presented an overview of different newly detected and described actors, bridging the domains of brains, nutrition, endocrinology and fertility in the cows’ adaptation processes. Examples are: leptin, resistin, gut peptides, Gh relin, fibroblast growth factor 21 (FGF 21) and osteocalcin. They have a different origin of secretion; for example, the adipose tissue (leptin and resistin), the abomasum (Gh relin), the intestines (gut peptides) or the liver (fibroblast growth factor 21, FGF 21); Figure 3 presents an

Table 1. An overview of various conditions impacting on energy balance (EB) and NEB.

<table>
<thead>
<tr>
<th>Domain of concern</th>
<th>Lactation stage</th>
<th>Specifications</th>
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</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>End of lactation</td>
<td>Forage quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concentrates; cereals</td>
</tr>
<tr>
<td></td>
<td>Dry period</td>
<td>Ration composition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantity of feed supplied</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minerals and vitamins</td>
</tr>
<tr>
<td>Animal health status</td>
<td>Dry period</td>
<td>Claw lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viral infections</td>
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<tr>
<td></td>
<td></td>
<td>Other infections: mastitis</td>
</tr>
<tr>
<td></td>
<td>Around parturition</td>
<td>Immune responsiveness (pro-inflammatory and inflammatory responses)</td>
</tr>
<tr>
<td>Management factors</td>
<td>Dry period</td>
<td>Feeding management errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cow groups in dry period</td>
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<tr>
<td></td>
<td></td>
<td>Housing ante- and postpartum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of mobility of dry cows</td>
</tr>
<tr>
<td></td>
<td>Lactation</td>
<td>Poor cow comfort</td>
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<tr>
<td></td>
<td></td>
<td>BCS ante- and postpartum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress conditions in herd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barn climatic conditions</td>
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<td></td>
<td></td>
<td>Heat stress conditions</td>
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</tbody>
</table>
overview of such actors. The preceding three
Figures make the picture of adaptation a rather
complex one, far from being fully understood.
Another factor of interest is carnitine. Carnitine
mediates the fat metabolism in the liver; carnitine
synthesis is dependent on feed intake. When feed
intake drops, carnitine synthesis decreases which
results in a poor fat metabolism in the liver. Choline
stimulates the synthesis of carnitine (Kumar-Dubey
2012).

Major triggers for a pathophysiological
development of NEB and ketosis are poor feed
intake ante- and postpartum, too high Body
Condition Score (BCS ≥ 4) antepartum, and BCS loss
postpartum. Preconditioning factors in this context
are: nutrition in the dry period and in the transition
period, animal health status in the dry period,
housing facilities ante- and postpartum, a lack of
mobility among dry cows, various stress conditions,
and the barn climatic conditions (including heat
stress). Given the previous sections, the role of
the immune system should not be underestimated.

EFFECTS OF NEB AND KETOSIS ON FERTILITY
The effects of NEB and ketosis on fertility have been
widely described in literature and are manifold.
Table 2 comprises the major effects of NEB and
ketosis on dairy cow fertility postpartum. These

effects may be direct or indirect. For example,
rations rich in protein induce circulating ammonia
and urea, which on their turn may damage liver
function. At the same time ammonia and urea are
toxic for follicles, as NEFAs are. Also the binding of LH
to ovary receptors is reduced (Butler 2000, 2012).
Management related factors too may play a role.
Putting heifers to pasture for the first time causes
a certain stress which may reduce their cyclicity. High
yielding cows show in average a shorter oestrus
duration and are less mounted than low yielding
cows; oestrus detection efficiency becomes crucial
in such herds. High yielding cows have a higher GH
blood level (14.2 vs 10.0ng/ml) and a lower insulin
blood level (35 vs 46μIU/ml) than low yielding cows.
The metabolism in high yielding cows is different
from that in low yielding cows. BCS is a good means
to assess early postpartum cow performance.
Small BCS loss (less than 0.5 unit) postpartum has
minor effect on the interval from parturition to first
ovulation, while large losses (≥ one unit) may have
great impact on that interval (30 days pp vs 50 days
pp) as well as on the number of days open (11 days
more) and pregnancy rates (Cardoso and others
2013, Inchaisri and others 2013).

Table 2. Major effects of NEB and ketosis on
fertility.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>No oestrus observed during 50 days postpartum at all</td>
<td>No oestrus observed shortly after parturition and no more until about 75 days postpartum</td>
</tr>
<tr>
<td>Oestrus observed shortly after parturition and no more until about 75 days postpartum</td>
<td>Cystic ovarian disease occurrence</td>
</tr>
<tr>
<td>Cows not conceiving after insemination</td>
<td>Early embryonic death</td>
</tr>
</tbody>
</table>
| Weak calves at following parturition, with potential fertility problems in their respective first lactation | Cows with hepatic lipidosis showed a retarded development of their oocytes (Wensing and others 1997, in Cardoso and others 2013). Follicle development from first stage to ovulatory stage has a certain duration; Brit (1992) proposed a duration of about 75 days. Follicles under the impact of a NEB or ketosis, especially in the second part of development, lack sufficient energy and will not always attain the ovulatory stage. Butler (2000, 2012) reported a strong positive association between early postpartum restart of ovulatory cycles and pregnancy rate. Once the nadir of the NEB has been passed, the energy supply becomes more positive and ovulation may again occur. Oocyte quality postpartum may be improved by
a ration low in carbohydrates and/or high in fat (Garnsworthy 2012) but such a ration could hamper the restart of the oestrous cycle. There seems to be variation between cows with respect to their individual liver oxidative, storage and export capacity (Jorritsma and others 2003). This may – at least partly - explain the variation in reproductive outcome among cows postpartum due to NEB and ketosis.

With respect to fertility disorders various associations with NEB and ketosis have been reported (Chastant-Maillard 2012). For example, subclinical metritis is associated with BHB blood levels, NEFAs, low dry matter intake two to three weeks prior to the metritis, a poor BCS, and other peri-parturient disorders. NEFAs have also been associated with abomasal displacement and metritis, while ketosis is associated with anoestrus, decreased pregnancy rates, mastitis and abomasal displacement (LeBlanc 2012a, 2012b). Ketosis on its turn leads to a certain degree of immune suppression which is reflected in a higher rate of mastitis (Suryasathaporn and others 2000). Finally, the situation may be further aggravated when ruminal acidosis occurs, because various reports have been published on the association between ruminal acidosis and other health or fertility disorders (Enemark 2008, Inchaisri and others 2013). Dong and others (2011) found that when ruminal acidosis occurs, bacterial endotoxins are released in the rumen and large intestines (lipopolysaccharides, LPS). This LPS is translocated to the blood circulation and provokes an immune response (increase of neutrophils, serum amyloid A, haptoglobins, LPS binding protein, C-reactive protein). LPS affects the metabolism by increasing blood glucose, NEFA and reactive oxygen species (cytotoxic for e.g. mammary gland cells), while feed intake decreases. The issues described above can play a role in lowered fertility.

**DIAGNOSIS AND PREVENTION**

Diagnosing NEB and ketosis in a herd can be done by conducting a clinical observation of fresh cows. This includes body condition scoring, rumen fill, faecal consistency, and undigested fibre in the faeces (Zaaijer and Noordhuizen 2003), if desired to be extended with a postcalving fertility check on ovary function. Cow side tests on ketosis are available which yields quicker results than the classic blood tests in the laboratory. Another option regards the milk recording forms every few weeks. In these forms we look for milk fat and milk protein levels in the fresh cows, their deviations from the herd means, the milk fat:protein ratio, and the litres of milk of individual cows on subsequent milk recording dates. The key is to determine whether there is a problem of NEB or ketosis in the herd, and not to find the last individual cow potentially affected. Table 3 shows some reference values for milk recording data in the detection of NEB or ketosis problems in a dairy herd. These values can be adapted to the local situation (Noordhuizen 2012).

<table>
<thead>
<tr>
<th>Situation</th>
<th>Potential cause</th>
</tr>
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<tbody>
<tr>
<td>Decrease in milk production in fresh cows &gt;8% since last milk recording date</td>
<td>NEB—ketosis</td>
</tr>
<tr>
<td>Increase of milk fat in fresh cows &gt;4.8 (this level may drop over subsequent milk recording dates below 3.5)</td>
<td>NEB—ketosis</td>
</tr>
<tr>
<td>Decrease of milk protein in fresh cows &lt;2.9</td>
<td>NEB—ketosis</td>
</tr>
<tr>
<td>Decrease in milk fat in fresh cows &gt;0.5 below the herd mean</td>
<td>NEB or acidosis</td>
</tr>
<tr>
<td>Decrease in milk protein in fresh cows &gt;0.3 below the herd mean</td>
<td>NEB or ketosis</td>
</tr>
<tr>
<td>Ratio milk fat:protein in fresh cows &gt;1.5</td>
<td>Ketosis</td>
</tr>
<tr>
<td>Ratio milk fat:protein in fresh cows &lt;1.2</td>
<td>Rumen acidosis</td>
</tr>
</tbody>
</table>

With respect to the prevention of NEB and ketosis, the emphasis should be on maintaining a stable dry matter intake during the last one or two weeks prior to parturition (the transition period), as well as after parturition. Among the issues of concern are palatable products and constantly available fresh clean drinking water of high quality. To optimise feed intake the following issues have been listed by DeVries (2011): free access to fresh feed all day, frequent deliveries of fresh feed, sufficient feed bunk space (75 to 90cm per cow) to minimise competition for feed, and in order to prevent detrimental feeding behaviour and aggression the topdressing of feed forage with grains or concentrates should be avoided. Feedstuffs learned and feeding patterns developed during rearing age pertain later in productive life.

Failed transition cow management is evidenced by over-conditioned cows (BCS ≥ 4; fatty liver), decreased feed intake around parturition, NEB and ketosis, health disorders (milk fever, abomasal displacement, mastitis, claw lesions, ruminal acidosis), milk production problems and reproductive disorders. The objective of an adequate transition cow management is to prepare the rumen function for lactation (especially with regard to motility, microflora, fatty acid ratio, proper pH, adequate rumen layers, functional papillae). A transition cow demands consistent

With regard to the ration, it is currently considered that restricted or controlled energy content in the ration during the far-off period, but even more particularly during the close-up period, is very promising for avoiding severe NEB and ketosis, and at the same time allowing an acceptable restart of cow fertility (LeBlanc 2012b, Cardoso and others 2013). Preliminary results of a large study by Zom (2014) in the Netherlands indicate that the feed intake capacity of cows at the end of the dry period has been overestimated in recent decades by using simulation or other mathematical models. Feed intake capacity was in average 10% lower several days antepartum than generally accepted, while on the days around parturition an additional drop of 15% was determined. No difference was observed between adult cows and heifers (Zom 2014). These researchers conclude that the energy density in the ration should be increased just before and after parturition (maize instead of grass; a minor portion of concentrates). They launched the idea of using sensors for measuring feed intake and rumination frequencies to identify cows in need of particular (feed) attention.

Furthermore, management can contribute further by avoiding changes in housing, group composition and stressful conditions, and providing ample space and sight of herd mates, in the group due to calve. From another preventive point of view, BCS should be stabilised at the end of lactation and during the dry period at a score 3.0 to 3.5 maximum, while BCS loss after parturition should be kept at less than one unit. The farmer should pay particular attention to rumen acidosis in cows with preceding NEB and ketosis, because it can worsen the situation. Moreover, cows with rumen acidosis may be at increased risk of mycotoxicosis (Enemark 2013) due to the destruction of rumen protozoa.

Finally, veterinarians should be aware of the fact that cows in a severe NEB or with ketosis frequently show poor or no ovarian activity (see earlier paragraphs). The administration of prostaglandin F2α for oestrus induction in such cows is hence useless and unnecessarily expensive. On the contrary, the search for fresh cows with cystic ovarian disease, as a result of poor follicle development without ovulation, is indicated to accelerate recovery of the ovary (Butler 2012). The follow-up of fresh cows during each farm visit, for example during a herd health and productivity management advisory programme, conducting the diagnostic activities named above, may further contribute to a better control of NEB and ketosis.

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