

## The impact of the oxidative status on the reproduction of cows and the calves' health – a review

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### Abstract

The profitability of cattle farming is largely determined by ensuring high-quality breeding animals for replacement and longevity in production. The provision of breeding animals requires adequate fertility of the cowherd and then intensive weight gain in the calf rearing period. For ensuring these demands, many management aspects must be considered. Continuous monitoring of the herd's health status, including redox status, is essential. This review aims to provide a summary of relevant scientific data published in the last few decades regarding the role of oxidative stress (OS) in infertility of dairy cows and developmental diseases in calves, the major predisposing factors, and possible prevention.

*Redox status, fertility, herd-health, dairy cattle*

Fertility of dairy cows is crucial for ensuring breeding animals for replacement, and unfortunately, the decline in cattle fertility is often attributed to increased milk yield (Smith et al. 2014). Reproductive performance may be depressed by several biogenic and abiogenic factors, and most probably results from a combination of various physiological and management factors (Lucy 2001). The conception rate may be low due to biotic reasons such as an unmaturred or unhealthy genital tract, low quality of oocytes, failures of implantation, or poor embryo development and health (Leroy et al. 2008; Al-Gubory et al. 2010; Walsh et al. 2011; Diskin et al. 2012; Healy et al. 2013). The major abiotic factors are the low effectivity of heat detection, improper insemination techniques, semen quality, feeding and housing technology including heat abatement (Senger 1994; Bage 2003; Chebel et al. 2004; Tóth et al. 2006; Walsh et al. 2011). Proper nutrition and eligible energy supply are also vital factors in the management of ruminants. Negative energy balance (NEB) and metabolic stress are risk factors for reproduction performance (Leroy et al. 2006; Könyves et al. 2009a,b; De Bie 2017). Oxidative stress (OS) develops when the excessively formed oxygen free radicals (Reactive Oxygen Species; ROS) exceed the capacity of the body's antioxidant (AO) defence mechanisms, which can cause cell damage or exacerbate diseases (Sies et al. 1985). In the periods of NEB, cows are vulnerable to OS (Abuelo et al. 2015, 2019; Elischer et al. 2015; Mikulková et al. 2020).

Calves may experience several physiological challenges after birth, during the milk feeding period and around weaning (Weary et al. 2008). The birth itself, the immature immune system, the high risk of contamination, and the transition from milk to solid feeds all act as stressors, usually exacerbated by environmental effects such as bad hygiene or heat stress (Weary et al. 2008; Hulbert and Moisé 2016; Kertz et al. 2017). Some of these factors can cause OS in calves (McGrath 2016; Vannucchi et al. 2019). The

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adverse effects of the above factors should be significantly reduced in order to produce good quality breeding animals for cow replacement. For effective management of this period, it is essential to have a better understanding of the physiological background.

Oxidative stress is currently an intensively researched area (Wen and Huang 2012). Despite the rapid growth of general knowledge, there are still many unexplored areas for OS in cattle, especially in calves. This review aims to gather the current knowledge regarding OS in cattle with particular attention to cow infertility and diseases of calves.

### **Relationship between fertility and redox status of cows**

Gestation and calving are physiological but challenging conditions for animals. It is vital for economic dairy cattle farming that the heifers calve first at 24–25 months of age (Donovan et al. 1998) and that cows become pregnant within 110–120 days after calving. Fertilization and development of the foetus are mainly affected by the feeding and health of the cow, as well as several additional management factors. The failure of insemination may be caused by OS (Celi et al. 2012).

The average duration of pregnancy is 279–288 days, affected by many factors, such as the breed, age, health status, sex of the foetus, and the season. If the duration of pregnancy is 10–15 days longer than the average for the specific breed, it is considered to be pathological. The fertilized oocyte migrates 72–96 h after fertilization from the ovarian duct to the uterus, and intrauterine life starts and lasts until calving. Approximately 40% of unsuccessful inseminations are due to early embryo death, and 7–8% of this is happening in the blastula stage, undetected by the farmers as it does not have any external symptoms. Also, early embryonic death occurs at the time of nidation, between days 16–32. Major causes of embryonic death include the inappropriate supply of essential nutrients, macro- and microelements, climatic factors, hormonal dysfunction of central or peripheral origin, and certain immunological factors (Haraszti 1993). Unregulated OS is also mentioned as a direct cause of early embryonic mortality (Rizzo et al. 2007; Jóźwik et al. 2012; Konvičná et al. 2015), which may cause failure in the implantation, however, the embryo may also be damaged in some other ways. For example, increased ROS production due to the activity of various inflammation mediators (e.g. cytokines), or even by the activity of a large number of neutrophils, may eventually lead to the death of the embryo. Oxidative stress may develop in heat stress, a primary cause of embryo damage in hot weather (Bernabucci et al. 2010; Jóźwik et al. 2012). In addition to several factors, OS may also play a role in uterine involution disorders, associated with infertility and diseases. In the case of endometritis, the high polymorphic nucleotide (PMN) count detected in the endometrium and also the elevated OS biomarker (advanced oxidation protein products; AOPP) suggest that OS is one of the causes leading to impaired fertility (Gabai et al. 2019).

The above may point to the fact that several factors can influence effective insemination and healthy foetal development, and OS may play a significant role in this.

### **Links between the health of new-born animals, the milk feeding period, and the redox status of the organism**

During birth, the new-born's respiratory system starts functioning and usually OS develops (Gaál et al. 2006; Mutinati et al. 2014; Ranade et al. 2014). Complications during calving can, directly and indirectly, endanger the life and further development of the new-born. First, dystotic calves are often born with low vitality (Vermorel et al. 1989; Besser et al. 1990; Barrier et al. 2013). Oxidative stress can usually be detected in the case of dystocia (Yildiz et al. 2011; Kandemir et al. 2016), although the opposite observations are also known (Yokus et al. 2007).

In new-born animals, due to their rapid development, protein oxidation processes often dominate (Ranade et al. 2014). The concentration of AOPP in blood plasma and AOPP/albumin ratio are progressively decreasing from birth to weaning, whereas a reverse trend is observed in albumin and thiol groups (Celi and Gabai 2015).

The early uptake of good quality colostrum, rich in immunoglobulins (Igs), nutritious substances and AO in sufficient quantities (4 litres) plays a crucial role in the health of new-born calves (Blum et al. 1997; Morin et al. 1997).

The absorption of Igs through the gut decreases by 50% at 6 h after birth (Leslie 2012). Failure in the passive immune transfer occurs in about 32–35% of calves (Weaver et al. 2000; Šlosárková et al. 2014). The low passive transfer may be due to poor quality of colostrum, but for example, severe acidosis at birth also causes 52% reduction in colostrum uptake and results in a 35% lower serum IgG level (Besser et al. 1990). Calving-related diseases are more likely to develop in calves with low levels of maternal IgG in serum (Donkersgoed et al. 1993; Waldner and Rosengren 2009; Leslie 2012).

However, providing maternal antibodies is not the only function of colostrum. Colostrum is rich in AOs, protecting the new-born from OS. It is reported that the production of colostrum can overload the cow's AO systems and may cause OS (Goff and Horst 1997; Abuelo et al. 2016), especially when a cow suffers from NEB after calving and metabolic stress develops. It harms the immune function, health and production in early lactation and may also contribute to the development of OS (Kehrli et al. 1989; Sordillo and Aitken 2009; Abuelo et al. 2019). Metabolic stress can often be detected before calving, and it may affect the health of calves as well. The rate of ROS formation after birth is higher in calves of cows with elevated non-esterified fatty acid (NEFA) values. Cows with OS have a higher blood concentration of haptoglobin, tumour necrosis factor alpha (TNF $\alpha$ ) indicating the animals' response to inflammation. Such calves have an impaired immune response to the lipopolysaccharide (LPS) challenge, an indicator of immunosuppression (Abuelo et al. 2019).

It is beneficial for the health of calves that AOs in colostrum reduce the cellular adverse effect of OS at birth. The concentration of ROS in the blood is lower in the first 3–7 days of life; however, at 2–3 weeks of age, it rises again (Gaál et al. 2006). Others have also pointed out the importance of this temporary ROS/AO imbalance (Albera and Kankofer 2010, 2011).

In modern calf rearing systems, calves are typically fed with milk replacer formula after colostrum and the AO content of these products varies widely (McGrath 2016). If milk replacers have a lower AO content, additional AO supplementation to calves fed in this way is recommended (Lindmark-Månsson and Åkesson 2000; Friel et al. 2002; Chen et al. 2003; Clausen et al. 2009; Soberon et al. 2012; McGrath 2016; Abuelo et al. 2019).

The high rate of weight gain in the early stage of life plays a vital role in later productivity of adult animals as a 5–10 kg increase in weight gain in the pre-weaning period resulted in a significantly increased production in the subsequent lactation (Soberon and Van Amburgh 2013; Van De Stroet et al. 2016). If a higher growth rate is achieved by the feeding of larger amounts of milk replacers, it will later have a negative impact on the uptake of solid feeds and hinder the development of the rumen (Suarez-Mena et al. 2011; Margerison et al. 2013; McGrath 2016).

### **The impact of weaning and management of the post-weaning period on the redox status of animals**

The weaning is technically the closure of the dairy calf rearing period. The weaning in animal husbandry differs from the natural process, as the change from milk feeding

to solid feeding takes place much earlier and mainly suddenly, without any or with a minimal transition period. This is a significant stress factor in young animals (Weary et al. 2008), which can deplete the body's AO defence capacity and lead to the development of OS (Ranade et al. 2014; Buchet et al. 2017). The triggering effect of weaning on OS development has also been observed in piglets (Yin et al. 2014). The weaning upsets the ROS/AO balance, which is later restored with the development of AO defence systems (Celi and Gabai 2015).

Daily feed rations typically contain a lot of fermented forages after weaning which mostly lack natural AO-rich fresh green feeds. Besides, environmental stress factors are common during this period, and therefore the AO requirements of calves are high (McGrath 2016). Therefore, additional AO supplementation during this period can help to maintain health and thus achieve a more intense weight gain (McGrath 2016)

### **The relationship between the most common calf diseases and the redox status**

The pre-weaning mortality rate of the calves is 15.9% in the USA, caused by perinatal deaths of calves (8.1%) and diseases caused by various pathogens (7.8%) (Leslie 2012), mainly diarrhoea and respiratory diseases (bovine respiratory disease complex [BRDC]) during this period (Windeyer et al. 2014). The concentration of lipid peroxides is high, and AO defence capacity is low in case of BRDC (Al-Qudah 2009; Joshi et al. 2018; Blakebrough-Hall et al. 2020). Calf scours are common and can cause significant economic damage through reduced weight gain, treatment costs, and mortality. By examining calves with the disease, it was found that OS can play a significant role in its development (Ranjan et al. 2006). Similar results were obtained in studies of calves sickened by *Cryptosporidium parvum*, as there was a significant increase in malondialdehyde (MDA) and decreased superoxide dismutase (SOD) and catalase (CAT) levels (Gaadee et al. 2018).

### **Biomarkers and monitoring of oxidative stress in cattle**

Although superoxide anion was discovered as early as the 1930s, research into the physiological effects of oxygen-originated free radicals and OS was most likely to be started by the discovery of the SOD enzyme in '60s (McCord and Fridovich 1969; Soares and Costa 2009). For detection of disbalance in capacity of AO defence system and ROS concentration, so called indirect methods such as measurement of glutathione peroxidase (GPx) and SOD activity, glutathione (GSH) and oxidised glutathione (GSSG) ratio are frequently used in research practice (Mikulková et al. 2019, 2020).

Currently used biomarkers represent different approaches in OS detection:

- 1) factors that linked to the existence of OS:
  - lipid peroxidation and nucleic acid or protein damage products such as MDA, reactive oxygen metabolites (dROM), F(2)-isoprostane 8-iso-PGF(2 $\alpha$ ), 8-hydroxy-2'-deoxyguanosine,
  - tests to detect the disintegration of red blood cells due to OS, such as the Kit Radical Libres which can be used to infer the AO capacity of blood plasma and red blood cells
  - tests for quantification of AOs such as SOD, GPx, GSH:GSSG, BAP, PAT;
- 2) metabolic parameters for detecting the increased fat mobilisation such as blood glucose, insulin, insulin-like growth factor, glycoalbumin, non-esterified fatty acids, beta-hydroxybutyrate;
- 3) parameters for detecting disorders of liver function such as aspartate aminotransferase, direct bilirubin, total bilirubin, cholinesterase;

- 4) tests for detecting inflammation-related factors, such as myeloperoxidase, calcium concentration, and acute phase proteins (Pastorelli et al. 2013; Sordillo and Mavangira 2014; Abd Ellah et al. 2016). According to Celi (2011), the most common diagnostic procedures used in practice for OS-testing are shown in Table 1.

Targeted OS studies match well various herd monitoring studies, such as ketosis monitoring, body condition scoring, production and fertility indicators, and disease monitoring which may point to metabolic stress in the herd. For this reason, it is an obvious option to analyse OS indicators in parallel with metabolic profile studies, to identify links between OS and metabolic changes (Mikulková et al. 2020).

Most of the methods developed so far are only suitable for individual detection of oxidative stress. However, herd-level monitoring is also vital in a modern farm-animal veterinary practice. Methods for monitoring OS on the herd level could be a key course of further research (Leblanc 2006; Sordillo and Mavangira 2014; Pišřková et al. 2019).

### **The importance of strengthening antioxidant defence and its implementation**

Antioxidants can function as an electron donor to free radicals and thus play an essential role in preventing the development of OS. On the other hand, AOs can eliminate the damages caused by ROSs help in restoring cell structure and function (Sies et al. 1985; Cadenas and Packer 2002). The primary AOs are enzymes such as preventive SOD, CAT, GPx, glutathione reductase, and the restorative lipase, protease, DNA repair enzymes, and transferase. The secondary AOs are typically vitamins and pro-vitamins (e.g. vitamin E, vitamin C, ubiquinol, carotenoids), microelements (e.g. selenium, manganese, zinc, iron, copper) and other substances having an AO effect (e.g. polyphenols and including bioflavonoids, melatonin, urate, bilirubin, albumin, amino acids, omega-3 and omega-6 fatty acids) (Palmieri and Sblendorio 2007; Spears and Weiss 2008; Mézes and Balogh 2009; Heidarpour et al. 2012; Celi and Gabai 2015; Talukder et al. 2017; Park et al. 2019). Ruminants can effectively absorb and synthesize ascorbic acid. However, some external and internal effects may inhibit the synthesis (e.g. heat stress, liver damage, intensive fattening, mastitis) or absorption (high levels of dietary iron, zinc, copper and pectin), when low vitamin C levels can be measured in plasma, and it is worth supporting the body with supplementation (Kleczkowski et al. 2005; Matsui 2012). In case of nutritional supply by vitamin C, it is essential to take into consideration that only by-pass additives are useable for this purpose because ruminal microorganisms can absorb the non-protected products.

Since ruminants are able to synthesize ascorbic acid, they are only likely to experience deficiency symptoms in the neonatal period, before synthesis reaches full capacity. Cummins et al. (1992) cited several published reports of vitamin C deficiency signs in young calves.

The carotenoids ( $\beta$ -carotene,  $\alpha$ -carotene, lutein, zeaxanthin, lycopene, and  $\beta$ -cryptoxanthin) are also primary factors in the defence against OS (Karancsi et al. 2015). Park et al. (2019) showed that the concentration of carotenoids in plasma is in a significant negative correlation with the OS biomarker 8-iso-PGF<sub>2</sub> $\alpha$  (Park et al. 2019). Professional colostrum feeding management plays a significant role in this regard, in that the plasma carotene level increases about fivefold from 0.05 (S.D. 0.04) to 0.27 (S.D. 0.14)  $\mu$ mol/l after the first colostrum intake in calves (Bouda and Jagos 1984). The plasma carotenoid level then subsequently decreases to the age of six weeks and increases again from the age of only two months, which highlights the importance of switching to solid feeds for natural AO supply (Bouda and Jagos 1984).

The GPx enzyme requires selenium for its function; therefore, selenium plays a key role in proper intrauterine and postnatal development. In cows, a lower marginal supply (<1  $\mu$ mol/l) is often found (Sordillo 2013). Selenium is able to pass through both the placenta and the

Table 1. Advantages and disadvantages of various biomarkers of oxidative stress (Celi 2011).

Biomarkers	Assay procedure	Advantages	Disadvantages
MDA (Malondialdehyde)	Colorimetry, luminometry, chemiluminescence, HPLC, GC/MS	Sensitive and reproducible	Non-specific product of lipid peroxidation; interferes with TBARS assay
TBARS (Thiobarbituric reactive substances)	Spectrometry, luminometry chemiluminescence	Rapid, popular, easy, and economical	Non-specific, non-reproducible, no quantitative relationship with lipid peroxidation
F2 - Isoprostane	EIA, ELISA, HPLC, GC/MS	Specific, reproducible, sensitive	Expensive, auto-oxidation of samples, sample derivatization required
ORAC (Oxygen radical absorbance capacity)	Fluorescence	Sensitive and covers a wide variety of AOs	Requires spectro-fluorimeter; AAPH used a free radical source undergoes spontaneous decay and it is sensitive to temperature
FRAP (Ferric reducing antioxidant power)	Spectrophotometry	Serum dilution effect not seen	Fe may generate free radicals; not every free radical reduces Fe; GSH is not measured
TEAC (Trolox equivalent antioxidant capacity)	Spectrophotometry	Extremely fast and simple	Results vary with sample dilution; AO used may interact with solvent molecules; specificity varies
TRAP (Total reactive antioxidant potential)	Chemiluminescence	Gives an idea of the rate of free radical formation	AO employed may not trap all types of free radicals Inhibited by sodium azide
ROMs (Reactive oxygen metabolites)	Spectrometry	Extremely fast, simple; only condensate 5-20 µl of plasma/serum required; can be performed directly in whole blood, inflammatory fluids, cell extracts and respiratory condensate	
BAP (Biological antioxidant potential)	Spectrometry	Extremely fast, simple and covers a wide variety of AOs; only 5-20 µl of plasma/serum required	Can be performed only in plasma and serum samples; hyper lipaemic samples can underestimate results

AAPH - 2,2'-azobis(2-amidinopropane) dihydrochloride; EIA - enzyme immunoassay; ELISA - enzyme-linked immunosorbent assay; GC - gas chromatography; HPLC - high-pressure liquid chromatography; MS - mass spectrometry; AO - antioxidant

udder barrier, but transmission through the placenta is much more effective. Therefore, it is also worth focusing on the supply of selenium to dry cows (Konvičná et al. 2015). Vitamin E plays a role in the neutralization of ROS by inhibiting the development of non-regulated inflammatory processes. A pro-oxidant reactive radical of vitamin E is formed, which is involved in the neutralization of ROS. Then, under normal physiological conditions, it is regenerated again into vitamin E in the presence of GPx and vitamin C. A week before calving, the level of vitamin E in plasma decreases by 50% and rises again only 3–4 weeks postpartum. This may be due to a reduction in the daily dry matter intake or the high vitamin E requirements of colostrum secretion. Supplementing cows with vitamin E before calving improves their AO status, reduces inflammation-related cytokine production and the development of mastitis (Konvičná et al. 2015). The concentration of AOPP is increased due to the peroxidation of plasma proteins, which can be reduced by a higher dose of vitamin E and selenium (Chauhan et al. 2014), demonstrating their combined AO effect. In light of these results, it can be concluded that supplementing milk replacer with selenium and vitamin E is important during the milk feeding period. It was shown that the OS-reducing effect of a milk replacer lacking in vitamin E and selenium was lower than that of whole milk (Soberon et al. 2012; Abuelo et al. 2019).

The AO supplementation should be carried out professionally, as AOs may become pro-oxidants and can cause the OS formation themselves (Mézès and Balogh 2009). Ascorbic acid may stimulate lipid peroxidation when it is in combination with iron or copper ions or hydrogen peroxide, providing an excess amount of Fe<sup>2+</sup> ions for the formation of hydroxyl radicals in the Haber-Weiss reaction (Kankofer 2001; Kleczkowski et al. 2005; McMichael 2007). The reaction is concentration-dependent *in vitro*, as ascorbic acid acts as a pro-oxidant at low concentrations and as an AO at higher concentrations (Gaetke and Chow 2003; McMichael 2007). In the presence of copper ion, vitamin E may also act as a pro-oxidant (Gaetke and Chow 2003). The use of vitamin E at higher doses may be dangerous for cows' health if applied to all cows within the herd regardless of their previous vitamin E level and OS status assessment. This is evidenced by an increase in the prevalence of mastitis cases in cows treated with vitamin E during their dry period. Unfortunately, this study has not been published yet, and the dosage was not reported in the cited literature (Bouwstra et al. 2010). Knowing the current redox status of animals is, therefore, crucial for the success of AO supplementation. Herd-level OS monitoring on live animals, carried out under practical conditions, is thus essential for the implementation of a professional AO supplementation (Carletti et al. 2007; Celi et al. 2010; Celi and Gabai 2015; Talukder et al. 2017)

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