Oxidative & Inflammatory stress in reproductive Sows

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One of the biggest challenges in swine production is keeping the modern, hyperprolific sow healthy and in good shape so that she can wean large, healthy litters and maintain her high reproductive performance.

Unfortunately, sows often suffer from stress and increased systemic inflammation around farrowing and during lactation. This leads to impaired feed intake and disturbed endocrine homeostasis, negatively affecting reproductive and litter performance.

The key to increasing the efficiency of pig production is to reduce the metabolic burden of sows while maintaining the reproductive performance of high-yield sows. A deep understanding of the complex interplay between environmental factors, sow well-being, health, and productivity is necessary to implement enhanced nutritional regimens and meticulous management practices.

Why does oxidative stress occur in today's sows?

Nowadays, hyperprolific sows produce between 30 and 40 weaned piglets per year and are at a higher risk of suffering from stress. What are the reasons?

A high number of piglets causes oxidative stress

Oxidative stress occurs when reactive oxygen species (ROS) are produced faster than the body's antioxidant mechanisms can neutralize them and cause damage to lipids, proteins, and DNA. During gestation, the sow needs high amounts of energy to provide for the fetuses. This energy is produced in the placental mitochondria. The placenta, therefore, is a place of active oxygen metabolism during gestation and a source of oxidative stress. In hyperprolific sows, a higher number of fetuses need even more energy to grow. Consequently, ROS production and the risk for intrauterine growth retardation (IUGR) increases (Figure 1). Moreover, evidence shows that the body's antioxidant potential is reduced in late gestation and after parturition (Szczubial, 2010), resulting in increased oxidative stress biomarkers (Yang, 2023). Increased milk production for large litters demands a substantial amount of energy, risking similar oxidative distress. Therefore, both the final phase of gestation and the subsequent lactation period are predestined for oxidative stress, which has been demonstrated by reduced TEAC (Trolox equivalent antioxidant capacity) levels during these phases (Lee et al., 2023).

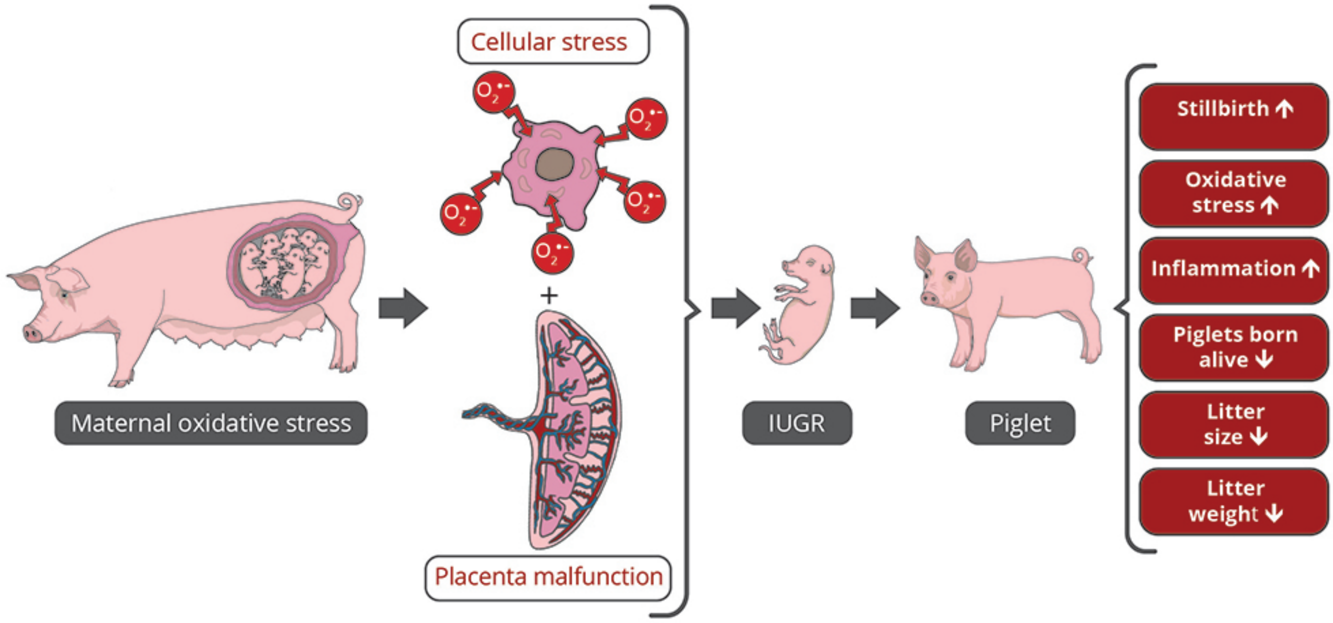

Figure 1. Illustration of the effect of oxidative stress on the fetus: intrauterine growth retardation (IUGR) (adapted from Yang et al., 2023)

Heat and ambient stress also contribute

The reproductive sow produces lots of heat. From the beginning of gestation, the sow's thermoneutral zone decreases. This, however, does not always correspond with the ambient conditions. Especially during the last days of gestation, the discrepancy is exceptionally high as everything is prepared for the newborn piglets, which need a temperature of about 27-35°C. The sow, on the contrary, would be happy with 18-22°C. Additionally, changes around farrowing – moving to the farrowing unit, social stress, change of feed, and the preparation for parturition – exert additional stress for the sows.

Why does the inflammation level increase?

After parturition, systemic inflammation is a normal phenomenon: the reproductive organs have sustained injuries during the parturition process and require remodeling. Inflammation is a natural and desired process, to repair the tissues and return to a normal status. However, inflammation is increased in modern sows, adversely affecting their inflammatory balance. Some possible underlying reasons are:

1. The high numbers of piglets need a lot of space in the uterus, often leading to damage of the uterine tissue and an inflammatory response in the sows. Lee et al. (2023) found significantly ($p<0.10$) higher TNF-α concentrations in sows with litters of 15-20 piglets than in sows with 7-14 piglets. TNF-α is a biomarker of inflammation.
2. Pathogenic infections – particularly infections of the reproductive tract – can induce a prolonged or excessive inflammatory state. A further reason can be the need for more obstetric interventions in hyperprolific sows, which can injure the birth canal or the uterus.
3. Imbalanced nutrition: Excessive backfat is associated with a higher expression of proinflammatory cytokines, and feed contaminated with mycotoxins can impair the sow's immunocompetence.

Biomarkers can inform us about the oxidative status

Biomarkers are naturally occurring molecules that help us identify diseases or physiological processes. They provide insights into the oxidative state and inflammatory processes.

Anti-oxidative biomarkers

To check the anti-oxidative capacity, the "beneficial" substances, or antioxidants, can be quantified. These substances can neutralize free radicals or be neutralized by them. Higher levels of antioxidants indicate better antioxidant capacity; when antioxidants are abundant, fewer oxidizable substances have undergone oxidation.

Examples of antioxidant biomarkers:

Total Antioxidant Capacity (T-AOC): represents the synergistic interaction effects of all antioxidants in a matrix (E.g., diet or body fluids). It's a global measure of non-enzymatic antioxidant efficiency. Various assays, like **Trolox Equivalent Antioxidant Capacity (TEAC),** which measures a substance's antioxidant capacity compared to Trolox, can measure T-AOC.

Glutathione Peroxidase (GSH-Px) belongs to the peroxidase family and converts hydrogen peroxide to water.

Catalase (CAT): scavenges ROS. Its activity can predict oxidative stress.

Superoxide Dismutase (SOD): catalyzes the dismutation of superoxide radicals to oxygen and hydrogen peroxide.

Oxidative biomarkers

Oxidative stress biomarkers, the 'negative' substances, can also serve as general biomarkers. These include free radicals with oxidant capacity or intermediate/final oxidation products. Ideally, their levels should be minimized.

Examples of oxidative stress biomarkers:

Thiobarbituric acid reactive substances (TBARS): to measure lipid peroxidation products in cells, tissues, and body fluids.

Reactive oxygen species (ROS) or free radicals: unstable, oxygen-containing molecules that react with other molecules in a cell. They might damage DNA, RNA, and proteins and cause cell death. **Hydrogen Peroxide (H_2O_2)** is a ROS produced during normal cellular metabolism, which causes oxidative damage at excessive levels.

Malondialdehyde (MDA): a final product of oxidative fat degradation and, therefore, a biomarker for lipid peroxidation.

Pro-inflammatory biomarkers

Like oxidative stress, the interplay between pro- and anti-inflammatory signals helps develop the proper immune response for the appropriate duration.

Examples of Pro-inflammatory biomarkers or molecules produced in the case of inflammation:

- **Plasma Adenosine Deaminase (ADA-1 and ADA-2)**: involved in immune regulation, with ADA-1 inhibiting pro-inflammatory responses and ADA-2 supporting immune cell functions.
- **Interleukins (IL-1α and IL-1β), IL-6:** IL-1α and IL-1β are associated with inflammatory diseases, IL-6: is produced during inflammation and acute-phase response.
- **Tumor Necrosis Factor α (TNF-α):** endogenous pyrogen that induces fever and promotes inflammation.
- **C-reactive Protein (CRP):** liver-produced acute-phase protein responding to inflammation.

Procalcitonin (PCT) is produced by the liver during infections and helps detect bacterial infections.

Examples of anti-inflammatory substances – the "good ones":

- **Interleukines – IL-4, IL-10**: inhibit the function of the macrophages and act, therefore, anti-inflammatory
- **Cortisol**: anti-inflammatory and immune-suppressive
- **ACTH**: stimulates the production and release of cortisol

Higher stress or infection level lowers performance in sows and piglets

As mentioned, hyperprolific sows suffer from higher oxidative stress, especially during late gestation, parturition, and lactation. Additionally, systemic inflammation occurs to repair the injured tissues to facilitate the healing of the birth canal and remodeling of the uterus to establish the subsequent pregnancy. To this purpose, an inflammatory cascade, triggered by the injuries due to gestation and parturition, involves the release of critical (pro-inflammatory) mediators such as TNF-α and IL-6, leading to the activation of acute phase proteins.

After triggering inflammatory pathways, anti-inflammatory pathways must also be activated to reestablish homeostasis in the reproductive organs (Serhan & Chiang, 2008). Alterations at the onset of anti-inflammatory pathways and exacerbated activation and maintenance of inflammatory pathways can lead to uncontrolled inflammation and the onset of reproductive disease in sows (Kaiser et al., 2018), as well as reduced feed intake and insufficient milk production, resulting in poorly growing piglets and lower weaning weights or piglets suffering from clinical infectious diseases such as diarrhea. If possibly homeostasis cannot be restored, the sow is at risk of contracting diseases like post-partum dysgalactia syndrome (PPDS), lameness, and impaired fertility.

Targeted use of polyphenols can mitigate inflammation and improve the oxidative

status of sows

There are several experiments showing the beneficial effects of natural compounds. Especially polyphenols, disposing of phenyl rings and two or more hydroxyl substituents, are perfect radical scavengers and proven antioxidants (Chen, 2023). Phytogenic substances that have anti-inflammatory effects can be found in the families of polyphenols as well as terpenoids, flavonoids, saponins, and tannins (Bunte et al., 2019; Ge et al., 2022; Ginwala et al., 2019; Santos Passos et al., 2022; Ambreen and Mirza, 2020).

Here are some examples showing the beneficial effects of phytochemicals:

1. Primiparous sows fed with Moringa oleifera leaf meal, rich in polyphenols, saponins, and tannins, illustrate the potential of phytomolecules: serum levels of T-AOC (total anti-oxidative capacity), were increased in late gestation and during lactation, while MDA was reduced. Additionally, piglets that received Moringa oleifera meal showed the highest serum CAT and SOD activities. The meal significantly decreased the farrowing length and number of stillbirths, while there was an increasing trend in the number of live-born piglets (Sun et al., 2020).
2. The polyphenol Daidzein, a member of the class of compounds known as isoflavones (200 mg/kg during gestation), increased the total antioxidant capacity (T-AOC) and the activities of glutathione peroxidase and superoxide dismutase. Additionally, it elevated the level of immunoglobulin G and increased the number of piglets born and born alive per litter (Li et al., 2021).
3. Glycitein, a polyphenol occurring in the isoflavone fraction of soy products, applied during late gestation and lactation increased the total antioxidant capacity and SOD activity during the first 18 days of lactation and the CAT and GSH-Px activity in mid-lactation. Plasma MDA level was reduced from late gestation to the 18^{th} day of lactation. The enhanced oxidative status of the sow resulted in a higher daily gain of the piglets and a higher weaning weight of the litter (Hu et al., 2015).
4. Meng et al. (2018) tested Resveratrol (300 mg/kg), a stilbenes polyphenol, in sows from day 20 of gestation until farrowing. They saw noticeably higher GSH-Px, SOD, and CAT activities, as well as lower contents of MDA and H_2O_2 in the placental tissue, improving the antioxidant status of sows and piglets.
5. Xu et al. (2022) fed silymarin to sows in late gestation. They observed that IL-1ß concentration in the blood sample on the 18^{th} day of lactation was reduced in the supplemented group. The altered fecal microbiota was associated with variations in inflammatory factors, suggesting that silymarin modulates microbiota in the gut and may improve the health of lactation sow.

Phytochemicals support sows against oxidative and inflammatory stress

The above-presented examples show that phytochemicals, particularly those developed to have a potent anti-inflammatory and anti-oxidative capacity, have a high potential to alleviate oxidative stress in pregnant and lactating sows and reduce inflammation when applied in sow diets. Consequently, a broader use of these natural substances should be considered to reduce the metabolic burden of sows and increase the efficiency of pig production.

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