Effects of Progressive Oxidative Stress on Sow Reproductive Performance and Its Nutritional Modulation Postprint

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Date: 2017-10-11T00:00:00+00:00

Abstract

Due to accelerated fetal growth and increased lactation intensity, the metabolic intensity of mammals gradually increases during the perinatal period, often leading to elevated oxygen free radicals and causing progressive oxidative stress. The impact of progressive oxidative stress on sow reproductive performance is mainly manifested in decreased farrowing performance, reduced lactation capacity, lower piglet survival rates, and compromised health status. However, standardized methods for evaluating progressive oxidative stress in sows are currently lacking. This review summarizes the causes of maternal perinatal oxidative stress, evaluation indicators, and its effects on sow reproductive performance, as well as measures to alleviate oxidative stress in sows under production conditions, aiming to provide a theoretical basis and technical guidance for mitigating oxidative stress and improving reproductive performance in sows within pig production systems.

Full Text

Impact of Progressive Oxidative Stress on Sow Reproductive Performance and Its Nutritional Manipulation

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Abstract: The perinatal period in mammals is characterized by gradually increasing metabolic intensity due to accelerated fetal growth and heightened lactation demands, which often leads to elevated oxygen free radicals and progressive oxidative stress. This progressive oxidative stress negatively impacts

sow reproductive performance through reduced litter performance, diminished lactation capacity, lower piglet survival rates, and compromised sow health. However, standardized methods for evaluating progressive oxidative stress in sows remain lacking. This review synthesizes current knowledge on the causes of maternal perinatal oxidative stress, evaluation indices, and the effects of oxidative stress on sow reproductive performance, while also examining practical measures for alleviating oxidative stress in production settings. The objective is to provide a theoretical foundation and technical guidance for mitigating oxidative stress and improving reproductive performance in sows.

Key words: progressive oxidative stress; sows; perinatal period; reproductive performance

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During pregnancy, mammals typically generate appropriate levels of reactive oxygen species (ROS) that are essential for gestation. However, as the fetus develops, maternal metabolic intensity increases correspondingly in late gestation, resulting in substantially elevated ROS levels and significantly heightened risk of oxidative stress [1]. In human medicine, extensive research has confirmed that various metabolic disorders in late pregnancy are closely associated with maternal oxidative stress during this period [2]; more critically, even apparently normal fetuses exposed to oxidative stress often exhibit increased susceptibility to metabolic diseases such as hypertension and diabetes later in life [3]. In livestock production, gestating and lactating sows, particularly primiparous ones, experience vigorous metabolism that can lead to oxidative stress during the perinatal period. Previous studies have documented changes in sow blood malondialdehyde (MDA), glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), and 8-hydroxy-2' -deoxyguanosine (8-OHdG) during late gestation, reflecting oxidative stress status from various perspectives [4-8]. Nevertheless, comprehensive analyses integrating these indices while simultaneously considering both oxidative and antioxidant markers are scarce, and standardized criteria for diagnosing sow oxidative stress have not been established. While correlations between oxidative stress and sow reproductive performance have been reported [4,8-9], the underlying mechanisms remain unclear. Furthermore, research on nutritional regulation to alleviate perinatal oxidative stress in sows is still in its infancy. Based on current research progress, this review examines changes in redox status throughout the sow reproductive cycle, proposes the concept of progressive oxidative stress in sows, analyzes its causes, and discusses evaluation indices for assessing oxidative stress. Building upon this foundation, we explore nutritional regulation strategies to mitigate oxidative stress in swine production, aiming to provide references for managing oxidative stress and improving reproductive performance during the reproductive cycle.

1. Progressive Oxidative Stress in the Mother

Sohal et al. [10] first proposed the concept of oxidative stress while studying human aging, observing that oxidative metabolic processes inevitably produce potentially harmful byproducts that accelerate organismal aging through effects on genetic and epigenetic events. Oxidative stress occurs when harmful stimuli from internal or external environments cause accumulation of ROS and reactive nitrogen species (RNS), triggering physiological and pathological responses in animal cells and tissues [11]. Under normal physiological conditions, cells produce small amounts of ROS necessary for metabolism, which are promptly cleared by the antioxidant system, maintaining a dynamic equilibrium between generation and elimination. During reproduction, appropriate ROS levels are required for oocyte maturation, follicular growth and ovulation [12-13], as well as placental angiogenesis [14]. Despite these physiological roles, sustained and massive ROS production during late gestation and peak lactation can lead to oxidative stress [12,15].

Progressive oxidative stress refers to the phenomenon of progressively increasing ROS production in female animals during critical reproductive stages including placentation, rapid fetal growth in late gestation, parturition, and lactation. Based on origin, ROS can be classified as endogenous or exogenous. Endogenous sources primarily include oxidative phosphorylation, erythrocyte metabolism, and mitochondrial ROS release [11], while exogenous sources encompass environmental and dietary factors. In human pregnancy, progressive oxidative stress is divided into three stages based on ROS levels: early gestation (1-12 weeks), when placental vessels are not yet formed and fetal growth relies mainly on carbohydrate metabolism, resulting in low ROS levels; mid-gestation (13-28 weeks), when placental vasculature gradually develops, establishing maternal-fetal connections that transport ROS to the placenta and fetus while placental and fetal metabolism intensify, causing gradually increasing ROS levels; and late gestation (29-40 weeks), when vascular formation ceases but placental mitochondrial numbers increase with enhanced oxidative metabolism, coinciding with rapid fetal growth that drives ROS levels to their peak [14,16].

In recent years, progressive oxidative stress during the perinatal period has gained attention in both human medicine and ruminant research. Human studies demonstrate close relationships between reproductive disorders during pregnancy and oxidative stress [17-18]. For instance, preeclamptic women exhibit elevated thiobarbituric acid reactive substances and reduced GSH-Px activity [19]. Similarly, dairy cows experience high incidence rates of mastitis and metritis during the perinatal and early lactation periods, severely affecting mammary health, milk yield, and quality [20]. Like ruminants and humans, perinatal sows also suffer from oxidative stress during late gestation and lactation [21-23], indicating that sows exhibit progressive oxidative stress throughout their reproductive cycle. However, no standardized classification of progressive oxidative stress stages specific to sows has been established.

2. Causes of Progressive Oxidative Stress in Sows

The development of progressive oxidative stress in sows is directly related to the progressive massive generation of ROS during the reproductive cycle and is also associated with insufficient antioxidant system activity. Both endogenous and exogenous ROS contribute to this condition. During normal pregnancy, fetal survival depends entirely on nutrient transport through the placenta. In late gestation, accelerated fetal growth increases placental metabolic intensity, triggering maternal adaptive changes such as increased uterine blood flow [24] and elevated blood glycerol, free fatty acids, and alanine [25], all indicating enhanced maternal metabolism that leads to increased endogenous ROS production. Additionally, dietary factors such as excessive unsaturated fatty acids or deficiencies in mineral elements (copper, zinc, manganese) and vitamins (E, C, carotenoids) can induce oxidative stress [11,21]. Environmental factors including high temperature, hypoxia, and nitrogen oxides can cause excessive free radical accumulation and damage the antioxidant system [26]. Beyond ROS overproduction from enhanced metabolism, decreased antioxidant system activity represents another important mechanism for ROS accumulation in sows [8-9].

Notably, since sow metabolic intensity positively correlates with litter size, and modern breeding has substantially increased both litter size and piglet birth weight [22], contemporary sows must maintain stronger metabolic activity during gestation. Concurrently, sow milk production has increased approximately fourfold [23], dramatically elevating metabolic intensity during lactation. Consequently, modern high-producing sows are more susceptible to oxidative stress.

3. Evaluation Indices for Sow Oxidative Stress

Although standardized diagnostic criteria for reproductive disorders induced by perinatal oxidative stress in sows remain unreported, monitoring changes in oxidative stress biomarkers can help assess redox status during the reproductive cycle. Excessive ROS accumulation attacks biological macromolecules—lipids, DNA, and proteins—generating MDA, 8-OHdG, and protein carbonyls. The enzymatic antioxidant system participates in ROS scavenging, which may reduce the activity of certain antioxidant enzymes [27]. Therefore, measuring blood MDA content, thiobarbituric acid reactive substances (TBARS), 8-OHdG levels, reduced glutathione (GSH) content, antioxidant enzyme activities, and T-AOC can indirectly reflect the degree of oxidative stress. Direct measurement of blood ROS levels via chemiluminescence provides more direct assessment of redox status.

Studies measuring plasma TBARS from gestation day 60 to lactation day 18 found no significant differences between stages, though values were numerically higher during lactation than gestation [4]. Other research showed no statistical difference in plasma TBARS between gestation days 109 and 93 [5]. Analysis of blood 8-OHdG and protein carbonyls from gestation day 60 to lactation day

18 revealed no differences across time points, though both were numerically higher on gestation day 109 [4], suggesting greater oxidative stress at this stage. Another study found no difference in blood 8-OHdG and protein carbonyls between gestation days 89 and 109, though protein carbonyls were numerically higher on day 109 [22].

Research demonstrates that antioxidant substances decrease while antioxidant enzyme activity and overall antioxidant capacity decline throughout the reproductive cycle: 1) Lipid-soluble antioxidants vitamin E and vitamin A follow a pattern of initial decrease followed by increase, being significantly lower on gestation day 110 than other gestational stages [23]. The substantial reduction in blood vitamin E during late gestation indicates diminished antioxidant reserves and oxidative stress, confirmed by other studies showing dramatic decreases in blood vitamin E on the day of parturition [5]. 2) Ferric reducing antioxidant power (FRAP), which measures the ability of plasma antioxidants to reduce Fe^{3+} to Fe^{2+}, is commonly used to assess plasma reducing capacity [28]. On the day of parturition, sow plasma FRAP and GSH-Px activity were lower than on gestation day 93, though not statistically significant [5], indicating weakened antioxidant capacity and more severe oxidative stress during parturition. However, other researchers found higher FRAP on gestation day 109 compared to day 93 [6], consistent with enhanced antioxidant capacity in women during late pregnancy [29], suggesting a higher yet stable redox state. Thus, the suitability of FRAP as an oxidative stress marker requires further validation. Additionally, some studies indicate that blood antioxidant enzyme activity remains unchanged during late gestation: the expression abundance of mRNA encoding GSH-Px in sow liver homogenate did not differ on gestation day 109 [7], suggesting that ROS-induced reduction in antioxidant substances does not necessarily cause decreased antioxidant enzyme activity. Research demonstrates that comprehensive consideration of both pro-oxidant and antioxidant systems, such as using ROS-T-AOC or oxidative stress index (OSi), can more accurately reflect oxidative stress status [30].

Current swine oxidative stress research has advanced to the molecular level. Expression profiling of genes encoding glutaredoxin (GRX) and thioredoxin (TRX)—GRX1 and TRX1—in various tissues of Gaoligongshan pigs revealed that overexpression of these genes can alleviate oxidative stress [31]. Recent studies examining antioxidant gene expression in piglet tissues found that GPX4 is more critical for antioxidant capacity than other enzymes such as GPX1, manganese-superoxide dismutase, and copper-zinc-superoxide dismutase [32], providing promising avenues for identifying more precise oxidative stress indicators.

In summary, elevated oxidative stress products during the perinatal period indicate severe oxidative stress in sows. Among the various indices, DNA damage marker 8-OHdG, protein damage marker protein carbonyls, GSH-Px, plasma vitamins E and A, and TBARS can all reflect redox status to some degree. ROS levels directly indicate oxidative stress severity, while FRAP and GSH-Px ac-

tivity may not accurately reflect oxidative stress status. Future research should focus on correlational analysis of these indices and detection of antioxidant genes at the molecular level to identify the most suitable markers for diagnosing sow oxidative stress.

4. Impact of Progressive Oxidative Stress on Sow Reproductive Performance

Extensive research confirms that oxidative stress substantially reduces reproductive performance in female animals [23,33]. Human medical studies demonstrate that excessive ROS in late gestation interferes with meiosis II in oocytes, inhibiting oocyte maturation, while concurrent reductions in GSH content suppress subsequent ovulation and fertilization [34].

The impact of progressive oxidative stress on sow reproductive performance manifests primarily as reduced litter performance, decreased lactation capacity, lower piglet survival rates, and poor sow health. Excessive free radicals attack oocytes, impede sperm-egg binding, delay embryo implantation and preimplantation mitosis, and inhibit embryonic development, thereby reducing litter size, increasing proportions of weak and stillborn piglets, and decreasing newborn survival rates [23,35-36]. Additionally, excessive free radicals increase metabolic burden, reduce mammary cell nutrient uptake, increase inflammatory factors in milk, and decrease immunoglobulin content, consequently reducing nursing piglet growth and survival rates [34,37-38]. summarizes the major adverse effects of free radicals on sow reproductive performance.

5. Nutritional Regulation Measures to Alleviate Progressive Oxidative Stress in Sows

From a nutritional perspective, oxidative stress during the reproductive cycle can be mitigated by supplementing sow diets with trace minerals to enhance antioxidant enzyme activity, and with antioxidant vitamins and plant extracts.

The enzymatic antioxidant system constitutes an important defense barrier in sows. Trace minerals including copper, iron, zinc, manganese, and selenium serve as active centers of antioxidant enzymes, and their adequate intake and accumulation are crucial for antioxidant capacity. Iron deficiency reduces sow antioxidant capacity, while iron or selenium supplementation significantly increases serum GSH-Px activity, decreases MDA content, and alleviates oxidative stress [39]. Supplementing diets with iron glycinate or ferrous sulfate monohydrate from 28 days before expected parturition to the day of farrowing significantly increased serum T-AOC and activities of GSH-Px and SOD while reducing MDA content. Based on comprehensive antioxidant indices, optimal supplementation levels are 80 mg/kg iron glycinate and 110 mg/kg ferrous sulfate monohydrate [39]. Additionally, zinc can reduce nitric oxide free radicals and mitigate RNS-induced oxidative damage [40].

Supplementation with antioxidant vitamins helps sows cope with oxidative stress. Adding 66 IU/kg vitamin E to sow diets from first mating through five reproductive cycles increased serum α-tocopherol and selenium content while reducing the incidence of mastitis-metritis-agalactia syndrome [41]. Combined selenium and vitamin E supplementation shows superior effects: 0.3 mg/kg selenium with 66 IU/kg vitamin E throughout gestation and lactation in primiparous sows increased the number of piglets born alive and weaning weight while improving piglet health status [42-43]. Combined vitamin E and C supplementation (250 IU vitamin E and 500 mg/kg vitamin C) from gestation day 108 to weaning day 28 enhanced sow cellular and humoral immunity [44]. Furthermore, vitamin C supplementation from gestation day 72 to parturition reduced prepartum fecal *E. coli* and increased *Lactobacillus* counts [45], benefiting sow health and reproductive performance.

Plant extracts have emerged as a research hotspot for alleviating sow oxidative stress. Due to their natural, residue-free, and potent antioxidant properties, plant extracts are gaining recognition as excellent antioxidants [46]. Antioxidant-active plant extracts include flavonoids, quinones, phenolic acids, nitrogen-containing compounds, terpenoids, and alkenoic acids, with phenolics and flavonoids being most extensively studied [47]. Oral administration of 8 g/day silymarin (a flavonoid extract) from gestation day 90 to 110 did not reduce 8-OHdG or protein carbonyl content on day 109, but significantly decreased protein carbonyl accumulation from days 90-109 and markedly reduced protein carbonyl content in liver homogenate on day 109, indicating partial alleviation of late-gestation oxidative stress [7]. Dietary supplementation with 200 or 300 mg/kg catechins (polyphenol-rich compounds with strong antioxidant capacity) from mating to gestation day 40 increased SOD and catalase (CAT) activities on the day of parturition while reducing MDA and hydrogen peroxide content, significantly decreasing average stillbirths per litter and increasing the number of piglets born alive [47]. Supplementation with flavonoid-rich antioxidants increased GSH-Px activity and reduced MDA content on day 4 post-weaning while significantly elevating estradiol and progesterone levels and markedly shortening the weaning-to-estrus interval [48]. Similarly, supplementation with antioxidant-rich soybean isoflavones significantly increased T-AOC and CAT activity on lactation day 21 while reducing MDA content, thereby increasing sow milk yield and piglet weaning weight [49].

Our laboratory has conducted extensive research on nutritional measures to alleviate sow oxidative stress. Results demonstrated that dietary supplementation with 2.2% konjac powder during gestation significantly increased serum GSH-Px activity while reducing ROS levels and 8-OHdG content, suggesting that konjac powder feeding helps mitigate oxidative stress and damage in pregnant sows [9]. Additionally, dietary supplementation with 15 g/t oregano essential oil throughout the reproductive cycle reduced serum TBARS and 8-OHdG content during late gestation and on the day of parturition while increasing GSH-Px activity [8], indicating that oregano essential oil enhances antioxidant capacity during

late gestation, alleviates oxidative stress, and helps maintain sow health.

In conclusion, like dairy cows and pregnant women, sows are highly susceptible to oxidative stress during the perinatal period due to substantially increased metabolic intensity. Adverse environmental factors in pig production further increase this risk. Comprehensive assessment incorporating both oxidative and antioxidant systems, combining indices of oxidative products, antioxidant enzyme activities, and ROS levels, provides more accurate evaluation of oxidative stress status. Meanwhile, exploring novel oxidative stress markers at the molecular level to identify the most suitable diagnostic indices will greatly benefit precise assessment of sow oxidative stress at various stages. From a nutritional regulation perspective, primary measures to alleviate oxidative stress include supplementation with trace minerals, vitamins, and antioxidant plant extracts.

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Note: Figure translations are in progress. See original paper for figures.