

Oxidative Stress in Sows and Effects on Reproductive Performance

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Take Home Message

Sows have increased oxidative damage especially during late gestation and lactation and increased oxidative damage is related to a reduced reproductive performance of sows. At the same time, the antioxidant defense substantially reduces during late gestation. Dietary antioxidant concentration should be checked and provided in adequate amounts especially for sows in late gestation and lactation which becomes very important if sows are heat stressed. Gestational group housing may affect reproductive performance of sows negatively but not through increased oxidative stress. However, regardless of social ranking in a group, sows reproductive performance is closely related to oxidative stress status. Current feeding program may do not provide enough antioxidants to sows in late gestation and lactation needing re-evaluation.

Introduction

Sows are under severe catabolic status especially during late-gestation and lactation. This is because there are greatly increased nutrient needs for fetal growth (McPherson et al., 2004; Ji et al., 2005), mammary growth (Kim et al., 1999; Ji et al., 2006), and milk production (Kim et al., 2000), whereas their nutrient intakes are insufficient during those periods (Kim et al., 2009). Catabolic condition increases the production of ROS causing increased oxidative stress (Bernardi et al., 2008).

Midwestern and Southeastern coastal areas in the US are where majority of sow farms are located (National Agricultural Statistics Service. 2008). Without proper cooling systems, hot and humid summer climate causes thermal heat stress which will cause reduction in reproductive performance and longevity of sows (Flowers et al., 1989; Johnston et al., 1999; Renaudeau and Noblet, 2001). Hyperthermia from heat stress is shown to stimulate ROS production and thus cause oxidative damages to sows (Ozawa et al., 2002; Matsuzuka et al., 2005). Increased oxidative stress is responsible for reduced reproductive performances and longevity of sows (Flowers and Day, 1990).

Oxidative damage is a strong indicator of health status and wellbeing of animals in relation to aging, stress, nutritional status, and disease. However, currently only limited information on oxidative damage status of sows is available. Previous research studies measured antioxidant levels to evaluate oxidative status of sows. Antioxidant levels, however, are not a direct measurement of oxidative damage status because their maternal levels are affected by needs for fetuses and milk production. Recent research has evaluated antioxidant levels (Mahan et al., 2007) or oxidative stress markers (Berchieri-Ronchi et al., 2010) to indirectly or directly evaluate oxidative status of sows.

This article is (1) to provide basis about oxidative stress, (2) to introduce recent findings in oxidative stress status of sows, (3) to discuss factors affecting the changes of oxidative stress, and also (4) to discuss the relationship of maternal oxidative stress to reproductive performance.

Oxidative Stress

Oxygen is the major source of reactive oxygen species (ROS) produced in metabolic reactions for cells to obtain energy from nutrient oxidation. Animal cells have pro-oxidant and anti-oxidant compounds that continuously generate and remove ROS during metabolism. Oxidative stress can be caused when generation of pro-oxidants is greater than a capacity of anti-oxidant systems in cells. Increased production of pro-oxidants can cause oxidative damages to nucleic acid basis in DNA, unsaturated fatty acids in membranes, and thiols in proteins, which all can damage cells and even cause cell death. Lipid peroxidation can cause injury to cellular membranes, DNA oxidation can lead to mutations, and protein oxidation can interfere with functions of cellular enzymes and increase protein turnover. In order to cope with oxidants, cells use anti-oxidants stored in cells which include glutathione and vitamin E.

Free Radicals: Reactive Oxygen Species

Reactive oxygen species are generated during normal aerobic metabolism occurring in the body. Thus, the process of generating energy from the oxidation of nutrients involves production of ROS which mainly occurs in mitochondria. The ROS are mainly generated from the Krebs cycle and the electron transfer chain in mitochondria. It is estimated that 1 to 2% of oxygen consumed in mitochondria are contributed to ROS generation. Reactive oxygen species include (1) superoxide anion ($O_2^{\cdot-}$), (2) hydroxyl radicals (HO^{\cdot}), (3) peroxy radicals (RO_2^{\cdot}), (4) alkoxy (RO^{\cdot}) radicals, (5) hydrogen peroxide (H_2O_2), and (6) singlet oxygen. All these ROS are pro-oxidants which can cause cellular oxidative damage.

Oxidative Damages to Nutrients

Lipids

Peroxidation of polyunsaturated fatty acids can be easily occurred by ROS. Peroxidation of these polyunsaturated fatty acids in cellular membranes can eventually cause damage in cellular function. Peroxidation of polyunsaturated fatty acids in one site can cause chain reaction propagating in cellular membranes resulting in severe damage on cellular membranes. Lipid peroxidation produces further ROS which can cause oxidative damages of proteins and DNA. Lipid peroxidation can be easily detected by measuring malondialdehyde in blood plasma.

DNA Oxidation

Biochemical reactions by mitochondrial enzymes such as α -ketoglutarate dehydrogenase and pyruvate dehydrogenase produce large amounts of $O_2^{\cdot-}$ and H_2O_2 . In addition, $O_2^{\cdot-}$ is also largely generated from reactions by NADPH oxidase. All these ROS can cause oxidative damage to mitochondrial DNA which can damage cell functions and even cell death. Hydroxyl radicals can react to nucleic acids modifying the base portion of the polymer which is responsible for genetic mutation. Quantification of modified bases in plasma and urine is a typical way of measuring oxidative DNA damage in an animal. Products of oxidative DNA damages include as 8-hydroxy guanosine,

thymidine glycol, and uric acid. Among them, 8-hydroxy guanosine is often used as an indicator of oxidative damage of DNA for its feasibility of detection (Collins, 2005). However, due to a large variation in 8-hydroxy guanosine in normal condition, sensitivity can be a shortcoming as a marker of oxidative damage of DNA. During the DNA repairing process, cellular enzymes breaks DNA at sites of 8-hydroxy guanosine. The breaks can be measured by the single-cell gel electrophoresis assay called the comet assay (Yeum et al., 2004).

Proteins

Oxidative damages in proteins can be occurred in many different ways. Three major reactions include (1) fragmentation of proteins at specific amino acids such as proline and histidine, (2) protein degradation by cellular protease after irreversible modifications in amino acids, such as histidine, and (3) production of disulfide of cysteine and sulfoxide of methionine. Damages to protein by ROS cause loss of biological functions of proteins in cells.

Antioxidants

An animal body produces antioxidants to effectively remove free radicals generated during normal metabolic processes. Ability of producing antioxidants is affected by the animal's genetic potential, dietary factors, and other environmental factors. There are various types of antioxidants available in an animal body including glutathione, uric acid, melatonin, thiols, ascorbic acids, polyphenols, carotenoids, and tocopherols, as well as enzymes including superoxide dismutase, catalase, and peroxidases. Effectiveness of antioxidants is related to specific type of targeting oxidative stress.

Oxidative damage to cellular membranes by lipid peroxidation can be effectively prevented by tocopherols which reacts with HO^\bullet and RO_2^\bullet , by carotenoids which react with singlet oxygen, and possibly by membrane bound proteins. Ascorbic acid and glutathione further stop chain reaction of lipid peroxidation.

Various antioxidants participate in response to oxidative damage occurring to protein. Oxidative damage to proteins causes irreversible or reversible loss of activity of protein such as enzymes. Glutathione is a small peptide with strong hydrophilic property which allows maintaining a high concentration in cells. Glutathione contains cysteine that can readily be oxidized and reduced during the metabolism. In the glutathione redox cycle, glutathione can be oxidized to glutathione disulfide by removing hydrogen peroxide or lipid peroxides. This process is catalyzed by glutathione peroxidase or other enzymes. Glutathione disulfide is subsequently reduced by glutathione reductase, using NADPH. Cellular NADPH, therefore, is the major source of reducing power for removing peroxides. Glutathione peroxidase is found in the cytoplasm and mitochondria of most cells. Tocopherols are found in cell membrane due to their lipophilicity. Tocopherols reduce lipid peroxidation and prevent further chain reaction occurring on unsaturated fatty acids that reside within the lipid bilayer. Superoxide dismutase exists in cell cytoplasm and in mitochondria functioning as a cellular antioxidant by eliminating superoxide anion. There is also an extracellular form of superoxide dismutase found in plasma, lymph, and synovial fluid. These extracellular enzymes function at cell surfaces.

Oxidative Stress in Sows

Oxidative Stress During Gestation and Lactation

Increased demands for energy and protein also increase oxygen use for animals during pregnancy and lactation. Increased oxygen use in metabolism generates ample production of ROS which cause oxidative stress of pregnant and lactating animals (Agarwal et al., 2003; Reyes et al., 2006). Research shows that increased oxidative stress is related to most frequent disorders in pregnancy (Hubel, 1999; Jauniaux et al., 2006; Myatt et al., 2004). It is possible that the high metabolic demands of pregnancy may induce the production of ROS by the placenta during pregnancy, although the placenta is a source of antioxidative enzymes and hormone systems to control placental lipid peroxidation in healthy pregnancy (Mueller et al., 2005). Our recent study (Berchieri-Ronchi et al., 2010) evaluated oxidative stress status of sows during gestation and lactation. In this study, blood samples were drawn from sows during d 30, 60, 90, and 110 of gestation (G30, G60, G90, and G110), d 3, 10, and 18 of lactation (L3, L10, and L18), and d 5 of post weaning (W5) periods. Lymphocytes were isolated from the fresh blood and cryopreserved in each time point. Oxidative DNA damage and the antioxidant status were determined in lymphocyte or plasma samples. This study showed that DNA damage is significantly increased from d 60 of gestation and maintained elevated oxidative DNA damage throughout the lactation period without complete recovery during the weaning period (Figure 1). The plasma concentration of antioxidants including tocopherol and retinoid dropped at d 110 of gestation and began to normalize towards end of lactation period (d 18) (Figure 2). Our study clearly indicates that sows are under systemic oxidative stress during late pregnancy and early lactation and the elevated oxidative stress status are not fully recovered until the weaning period. This may also be related to insufficient availability of tocopherol and retinoid during these periods.

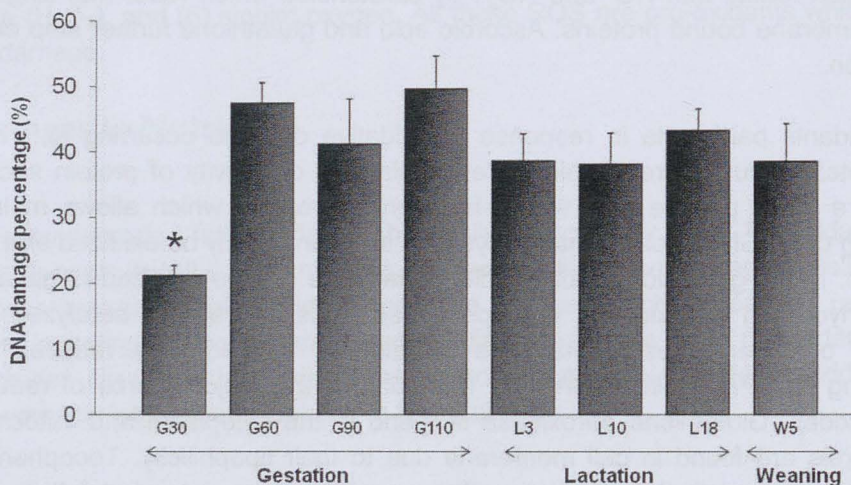


Figure 1. Lymphocyte DNA damage in sows during gestation and lactation; with lower ($P < 0.05$) endogenous DNA damage at d 30 of pregnancy (21%) as compared with those of the other time points (38 to 47% lesion); * $P < 0.05$ vs. G60, G90, G110, L3, L10, and W5. Data are expressed as mean \pm SD. Value with an asterisk is significantly different ($p < 0.05$). The assay used was the single cell gel electrophoresis (Berchieri-Ronchi et al., 2010).

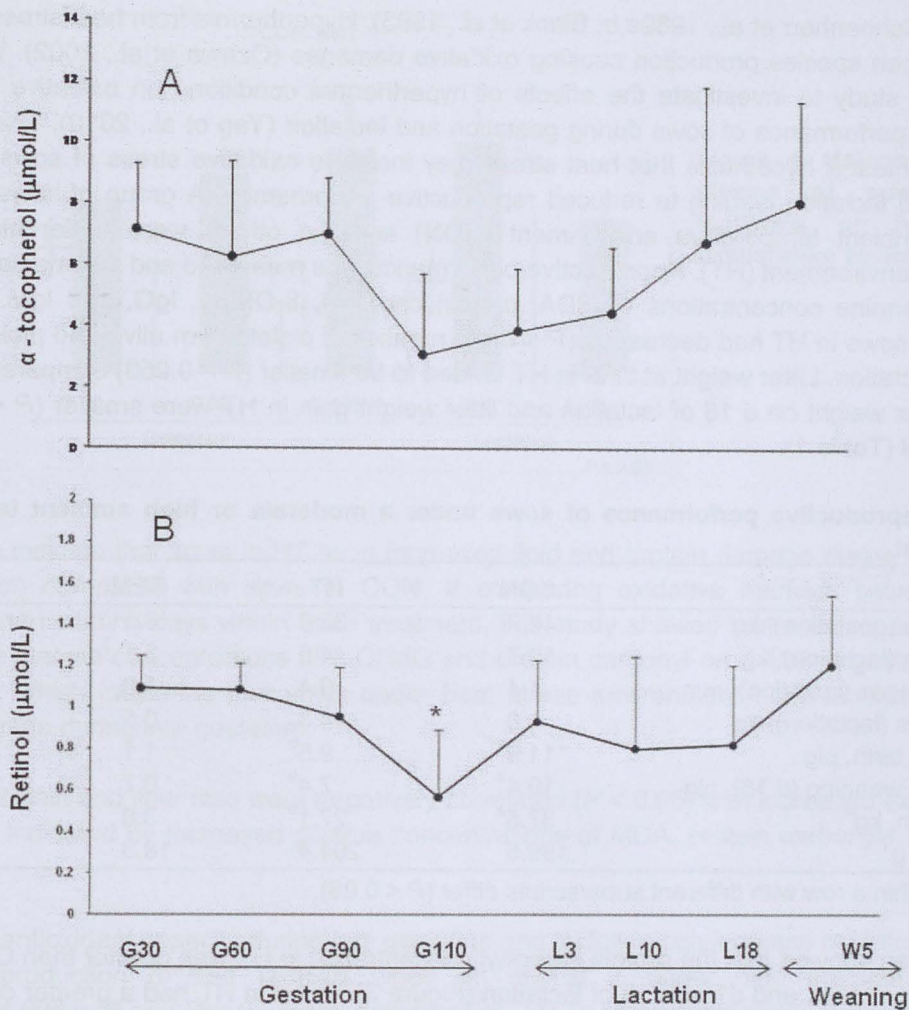


Figure 2. (A) Plasma concentrations of α -tocopherol in multiparous sows. Data are expressed as mean \pm SD. Values with an asterisk or different letters are different ($P < 0.05$). The analyses were performed using HPLC systems. Student t-test method used for normal distribution statistical analyses. (B) Plasma concentrations of plasma for retinol; G110 * $P < 0.05$ vs. G30, G60, W5. Data are expressed as mean \pm SD. Values with an asterisk or different letters are different ($P < 0.05$). The analyses were performed using HPLC systems. Student t-test method used for normal distribution statistical analyses (Berchieri-Ronchi et al., 2010).

Oxidative Stress Under Hyper-thermal Conditions

Hot and humid summer climate causes heat stress reducing reproductive performance and longevity of sows (Flowers et al., 1989; Johnston et al., 1999). Heat stress would cause a negative effect on reproductive performance of sows during gestation and lactation. Studies showed that heat stress diminished hypothalamo-pituitary gonadal axis to secrete FSH, LH, and delayed puberty in gilts (Flowers et al., 1989; Flowers and Day, 1990). Heat stress may affect early development of embryos (Edwards et al. 1968) causing small litter size, increased number of stillborn, and reduced birth weights (Omtvd et al., 1971; Johnston et al., 1999; Renaudeau and Noblet, 2001). Studies have shown that lactating sows exposed to high temperatures had reduced feed intake and milk

production (Schoenherr et al., 1989a,b; Black et al., 1993). Hyperthermia from heat stress stimulates reactive oxygen species production causing oxidative damages (Ozawa et al., 2002). We recently conducted a study to investigate the effects of hyperthermal conditions on oxidative status, and reproductive performance of sows during gestation and lactation (Yan et al., 2010). This study was conducted to test a hypothesis that heat stress may increase oxidative stress of sows during late gestation and lactation leading to reduced reproductive performance. A group of sows was under moderate ambient temperature environment (CON) and the others were under high ambient temperature environment (HT). Reproductive performance was measured and plasma samples were used to determine concentrations of MDA, protein carbonyl, 8-OHdG, IgG, and IgM. This study showed that sows in HT had decreased ($P < 0.05$) number of piglets born alive and piglets per litter on d 18 of lactation. Litter weight at birth in HT tended to be smaller ($P = 0.050$) compared with those in CON. Litter weight on d 18 of lactation and litter weight gain in HT were smaller ($P < 0.05$) than those in CON (Table 1).

Table 1. Reproductive performance of sows under a moderate or high ambient temperature environment.

Item	CON	HT	SEM	P-value
BW changes (gestation), kg	46.7	35.0	6.5	0.114
BW changes (lactation), kg	-12.7	-4.5	5.1	0.130
Backfat changes (lactation), mm	-1.4	-0.4	1.0	0.333
ADFI of sows (lactation), kg	4.6	4.3	0.5	0.478
Litter size at birth, pig	11.9 ^a	9.5 ^b	1.1	0.045
Litter size at weaning (d 18), pig	10.4 ^a	7.4 ^b	0.7	< 0.001
Litter Wt gain, kg ⁴	37.5 ^a	27.1 ^b	3.8	0.013
Piglet ADG, g	199.5	204.4	18.3	0.794

^{a-b}Means within a row with different superscripts differ ($P < 0.05$).

This study also showed that the protein carbonyl concentration in HT was greater than CON on d 90 and 109 of gestation, and d 1 and 18 of lactation (Figure 3). Sows in HT had a greater concentration of MDA on d 90 and 109 of gestation, and d 1 of lactation than sows in CON (Figure 4).

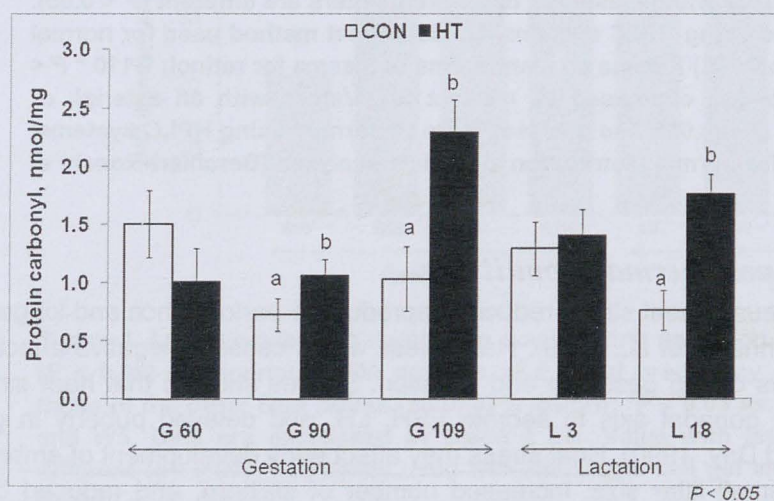


Figure 3. Protein carbonyls in plasma of sows under a moderate or high ambient temperature environment.

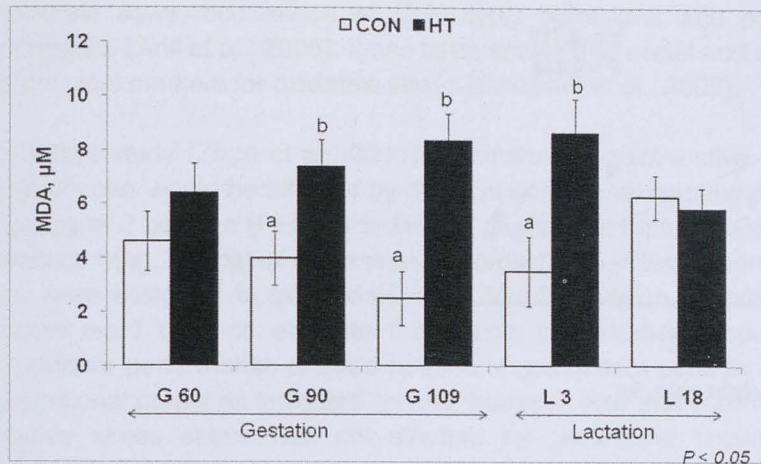


Figure 4. Malondialdehyde in plasma of sows under a moderate or high ambient temperature environment.

These data indicate that sows in HT have increased lipid and protein damage during late gestation and lactation compared with sows in CON. If comparing oxidative markers between different gestating and lactating days within each treatment, this study showed that sows under heat stress had greater plasma concentrations of 8-OHdG and protein carbonyl on d 109 of gestation than the other days, which indicating that sows under heat stress environment have increased DNA and protein damage during late gestation.

Litter weight gain and litter size were negatively correlated ($P < 0.05$) with increased oxidative stress to sows as indicated by increased plasma concentrations of MDA, protein carbonyls, and 8-OHdG (Figure 5).

Decreased antioxidant capacity during late gestation and lactation can increase oxidative damage by increased production of free radicals when an animal is under high ambient temperature environment (Mitchell and Russo, 1983; Ozawa et al., 2002; Matsuzuka et al., 2005). This indicates that oxidative stress is one of major stress responses caused by heat stress. Thus, sows under heat stress would have increased protein turnover due to increased oxidative damage to cellular proteins, increased cell death due to increased peroxidation of membrane lipids and increased DNA mutation and breakdown which can together interfere fetal development, mammary gland development, and milk production as shown as reduced number of piglets born alive, and reduced litter weight gain from sows under heat stress as shown in Yan et al. (2011). Increased oxidative stress during the period of embryonic implantation may cause increased embryonic death which can be related to a reduced litter size for sows under heat stress. This study shows that sows were under elevated oxidative stress during the late gestation and lactation periods when they were housed in a heat stress environment. Increased oxidative damage to lipid, protein, and DNA was one of the major contributing factors for reduced reproductive performance of sows under a heat stress environment.

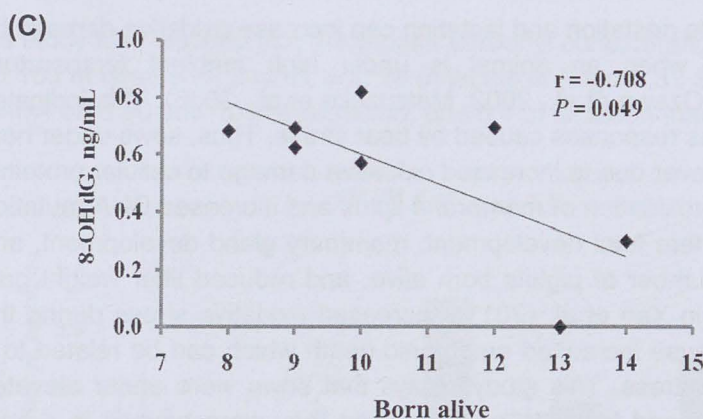
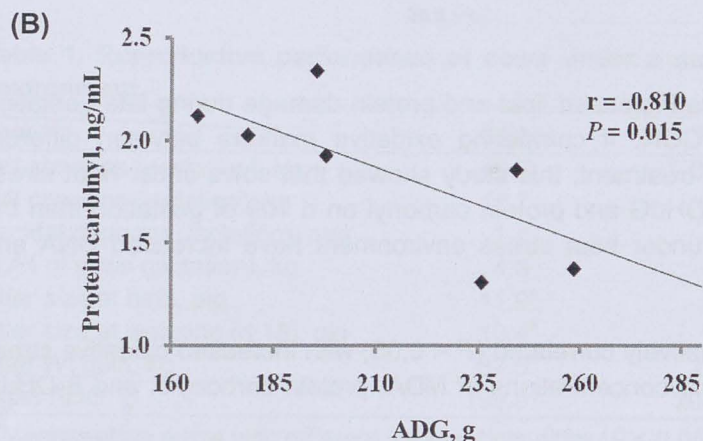
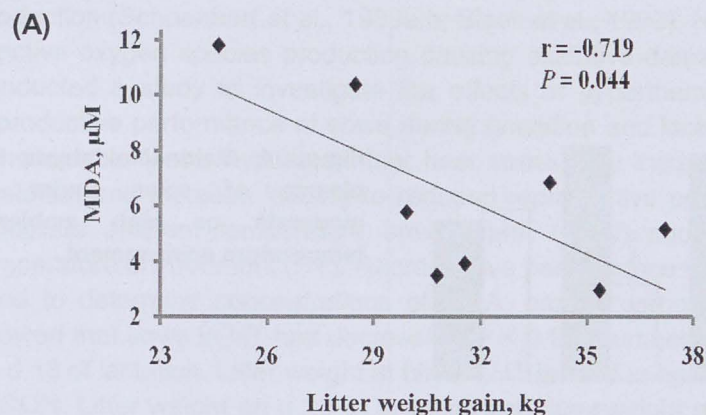


Figure 5. Correlations of reproductive performance with oxidative stress indicators for sows in a high ambient temperature environment. (A) Litter weight gain during lactation and MDA concentration on d 60 of gestation; (B) average daily gain of individual nursing piglets and protein carbonyl concentration on d 18 of lactation (C); and born alive per litter and 8-hydroxy-deoxyguanosine (8-OHdG) concentration on d 3 of lactation.

Oxidative Stress and Social Behavior

Gestation crate has widely been used in order to control individual energy intake especially benefiting lactation performance. However, concerns with potential interruption of animal wellbeing suggest the removal of gestation crates. Rapid urbanization reduces societal support and understanding of swine production, which may also play a role in increasing societal pressure to change current gestation housing system. However, group housing of sows under controlled feed allowance could also potentially increase aggressive behavior between sows, health risks of low

dominance sows, occurrence of stereotypic behaviors, and possible reduction in reproductive performance (Anil et al., 2005). It has been shown that social and behavioral stresses are associated with physical markers for oxidative stress (Eskiocak et al., 2005).

Our recent study (Zhao et al., 2011) determined if reproductive performance and oxidative stress status of sows would be affected by different gestational housing systems. Sows were housed either in groups of 3 per pen (PEN) or individual gestational crates (CON) on d 35 of gestation. Behaviors (standing, lying, eating) of sows were recorded from video observation for the first 4-d period after sows were assigned to treatments on d 35 of gestation. Reproductive performance and plasma samples were used to evaluate the effects of gestational housing. This study concluded that reproductive performance of sows housed in gestational pens tended to be inferior to sows housed in gestational crates as indicated by total born per litter and litter weight at born (Table 2). However, oxidative stress status was not affected by gestational housing indicating that the effects of gestational housing on reproductive performance of sows may not be directly related to oxidative stress status. Oxidative damages to protein and DNA were further increased during late gestation and lactation regardless of gestational housing.

This study further determined if social ranks of gestating sows housed in group would affect their oxidative stress status, immune status, and reproductive performance. The social rank of sows within a pen was determined by observing their aggressive behavior for a 4-d period after mixing. Sows within a pen were classified into high-, middle-, and low-ranking groups (HR, MR, and LR) according to their percentage of winning interactions. Sows in LR showed greater litter size and litter weight than sows in HR even though their BW was inferior to sows in HR. However, sows in LR has decreased farrowing rate and increased mortality. Sows in LR had higher DNA damage compared with HR during late gestation and lactation, which could be one of major reasons to their poor farrowing rate or mortality (Table 3). The study concluded that within each rank, it was all shown that the reproductive performance was related to oxidative status of sows regardless which rank they were in (Figure 6).

Table 2. Reproductive performance and oxidative stress status of sows housed from gestational crates and pens.

Item	CON ¹	PEN ¹	SEM	P-value
BW changes (gestation), kg	41.5 ^a	35.7 ^b	3.5	0.093
BW changes (lactation), kg	-8.6	-9.2	3.4	0.798
ADFI of sows (lactation), kg	4.7	4.4	0.3	0.362
Litter size at birth, pig	11.0	10.3	0.6	0.190
Litter size at weaning, pig	9.0	8.2	0.9	0.520
Litter weight at birth, kg	16.8 ^a	15.2 ^b	0.9	0.089
Litter weight gain, kg	33.2	31.7	2.5	0.572
Malondialdehyde (d 109), μ M	5.52	6.01	0.80	0.547
Protein carbonyl (d 109), nmol/mg	1.88	1.63	0.36	0.610
8-OH-deoxyguanosine (d 109), ng/mL	0.94	1.10	0.14	0.347

^{a-b}Means within a row with different superscripts differ ($P < 0.05$).

Table 3. Reproductive performance of sows from different social ranks.

Item	HR	MR	LR	SEM
BW, d 35 of gestation, kg	256.3 ^a	237.6 ^b	233.8 ^b	6.1
BW, d 18 of lactation	275.2 ^a	252.2 ^b	247.9 ^b	6.5
ADFI of sows during lactation, kg	4.3	4.8	4.3	0.3
Litter size at birth, pig	9.6	10.3	11.2	0.7
Litter size at weaning, pg	7.2 ^a	8.2 ^a	9.6 ^b	0.6
Litter birth weight, kg	13.6 ^A	16.3 ^B	16.6 ^B	1.0
Litter weaning weight, kg	43.1 ^A	47.8 ^{AB}	51.8 ^B	3.4
ADG of piglets, g	233.3 ^A	211.7 ^{AB}	207.0 ^B	11.3
Farrowing rate, %	91.7	95.7	72.0	
Sow mortality rate, %	0.0	4.3	4.0	

^{a-b}Means within a row with different superscripts differ ($P < 0.05$).

^{A-B}Means within a row with different superscripts tend to differ ($0.05 \leq P < 0.10$).

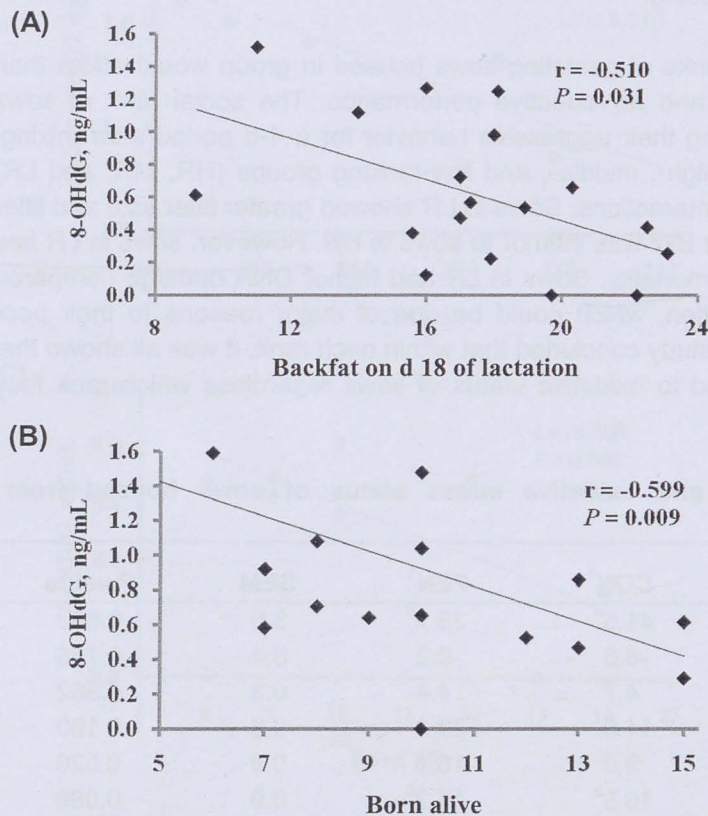


Figure 6. Correlations between reproductive performance and oxidative stress indicators for sows in high-ranking group. Backfat thickness at d 18 of lactation and 8-hydroxy-deoxyguanosine (8-OHdG) concentration on d 60 of gestation (A), born alive per litter and 8-OHdG on d 109 of gestation (B).

Conclusions

In summary, our recent research indicates that sows have increased oxidative damage during late gestation and lactation. At the same time, the antioxidant defense substantially reduces during late gestation. When sows housed under heat stress environment, they have increased oxidative damage to lipid, protein, and DNA during late gestation and lactation, which is one of the major contributing factors for reduced reproductive performance of sows under a heat stress environment.

The gestational housing systems (crate vs pen) do not affect oxidative stress status and maintenance behavior of sows. When sows are housed in gestational pens, they tend to have inferior reproductive performance compared sows housed in gestational crates. At the same time, they have increased protein and DNA damage during late gestation. For all social ranks, it is shown that the reproductive performance is related to oxidative status of sows. Sows in low-ranking showed greater litter size and litter weight than sows in high-ranking, even though body weight of sows in low-ranking was inferior to sows in high-ranking. However, sows in low-ranking has decreased farrowing rate and increased mortality compared with others. Dietary antioxidant concentrations need to be re-evaluated for its sufficiency in sow diets especially to prevent excessive oxidative stress during late gestation and lactation.

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Hormel Foods – Feed Division

Dennis Dieterich

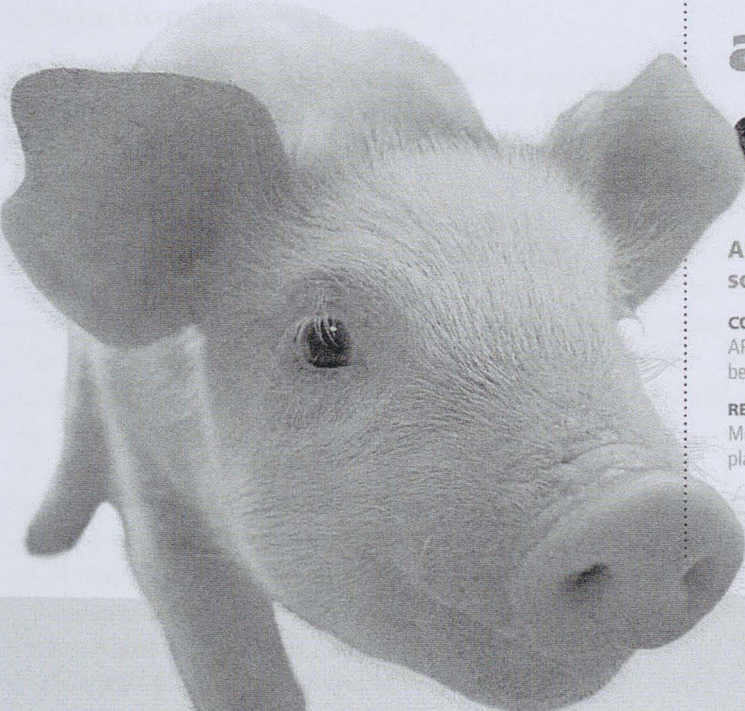
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