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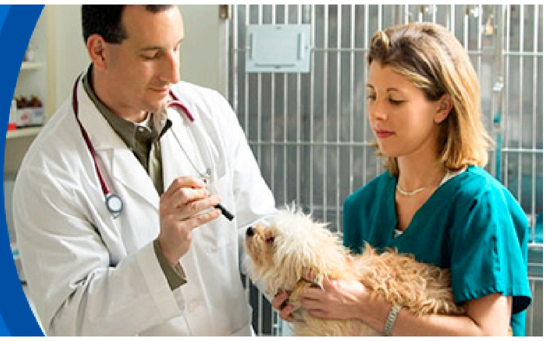

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Oxidative stress and its effects on reproductive performance in thermally-stressed ewes

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Abstract
This paper reviewed the impact of thermally-induced oxidative stress on reproduction in ewes. Thermally-induced oxidative stress is associated with excess generation of reactive oxygen species (ROS) during aerobic respiration and metabolic activities within the body. Excess ROS have been implicated in pathophysiologic mechanisms impairing reproductive processes, including changes in cyclic luteal and endometrial processes, poor follicular development, ovulation, fertilisation, embryogenesis, embryonic implantation, and placental differentiation and foetal growth. High levels of ROS during pregnancy result in pregnancy disorders such as spontaneous abortions, embryopathies, pre-eclampsia, foetal growth restriction, pre-term abortion and low-birth weight. Thermally-induced stress occurs as a result of extreme cold and hot temperatures, and its impact on animals is determined by nature of management practices being used in the farm. Heat stress suppresses reproductive hormonal expression and activities, resulting in poor reproductive performances, including the exhibition of poor oestrus behaviour and mating ability; while cold stress suppresses reproductive neuroendocrine axis, which adversely affects conception rates and mating behaviours. Other oxidative stress factors exerting negative effects on reproduction are poor nutrition, solar radiation, environmental pollutants, high ambient temperature and high relative humidity, expressed as temperature-humidity-index. The stressors contribute to adverse pregnancy outcomes, increase in the susceptibility of offspring to disease by compromising the offspring immune status and overall reproductive performance in ewes. The link between oxidative stress and reproductive processes such as spermatogenesis, oogenesis, fertilisation, embryonic development, implantation and foetal growth are critical therapeutic and prophylactic interventions in reproductive medicine. The role of oxidative stress in reproductive processes and the state of knowledge on the association between oxidative stress and pregnancy outcomes in ewes are elucidated. It is concluded that oxidative stress is an important silent condition undermining reproductive performance in sheep resulting in serious economic loss. Reduction of its impacts will enhance productivity and performance in ewes.

Keywords: Environmental stressors, oxidative stress, reactive oxygen species, reproduction, pregnancy, oestrus cycle, ewes.

Introduction

Sheep production form an important component of the livestock economy among rural populations in Africa, including Nigeria. Apart from their socio-cultural roles as sources of meat and food security, they are important rural financial resources, serving as cash savings and are used in festive activities. Sheep contribute 11% of the meat industry in Nigeria. Their production is an important component of livestock production in many parts of the world, where they are raised for mutton, milk, wool and hides and skins. In Australia, sheep production is an important source of mutton, wool and milk. In the Mediterranean countries, sheep milk is rated higher for nutritive value and cheese processing outputs than cow milk. Therefore, sheep milk is more expensive than cow milk. The Mediterranean countries have a long history of consumption of sheep milk as they associate it with longevity. Thus, sheep production forms an important part of the integrated agricultural economy across the world [1].
Various management systems are employed in sheep production in tropical environments. In Nigeria, traditional management system such as nomadism, transhumance and agropastoralism are among the common methods used, where animals are raised and fed through herding and open grazing and feeding of animals on crop-residue with little or no supplemental feeding [2].

The production systems expose animals to harsh, tropical climatic conditions, presenting seasonal variability in feed quality and supply often resulting in nutritional stress. The experience extreme weather conditions throughout the year, predisposing them environmental stressful conditions and diseases. Nutritional stress, environmental stress and diseases compromise the productivity of livestock and, especially, their reproductive performance. Nutritional stress is associated with underfeeding due to the seasonal variation in feed quality and availability that brings about roaming and scavenging of food through nomadism and transhumance practices. Consequently, there is an increase in the incidence of reproductive disorders and infertility in animals [3, 4, 5] and in women [6].

Environmental conditions precipitate thermal (hot and cold) stress as the result of extreme weather conditions due to climatic changes, which subject the animals to oxidative stress that undermine the reproductive performance. Oxidative stress is also associated with tropical diseases especially ecto- and endo-parasitism which predispose animals to changes in the vulgaris of weather such as changes in ambient temperature and humidity. In tropical countries this situation breaks the weather into two main weather conditions, *viz*: hot and dry seasons. Both seasons are characterized by variations in disease burdens on animals due to differences in changes in management systems, accessibility of good nutrition and water, thus, predisposing them to oxidative stress. The un-favorable conditions associated with management systems such as nomadism and transhumance practices cause varying levels of oxidative stress, which undermine the productive capacity of ewes and result in poor reproductive performance as well as huge economic loss. Measures aimed at ameliorating oxidative stress in sheep production are, thus, crucial for the sustainability of their production in tropical environments. Such measures are required to interfere in the pathophysiologic mechanisms underlying oxidative stress resulting in excess generation of ROS, which adversely affect reproductive performance in ewes. This paper reviews oxidative stress associated with changes in environmental conditions and its adverse effects on reproductive performance in sheep exposed to thermal stress.

Oxidative Stress

Oxidative stress (OS) plays a crucial role in the mechanism of diseases arising from extreme environmental conditions. It occurs as result of imbalances in the redox (reduction and oxidation) reactions due to the production and scavenging of ROS [7, 8]. Redox reactions involve the transfer of electrons between molecules during metabolic and aerobic respiration due to cellular response to endogenous and exogenous stimuli [7, 8, 9]. Excessive endogenous stimuli such as disease conditions, increased aerobic respiration and metabolic activities; and exogenous stimuli including environmental disrupting substances, thermal stress, wind speed and solar radiation. These stimuli increase the generation of reactive species, comprising oxygen and nitrogen free radical species as by-products, resulting in oxidative stress [7, 8, 10]. Although reactive species play a central role in normal cellular function in providing an important feed-back loop between metabolic activity and regulation of cellular functions, excess production of ROS in the body exerts deleterious effects in the body and overall performance [11]. The ROS arise due to an imbalance between pro-oxidants and antioxidants in stressful conditions, as a result of increased antioxidant utilisation, impaired buffering capacity or immune dysfunction [8, 11]. Though several reactive molecules are produced in the body, ROS and reactive nitrogen species (RNS) are the most important. ROS comprise superoxide, hydroxyl radical, peroxyl radical, while the RNS include nitrogen oxide and peroxynitrite. These species are generated continuously in small quantities during normal aerobic respiration and metabolic activities in the body. The reactive species are involved in several physiological processes, including protein phosphorylation, activation of transcription factors, cell differentiation, apoptosis, oocyte maturation, steroidogenesis, cell immunity and cellular Defence against pathogens [11, 12]. The effects of ROS on cells become deleterious when they are generated in excess, resulting in oxidative stress, when there is an imbalance between ROS and antioxidant activities. Oxidative stress is common in animals exposed to extreme environmental conditions such as excessive thermal, wind speed and solar radiation [8].

Heat stress impairs animal performance, and has been implicated in promoting oxidative stress, either through excessive ROS production or decreased antioxidant defenses [13]. Some diseases like sepsis, ketosis, mastitis, and enteritis, and pneumonia, respiratory and joint diseases are associated with excess ROS [11]. Excess ROS generation also causes infertility and poor reproductive performance in animals [14]. The significant roles of ROS in the pathogenesis of reproductive disorders have been reported and these include attack on the fluidity of the sperm plasma membrane and DNA integrity in the sperm nucleus; induced DNA damage which may accelerate the process of germ cell apoptosis, leading to the decline in sperm counts associated with male infertility [15, 16, 17].

In female, ROS mediated the pathophysiology of endometriosis and unexplained infertility with high follicular fluid ROS levels, resulting in negative IVF outcomes, apparently responsible in *hydrosalpinges* fluid mediated embryo toxicity as well as poor *in vitro* embryonic development. In the female, oxidative stress has been reported to influence oocyte development, maturation, follicular atresia, *corpus luteum* function and luteolysis [18]. Though ROS may play a significant role in the modulation of gamete interaction and successful fertilization, excess ROS reduce oocyte and embryo quality both *in vitro* and *in vivo*. The ROS exert considerable impact on post-fertilisation development, such as cleavage rate, blastocyst yield and quality, which are indicators of assisted reproduction outcomes [19]. Oxidative stress has been reported to cause embryo resorption, placental degeneration with subsequent alteration in maternal-foetal exchanges, delay in foetal growth, pregnancy interruption, and still-births during pregnancy [20]. Excess ROS generation modulate the microenvironment in the female, resulting in follicular, *hydrosalpinges* and peritoneal fluid accumulation. It interferes with implantation and early embryo development, and causes embryo toxicity due to poor *in vitro* embryonic development, resulting in poor pregnancy outcomes [15, 21]. Oxidative stress is implicated in pathophysiology of endometriosis and unexplained infertility, and high concentrations of ROS in follicular fluid is reported to be associated with negative *in vitro* fertilisation (IVF) outcomes [15]. The ROS also cause DNA damage, resulting in various genomic defects due to telomere shortening; for example, aplastic anaemia in the bone marrow and progressive fibrosis in the lungs and liver [22, 23, 24]. The ROS undermine the development of germ cells, which adversely affects the quality of ovum production. They also induce oocyte implantation disorders, endometriosis, embryo resorption, placental degeneration with subsequent alteration in maternal-foetal exchanges, delay in foetal growth, pregnancy interruption and stillbirths in sheep [20, 25, 26]. In female animals, oxidative stress has been associated with irregular oestrous cycle, polycystic ovary syndrome, endometritis, infertility, poor embryo development and pregnancy failure [14]. Pregnancy, especially at the last trimester and early lactation has been associated with oxidative stress due to higher nutrient demands for rapid foetal growth and the production of large amounts of colostrum and milk [27]. The ROS exert negative impact on weight gain and nutrient utilisation in ewes, especially during the last trimester of pregnancy, and at the onset of lactation, when the body requirements for micronutrients and antioxidants are very high, but the supply is grossly inadequate [28].

The indices of oxidative stress have a strong correlation with infertility in the females. The ROS levels and selenium-dependent glutathione peroxidase activity in follicular fluid are directly correlated with pregnancy rates, while lipid peroxidation, total antioxidant capacity, and superoxide dismutase activity have strong correlation with oocyte fertilisation and pregnancy rates, following IVF and other assisted-reproductive techniques [21]. However, the oxidative stress maker in granulosa cells, 8-hydroxy-2-deoxyguanosine shows negative correlation with embryo quality following IVF [21].

Oxidative stress is associated with infertility in rams and other male animals. Normal ROS levels modulate the fertilizing capabilities of the spermatozoa, but excess ROS above the physiological levels result in structural and functional damage, which may lead to motility loss, premature acrosomal reaction, lipid peroxidation, apoptosis, and DNA damage [18, 21]. Oxidative by-products generated by ROS include 8-oxo-7,8-dihydroxyguanosine, which cause lipid peroxidation, RNA transcripts damage and cause DNA fragmentation with a resultant mutagenic effect and overall negative effects on sperm quality [29]. The compound also causes negative impact on the success rates of assisted-reproductive techniques such as artificial insemination (AI), *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) [30]. Oxidative stress reduces sperm count due to germ cell apoptosis, resulting in male infertility in animal models and humans [15, 31, 32, 33]. Furthermore, it has been reported that the generation of ROS, including superoxide anion, hydrogen peroxide and hydroxyl radicals during oxidative stress, increases the decay of sperm membrane lipid and DNA, and increases DNA strand breaks [30]. Damages to sperm membrane and DNA by excess ROS result in necrozoospermia, asthenozoospermia, and DNA fragmentation in sheep, man and other mammals [21, 32, 33, 34, 35]. Excess ROS impair overall sperm production and function due to oxidative damage to somatic cells and spermatozoa [21, 23, 31, 36]. They are associated with erectile dysfunction, sperm damage and motility in animals and men [37, 38].

Reactive Oxygen Species and Reproductive Performance in Sheep

Thermal stress comprising heat and cold stress is associated with oxidative stress and poor reproductive performance in ruminants [39, 40].

Heat and cold stress are very serious conditions that occur when the body can no longer maintain a normal temperature. They result in serious illnesses and injuries, permanent tissue damage or death. Heat stress is associated with tropical or hot environments, while cold stress is associated with cold or temperate environments. In tropical climates such as occur in Nigeria, seasonal climatic variations exist, often with extreme weather variations. The two main seasons that could be classified in most northern parts of Nigeria are the dry (November – May) and rainy seasons (June – October). The dry season has no rain, and, therefore, lacks precipitation. It is further classified into cold-dry with hazy (harmattan) winds (November – February), and extreme hot period (March – May) [41]. The rainy season has rainfalls and, therefore, higher precipitation and there may be high relative humidity and high temperature (June – August) or high relative humidity and low ambient temperatures (September - October) [41]. The resultant temperature-humidity index (THI), which is an expression of heat load, has deleterious effects on overall sheep performance [42].

Cold stress is induced by low temperatures, high wind speed, high relative humidity, and/or contact with cold water or surfaces, while heat stress is characterized by high temperatures, low wind speed and moderate/high relative humidity. A cold environment forces the body to function harder to maintain its temperature as it draws heat from the body, while a hot environment results in the body functioning harder to dissipate heat. Oxidative stress adversely affects sheep productivity especially in both temperate and tropical environments. The high prevalence of pests and diseases, solar radiation, thermal and nutritional stress are important predisposing factors to oxidative stress in ruminants. Multiple stresses acting concomitantly are reported to exert more severe negative effects on all reproductive parameters than individual stress factors (Fig. 1) [43].

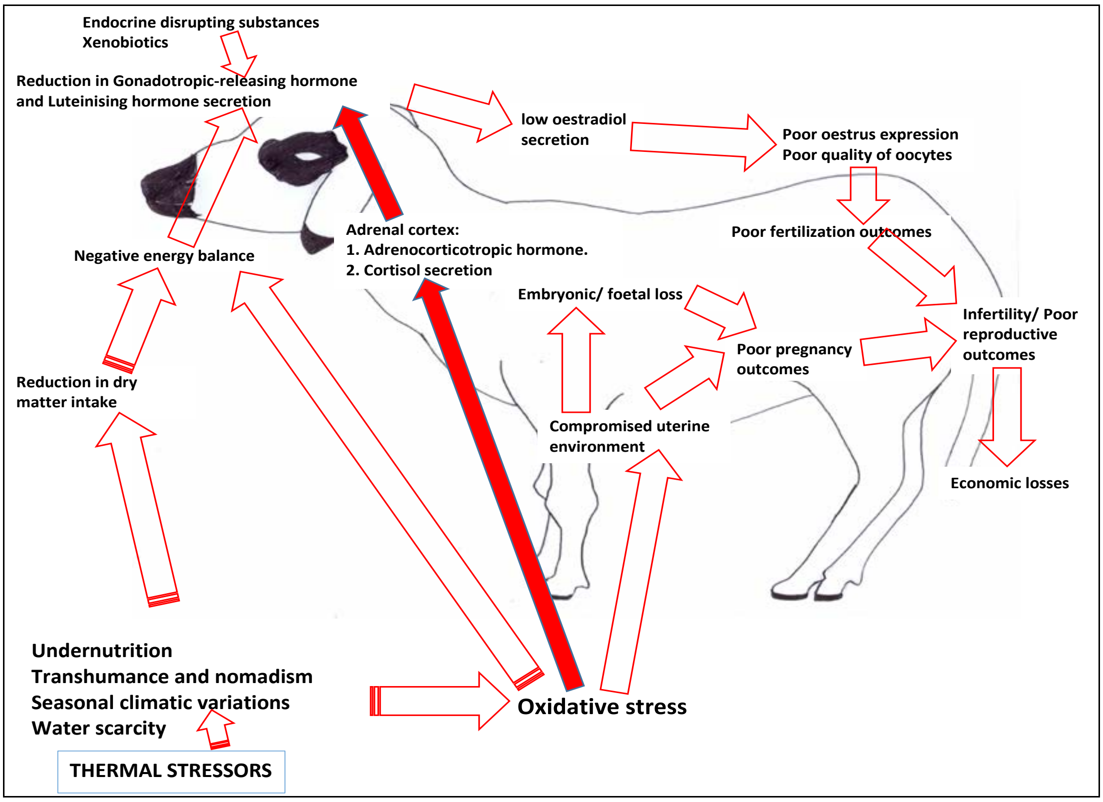

Fig 1: Oxidative stress and its effects on reproductive performance in ewes.

Heat Stress

Heat stress is one of the major factors exerting major negative effects on reproductive performance in ewes and other ruminant species. Although studies on the effects of heat stress on various reproductive parameters have been carried out extensively in cows [44 - 50], its impact on reproductive parameters in the ewes are poorly documented. In a study carried out in Brazil, lower birth and weaning weights in lambs in tropical environments were obtained when compared with those in temperate climate, demonstrating the negative impact of tropical heat stress on reproduction [51]. Heat stress lowers the productive and reproductive efficiency of animals [52]. In other countries, such as Nigeria, sheep productivity is low due to a variety of factors, including the effects of environmental stress, disease burdens, nomadism and undernutrition [53]. Furthermore, it has been shown that elevated rectal temperature, mean maximum and minimum temperatures and relative humidity compounded by feed scarcity during the dry periods of the year are responsible for poor conception rates among ruminants [53]. However, there are no specific information regarding the impact of oxidative stress on conception rates in sheep.

Heat stress reduces libido, fertility, and embryonic survival in ruminants [54]. It also reduces foetal growth and alters the endocrine status of the dam during late gestation [55]. Heat stress changes the endocrine status of sheep to reduce follicular activities and ovulatory mechanism, with a decrease in oocyte and embryo quality [56]. It also results in a decrease in basal metabolism, which subsequently reduce the production of hormones like thyroxine, growth hormone, and glucocortcoids. Heat stress is associated with decrease in electrolyte concentrations such as sodium and potassium in the body and also decrease the production of volatile fatty acids and alters the ratio of acetate/ propionate, and a decline in ruminal pH [55]. Heat stress during summer months has also been reported to reduce the duration and intensity of oestrus in cows, resulting in fewer successful inseminations and poor insemination outcomes [56, 57]. Heat stress during summer in cows affects the hypothalamic-gonadal axis by reducing the luteinising hormone (LH) levels, including its pulse amplitude and frequency [58, 59]; reduced estradiol secretion by dominant follicle and may demonstrate similar effects in ewes [60, 61, 62]. It lowers plasma inhibin concentration and a relatively higher plasma concentration of follicle stimulating hormone (FSH) levels, resulting in reduced folliculogenesis and poor oestrus behaviour [61]. The reports on the effects of heat stress on plasma progesterone are somewhat inconsistent in cyclic ewes and dairy cows; and were associated with the differences between the rate of luteal production and the rate of hepatic metabolism, which are both affected by changes in dry matter intake [56, 63, 64, 65, 66].

Heat stress in summer lowers the progesterone levels during the luteal phase, which results in poor follicular development, abnormal oocyte maturation and causes embryonic mortality [56, 67]. Although the mechanisms through which heat stress alters the concentrations of circulating reproductive hormones are not known, it has been postulated that increased corticosteroid secretion may be involved through its inhibition of GnRH and, thus, LH secretion [59]. Heat stress is an important factor in gametes and embryonic development and the interaction of such gametes during fertilisation occurs in ruminants. Spermatogenesis is a temperature-sensitive process where temperatures below the normal body temperatures are required. Oocyte development is also influenced by temperature [68]. Heat stress influences the uterine environment through increased uterine temperature, reduced blood flow and reduced endometrial prostaglandin secretions, which result in the inhibition of embryonic development, poor implantation, and premature luteolysis and increase in early embryonic loss, and in overall reduction in the proportion of successful inseminations [56, 69]. Heat stress is reported to affect follicular development through the delay in follicle selection and lengthening of the follicular wave, which in-turn affect the overall oocyte quality and follicular steroidogenesis

[46, 70, 71, 72, 73]. The reduction in food intake occasioned by heat stress and lowered body metabolic activities affects the overall energy balance, resulting in lower LH secretion and decreased dominant follicular size, which may contribute to anovulation in postpartum dairy cows and increase in infertility [56].

A study found the percentage of fertilized ova of 40.7% was significantly lower in ewes subjected to higher temperatures of 32ºC than the ewes in the control with fertilized ova of 94.2% [16]. The study also found higher percentage of 55.6% of morphologically-abnormal ova, from 3.8% in the control. The zygote was found to be most sensitive to the harmful effects of high ambient temperature during the initial stages of cleavage before implantation in the uterus [16].

Other studies have associated high ambient temperature with decrease in feed intake efficiency and utilization, disturbances in water, protein, energy and mineral balances, enzymatic reactions, hormonal secretions and blood metabolites, which also impact negatively on reproductive performance [35, 37, 52, 55, 74, 75, 76]. Elevated ambient temperature negatively affects the suprachiasmatic nucleus (SCN) in the brain, which impacts its ability to regulate the circadian and seasonal rhythms of most biological functions, and reproduction, including the phasic and tonic release of hormones, oestrus and gonadal size [37]. Adverse ambient temperature disrupts endocrine function by suppressing oestrus behaviour through a decrease in GnRH/LH pulse frequency and amplitude, with deleterious consequence on fertility in ewes [77]. It was also found in another study that heat-stressed pregnant ewes had lambs with lower birth weight of 3.18 kg., when compared with ranged pregnant ewes (4.57 kg.), while those on restricted feeding had 4.16 kg and dwarfed lambs among the heat-stressed ewes, irrespective of their level of nutrition [78].

Another study showed that the effects of heat stress on the reproductive function in both female and male ruminants are dependent on its severity [79, 80]. Such effects include reduced intensity of behavioural oestrus and low fertility in females, compromised sperm output and increased sperm abnormalities in males. Cows subjected to heat stress had reduced fertility due to changes in endocrine activities, such as reduced estradiol secretion and changes in plasma progesterone concentrations. Such changes reduce the follicular activities and alter the ovulatory mechanisms, leading to a decrease in oocyte and embryo quality, and the entire uterine environment with concomitant effect on implantation [56]. They reported that lactation increases the sensitivity of females to heat stress because of the associated increase in heat production during lactation, occurring due to high metabolic activities. It has been reported that heat stress generally impairs reproductive performance and immune response in livestock [74].

In assisted-reproductive techniques in animals, the production of embryos through superovulation is reduced during heat stress, affecting the success rates of *in vitro* fertilisation (IVF). This occurs as a result of reduced super ovulatory response, lower fertilization rate and reduced embryo quality and viability [78, 79]. The effect of heat stress on the reproductive processes in ewes, essential for embryonic development causes reduced oestrus behaviour expression, changes in follicular development, limiting oocyte performance, and impeding overall embryo growth in the dam [81].

Heat stress has also been associated with compromised passive and cell-mediated immunity in ewes exposed to heat stress during the dry period and fed on their dams' colostrum [65, 81]. Thus, may also have similar impact on kids, born to sheep exposed to heat stress. Heat stress significantly increase in the packed cell volume (PCV) ($P<0.05$) but does not significantly alter the total serum thyroxin and triiodothyronine levels in sheep, exposed to heat stress conditions [82]. The rise in PCV is considered as an adaptation mechanism for cooling.

Cold Stress

Cold stress is associated with lower environmental temperatures below the thermo neutral zone when the difference in core body temperature in animals is considerably higher than the environmental temperature. Cold stress has been reported to exert minimal negative effects on reproduction in animals [55]. It is associated with a general reduction in body activities due to lower body temperature. It increases basal metabolism as a measure of generating heat to maintain the body temperature [83]. Increase in metabolic activities in the body results in increased generation of ROS which induce oxidative stress with its consequential adverse effects on reproductive performance. Cold stress may lower conception and pregnancy rates in ewes as reported in heifers [84].

Multiple Environmental Stressors

Multiple environmental stressors, including seasonal effects, also exert deleterious effects on reproduction in ewes. It has been reported that lower reproductive values in ewes subjected to multiple environmental stressors have been obtained, when compared to the control group [43]. There was a significant difference ($p<0.05$) in the percentages of ewes exposed to multiple environmental stressors (41.7%) and the control group with 66.67%. The oestrus duration (in hours) was significantly higher in the control ewes (32 hours) than ewes in multiple-stressed group (14.4 hours). The conception and lambing rates also dropped significantly from 83.3% in the control group to 50% for the multiple-stressed group. The birth weight was not significantly different between the control and the multiple stressed group. The above study showed poor reproductive performance values in ewes exposed to multiple environmental stressors such as thermal, nutritional and walking stress. Sheep in Nigeria are commonly raised under similar conditions especially in the dry season of year when feed supply is inadequate and animals are walked for long distances in search for food.

Seasonal Effects

A study compared the outcomes of Santa Ines ewes in Brazil under dry and rainy season conditions and found that there was no difference ($P > 0.05$) in expression of oestrus (86.8 and 98.3%), pregnancy rate (86.8 and 90.9%), lambing (76.3 and 83.6%), abortion (9 and 7.4%), fecundity (86.8 and 96.3%), birth (103.4 and 110.8%), abortion rates (9.0% and 7.4%) and prolificacy (113.7 and 115.2%) [85]. However, lamb mortality differs significantly ($P > 0.05$), 26.6% for the dry season group A, and 49% for rainy season group B. Ewes raised in the dry season (group A) had higher average live weight at the end of the reproductive season and during the final third of pregnancy ($P < 0.05$) than those raised in the rainy season (group B). The average daily weight gain was higher for ewes raised in the dry season (98.3 ± 0.009) than in the weight season (8.3 ± 0.008). The live weight during the final third of pregnancy was higher in the dry season group (49.0 ± 1.07) than in the rainy season group (41.4 ± 0.84). The other parameters were not significantly different: postpartum live weight gain of 39.7 ± 0.98 for dry season group and 36.0 ± 0.78 for the rainy season group, lamb live weight at birth of 3.2 ± 0.12 for dry season group and 3.0 ± 0.09 for the rainy season group, male lamb live weight from singletons (kg) of 3.3 ± 0.13 for dry season group and 3.1 ± 1.0 for the rainy season group, females from singletons (kg) 3.5 ± 0.13 for dry season group and 3.0 ± 0.09 for the rainy season group, males lamb weight from twins live weight (kg) 2.9 ± 0.08 for dry season group and 2.4 ± 1.0 for the rainy season group, and females lamb weight from twins live weight (kg) of 2.2 ± 0.092 for dry season group and 2.6 ± 0.091 for the rainy season group.

The above studies highlight the variations in the negative effects of oxidative stress associated with environmental stressors, which are common problems facing sheep production in developing tropical countries such as Nigeria. The practice of extensive management system through walking of animals for long distances, poor nutrition especially during the late dry season, high thermal stress and solar radiation are important stressors compromising reproductive performance of sheep. Studies in Nigeria regarding the impact of oxidative stress on reproductive performance in ewes have not been adequately documented.

Concluding Remarks

Oxidative stress remains an important condition undermining reproductive performance in sheep. It is a silent cause of economic loss through poor oestrus behaviour and mating, poor fertilisation and overall pregnancy outcomes. It exerts and retards lambs' growth and development, including compromise of the ability of sheep to resist diseases and other stressful conditions. There are measures, such as the use of antioxidants, aimed at minimizing the effects of oxidative stress, posed by environmental stressors on reproduction. Such measures may be beneficial in ameliorating the negative impact of oxidative stress and may enhance sheep productivity.

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Conflict of Interest

The authors declare that there is no conflict of interest associated with this review article.

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