



# Harnessing the value of reproductive hormones in cattle production with considerations to animal welfare and human health

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## Abstract

The human population is ever increasing while the quality and quantity of natural resources used for livestock production decline. This calls for improved product efficiency and the development of improved and sustainable cattle production methods to produce higher quality products to satisfy the demands of both the modern and transient world. The goal of this review was to summarize the interactions, challenges, and opportunities in cattle production relating to their endocrine system, and how reproductive hormones and others impact economically important traits, animal welfare, and human health. A comprehensive literature search was conducted with a focus on analysis of natural hormones and the use of exogenous hormone administration for reproduction, growth, and development of beef and dairy cattle. Hormones regulate homeostasis and enhance important traits in cattle, including fertility, growth and development, health, and the production of both meat and milk products. Reproductive hormones such as testosterone, estradiol, progesterone, and related synthetics like trenbolone acetate and zeranol can be strategically utilized in both beef and dairy cattle production systems to enhance their most valuable traits, but the impact of these substances must account for the welfare of the animal as well as the health of the consumer. This scientific review provides a comprehensive analysis of the bovine endocrine system's impact on food animals and product quality which is vital for students, researchers, livestock producers, and consumers. Although important advances have been made in animal science and related technological fields, major gaps still exist in the knowledge base regarding the influence of hormones on the production and welfare of food animals as well as in the public perception of hormone use in food-producing animals. Filling these gaps through transformative and translational research will enhance both fundamental and applied animal science to feed a growing population.

## Lay Summary

The animal production industry is responsible for providing products like meat, dairy, and egg products to the growing human population of the world. Within each sector, there are production practices that can improve the overall productivity of the animals and contribute to their welfare. One such avenue for enhanced production is the inclusion of hormones. Hormones are naturally produced within the body by the endocrine system which helps initiate many life processes and transition the body to different stages of production. Hormones influence many important traits such as growth and development, milk production, fertility, and health within the cattle industry. Exogenous hormone use in animals has proven to improve a number of traits and qualities of animal products, but it has also struck up controversy. There are wide deficiencies in the full understanding of roles, applications, and implications of hormones in livestock, making it of high importance for further exploration. In this review, the mechanisms of hormones and their broad uses are explored to provide more context to the conversation of hormone use in animals. Knowledge of endocrinology is powerful and can aid in the advancement of fundamental science and animal development and production.

**Key words:** cattle, hormones, milk production, meat nutritive value, welfare

**Abbreviations:** ACTH, adrenocorticotropic hormone; VP, arginine vasopressin; AI, artificial insemination; ANS, autonomic nervous system; CL, corpus luteum; CRH, corticotropin-releasing hormone; ET, embryo transfer; E2, estradiol; FSH, follicle stimulating hormone; FFA, free fatty acids; GnRH, gonadotropin releasing hormone; GH, growth hormone; GHIH, growth hormone-inhibiting hormone; GHRH, growth hormone-releasing hormone; HSL, hormone sensitive lipase; HPA, hypothalamic–pituitary–adrenal axis; IgG1, immunoglobulin G1; IVF, in vitro fertilization; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; MGA, melengestrol acetate; NSAID, non-steroidal anti-inflammatory drugs; P4, progesterone; CIDR, progestin controlled internal drug release; PGF2 $\alpha$ , prostaglandin F-2 $\alpha$ ; rBST, recombinant bovine somatotropin; SCNT, somatic cell nuclear transfer; TRH, thyrotropin-releasing hormone; TBA, trenbolone acetate; T3, triiodothyronine; USDA, United States Department of Agriculture; FDA, United States Food and Drug Administration

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## Introduction

Livestock systems are a principal component of global agriculture requiring a large fraction of the world's agricultural land, which is valued at \$1.4 trillion (Thornton, 2010). In 2017, U.S. agricultural exports totaled \$138.2 billion, an increase of 2.6% above the previous year (Persaud, 2019). Additionally, U.S. agriculture and food-related industries contributed over \$1 trillion in GDP with farms alone being \$134.7 billion of this total (USDA, 2021). Cattle production is a cornerstone of livestock systems with beef and milk products being staples in the diets of consumers. As the global population grows and developing countries strive to consume more meat, there is an increased demand for animal protein and milk to maintain good nutrition and diets of consumers (FAO, 2006; Thornton, 2010). Increasing animal production requires efficiency and improvement of animal traits such as fertility, growth and development, carcass quality, and milk production.

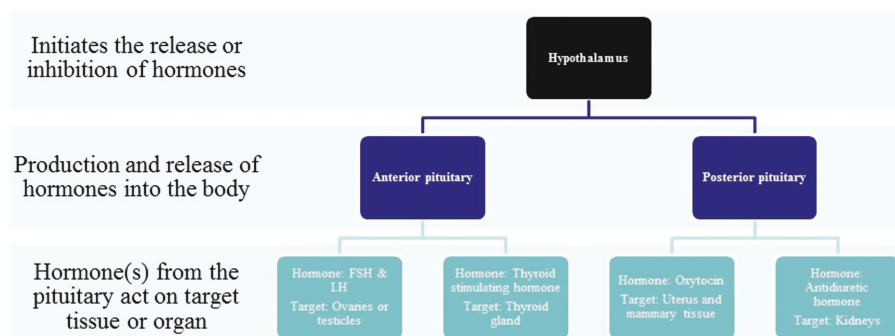
To meet global demands, there must be a universal effort to improve cattle production and environmental sustainability. Farmland is becoming scarce, and it is difficult to find new lands for ranching systems, grazing fields, and row-cropping (i.e., corn and soybean). Between the years of 2001 and 2016, approximately 11 million acres of farmland was converted for other uses to include both urban and residential purposes (Freedgood et al., 2020). The valuation of arable U.S. farmland has increased to \$3,160 per acre in 2019, nearly a 2% increase from the previous year. Pasture land was valued at \$1,400 per acre with a similar 2.2% increase from the year previous (USDA/NASS, 2019). Overuse of pastures and/or overgrazing lowers the quality of pasture forage, which decreases the nutrient value of that forage. With increasing herd sizes, there is a concern for maintaining animal health, welfare, and concern for current consumer attitudes towards these factors. The climate and weather conditions can complicate production problems with new challenges such as heat stress, water supply limitations, insufficient nutrients, plant toxicity, and parasites, all of which increase costs for producers. Today's research should aim to increase animal production while maintaining animal well-being and disease tolerance, while also minimizing land usage and accounting for environmental impacts.

The United States Department of Agriculture (USDA) states that although livestock production occurs in all U.S. states, Texas, California, Iowa, Kansas, and Nebraska maintain the highest sale values of their livestock and their products ((USDA, 2021). Leaders within government, private, and educational institutions have expressed the need for

improved forage utilization, disease control, food safety, and improved management strategies. Moreover, there has been an emphasis on short-term production systems rather than improving long-term sustainability towards improved energy usage and climate control. Researchers often utilize biotechnological and chemical approaches to provide resolutions to these issues. Research in the areas of endocrine hormones and the concentrations of hormone secretion are appropriate with the current and future needs in cattle production. Animal health and welfare are additional avenues of research opportunities. These could determine better practices for improved production traits, examining stress and pain intensity and their relationship with immunity and energy balance in animals.

There is evidence that hormone usage improves animal production efficiency, management, and utilization of resources. An example would be the use of recombinant bovine somatotropin, rBST, to increase milk yield in dairy cattle (Flores et al., 2019). However, the general consumer associates negative connotations with the use of hormones in a production setting (McGlone, 2001). The public sector has communicated their concerns with the use of hormones in the livestock production industry (Stock et al., 2015). In response to satisfying misinformed public perceptions, there is a rise of organic production systems and non-hormone-promoted animal products, and these systems typically do not incorporate efficiency. Therefore, it is important to provide honest scientific knowledge to properly educate the public about hormone usage in cattle production, how they are produced, transported, their mode of action, and how they are utilized and removed from the animal's body. This allows the consumer to gain factual knowledge and awareness of how food is raised then formulate their own opinion based on unbiased sources.

Hormones are signaling molecules that are secreted by endocrine glands to perform specific functions in cells and tissues (Figure 1). The principal endocrine organs are the hypothalamus, pituitary, gonads (ovary and testes), uterus, pancreas, thyroid, and adrenals (Hiller-Sturmhöfel and Bartke, 1998). Most hormones in mammals are triggered for release by the hypothalamus which also controls the feedback cascades of subsequent hormone secretions from the other endocrine glands (Hiller-Sturmhöfel and Bartke, 1998). The hypothalamus itself secretes a number of hormones: growth hormone-releasing hormone (GHRH) and gonadotropin-releasing hormone (GnRH) from the arcuate nucleus; and corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone from the



**Figure 1.** Endocrine regulation. The hypothalamus controls the production and regulation of hormones by acting upon the anterior and posterior pituitary gland. Specific hormones are produced by the specialized cells in particular portions of the pituitary.

paraventricular nucleus (Castro and Melmed, 2003; Malagon et al., 2006).

In the cattle production industry, several naturally occurring hormones are commercialized, including GH (rBST), prostaglandin (Lutalyse and Estromate), and Progestin (controlled internal drug release [CIDR]). All of these are widely utilized in estrous synchronization protocols. There are synthetic hormones available such as Zeranol, a non-steroidal form of estrogen and trenbolone acetate (TBA), which acts like testosterone (Jeong et al., 2010). Cloprostenol, or Estromate, is a synthetic form of PGF2 $\alpha$  in which studies have shown that it can induce luteolysis in dairy heifers (Pfeifer et al., 2009; Leonardi et al., 2012).

There are three synthetic hormones that are currently approved by the Food and Drug Administration (FDA): zeranol (estrogenic), trenbolone acetate (androgenic), and melengestrol acetate (MGA) for the feedlot sector of the beef industry. The first two are primarily used as growth promoters and are administered as implants, whereas the MGA is a progestin (oral feed additive) that suppresses estrus and ovulation (used in feedlot heifers) and can be used in estrous synchronization protocols. Somatotropin or growth hormone (GH) is a protein hormone that acts on the liver to trigger production of insulin-like growth factor-1 (IGF-1), which stimulates the growth of bone and muscle by increasing growth efficiency through increased lean muscle accretion, but it also increases milk production in lactating females (Simmons et al., 1990). The toughness of meat, as measured by the Warner-Bratzler shear force test, appears to increase slightly in cattle that were implanted with hormonal growth promoters, but not enough to compromise tenderness (Lean et al., 2018). Recombinant bovine somatotropin not only improves milk production, but it also reduces the occurrence of mastitis-infected cows (Eppard et al., 1996). Uses of GnRH, P4, and PGF2 $\alpha$  are extremely useful in estrous synchronization protocols such as Ovsynch and 7-day Cosynch + CIDR; these protocols increase the service rates of the herd and improve reproductive performance.

Hormone expertise and research are crucial for enhancing both the knowledge and application to real world problems in the industry. Hormone concentrations can be used to ascertain the current physiological challenges and welfare status of an animal. The evaluation of hormones through assays can provide indicators of reproductive performance and success among animals and their progeny (Post et al., 1987). Treatments can be introduced to improve reproductive performance and the efficiency of production. For example, GH and insulin are key indicators involved in fatty acid release in adipose tissues. Insulin can aid in diagnosing animals predisposed to conditions of insulin resistance, ketosis, and fatty liver disease in dairy cattle (Kirovski and Sladojevic, 2017). It has been demonstrated that early lactating cattle experience an increase in GH and hepatic function indicators such as albumin, in addition to a decrease in Triiodothyronine (T3), glucose, and urea (Djoković et al., 2015). Hormones like insulin can potentially provide therapeutic or medicinal benefits to metabolic disorders in dairy cattle (Sakai et al., 1993). A recent study using subcutaneous adipose tissue samples of dairy cattle demonstrated that the anti-lipolytic action of insulin increases insulin resistance of periparturient dairy cows during the first month after parturition (De Koster et al., 2018). The results showed that decreased free fatty acids (FFA) and glycerol levels coincide with increased insulin lev-

els. This is explained by the presence of insulin binding to hormone sensitive lipase (HSL), which prevents glucagon from binding and therefore in the interruption of the FFA release mechanism caused by glycogen.

With regard to human medicine and its ties to animal hormones, insulin therapy initially was labor intensive. Hormone extraction from slaughtered animals is not efficient, but recent innovations in the technology have allowed for efficient and economic synthesis of recombinant insulin analogs. Other developments of new hormone technologies for such uses, as in vitro fertilization (IVF), have enhanced scientific knowledge and research by improving understanding of the mechanisms involved in embryogenesis and fetal growth and development for both humans and animals. These technologies have facilitated steps to upgrade quality of gametes, zygotes, and embryos, and use of surrogates to develop animals with improved muscling, growth, and productivity (Ventura-Juncá et al., 2015). This technology has significantly altered the methodology used for this scientific research for which its developer, Sir Robert Edwards was awarded the Nobel Prize in Physiology or Medicine in 2010. It is imperative that we advance hormone research further to improve management practices, ultimately leading to improved productivity, product quality, efficiency, sustainability, and welfare of cattle.

## Hormones and Animal Welfare

Animal welfare is a crucial aspect of food safety and the desire to produce the best quality products. Welfare is a high priority issue and has led to changes in government regulations and consumer preferences over time. However, the definition of animal welfare is highly variable among producers, industry experts, veterinarians, and consumers. There are five basic freedoms that should be provided to animals: the freedom from thirst and hunger, freedom from discomfort, freedom from pain, injury, and disease, freedom from fear or distress, and freedom to express normal behavior (Brambell, 1965). According to the American Veterinary Medical Association, animal welfare is the human responsibility to provide proper housing, management, disease prevention and treatment, responsible care, humane handling, and, when necessary, humane euthanasia (AVMA, 2018). Animals must be provided adequate amounts of clean, fresh water and food. Shelter and care should be provided and should be free of potential hazards that could inflict injury and disease. All animals should be provided enough space to perform normal behaviors such as, lie down, stand up, and turn around. The living environment should be calm, provide adequate lighting, and avoid unnecessary stressors such as loud noises.

Combining these ideas helps create a holistic view of animal welfare. Variability in this area stems from how producers raise and manage their herds because every operation is managed differently. Despite on the farm practices consumers want to see “happy” cows and producers want their livestock to produce. Animal welfare is not only of value for ethical standards and beliefs, but also helps elevate production and provide healthier foods for human consumption. Hormones aid in the enhancement of farm productivity by improving breeding efficiency and increasing production and product quality (Lacasse and Ollier, 2015; Reineri et al., 2018). Happiness is not measurable in animals, so we must attain information about the animal’s well-being through other means

such as biological or physiological indicators. Researchers are indeed capable of determining other factors such as stress levels by measuring hormone levels in their systems. New techniques are being created to improve the sensitivity and accuracy of these technologies to enhance our understanding of animal wellbeing.

Improvement of management and animal handling protocols can then be developed from learning what stressors intensify cortisol levels, for instance, and how to reduce them. The North American Meat Institute created audit criteria and recommendations to identify problems when it comes to animal handling, welfare, and harvesting plan procedures for turkey, chicken, cattle, swine, and sheep species. Audits that review rendering practices, facilities, and the handling of animals can encourage change and reduce instances of animal mistreatment and improve animal care (Grandin, 2000; Whytt et al., 2003). Additionally, there are new adjustments on how hormone levels are detected, using factors such as increasing detection sensitivity, decreasing invasive procedures, and improving welfare-friendly approaches of data collection from the herd.

Animal welfare can be quantified using a combination of diverse, minimally invasive measurements including changes in heart and respiratory rates, pupil dilation, behavioral changes, and by detecting hormone levels in their biological system via blood, urine, and saliva. Hair samples are commonly utilized to assess the long-term stress levels of animals because of their reliability and the ease of acquisition of hair samples (Heimbürge et al., 2019). Biomarkers found on the hair samples can be indicative of a variety of potential stressors, to include pathological conditions, but variation occurs with the age, sex, and production level of the animal, i.e., pregnancy (Heimbürge et al., 2019). In addition, physiological changes in the animal can be evaluated to quantify stress. Animal care has been a topic of controversy for years and many techniques and studies have been performed to increase our understanding of animal husbandry and food production. Bruising of carcasses indicates inferior animal care pre-slaughter and decreases carcass value and profits at slaughter (Huertas et al., 2015). Commonly, bruising will occur during loading, transport, or unloading of the animals. A recent study showed that animal welfare training for truck drivers decreased the amount of deep/severe bruising (Huertas et al., 2018). Bruising caused in transportation increases cortisol in animals (De Freslon et al., 2014). Short-term transportation and holding systems elicit changes in stress response in cattle (Odore et al., 2010).

In a study performed in 2010, one group of cattle were raised in a tie-barn and another in a loose-housing system (Odore et al., 2010). In this study, hormone concentrations were evaluated by sampling the blood of the two groups to study the blood serum changes that were induced by stressors. Those in the tie-barn showed significant increases in blood cortisol levels, whereas the loose housed group did not. Both groups had significant increases in blood cortisol concentrations when transported on a double-decker truck for 45 min. In a later study, heifers were given oxytocin injections to observe endocrine system modulation of blood serum cortisol concentrations as compared to untreated groups (Barros et al., 2016). The use of exogenous oxytocin induced a reduction of serum cortisol levels in the treated heifers. Utilizing hormones as an indicator of animal welfare is valuable for the improvement of animal well-being and improving livestock rearing practices.

Within the United States, the FDA provides information for all approved hormonal products, implants specifically, which can enhance efficiency and productivity of the animal. Hormones used in the food animal sector undergo testing to demonstrate their safety. Manufacturers of these drugs are required to demonstrate that hormones are present in animal tissues at appropriate levels; appropriate meaning that it is present at a level that should not cause detrimental effects on human health after ingestion. Information for each of these implants is available in the Code of Federal Regulations, Title 21, in parts 522 and 556. In a survey study performed in 2013, more than 80% of veterinary practitioners agreed that hormones improve fertility and farm business profitability, but suggested that improvements in herd genetics and welfare could combat fertility issues that producers experience (Higgins et al., 2013). However, other countries do not share the same views as the United States when it comes to the use of hormones in animal production. Much of the European Union has placed a ban on hormone used for promoting growth (Stephany, 2001). The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) set global standards for food additives like contaminants, drugs, and toxins. They set limits to these hazards and risks such that producers can market their products world-wide if they fit within the given limits or standards. While we are always seeking to improve livestock management and care practices, welfare is always at question.

Castration and disbudding of calves are common practices among most livestock operations and they can be painful procedures (Rodriguez-Martinez et al., 1997). The efficacy of an anti-gonadotrophin-releasing factor vaccine vs. band castration methods has been explored. In one study, calves that were treated with the vaccine had a higher average daily gain and final body weight than that of the banded calves (Marti et al., 2015). It was also found that undesirable sexual and aggressive behaviors were appropriately reduced in the vaccinated group (Marti et al., 2015). These positive results make the animals easier to manage, improve growth, and thus enhance production. Disbudding reduces injury among the mature animals and others in day-to-day life making it easier to work with the cattle in a production setting. In a study performed in 2015, calves were given firocoxib, a non-steroidal anti-inflammatory, or placebo of saline solution to evaluate animal stress indicators after disbudding (Stock et al., 2015). Within the first 24-h period, no differences in cortisol were noted between the treatment and placebo groups. Calves in the placebo group showed increased levels of cortisol 48 h after the procedure had taken place. Utilization of hormones in the beef and dairy industry is growing and has proven to increase productivity and welfare in several areas. Adopting the best practices of animal welfare in cattle production and educating the consumer to these benefits will have a positive impact on the cattle industry.

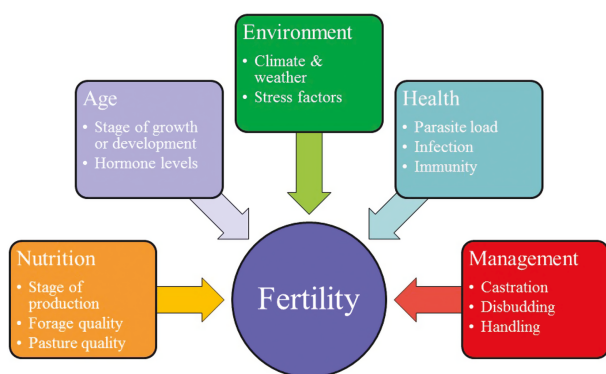
## Hormones and Economically Important Traits for Cattle Production

### Fertility

High fertility is defined as the ability to produce viable offspring and it is essential for reproductive efficiency in cattle production. Heritability of some reproductive traits is only 5%–10%, and they can be influenced by environmental

factors such as housing, management, nutrition, transportation, and climate (Figure 2). Scrotal circumference can be an indicator of reproductive productivity and value when evaluating a bull for breeding purposes. Scrotal circumference is a highly heritable trait in *Bos taurus* cattle with a range of 0.36 to 0.71 (Latimer et al., 1982; Bourdon and Brinks, 1986; Morris and Wilson, 1997). Scrotal circumference in sires is also correlated with earliest onset of puberty in that sire's daughters (Smith et al., 1989). Bull fertility may be defined as the ability to produce viable, motile spermatozoa that can successfully fertilize and activate the ovum and support subsequent embryo development. In males, spermatogenesis, testosterone production, and testicular function play key roles in fertility. On average, blood serum testosterone levels in a healthy bull will range from approximately 0.47 to 4.04 ng/mL (Santos et al., 2004; Souza et al., 2011; Bolado-Sarabia et al., 2018). Ranges will vary among breed, season, and age. Bulls, for example, that have been immuno-castrated will have lower blood serum testosterone levels of approximately 0.22 ng/mL (Bolado-Sarabia et al., 2018). These factors can be analyzed via a breeding soundness exam. Bulls must have normal sperm morphology and motility, semen samples should be free of foreign materials such as blood or urine, and the animal should be healthy and free disease, injuries, or major conformational defects. When turned out with females, bulls must have the libido to service the herd and the ability to mount the females.

In cows and heifers, fertility is the ability to enter the estrous cycle and successfully maintain pregnancy until calving and maintain calving pattern. Calving intervals tend to fall within a 12- to 13-month timeframe (Arbel et al., 2001). For beef cattle, females begin to re-cycle and be rebred within 45–60 d of calving to maintain this calving interval. In dairy cattle, it is important for females to rebreed approximately 60 d postpartum to maintain production goals. However, this may take longer time in some situations such as high producing dairy cattle. The estrous cycle is composed of four phases: estrus, metestrus, diestrus, and proestrus. Proestrus and estrus comprise the follicular phase and are characterized by an increase in estrogen production by the granulosa cells in the follicles. Estrus, commonly known as “standing heat,” occurs when the female is receptive to breeding, estrogen levels are heightened, and a dominant follicle releases an oocyte. For breeding with artificial insemination (AI), the



**Figure 2.** Factors influencing fertility. A multitude of factors can affect the fertility of an individual animal. Nutrition, age, environment, health, and management play a role in contributing to the success or hindrance of fertility.

highest conception rates are obtained during the last half of standing heat (O'Connor, 2016). Metestrus is the period between ovulation and the formation of the corpus luteum (CL). Diestrus is known for the characteristic presence of a fully functional CL on the ovary, high levels of progesterone of approximately  $\leq 4.5$  ng/mL serum, and a lack of reproductive behavior (Snook et al., 1971). Metestrus and diestrus comprise the luteal phase, with diestrus being the longest. If the female is not bred, PGF2 $\alpha$  causes the CL to regress, and the female enters proestrus which resets the estrous cycle (Senger, 2012). It is critical to properly manage estrous cycles and the beginning of puberty because with an earlier onset of puberty and proper management of heifers, females can be reproductively active and efficient for a longer productive life as a cow and provide greater profits.

Hormones play critical roles in the endocrine regulation of the reproductive system and overall fertility of mammals. Puberty is initiated by Kisspeptin, produced by the hypothalamus, which stimulates the production and secretion of GnRH which in turn signals the release follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary (Ahmed et al., 2009). These glycoproteins target the gonads to support gametogenesis and induce certain reproductive behaviors (Kumar and Sait, 2011). In females, FSH targets the ovary to initiate the development of the ovarian follicle and stimulates granulosa cells to produce estradiol (E2), which induces estrus. Additionally, the CL is responsible for producing progesterone (P4) which is responsible for allowing the endometrium to accommodate the developing fetus. The PGF2 $\alpha$  is secreted by the endometrium and targets the CL, resulting in regression and thus decreasing P4 secretion if attachment of the hatched blastocyst after the elongation has not occurred (Papich, 2016). The LH targets the theca interna and luteal cells to regulate ovulation in females (Shoham, 2002). In males, FSH targets the testes, specifically the Sertoli cells, which support spermatogenesis. The LH targets the Leydig cells to produce testosterone in males, which is responsible for libido, development of secondary sexual traits associated with puberty, and support of spermatogenesis (Chen et al., 2009).

The dairy cattle industry relies heavily on the use of assisted reproductive technologies for estrous synchronization, AI, and embryo transfer (ET) to improve productivity and efficiency of their herds. A dairy cow, on average, stays in the milking herd for approximately 305 d a year and spends 60 d in the dry herd. This number can vary from farm to farm and there are documented advantages to shorter and longer dry periods (Bar-Anan and Soller, 1979; Holmann et al., 1984; Dijkhuizen et al., 1985). Estrous synchronization is a valuable tool in bringing non-cycling, anestrus, females into heat. The Ovsynch protocol series of hormonal injections is the preferred estrous synchronization protocol in the dairy industry (Carvalho et al., 2018). For this protocol, the producer administers an injection of GnRH and inserts a CIDR on day 0 and then removes the CIDR and gives an injection of PGF2 $\alpha$  on day 7 (Pursley et al., 1997). Forty eight hours after the injection of PGF2 $\alpha$ , the producer administers a second injection of GnRH, followed by the timed AI 8 to 18 h after the second injection of GnRH (Pursley et al., 1997).

The Ovsynch protocol can eliminate the need for heat detection. This is due in part to the reductions of labor inputs by synchronizing all the cows onto the same breeding schedule while also reducing missed heats. However, producers should

observe their herd for signs of estrus even when utilizing an Ovsynch protocol to reduce the potential for missed services. The Ovsynch protocol yields 30%–40% pregnancy rates and variation in success can be contributed to factors such as heat stress and parity (Cartmill et al., 2001; Tenhagen et al., 2004). To further bolster the effectiveness, producers may choose to administer two treatments of PGF2 $\alpha$  2 wk apart to encourage a full luteal regression before the onset of the Ovsynch protocol, thus improving subsequent pregnancy rates (Borchardt et al., 2018). Timed AI yields a higher pregnancy rate per treatment than breeding on visual signs of estrus only (Celeghini et al., 2008).

The beef cattle industry has been slow to adopt assisted reproductive technologies, with only 7.6% of beef cattle producers utilizing these programs (Lamb and Mercadante, 2016). The reluctance to use assisted reproductive technologies by this sector of the industry has been attributed to variable pregnancy rates among other factors. The average pregnancy rate from the 7-d Co-Synch + CIDR timed AI is around 50% (Larson et al., 2006). These variable rates deter beef producers from adopting these technologies because herd bulls can achieve greater conception rates. However, the 50% pregnancy rate is the percentage of the herd getting pregnant on a single day, early in the breeding season. Therefore, calves are weaned at heavier weights and females are more likely to calve early, allowing them more time to be bred in the next breeding season, increasing profitability of the herd. The 7-d Co-Synch timed AI is the most common estrous synchronization protocol used among beef cattle producers (Geary et al., 2001). In a traditional 7-d Co Synch + CIDR timed AI protocol, an injection of GnRH is administered and a CIDR that supplies progesterone is inserted on day 0. On day 7, the CIDR is removed and an injection of PGF2 $\alpha$  is administered. Sixty to 66 h after the injection of PGF2 $\alpha$  and CIDR removal, the producer can perform timed AI and administer GnRH to ensure the timing of ovulation. This protocol eliminates the need for heat detection requires the producer to work their cattle through the chute only 3 times, and yields pregnancy rates comparable to Ovsynch (Pursley et al., 1997; Geary et al., 2001).

Additionally, it is important to know that cattle that are predominantly *Bos indicus* or *Bos indicus*-influenced will not respond as well to hormone protocol compared to *Bos taurus* cattle. Other protocols have been developed for *Bos indicus* breeds and crosses (Sá Filho et al., 2009; Oliveira et al., 2019; Madureira et al., 2020). Beef cattle producers who have adopted assisted reproductive technological protocols are often elite seedstock and club calf producers. In other countries, assisted reproductive technologies such as estrous synchronization, timed AI, ET, and somatic cell nuclear transfer (SCNT) are more widely adopted compared to those in the United States.

### Growth and development

Economically efficient cattle production is dependent on the rates of fetal development, growth, age at puberty, and development of desirable carcass traits; all of which are under the influence of the GH axis (Armstrong et al., 1995; Jenkinson et al., 1999). The loop of this axis starts at the hypothalamus, where GHRH is secreted and travels to the anterior pituitary to stimulate the release of GH (Carter-Su et al., 1996). When GH reaches the liver and other target tissues, it stimulates the secretion of IGF-I (Laron, 2001). The IGF-I signals its target

tissues to promote bone proliferation, muscle development and growth, and the breakdown of adipose tissue (Carter-Su et al., 1996). The IGF-I is produced throughout life, but it is at its greatest synthesis and secretion levels during periods of growth. Once IGF-I reaches a threshold concentration in circulating blood, they signal the hypothalamus to secrete growth hormone-inhibiting hormone (GHIH; also called somatostatin) which decreases or stops the release of GH from the anterior pituitary (Jenkinson et al., 1999). During animal growth, cells in tissues and organs, including bones and muscles, proliferate and change the body weight, composition, and fat deposition in animals.

The maintenance and regulation of the GH axis is directly responsible for the process of growth in the body (Devesa et al., 2016). It has been previously demonstrated that growing cattle immunized with a GHRH antagonist experienced a decreased rate of gain, reduced skeletal muscle, increased fat deposition, and decreased feed efficiency (Simpson et al., 1991). In the cattle industry, producers expect cattle to consistently reach certain body weights at specific time points in the production process. For example, d205 weight, yearling weight, and average daily gain are common variables used by producers to determine input costs versus potential value of their cattle. At these time points, the concentrations of GH in the blood of these animals are greater due to GH being elevated in early life and puberty when rapid growth occurs. The influence of the GH axis during fetal development is still unclear. Exogenous GH has been demonstrated to increase fetal weights during late gestation, but placental size was not altered, suggesting that GH plays a vital role in late gestation fetal growth (Jenkinson et al., 1999). Cows supplemented with GH in the third trimester had increased levels of GH in their colostrum, which resulted in calves absorbing more growth factors and hormones (Phomvisith et al., 2017). The concentrations of GH in colostrum affect calf growth and development beyond puberty. GH is responsible for body composition, more specifically the bone: muscle: fat ratios which ultimately defines the value of an animal's carcass at slaughter.

In the beef industry, hormonal implants are used in both yearling stocker operations and feedlots to increase the rate of growth and improve body composition in finishing steers and heifers (Stewart, 2013). Implants contain a mixture of synthetic estrogen and testosterone, such as zeranol and trenbolone acetate (Stewart, 2013). These exogenous hormones upregulate production of GH in implanted cattle, which leads to quicker closure of bone plates and therefore allows the animal to begin putting on muscle and formation of desirable fat deposits, such as intramuscular fat or marbling (Meinhardt and Ho, 2006). Cattle treated with these implants consistently have increased average daily weight gain and improved muscle to bone growth ratio, larger rib-eye area, and a leaner carcass (Huck et al., 1991). Androgenic implants are used in heifers, estrogenic products are used in steers to increase feed efficiency and daily gain, up to 5%–15% and 25%, respectively (Perry et al., 1991; Dunshea et al., 2005). Moreover, estrogenic or androgenic implants play a significant role on pre-weaning growth of cattle. Beta agonists manipulate the metabolism of fat by promoting the breakdown and usage of fat, therefore decreasing the fat composition of the carcass, leading to a leaner, more desirable cut (Muir, 1988). Growth promoters increase protein synthesis in the muscle and decrease rates of fat deposition in muscle. Additionally,

growth hormones can impact meat palatability and tenderness score, positively or negatively. The manipulation of GH through alternate pathways can be beneficial in increasing the profitability of an animal. However, due to recent consumer concerns, less invasive and more natural mechanisms of altering growth need to be explored.

The demand for high quality food continues to rise but the amount of land for production is declining. This strain on the environment and limited resources also raises the concern of greenhouse gas emissions created by cattle production. Research has shown that cattle actually produce less greenhouse gas emissions as compared to the combustion of the feedstuffs or agricultural byproducts they consume (Rusomano et al., 2012). This serves the environment well and demonstrates the ecological importance of supporting the livestock industry due to the utilization of by-products that would ultimately be wasted. Growth-promoting technologies have been used for many years in the cattle industry to enhance feed efficiency and weight gain with initial investigations in the efficacy of growth promotors, like somatostatins, beginning as early as the 1920s in rodent models and livestock models in the 1950s (Turman and Andrews, 1955; Brumby, 1959; Courtheyn et al., 2002). Use of exogenous hormones may aid in the reduction of greenhouse gas released by increasing productivity of livestock which would reduce herd sizes. Research is needed in this area to provide a greater insight into the potential for success of exogenous hormones on the reduction of greenhouse gas production by cattle.

Producers can increase the production efficiency of their cattle by targeting the GH axis. Currently, there are implants, feed additives, and exogenous GH injections available to cattle producers to increase animal growth. The rBST is an injectable synthetic form of GH that increases milk yields in dairy cattle by providing more nutrients to the mammary gland stemming from the elevated levels of circulating IGF-I (Bauman and Currie, 1980). Treating dams with rBST 124–220 d post-partum leads to increased milk yield and heavier calves being weaned without compromising reproductive efficiency (Armstrong et al., 1995). In 1993, the FDA approved Monsanto's rBST, Posilac, for commercial use. In the first 20 yr of its approval, over 35 million dairy cows received rBST (Collier and Bauman, 2014). Due to consumer misconceptions, the usage of rBST in the dairy industry has become stigmatized, thus drastically decreasing usage in recent years (Kecinski et al., 2018). Contrary to the negative connotations, rBST could be of great value when it comes to the reduction of feed additives for dairy cattle (Capper et al., 2008). It has been demonstrated that the use of rBST can increase milk yields without hindering pregnancy rates in Holstein cattle under heat stress conditions (Jousan et al., 2007). This increased productivity means that there is potential for a reduction in herd size, thus reducing the carbon footprint of the herd.

### Animal health

The health of cattle depends on a diverse array of environmental factors including nutrition, reproduction, and management styles. Animals become ill when the pathogen load exceeds what their immune system is capable of thwarting. The structure of the ruminant placenta restricts calves to minimal antibodies at birth, which makes it imperative that calves receive quality colostrum within 24 h of birth. The main immunoglobulin found in colostrum is immunoglobulin G1 (IgG1), along with other components such as cytokines

and leukocytes (Chase et al., 2008). Once ingested, high levels of corticosteroid allow the colostrum to be absorbed by the calves' intestinal cells, initiating the early developmental of their immune system (Sangild, 2003). Leukocytes work to develop antigen-presenting cells, important for immune responses to pathogens and vaccines. However, newborn calves do not receive all the immunoglobulins from maternal colostrum that are necessary to develop full immunity; therefore, vaccines are administered within specific time-frames to aid in immune system development (Weaver et al., 2000).

When cattle experience changes in their homeostatic balance, they become stressed. Stress is defined as behavioral and physiological changes caused by stimuli that affect an organism's well-being (von Borell, 2001). Exposure to stressful environments triggers hormonal responses from the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Stewart et al., 2010). When stressed, the sympathetic nervous system, via the ANS, is activated and results in the "fight or flight" response. This response could be short or fast in its nature and is driven by the catecholamines (epinephrine, norepinephrine, and dopamine) synthesized in the adrenal medulla. Epinephrine and norepinephrine have a half-life of approximately 0.25 to 1.0 min and are responsible for increasing energy supplies, heart rate, respiratory rate, vasoconstriction, and vasodilation (Jones and Robinson, 1975; Stewart et al., 2010).

Detecting the presence of cortisol in animal products and secretion concentration in live animals can also determine whether animals were subjected to chronic levels of stress (Nemeth et al., 2016; Heimbürge et al., 2019). The parvocellular neurons in the hypothalamus secrete CRH and arginine vasopressin (VP) to initiate the HPA cascade (Whitnall, 1993). The CRH and VP cause the release of ACTH from the anterior pituitary that binds to the melanocortin receptors in the cortex of the adrenal glands to produce glucocorticoids. The main glucocorticoid is known as cortisol, and it acts on liver, muscles, and adipose tissue to supply the organism with fuel during stressful conditions. In comparison to the brief half-life of catecholamines, cortisol plasma clearance takes a longer amount of time. In one study, cows returned to basal cortisol concentrations 120 min after exposure to the milking machine (Negrão et al., 2004). This type of investigation strengthens the value of using salivary and plasma cortisol measurements as indicators of fear, stress, pain, or discomfort in cattle.

Adversely, an increase in glucocorticoids is related to a decrease in the immune system function. It has been found that calves that are suddenly weaned experience an increase in plasma cortisol and noradrenaline concentrations, along with a corresponding reduction of the immune function (Hickey et al., 2003). Calves exposed to early stress could experience compromised immune function; therefore, research is evaluating the use of non-steroidal anti-inflammatory drugs (NSAID) during stressful conditions to reduce pain or discomfort and support the immune system. For example, Meloxicam administration during knife castration or castration and branding was shown to mitigate the pain related to these management practices in cattle (Meléndez et al., 2018). In addition, pregnant dairy cows exposed to heat stress during late gestation had calves with lower birth weights. These offspring, when mature, produced less milk in the first lactation as compared to the offspring from non-heat stressed cows (Monteiro et al., 2016). These results suggest that even exposure to stress while

in utero has detrimental consequences upon offspring which could be related to an increase in stress hormones during gestation.

Higher levels in stress hormones, such as cortisol, epinephrine, norepinephrine, and dopamine, influence cattle physiology and behavior, such as a temperament-display of a more nervous behavioral pattern as evaluated by their exit and pen scores (Sánchez-Rodríguez et al., 2013). Additionally, previous research has indicated that temperamental beef cows have higher cortisol levels and reduced pregnancy and calving rates as compared to less temperamental cows (Cooke et al., 2012). Previous studies have demonstrated an increase in fetal plasma cortisol concentrations caused by maternal uterine blood flow reduction (Bocking and Harding, 1986; Sue-Tang et al., 1992). An increase in this corticoid initiates parturition by enabling the placenta to synthesize PGF<sub>2</sub> $\alpha$ , leading to CL regression and myometrial contractions (Senger, 2012). Such an increase in fetal cortisol could cause pregnancy termination at any stage of gestation (Giri et al., 1990). Animals exposed to hot environments have increased cortisol concentrations, causing higher body temperatures (Dobson and Smith, 2000). Animals with higher body temperatures showed a reduction in uterine blood flow and an increase in peripheral blood flow in order to increase heat dissipation (West, 2003). Studies evaluating cow-calf separation have shown that calves tend to have higher cortisol levels than that of their dams when removed from one another (Acevedo et al., 2005; Newberry and Swanson, 2008). However, when restricted suckling protocols are utilized, calves can acclimate to their routines quickly and stress parameters decrease (Rasby, 2007; Orihuela and Galina, 2019). By using this technique in conjunction with the use of familiar surroundings and/or pen mates, calves are able to transition away from their dams in a less stressful manner (Færevik et al., 2007; Newberry and Swanson, 2008). Thus, an increase in plasma cortisol concentrations can have profound influences on reproductive health, performance, and behavior.

### Production

Hormones play a vital role in the growth, development, reproduction, and social behavior of both beef and dairy cattle production sectors. Carcass traits are economically important and include quality grade, yield grade, ribeye area, and back fat thickness. Quality grade is determined by the amount of marbling on the surface of the ribeye between the 12th and 13th ribs (Hale et al., 2013). Marbling, or intramuscular fat, is the dispersion of fat within lean tissue (Griffin and Savell, 2018). The more marbling the ribeye contains, the higher quality grade the carcass receives. Yield grade is the estimate of trimmed retail cuts that a carcass is likely to yield. It is determined by external fat thickness, percentage of internal fat, ribeye size, and carcass weight. Yield grades are denoted on a 1 to 5 scale (Hale et al., 2013). The lesser the yield grade, the leaner the carcass. Carcasses with a yield grade higher than 3 are oftentimes discounted. Ribeye area is the surface area of the longissimus dorsi muscle which is sectioned between the 12th and 13th ribs. This area is the last location on the carcass where muscle and fat deposited. Back-fat thickness is measured as the amount of fat between the 12th and 13th ribs. The muscle of beef cattle is composed of water, high-quality protein, carbohydrates, B vitamins, iron, zinc, phosphorous, selenium, omega-3 polyunsaturated fats, riboflavin, and pantothenic acid. Red meat generally is low

in fat content, it is highly digestible protein, and it contains many vitamins and minerals that are essential for human health (Holt et al., 2007).

Composition of meat varies based on the animal's breed, age, gender, plan of nutrition, and environment. However, carcass traits can be manipulated using hormones which may improve qualities for ever-changing consumer preferences. Growth hormone is essential for growth and development and ultimately impacts carcass traits because GH increases muscle mass and strength, bone density and cardiac output, and decreases adipose tissue accretion (Velloso, 2008; Bartke et al., 2013). Estrogen, progesterone, testosterone, zeranol, and trenbolone acetate are hormones that are approved for use in implants for cattle in the beef industry by the FDA. These hormones promote muscle growth at the expense of fat deposition with less feed consumed, thereby allowing cattle producers to produce leaner beef with fewer resources (Johnson et al., 2013). They reduce production cost and number of animals required, allowing for price competitiveness of beef with other forms of protein. Implants increase growth rates 8% to 20%, improve feed efficiency 5% to 20%, as well as increasing lean tissue mass by 3% to 10%. The hormones are metabolized and excreted by the animal, ensuring that there are no residues in edible tissues (Johnson et al., 2013). When the time comes for slaughter, there can be issues with dark cutting. When a carcass cuts dark, there has been a great amount of physical stress to that animal prior to slaughter. The muscles become depleted of glycogen. Under normal circumstances, glycogen would convert to lactic acid and allow for the pH to drop to a more acidic level. Without enough glycogen, the conversion cannot take place and allow for the pH to change. This alters the meat quality, making it unacceptable for human consumption.

Milk production begins with the growth of the mammary gland, which is stimulated by GH, prolactin, estrogen, and progesterone (Lacasse et al., 2016). GH and prolactin facilitate the rapid proliferation of mammary cells to prepare the gland for lactation and increases blood flow and glucose levels in the mammary tissue. Oxytocin facilitates the letdown of milk when the udder is stimulated by a calf suckling or by a producer that is cleaning and prepping the teats prior to milking (Akers and Lefcourt, 1984). Nutrients from non-mammary tissues are redirected to the mammary system by GH, prolactin, and leptin. Prolactin increases the absorption of calcium and facilitates the uptake of long-chain fatty acids for milk fat synthesis (Ajibade et al., 2010). Leptin plays a regulatory role in energy metabolism by stimulating energy expenditure and suppressing food intake (Block et al., 2001; Morrison et al., 2001; Liefers et al., 2003). Produced by adipose cells, high levels of leptin stimulate the hypothalamus to suppress hunger.

### Hormones in Food Animals and Human Health

Since the early 1950s, exogenous anabolic promoters have been used to improve feed efficiency, weight gain, and milk yield of cattle in the U.S. Exogenous growth promoters including anabolic hormones (androgens), estrogens, glucocorticoids, progestogens, and synthetic compounds, such as TBA and MGA (Yang et al., 2009). For instance, MGA is a feed additive that is fed to suppress estrus cyclicity of heifers in a feedlot setting. Once these exogenous hormones are administered, the cow's system utilizes the time-released effect by



absorption through epithelial cells of the ear, or muscle tissue in the neck, thence to the blood where it is transported to various target tissues and organs. Once these exogenous hormones reach the target tissues or organs, the tissues respond to produce the outcome of increased growth, milk yield, or fat deposition in cattle. From the application of exogenous hormone promoters in the beef and dairy industries, consumers express growing concern that the hormones may be impacting the environment, quality of food products, and human health (Wandel and Bugge, 1997).

As a result of consumer concerns on the uses of exogenous hormones in the livestock industry, there has been a growing concern of residual hormones in beef and milk and their effects on human health and the environment. These health concerns include a slightly younger age of pubertal onset in girls and an increase in estrogen-related diseases attributed to the excessive consumption of animal proteins like milk and meat (Yermachenko and Dvornyk, 2014). However, research has demonstrated that the tissues of calves, steers, and heifers treated with exogenous growth hormone promoters, such as estradiol, testosterone, and progesterone, when given at proper administration levels, do not lead to toxic or harmful levels of hormonal residues in their tissues (Hartmann et al., 1998; Jeong et al., 2010). For example, the average man produces 210 to 480 µg/d of testosterone (Joint FAO/WHO Expert Committee on Food Additives, 1999). In non-hormone-treated animals, residues will range from about 0.006 to 0.029 µg/kg, whereas hormone-treated animals will have residues ranging from 0.031 to 0.360 (Paris et al., 2006). When treated meat is ingested, the present residues will range from about 0.0093 to 0.108 µg/d (Paris et al., 2006). These research findings indicate that effects of implanting, orally supplementing, or injecting beef and dairy cattle with these exogenous hormones apparently have no carry-over effects on human health. The use of these exogenous hormones in the livestock industry is not the cause of human disease or the effects on human health.

Due to the current market trend towards organic products, producers are having to eliminate the use of hormones in their herds to ensure the profitability of their milk and milk products (Kolodinsky, 2008). Milk yield is the most monitored trait in the dairy production sector. Hormones are necessary for milk production for a number of reasons. Milk is composed water, fats, proteins, lactose, vitamins, and minerals, including the most abundant ones of calcium and potassium. The diet of the animal greatly affects the composition of milk. The rBST positively affects mammary growth and increases milk production in dairy cattle. rBST has been deemed safe by the FDA both for the cattle receiving rBST and for human consumption; however, it is no longer widely used due to consumer misconceptions. In a survey conducted in 2012, researchers found that consumers were willing to pay more for milk that was rBST-free, but surprisingly the labeling of the milk did not cause a differential effect on how consumers valued the half-gallon size of milk (Wolf et al., 2011).

Use of exogenous hormones, particularly rBST, contributes little to no negative effects on human health. The way these exogenous hormones are administered, how the human body digests them, and the recommended withdrawal periods established by the USDA and the FDA for each of these growth hormone promoters prevents human health effects. Many these hormones are delivered in a pellet form which are implanted under the skin of the ear and are time-released.

The highest concentrations of these hormones are in the ear and are slowly released throughout the animal's body for 90 to 120 d. Once this time period is up, normally during the feedlot phase of the cattle industry, cattle must go through a withdrawal period to allow the residues to be metabolized and excreted from the animal's system prior to harvest (NRC, 1999). In the dairy industry, the FDA has specified no withdrawal period for rBST or when human consumption of meat and milk can occur, thus indicating that there is no scientific evidence of detrimental effects on human health because it is not bioactive upon oral ingestion (WHO, 2013; FDA, 2019). The rBST is a bulky protein that is easily broken down by digestive enzymes in the human gastrointestinal system (FDA, 2019). Furthermore, the human system will not recognize rBST because of its bulky structure as a large protein, and that is distinctly different from human somatotropin (WHO, 2013; FDA, 2019). In conclusion, the human body can metabolize this protein and the residue is not utilized due to its foreign nature. Even as an exogenously supplemented hormone, it does not have any detrimental effects on human development and health.

The use of hormones in beef and milk production is specifically regulated by the FDA which approves an animal drug or hormone after studies have shown that the food products (milk and meat) from treated animals is safe for human consumption, and that the drug/hormone does not harm treated animals, nor the environment (FDA, 2019). Even further, the dairy industry concurring with consumer preferences has implemented a "zero tolerance level," with residual artificial hormones or antibiotics in cow's milk. Milk is regularly tested for minute amounts of artificial hormones and antibiotics before being pasteurized and homogenized to produce dairy consumables: milk, cheese, yogurt, butter, etc. This is not to say that there are no endogenous hormones secreted by the cow itself. Some of these naturally occurring hormones include bovine somatotrophin (bST, or otherwise referred to as GH), E2, P4, oxytocin, prolactin, and IGF-1. In 2018, the FDA determined that hormone concentrations are low in milk and the hormones present are easily digestible by humans. Additionally, milk contains very low concentrations of endogenous hormones, which are not at high enough concentration to elicit detrimental effects on human life or health. However, one of the most predominant estrogens found in cow's milk, estrone, has been quantified in low quantities in milk as compared to other more concentrated products such as butter or yogurt (Hartmann et al., 1998; Ganmaa et al., 2004).

## Conclusions

Sustainable, efficient, and profitable production of cattle, the key livestock for meat and milk production, is essential for feeding the globe. Synthesized within and secreted from the endocrine glands, hormones are critical for animal life in addition to the production of cattle with economically important traits and wholesome meat and milk. An increase of stress hormones in livestock production leads to a decrease in meat quality and milk yield and affects behavior and temperament resulting in problems in farm management and animal welfare. So, hormones can be measured to determine the status of animal welfare and to develop the best production systems. Also, hormones can be used to increase quantity and quality of meat and milk. For example, GH is an economically important hormone that aids in lean muscle accretion,

decreases in adipose tissue deposition, and increases in overall efficiency of the animal. Further, GnRH, P4, and PGF2 $\alpha$  can be used in combination to improve reproductive efficiency through synchronizing estrus. Commercialized forms of hormone products such as Factrel, CIDR, and Lutalyse can aid in decreasing labor costs. Through hormone biotechnology, efficiency of cattle reproduction and production as well as product quality can all be increased to improve food security on a global scale.

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## Conflict of Interest Statement

The authors declare no real or perceived conflicts of interest.

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