Influence of nutrition, body condition, and metabolic status on reproduction in female beef cattle: A review

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ABSTRACT

Nutrition is of fundamental importance in reproductive function of female beef cattle. Nutrition determines live weight (LW) and body condition score (BCs) and both were found more than 50 years ago to underpin fertility in pubertal heifers and postpartum cows. In heifers, LW at weaning and average daily gain (ADG) after weaning determines age and LW at puberty, and subsequent lifetime fertility. In cows, BCS at parturition is the most important factor that determines the period to re-conception postpartum. Nutrition establishes systemic metabolic homeostasis. Metabolic hormones such as leptin, IGF1 and Ghrelin act as signaling factors that regulate activity of GnRH neurons in the hypothalamus. The release of GnRH and function of the reproductive

endocrine system is determined by the balance of positive signals (IGF1, leptin) and negative signals (Ghrelin) at GnRH neurons. Metabolic factors also directly influence ovarian follicles, oocytes and embryos. Saturated fatty acids (FAs) are detrimental to oocytes and embryos whilst unsaturated FAs may be beneficial. The ratio of FAs (saturated, monounsaturated, polyunsaturated) is likely the key to optimal reproductive function. Nutrition controls the levels of metabolic hormones (leptin, IGF1, Ghrelin) and metabolic factors (FAs) and both have major roles in reproduction in female beef cattle.

1. Introduction

Wiltbank and colleagues were the first to report that reproductive function in female beef cattle is strongly influenced by nutrition [1]. Mature Hereford cows fed a high energy diet before and after calving had a substantially greater re-conception rate than cows fed a low energy diet [1]. Whitman [2] conducted a separate analysis using the same data which showed the body condition of cows at calving was the key determinant of postpartum re-conception, rather than changes in live weight (LW) before and/or after calving. These landmark studies stimulated global research on the interrelationships between nutrition, metabolic condition, and re-conception in the postpartum cow.

Young heifers are highly important for continued genetic improvement in beef production systems. Proper nutritional management of heifers early in life is critical for age at puberty and lifetime reproductive performance [3-6]. Indicators of future fertility are LW at weaning and average daily gain (ADG) after weaning [7-9]. Optimal timing of puberty in beef heifers requires an ADG of 0.6 to 0.7 kg/day [7].

In heifers [10,11] and cows [12,13] nutrition determines systemic metabolic homeostasis and it also regulates the ratio of adipose tissue and muscle. Metabolic hormones from adipose (leptin), liver (IGF1) and gut (Ghrelin) are now recognized as major regulators of reproductive function in females [10,14-16].

The present paper brings together studies on nutrition, body condition, metabolic status, and reproduction in heifers and cows. There has been a progressive increase in understanding of how nutrition establishes the balance of metabolic hormones which act at the brain to exert control of the reproductive endocrine system [17]. Nutrition also influences the amounts of metabolic substrates that act directly at ovarian follicles, oocytes and embryos. The paper cites early studies which have remained fundamental and stimulated research that has produced major advances in the nutritional management of female beef cattle for fertility. Many of the references are highly cited in the literature and have been brought together for the first time in the present paper.

2. Young heifer

Reproductive organs are the last major organs to develop and therefore can be influenced by nutrition and LW early in life [18]. Nelore (*Bos indicus*) heifers that reached puberty had a higher reproductive tract score (RTS) compared with heifers that had not reached puberty [9,19]. Other studies in beef heifers reported that RTS at first mating was associated with a higher pregnancy rate, greater calf weaning weight, and higher re-conception at the second mating [20,21]. In one study, a combination of RTS and pelvic area provided a better prediction of fertility than RTS alone [22].

The nutritional management of *Bos taurus* beef heifers to attain puberty, conceive, and achieve first calving at around 2 years is highly important as it optimizes lifetime reproductive performance [6,23]. As already noted, LW at weaning, and ADG after weaning, are strongly related to age and LW at puberty [7,8]. *Bos indicus* (Brahman) heifers on improved pastures achieved puberty at an earlier age than heifers on standard pastures [11]. Similarly, Nelore (*Bos indicus*) heifers that received a feedlot diet after weaning reached puberty earlier than the breed average [24]. Improved nutrition after weaning reduced age at puberty in Nelore heifers genetically selected for delayed puberty; however, puberty still occurred later than in heifers genetically selected for early puberty [25]. Nutrition and LW gain in young heifers is related to the deposition of adipose tissue and BCS [19]. Heifers with improved feed conversion efficiency tend to be relatively lean and reach puberty later than the breed average [26]. This presents a potential dilemma in the genetic selection and breeding of efficient cattle for improved sustainability, but without compromising fertility (see Section 4).

3. **Postpartum cow**

The resumption of fertile ovarian cycles after calving is critically important in order for cows to re-conceive and calve annually. Ovarian follicular growth and ovulation during postpartum rely on the re-establishment of normal patterns of gonadotrophin secretion [27]. The secretion of LH is low immediately after calving and a progressive increase in LH pulse frequency and amplitude leads to the first ovulation postpartum [28,29]. Suckling delays the return of LH secretion necessary for ovulation [30,31]. Suckling does not influence the LH response to exogenous GnRH indicating that suckling-induced suppression of LH acts at the brain [32]. Removal of the suckling stimulus by early weaning can be used to induce resumption of cyclic ovarian activity in postpartum beef cows [33,34].

Many studies have looked at the relationship of nutrition and body condition score (BCS) to reproduction postpartum in beef cows. This followed early recognition of the importance of nutrition [35]. It can be concluded from these studies that BCS at calving is arguably the single most important factor linked to the timely resumption of fertile ovulations postpartum [36-39]. Morrison and coworkers [40] reported that changes in LW and BCS in the last trimester of pregnancy were of lesser importance than actual BCS at calving in determining re-conception postpartum in beef cows. Cows with moderate to good BCS at calving can undergo a decline in BCS when suckling postpartum, yet have a higher re-conception rate than cows with poor BCS at calving [41,42]. In fact, cows with poor BCS at calving were reported to lose less body condition postpartum but still had lower fertility [41,42] (Figure 1). Cows with relatively good BCS at calving tend to wean heavier and healthier calves and this has important implications for young heifers destined to become breeders [43]. The BCS of cows provides a good index of subcutaneous fat and metabolic condition [44].

[INSERT FIGURE 1]

4. Feed efficiency and reproduction

Research on feed utilization efficiency in beef cattle was pioneered by Paul Arthur and Robert Herd [45-51]. The efficiency of feed utilization is of fundamental importance in the selection and breeding of cattle that require less input, and therefore less cost, per unit of production output [49]. Feed utilization efficiency in young cattle is a measure of the difference between actual feed intake and the expected intake based on metabolic body weight and growth [52]. This is expressed as net feed intake (NFI) or residual feed intake (RFI) [53]. Differences in RFI among cattle are thought to be due to differences in appetite, digestion, metabolism, thermoregulation and general activity [54-56].

After 1.5 generations of selection for RFI Angus cows with relatively low RFI (good feed efficiency) tended to have less rib fat than cows with high RFI [53]. Similarly, Angus heifers divergently selected for low RFI for 3 generations had approximately 50% less fat at the rump and ribs [56] (see also [26]). Given that adipose mass determines blood concentrations of leptin which has a positive action at GnRH neurons (Section 5), cows and heifers with a low RFI (more efficient) would be predicted to have reduced reproductive performance. Indeed, Angus, Angus crossbred, and Hereford heifers with a relatively high RFI (less efficient) showed earlier puberty than contemporary heifers with a low RFI [57] (see also [26]). A similar finding was reported for Angus-Hereford and Charolais-Maine Anjou heifers [57]. Cows of the latter genotypes with low RFI conceived and calved later than cows with a high RFI [59]. In contrast to these findings of a negative relationship between feed efficiency and fertility in heifers and cows, Arthur and coworkers [53] did not find a relationship between RFI and reproductive performance in Angus cows. Blair and coworkers [60] also did not find a relationship between RFI and fertility in Angus heifers sired by either low RFI or high RFI bulls. Notwithstanding the latter studies, it is biologically sound to hypothesize that female cattle with high feed utilization efficiency (low RFI), associated with reduced adipose tissue and reduced leptin in blood [61-64], would have lower fertility. Fertility and calving rate are main drivers of profit in beef enterprises and these traits are in potential conflict with the selection of cattle for feed utilization efficiency. There is an urgent need for research on how improvements in feed utilization efficiency can be achieved without compromising fertility in breeder cattle.

5. **Metabolic hormones and reproduction**

The central role of the liver in modulating reproductive function in females through secretion of IGF1 is arguably the best understood relationship between a metabolic organ and reproduction. Ovarian follicles have an absolute reliance on blood derived IGF1 to complete growth and maturation before ovulation [65-67]. At cells, IGF1 binds to IGF1 receptors (IGF1R) and IGF1R haplotypes are associated with age at puberty in Brahman heifers [68]. Brahman heifers [13] and postpartum Droughtmaster cows [14] on improved subtropical pastures had elevated blood IGF1 which was associated with earlier age at puberty and shorter postpartum anestrus, respectively. Elevated IGF1 early in life was related to earlier onset of puberty in Parda de Montaña and Pirenaica beef heifers [69,70]. Relationships between disorders of the liver and ovarian function have been extensively studied in dairy cows. In the 'fat cow syndrome' [71] fat accumulates in hepatocytes and disrupts normal liver function. This leads to reduced secretion of IGF1 and a lack of normal ovarian follicular activity [72]. Cows in positive energy balance have greater blood concentrations of IGF1 compared with cows in negative energy balance that have reduced IGF1 [73-75]. Negative energy balance and reduced IGF1 is associated with reduced fertility [73-75].

Adipose is an important endocrine tissue that impacts reproduction primarily through leptin [76,77]. Arguably the most important role of leptin in beef cattle is control of the onset of puberty [78]. Leptin acts through the receptor GPR54 which is present on kisspeptin (KISS1) neurons in the hypothalamus [79,80]. Kisspeptin binds to GnRH neurons and stimulates GnRH release [81] (Figure 2). As prepubertal heifers grow and mature they deposit adipose which leads to increasing concentrations of leptin in blood. Leptin then reaches a threshold and stimulates sufficient kisspeptin release for pubertal maturation of GnRH neurons. The leptin-kisspeptin-GnRH neuron pathway provides the endocrine explanation for the critical BW hypothesis which links body condition (fat-muscle ratio) to puberty in females [82]. The release of LH after injection of kisspeptin has been demonstrated in cows and heifers [83]. In a recent report, leptin was shown to regulate GnRH receptors on gonadotrope cells in the anterior pituitary gland [84], suggesting that leptin can act at both the brain and pituitary.

[INSERT FIGURE 2]

The hormone Ghrelin is secreted by the gastro-intestinal tract ('gut') and has been implicated as a metabolic signal for feed intake and energy balance [85,86]. Blood concentrations of Ghrelin in cattle are elevated during restricted feed intake and negative energy balance [87,88]. Ghrelin receptors are present in the hypothalamus and it has been proposed that Ghrelin pathways also regulate GnRH neurons.

Insulin and glucose are other metabolic hormones and metabolic factors which are influenced by nutrition and impact on reproduction in female beef cattle [89,90]. Brahman heifers on improved subtropical pastures had greater blood concentrations of insulin and glucose than heifers on standard pastures [11]. Droughtmaster cows that calved in BCS 3.0-3.5 (scale 1-5) had greater blood concentrations of insulin and glucose than cows in BCS 2.0-2.5 [13]. The Brahman heifers on improved pastures showed puberty earlier and the Droughtmaster cows with higher BCS had a shorter postpartum anestrus. Insulin stimulates cellular uptake of glucose which reduces blood concentrations. The finding that insulin and glucose were both elevated in heifers and cows on good nutrition was interpreted to indicate that these animals had a different insulin-glucose metabolic homeostasis setting than their contemporaries on poorer nutrition [11,13]. Parda de Montaña heifers with elevated glucose at weaning had an earlier age at puberty [69]. It was proposed that *Bos taurus* and *Bos indicus* cattle may differ in the effects of insulin and IGF1 on reproductive function [91].

6. Integration of metabolic hormone action at the brain

The mechanisms whereby leptin, IGF1 and Ghrelin interact at the brain to regulate the activity of GnRH neurons are not fully understood. Present information indicates that leptin and IGF1 stimulate GnRH secretion whilst Ghrelin suppresses GnRH secretion. Receptors for IGF1 are found on GnRH neurons and IGF1 can directly influence GnRH secretion [92]. The positive action of leptin on GnRH is mediated by the neuropeptides kisspeptin, galanin-like peptide (GALP) and proopiomelanocortin (POMC, precursor of α-MSH) [93-95]. The negative actions of Ghrelin are mediated by neuropeptide Y (NPY) [96]. This understanding of neuropeptide mediation of metabolic hormone signaling is likely an oversimplification and new information will emerge from further studies [15].

A model for pubertal transition in heifers proposes that before puberty Ghrelin predominates and NPY mediates a suppressive action on GnRH neurons [97] (Figure 3). As heifers grow and deposit adipose tissue, leptin increases and kisspeptin, GALP and POMC collectively start to have a stimulatory action on GnRH neurons. During the prepubertal-pubertal transition the balance shifts to leptin dominance which leads to increased GnRH secretion and activation of the reproductive endocrine system [97-100] (Figure 4). Target of rapamycin (mTOR) and Creb1-regulated transcription coactivator-1 (Crtc1) are thought to be involved in the actions of leptin at the brain in mammals [10,97,101].

[INSERT FIGURE 3]

[INSERT FIGURE 4]

The gonadostat hypothesis for puberty proposed that sensitivity of the hypothalamus to estrogen negative feedback declines at the pubertal age in females, and is followed by increased gonadotropin secretion and initiation of cyclic ovarian activity. This hypothesis was initially tested in rats [102] and later in beef heifers [103]. Given contemporary knowledge concerning the balance of positive and negative signals at GnRH neurons, it is feasible that the pubertal increase in gonadotropin secretion occurs as a result of greater stimulatory action at GnRH neurons, without a change in sensitivity *per* se to estrogen negative feedback . The gradual increase in LH secretion from 1 week of age until puberty in Hereford-Friesian heifers, without a notable increase around puberty [104], would be consistent with a progressive increase in positive signaling at the hypothalamus from leptin in growing heifers that are depositing adipose (Section 4).

7. Follicles, oocytes and embryos

The metabolic environment of ovarian follicles has a major influence on growth and maturation of oocytes, and also subsequent embryonic development [105-110]. Particularly important is the fatty acid (FA) profile of both follicles and oocytes [111]. The present consensus is that saturated FAs are detrimental to oocyte and embryo development and unsaturated FAs could be beneficial [106,112-117]. Cumulus cells surrounding oocytes have particularly high concentrations of FAs and it was suggested the cumulus accumulates FAs as a mechanism to protect oocytes for saturated FAs [118,119].

Prepubertal heifers were reported to have lower amounts of FAs in follicular fluid than cows and cow oocytes had greater lipid content [120]. It was suggested that these differences could explain the higher quality of oocytes from cows compared with heifers. It was also proposed that the relative amounts of different FAs (saturated, monosaturated, polyunsaturated) determine oocyte fertilizing capacity and embryo developmental potential [120,121]. The latter study [120] utilized slaughterhouse ovaries and the genotype and condition of heifers and cows was unknown. Lactating Holstein-Friesian cows had greater amounts of saturated FAs in follicular fluid than heifers which was thought to explain reduced fertility of oocytes from cows [106]. Further studies are required to elucidate relationships between the FA profiles of blood, follicular fluid, and oocytes, and impact on oocytes and embryos. Profiling of the metabolome in different fluids could provide some of the answers [106,122-124].

Dietary intervention has been used to influence the endogenous FA profile in lactating dairy cows. It would appear that diets high in unsaturated FAs can improve oocyte and embryo quality in high milk yield cows [120,125-126]. Notwithstanding these findings, further studies are required to better understand how dietary intervention can help achieve a positive FA balance in lactating cows [127].

8. **Summary**

A large body of knowledge has accumulated over the past 50 years on relationships between nutrition, metabolic condition, and reproductive function in beef cattle. It has become apparent that nutritional management should be used strategically to keep cattle in positive energy balance, rather than a ‘rescue’ strategy for cattle that have entered negative energy balance. In young heifers, this means ensuring an optimal LW and BCS at weaning and an ADG of 0.6 to 0.7 kg/day from weaning to puberty. Heifers should ideally have 2 to 4 ovarian cycles before their first mating [128]. Mating should occur early in their first breeding season to allow sufficient time for a return to fertile cycles and re-conception to establish annual calving. First-parity cows need particular nutritional attention in the third trimester of pregnancy to ensure a BCS of 3.0 to 3.5 (scale 1-5) at parturition. This can help prevent an extended period of postpartum anestrus in suckled first-calf cows that have yet to reach mature body size. The activity of adipose tissue, liver and 'gut' reflects metabolic condition. Hormones from these tissues (leptin, IGF1, Ghrelin) are important regulators of reproduction both in the brain and at somatic tissues. The ratio of fatty acids (saturated, monounsaturated, polyunsaturated) in follicular fluid determines oocyte quality and embryo development. A balance is needed between nutrition, metabolic condition, production (meat, milk), and reproduction. The genetic selection and breeding of dairy cows for high milk yield has pushed lactating cows into clinical negative energy balance (poor metabolic health) and severely disrupted the metabolic resilience boundary that balances production with reproduction [129]. The selection of beef cattle for high feed utilization efficiency [130] produces leaner animals and has the potential to reduce fertility in females. The experience in dairy cattle, and to a lesser extent beef cattle, provides a salient lesson that there are limits to the capacity of cattle to achieve high production, and also reproduce. The body of knowledge now available on relationships between nutrition, metabolic condition and reproduction, provides the opportunity to develop new strategies that achieve production imperatives without compromising fertility in female beef cattle. This will require a complementary blend of genomics and management.

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Figure legends

Figure 1. Relationships between BCS at calving, change in BCS postpartum, and the probability of pregnancy in multiparous Nelore beef cows mated using fixed-time AI at day 42 postpartum. The cows with highest BCS at calving were the cows with greatest loss of BCS postpartum and cows with the lowest BCS at calving were the cows with lesser loss, or gain, of BCS postpartum (Adapted from [42]).

Figure 2. Model for the role of kisspeptin and Kiss1 neurons in mediating the effects of leptin on GnRH secretion (Adapted from [14]).

Figure 3. Model for the actions of Ghrelin and leptin during energy insufficiency (Ghrelin) and energy sufficiency (leptin) that can be used to conceptualize the roles of Ghrelin and leptin before and after puberty (Adapted from [97]).

Figure 4. Model for the interrelationship of leptin, kisspeptin (Kiss), POMC and NPY during the prepubertal-pubertal transition in heifers (Adapted from [98]).

Figure 1

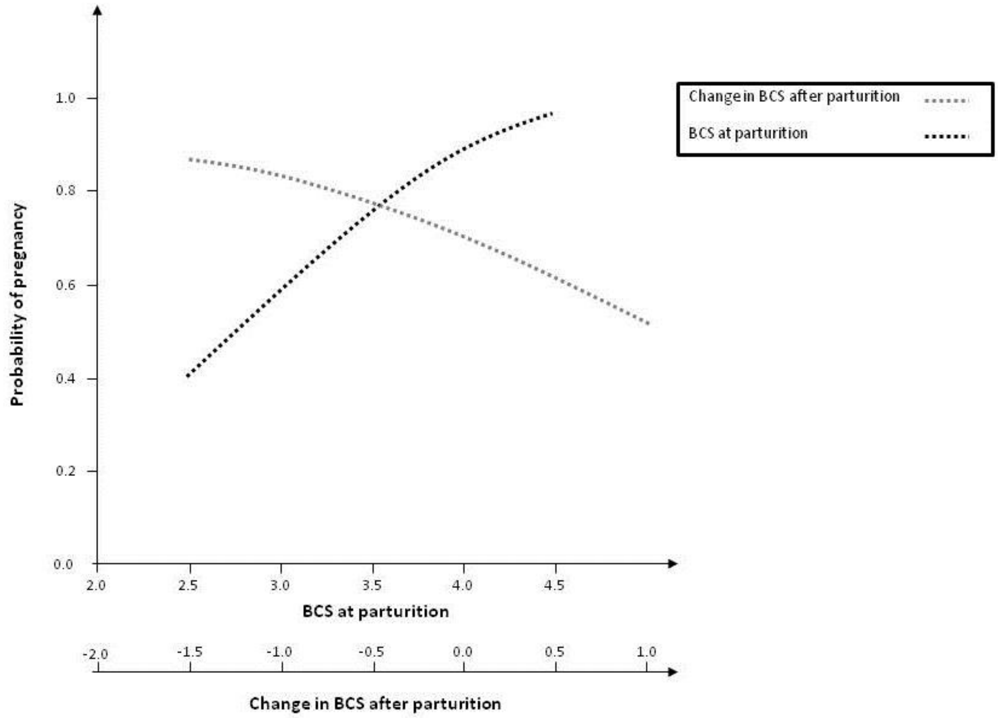
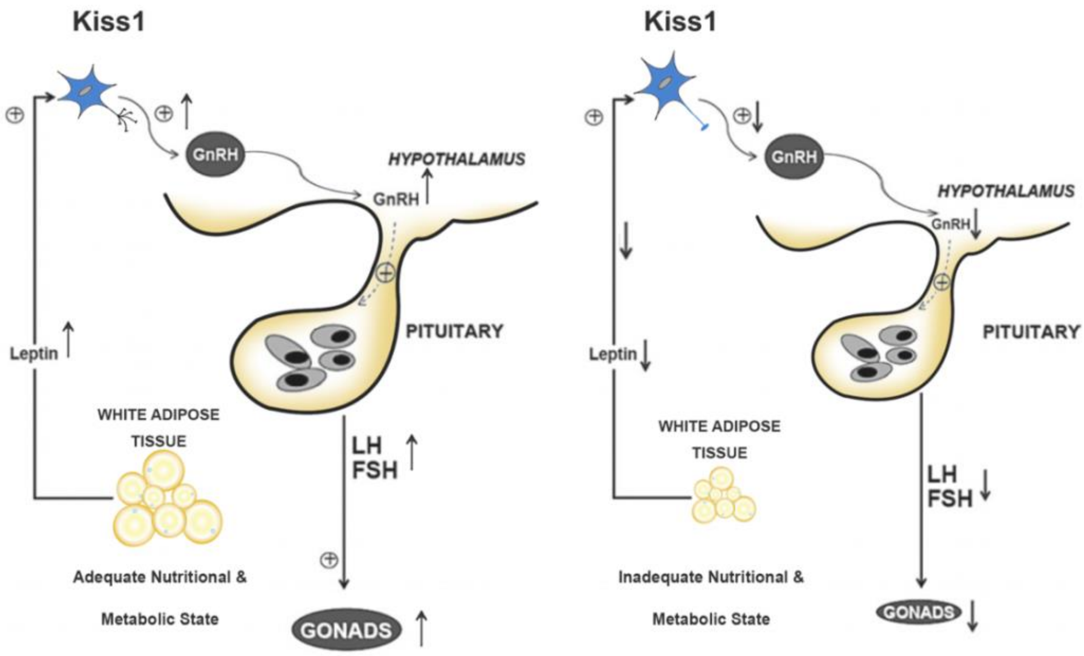

Probability of pregnancy
1.0
0.8
0.6
0.4
0.2
0.0
2.0
2.5
3.0
3.5
4.0
4.5
BCS at parturition
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
Change in BCS after parturition
Change in BCS after parturition
BCS at parturition

Figure 2



Kiss1
GnRH
HYPOTHALAMUS
GnRH
PITUITARY
Leptin
WHITE ADIPOSE TISSUE
LH
FSH
Adequate Nutritional & Metabolic State
GONADS
Kiss1
GnRH
HYPOTHALAMUS
GnRH
PITUITARY
Leptin
WHITE ADIPOSE TISSUE
LH
FSH
Inadequate Nutritional & Metabolic State
GONADS

Figure 3

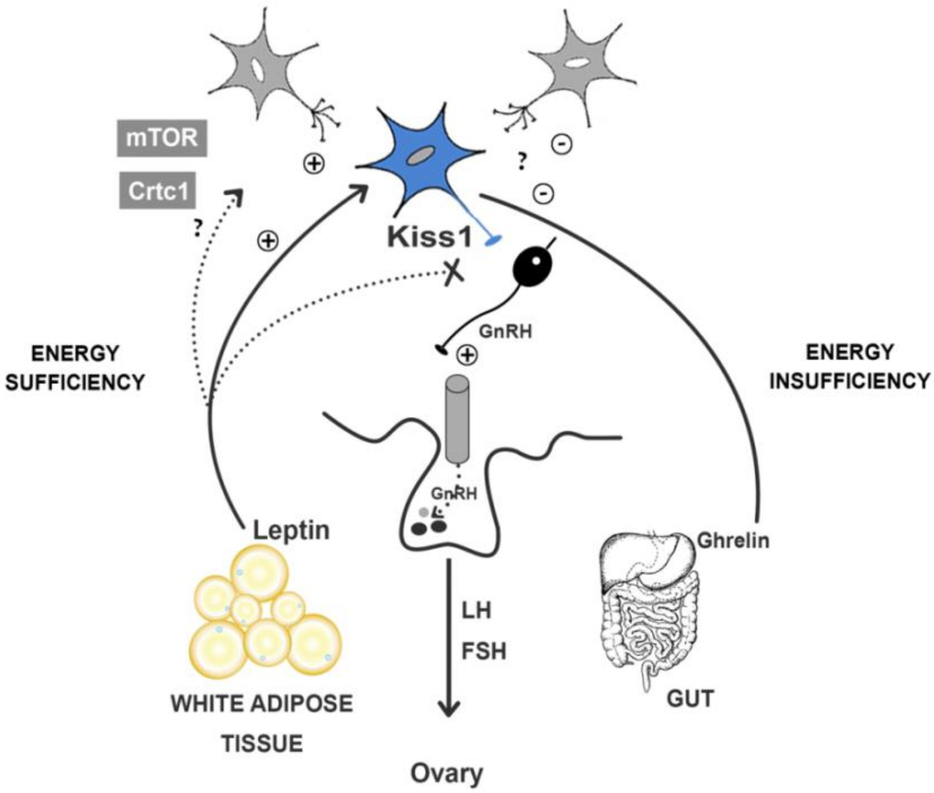
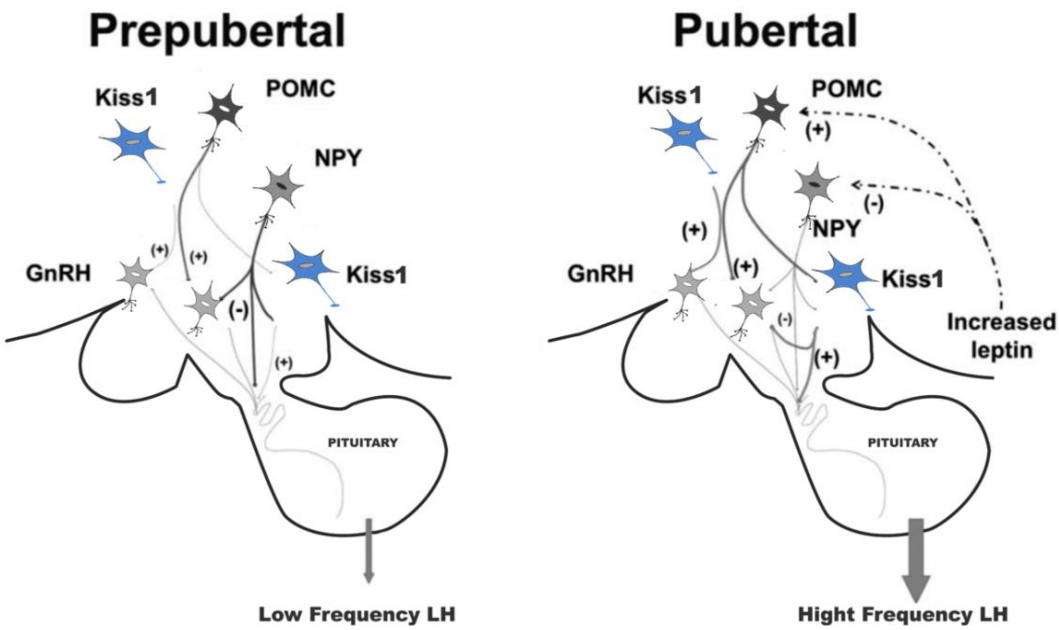

mTOR
Crtc1
Kiss1
GnRH
ENERGY SUFFICIENCY
ENERGY INSUFFICIENCY
GnRH
Leptin
Ghrelin
LH
FSH
WHITE ADIPOSE TISSUE
GUT
Ovary

Figure 4



Prepubertal
Kiss1
POMC
NPY
GnRH
(+)
(+)
(-)
Kiss1
(+)
PITUITARY
Low Frequency LH
Pubertal
Kiss1
POMC
(+)
(-)
NPY
(+)
GnRH
(+)
Kiss1
(-)
(+)
Increased
leptin
PITUITARY
Hight Frequency LH

Influence of nutrition, body condition, and metabolic status on reproduction in female beef cattle: A review

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AUTHOR AGREEMENT

All authors contributed equally to the conceptual framework and structure of the manuscript