Acta Scientific Veterinary Sciences (ISSN: 2582-3183)

Volume 4 Issue 1 January 2022

Mini Review

Lesser Explored Approaches for Ovulation Induction in Cows

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Received: : August 13, 2021

Published: December 10, 2021

Abstract

Ovulation induction in cattle has been traditionally done using either GnRH or hCG. Some of the uncommon approaches for ovulation induction include the use of insulin, prostaglandins, anti-estrogens, anti-prolactin's and aromatase inhibitors which are briefly described in this mini-review. Experiments mentioning the use of these agents have utilized only small numbers of animals and large clinical trials are needed to validate their clinical use.

Keywords: Ovulation; Cows; Insulin; Prostaglandins; Anti-estrogens; Anti-prolactin; Aromatase Inhibitors

Introduction

Ovulation induction in cattle is required in clinical cases of delayed ovulation, follicular ovarian cysts and in estrus synchronization programs. Ovarian cysts in cows are a result of ovulation failures [1]. Traditionally ovulation has been induced in cows using hCG or GnRH [2-5]. Such therapies usually initiate or potentiate the LH surge with resultant ovulation. The mechanisms of ovulation in cattle are complex and during past several years some other approaches have been evaluated for induction of ovulation in cows and these are mentioned in this mini review.

Insulin and glucose

Anovulation possibly originates on account of a poor preovulatory surge of LH although estradiol concentrations are high [6], possibly originating because of lack of progesterone priming, suckling, season and a variety of other factors. The LH surge is also affected by the circulating levels of glucose, insulin and insulin-like growth factors [7]. The LH secretion has been considered to be also regulated by insulin. One study hypothesized that hypoinsulinemia during early lactation originates because of low nutrition, resulting in delayed ovulation [8]. Another study indicated that acute elevation in insulin during the preovulatory follicular wave decreased percentage of large follicles that ovulated, particularly when combined with increased LH and also reduced fertilization of ovulated oocytes [9]. In a small trial, dairy cows with delayed ovulation were administered 500 ml of 25% dextrose IV at estrus along with insulin (5 ml of bovine insulin) and it was found that 30 of the 50 cows treated with such a treatment had timely ovulation and conceived subsequently [10]. Single subcutaneous application of 0.25 IU/kg human insulin to estrus synchronized Holstein cows had a positive effect on follicle development [11]. Estrus induction rate of acyclic buffaloes was improved by pretreatment with insulin for 3 days

before GnRH injection and this also increased the diameter of the dominant follicle [12]. Also low levels of plasma triiodothyronine (T3) and plasma thyroxine (T4) were recorded in cows with ovarian cysts and oral administration of levothyroxine improved the thyroid hormones [13].

Prostaglandins

The increase in intra-follicular fluid pressure and follicle wall thinning that precedes ovulation is known to have significant roles of prostaglandins [14] and thus prostaglandins can possibly be used as agents to facilitate ovulation. Presence of luteal tissue during transition of the follicle to ovulatory stage might hamper the process of ovulation [15]. Intravenous administration of cloprostenol at artificial insemination to high producing lactating dairy cows resulted in a 4.2 fold increase in the ovulation rate in heat stressed repeat breeder cows inseminated during the warm period [16]. Two recent studies [17,18] collected bovine ovaries by ovariectomy and evaluated the regulation pattern of prostaglandin family members (PGF2, PGE2, their receptors and enzymes) and the patterns of hypoxia-inducible factor-1alpha (HIF1A), inducible nitric oxide synthase (iNOS) and endothelial (eNOS) isoforms. These studies concluded that prostaglandins and other paracrine factors (HIF1A and NOS isoforms) are modulated and regulate the final ovarian follicle maturation and ovulation. Clinical trials on prostaglandin administration at the time of insemination need to be conducted to validate the use.

Antiestrogens

Two mixed antagonist-agonists of estrogen (Tamoxifen and clomifen) belong to the group of type I anti-estrogens [19]. Such antagonists partially inhibit the action of agonists, but due to their own inherent weak agonistic properties, they also induce, to some extent, estrogenic responses. Their action may directly affect the pituitary gland to stimulate estrogen-dependent LH release [20]. Scientific reports on the use of tamoxifen and clomiphene in bovine models are sparse. The authors have in limited clinical cases tried oral administration of 40-80 mg of tamoxifen to parturient cows with excessive vulvar edema with limited success. Clomiphene has been marketed to a limited extent for use in anestrus cows. In order to close the rumeno-reticular groove for passage of this drug directly to the reticulum a 1% copper sulfate drench has been suggested. Oral administration of 300 mg of clomiphene citrate resulted in induction of estrus in cows and buffaloes [21,22] however, the results were inconsistent with the drug being more effective in heifers [22,23]. Oral administration has also been suggested for repeat breeding cows [24] and cows with cystic ovarian disease [25]. In cattle and buffaloes where ovulatory failures have been confirmed in the previous estrous cycle or is speculated, clomiphene should be started preferably 1 day before expected estrous (300 mg) and continued until the onset of estrous. It is expected that the up-regulation of receptors would facilitate LH release and ovulation. Mid cycle oral administration of clomiphene citrate to cows resulted in marginal increase in ovulatory rates in anovulatory cows [26]. Clomiphene has been a drug of choice for ovulation induction in human subjects and some patients show resistance towards the effects of clomiphene. In such cases, metformin, an insulin sensitizer, has been advocated to be combined with clomiphene, for ovulation induction in patients with polycystic ovarian syndrome [27,28]. Insulin sensitizers improve hyperinsulinaemia and hyper-androgenism in treated women [29]. Therapeutic trials using metformin for ovulation induction in cattle and buffaloes are not available. Oral administration of 2000-4000 mg of metformin to cows showed some promise but the results were inconsistent [10].

Antiprolactins

Warm weather has been known to affect the ovulation in dairy cows with the incidence of ovulation failures being 3.9 times higher during the warm season [30]. Heat stress is considered to elevate the plasma prolactin [31] and thus the administration of antiprolactin bromocryptine has been suggested by some clinicians to help in ovulation induction in repeat breeder cows during summer season. The oral administration of 10-20 mg 12 h before and at the time of AI has however yielded inconsistent results [10]. In a previous study on Holstein cows the subcutaneous administration of 80 mg of ergocryptine in 50% ethanol resulted in decrease in plasma prolactin within 2 h and lasted for 5 days [32] yet the milk production was not affected. The oral administration of bromocryptine to ewes has shown to decrease the plasma prolactin without any significant effects on LH surge [33]. The administration of antiprolactins in ovulation induction therefore remains to be validated for ovulation induction in cows.

Aromatase inhibitors

A new class of drugs that has been largely experimented in human subjects is aromatase inhibitors. These agents block estrogen

biosynthesis, thereby reducing negative estrogenic feedback at the pituitary. Anastrazole and letrozole are approved for human therapy of breast cancer in many countries and are considered higher class (third-generation) aromatase inhibitors. Letrozole and anastrozole have greater potency and, reduce estrogen levels by 97% to 99% when administered to human females [34]. Blockage of aromatase prevents the conversion of androgens to estradiol and thus the estrogen decreases precipitously and their negative feedback on the hypothalamic/pituitary axis is prevented. Probably, this stimulates gonadotropin secretion, ovarian follicle growth and consequent ovulation. Only a limited number of studies have been conducted on the use of letrozole in animals. In a study in Canada heifers were administered 125 µg kg^{-1} to 500 µg kg^{-1} of letrozole intravenously 4 days after follicle ablation and the follicle growth and hormone levels were monitored. Treatment with letrozole resulted in elevated levels of plasma LH [35]. Placement of an intra-vaginal device containing 1 gm letrozole to heifers resulted in a reduction in estradiol concentration, delay in ovulation by 24 h but a subsequent better formation of corpus luteum [36]. An intravaginal device containing 3 g of letrozole for 4 days starting on Day 0, 4, 8, 12, or 16 resulted in a greater ovulation rate and greater synchrony of ovulation than in heifers not given letrozole [35,37]. The authors concluded from their studies on cattle that aromatase inhibitors are a new class of drugs that offer advantage of controlling estrus and ovulation [38]. Clinical trials on the use of letrozole for ovulation induction and ovarian cysts therapy in cows need to be conducted.

Conclusions

From the various alternative molecules evaluated in this study it can be concluded that anti-estrogens and aromatase inhibitors appear to be promising molecules for ovulation induction in cows.

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