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Lights on Drugs Used for Treatment of Ovarian Disorders in Farm Animals

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Abstract: Ovarian functional disorders are the most frequently observed clinical entities in buffaloes and cattle. Among these disorders, delayed onset of puberty, anestrous, ovariancysts, persistent corporalutea and inactive ovaries are of great economic importance. The therapy of most ovarian pathologies except for functional disorders appears to be difficult. Among therapeutics used for controlling functional ovarian disorders, prostaglandins, minerals, vitamins and hormonal supplementation, gonadotrophin releasing hormones (GnRH and hCG), Bovine growth hormone-releasing factor (bGRF) and Somatotropin are successively used. GnRH, PGF2α and progesterone based protocols are used for treatment of anestrous animals. Good ovarian response was monitored by ultrasonography following using progesterone releasing intravaginal device (PRID) protocol than OvSynch in buffaloes suffering from inactive ovaries. GnRH administration is the most common option for treatment of follicular cysts in dairy cows, PGF2α is used for treatment of cows suffering from PCLand give sustisfactoryresults as indicated by a high percentage of animals became normal. The PRID and Ovsych estrous synchronization protocols were successfully used for the treatment of buffaloes with inactive ovaries during the low breeding season as indicated by an increase in overall pregnancy rate and reduction in days open and calving interval. It cloud be concluded that bGRF is the best treatment for delayed onset of puberty, GnRH, PGF2α and progesterone based protocols for anestrous, GnRH for follicular cysts, PGF2α for PCL and PRID and OvSych for inactive ovaries.

Key words: Farm Animals · Ovarian Disorders · Delayed Puberty · Cystic Ovaries · Persistant Corpus Luteum · Inactive Ovaries

INTRODUCTION

Reproductive disorders such as delayed onset of puberty, poor estrous expression, longer postpartum ovarian quiescence and lower conception rates are the main causes of low reproductive efficiency in farm animals[1].

The ovaries and ovarian structures of buffaloes are inherently smaller compared to cows. It was reported that seasonal ovarian hypofunction and ovarian pathologies limit the breeding value of these important species and subsequently estrous cycle and pregnancy [2, 3].

The onset of puberty is the result of a series of complex developmental events that occur within the reproductive endocrine axis. Those events include a high frequency rhythm of gonadotrophin releasing hormone (GnRH) secretion, a rise in basal luteinizing hormone (LH) secretion[4] and paracrine factors such as growth hormone (GH) and insulin-like growth factor 1(IGF-1) which can also modify synthesis of GnRH and subsequently action on the pituitary gonadotrophins [5].

Buffalo heifers treated with bovine growth hormone-releasing factor (bGRF) showed earlier puberty onset than in control animals [6]. It was found that exogenous GRF may increase the synthesis and release of endogenous GH, which may help in the development of whole body structure including the reproductive organs leading to early maturation of gonads and production of progesterone in the ovary resulting early transient increase in plasma progesterone concentration followed by commencement of progesterone cycles signaling early onset of puberty in GRF-treated heifers [7].

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Anestrous is still a big dilemma in buffalo reproduction which is associated with lower peaks of FSH and LH and inherently suboptimal functioning of hypothalamus-pituitary-gonadal axis [8]. The estrous synchronization has been employed to resolve problem of anestrus in buffaloes but their results are variable. Progesterone based synchronization protocols have been combined with different gonadotrophins to achieve the maximum results in small and large ruminants [9].

Cystic ovarian follicles (COF) are defined as fluid filled follicular structures which are more than 17 mm in diameter persisting for more than 6 days without ovulation and no corpus luteum (C.L) detectable by ultrasound and clearly interfering with the normal ovarian cyclicity [10, 11]. The etiology, pathogenesis and efficiency of the treatment of COF in dairy cows have been studied extensively. The pathogenesis of COF is due to the lack of a pre-ovulatory LH surge, insufficient in LH magnitude or LH surge at the wrong time during dominant follicle maturation [12-15]. Treatments for COF are numerous and variable and have changed considerably over the years.During earlier times, the manual rupture of COF was advocated, yet during the past several years single or combination hCG, GnRH, progesterone and prostaglandins have been frequent in clinical practice. Other therapies include estrogen receptor blocker clomiphene citrate and transvaginal ultrasound guided cystic follicle aspiration. Among the various therapies suggested the OvSynch treatment appears to be the most logical approach as compared with other hormonal treatments, yet the pregnancy rates with timed inseminations following therapy with the OvSynch treatment are low [16].

Different hormonal treatments were used for follicular cysts in dairy cows with the most common option is GnRH administration, which results in a rapid increase in LH secretion and luteinization of the cysts [17]. The success of therapy in terms of disappearance of COF with different hormonal treatments is good, yet the establishment of pregnancy requires variable times due to formation of new COF and pathological alterations that occur in the uterus with long term persistence of COF [18]. It would be profitable to treat multiparous cows having cysts very early in the postpartum period, while treatment of primiparous cows should be delayed, at least until the end of the preservice period, to provide the opportunity for spontaneous recovery [19]. Other widespread options are OvSynch and PRID or CIDR progesterone based protocols [20].

Persistent corpus luteum (PCL) type I and type II were defined as delayed luteolysis of corpus luteum with milk progesterone = 3 ng/mL for 19 d, during the first estrous cycle postpartum and subsequent estrous cycles before AI, respectively [21].Luteal cysts are characterized by enlarged ovaries with one or more cysts with thicker walls because of lining of luteal tissue [22]. They are differentiated from follicular cysts by color Doppler or B-mode sonography for the selection of treatment [23]. The most common causes of PCL may be due to inadequate prostaglandin release at days 14-15 or late ovulations resulting in immature corpora lutea that are 5 days old at the time of prostaglandin release or embryonic loss after the time of maternal recognition of pregnancy or chronic uterine infections resulting in destruction of the endometrium and therefore a diminished prostaglandin release.

This work aimed to throw lights on some drug used for controlling ovarian disorders in farm animals.

The Delayed Puberty: Many techniques have been approached to advance puberty in farm animals by mimicking the hormonal changes occurring around puberty which may induce sexual maturity in animals.

- *Growth hormone-releasing factor (GRF):* Buffalo heifers treated with bovine growth hormone-releasing factor (bGRF) at the dose rate of 10 µg/100 kg body weight intravenously (i.v.) at an interval of 15 days for 9 months showed puberty onset at an age of 887.5 ± 17.5 days, while control buffalo heifers reached puberty at 946.0 ± 26.3 days of age [24].
- *Growth hormone:* There are several reports dealt with the effect of growth hormone on cow and ewe puberty. Radcliff *et al*. [25] found that manipulation of recombinant bovine somatotropin improved the heifer's growth and reduced age at first calving. In sheep, early puberty was attained in Barki ewe lambs treated with somatotropin [26]. Puberty was first attained 7 and 10 weeks after the start of the experiment in Rahmani ewe lamb treated with somatotropin and control groups, respectively [27].

Anestrous: Different estrous synchronization protocols with or without timed insemination (TAI) have been utilized for reduction of postpartum anestrus.

- *Progesterone based estrous synchronization protocol:* In this protocol, progesterone releasing intravaginal device (PRID) containing 1.55g progesterone in inert silicone elastomer coil was inserted in on day 50 postpartum anestrous Bulgarian Murrah buffaloes with inactive ovaries. At day 7, the coil was withdrawn and 500 mg cloprostenol (PGF2α) and 500 IU Folligon (PMSG) were administrated and 1500 IU hCG was injected intramuscularly48 hrs later. The animals were artificially inseminated 16hrs after hCG administration [28]. There is another progesterone based estrous synchronization protocol which is called controlled internal drug releasing devices (CIDR) in which 1.38g progesterone were inserted in buffaloes intravaginally for 7 days and animals were injected 2ml of PGF2α (Cyclomate) one day 7 [9].
- *OvSynch protocol:* In this protocol, buffaloes were treated with 100µg Depherelin / ml (GnRH) on day 0, 500 mg cloprostenol on day 7, followed by1500 IU hCG on day 9. The animals were artificially inseminated 28hrs after hCG administration [28]. In another protocol, Holstein dairy cows treated with 100 g gonadorelin / mL (GnRH) followed by PGF2α (250 g cloprostenol/mL) 7 days later. A second dose of (GnRH2) was administered 56 h after PGF2α and cows were inseminated 16-18 hrs after the second GnRHtreatment [29]. When the later protocol was compared to the same protocol initiated at random stages of the estrous cycle (40±2 days postpartum, it was clear that initiating the OvSynch protocol 6 days after estrus during the first 40 days postpartum resulted in a greater pregnancy rate at the synchronized estrus and increased fertility compared with control cows during heat stress.
- *Equine chorionic gonadotropin synchronization protocol:* The effect of CIDR and eCG on estrous response, ovulation and pregnancy rates in anestrous buffaloes was equally effective although CIDR induced estrus within 42 hrs after its removal with tight synchrony as compared to 72hrs after eCG injection [9]. In all these protocols, the ultrasonography diagnosis revealed a larger follicle, clear induced estrous signs, easier cervical passage, higher ovulation and pregnancy rates in PRID protocol than OvSynch in Murrah buffaloes with inactive ovaries [29].

Cystic Ovaries

- *Needle aspiration:* Single transvaginal-guided needle aspiration of ovarian follicular cysts is a safe and good alternative method against the manual active rupturing of cysts during transrectal palpation[30]but there is a tendency of the cyst to reform and cows may develop clinical mucometra [18]. Regimens suggested to resolve mucometra include oral 3-10 g of potassium iodide for 5-10 days [31] or injectable administration of elemental iodide [32] or uterine lavage [33].

Progesterone treatment

- *progesterone administration:* A single injection of 200 mg of progesterone administered to lactating Holstein and Jersey cows with ovarian follicular cysts reduced the lifespan of the cyst by 12 days, from 29.8 ± 2.3 days in control cows to 17.2 ± 1.8 days in progesterone-treated cows and in some cases was followed by ovulation of a new follicle. Progesterone treatment also tended to alter the frequency of subsequent follicular event[34].
- *CIDR:* Treatment with CIDR proved effective in restoring ovulation and reestablishing normal cyclicity in beef donor cows with cysts persistent for a long period[35].Progesterone works against follicular cysts by restoring the responsiveness of the hypothalamus to the positive feedback of estradiol, resulting in normal estrus and ovulation within 7 days after the implant is removed[17].
- *Progesterone and estradiol Benzoate:* Progesterone and estradiol Benzoate treatment administered using a PRID have a high rate of therapeutic effectiveness in cows with OC. Treatments with progesterone releasing intravaginal devices (PRID) in combination with estradiol benzoate for 12 days evidenced therapeutic efficacy in resolving OC in postpartum dairy cows [36]. Moreover, when progesterone is used for estrous synchronization after embryo collection instead of PGF2α, the proportion of cows developing OC decreased from ~25% to <3%[17].
- *GnRH analogues:* GnRH is most effective for returning cows with anovulatory follicular cysts to a normal cyclic ovarian condition [17]. The epidural administration of lecirelin (a GnRH analogue)

promotes the remission of follicular cysts and an improvement of reproductive parameters [37]. A single injection of 20 µgbuserelin and 200 µgfertirelin have equal therapeutic effects in lactating cows having OC [38]. A recent study found beneficial effects of a single IM administration of 0.1 mg lecirelin acetate in the therapy of cows suffering from OC [39].

- *hCG and GnRH analogues:* They have been used to treat ovarian cysts and both appear to be equally effective with regards to treatment response and fertility [40] but the next estrus would occur 5-21 days after treatment [41]. GnRH and hCG elicit equivalent endocrine and clinical responses, but GnRH has an advantage over hCG in its minimal antigenicity [42]. The treatment of OC with hCG is somewhat more effective than a treatment with hCG + P_4[43].
- *PGF2α:* Drost and Thatcher [41] recommended luteolytic doses of PGF2α as the ideal treatment for luteal cyst, with estrus being evident within 3-5 days. Intervals from treatment to resumption of ovarian activity are affected by the characteristics of ovarian cysts, with a faster recovery for the luteal type [14]
- *GnRH plus Cloprostenol* (CLP*):* CLP 14 days later is effective in resolving cysts with significantly higher percentages of ovulation rates, returns to estrus and pregnancyrates and a much lower level of cystic persistence. However, currently GnRH followed by PG 7-10 days later is a routinely used therapy for OC [18].
- *OvSynchprotocol:* Some relatively recent protocols for synchronization of ovulation, commonly referred as OvSynch, followed by timed artificial insemination performed 16-20 h after the 2nd GnRH injection, yields pregnancy rates of about 25% in cows suffering from OC [44] . Amer and Badr [45] used OvSynchprotocol as a treatment for OC and found it to be effective in curing the cystic condition and got the previously cystic animal pregnant after AI. Dairy cows with cystic ovarian follicle were treated with 1 500 IU hCG on day 0 (second ultrasound), $PGF_2\alpha$ 500 mg on day 7 and 100 g GnRH (Depherelin) 48 hours later. Significant improvement of cumulative oestrous activity and ovulation rate were indicated in animals subjected to hCG-PGF2-GnRH administration thannon-treated animals. The used hormonal protocol could decrease cystic ovarian follicle persistence in dairy cows [28]. Treatment of cows with OC with CIDR intra vaginal placement, GnRH followed by $PGF_2\alpha$ 7 days later resulted in recruitment of new healthy follicles, synchronization of ovulation and resulted in a marked improvement in pregnancy rate [46]

Persistent Corpora lutea: Sahiwal cows suffering from PCL were treated with 2 ml of Dalmazin (PGF2α) intramuscularly on the same day of checking the condition of genitalia for PCL and this was also confirmed by progesterone assay in weekly blood samples for three weeks. It was found that 85% of animals suffering from PCL and treated with PGF2α became normal and consequently 60% were pregnant at first service whereas 25% were repeat breeders [47].

Inactive Ovaries: Ahmed *et al.* [48] supplemented Egytian buffalo cows suffering from ovarian inactivity with Ovitone; 20g mixture of phosphorus, trace elements, vitamins and lasalocid for 10 successive days. Ovitone gave favorable response represented by the conception rate (58.33 %) as compared to other hormonal treatments such as PMSG (58.33 %) and GnRH (62.07 %). The ovarian rebound as monitored by estrous signs 7-10 days post-treatment were 79,72 and 71 % for the previous treatments, respectively.

In conclusion, bGRF is the best treatment for delayed onset of puberty in heifers, GnRH, PGF2α and progesterone based protocols for anestrous as the ultrasonography diagnosis revealed a larger follicle, clear induced estrous signs, easier cervical passage, higher ovulation and pregnancy rates in PRID protocol than OvSynch, GnRH is most effective therapy for returning cows with anovulatory follicular cysts to a normal cyclic ovarian condition, PGF2α for PCL as indicated by a high percentage of animals became normal and, The PRID and OvSych estrous synchronization protocols for inactive ovaries.

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