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Efficacy of three hormonal treatments for cystic ovarian disease and subsequent reproductive performance in dairy cows

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ABSTRACT

Cystic ovarian disease (COD) is a common ovarian disorder that causes major reproductive failure in dairy cows leading to significant economic losses in the dairy industry. This study aimed to evaluate the efficacy and the response of cows with ovarian cysts to three different treatments regardless of the cyst type. At 50 days postpartum, were considered to have an ovarian cyst when possessing a follicle with a diameter ≥ 17 mm in the absence of a corpus luteum in two ultrasonographic examinations performed at 7 days intervals. In the second examination considered (Day 0), 51 cystic Holstein cows were assigned randomly into one of 3 treatment groups.; GnRH group (*n*=12) treated with 100 µg gonadorelin as a single dose, GP group (*n*=12) received (100 µg gonadorelin on day 0 followed by 500 µg of cloprostenol sodium on day 7, CIDR group (*n*=12) treated with intravaginal progesterone-releasing insert CIDR on the day 0: and 100 µg gonadorelin then an injection of 500 µg cloprostenol sodium IM on day 7. The CIDR was removed on day 8, and a second GnRH injection was given on day 9. From day 9, animals were observed for estrus and inseminated with proven frozen-thawed semen. Control Group (*n*=15) represents cows that did not receive any treatment. Pregnancy was confirmed by ultrasound on day 28 post-insemination. Results showed that the GP group achieved the highest estrus induction rate (EIR). Thus, 44.4% of treated cows come in estrus less than 10 days and 100 % by day 20. While GnRH group showed EIR with 25% in less than 10 days and 62.5 % at the day 20. The CIDR group showed EIR (0%) in less than 10 days and 100 % at the day 20. Total conception rate (3 cycles after treatment) GP recorded (88.9%) GnRH group (87.5%) and CIDR (85.7%), while pregnancy rates (PR) was highest (66.7%) in GP protocol compared to GnRH (58.3%), and CIDR (49.9%). In conclusion, our results showed that the (GP group) had the best reproductive performance (earliest and highest estrus induction rate and highest pregnancy rate after treatment regardless of the type of the cyst.

Keywords: Cystic ovarian disease; GnRH; CIDR; Estrus

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1. Introduction

The improvement of dairy production of lactating cows has a negative effect on fertility. Thus, higher milk production is commonly associated with reduced fertility in dairy cows (Butler, 2003). Cystic ovarian disease is a common ovarian illness that causes major reproductive failure in dairy cows, resulting in substantial financial losses for the dairy industry. The incidence of cystic ovarian diseases is considered to be 10%, with studies ranging from 2.7 to 30% (BorȘ & BorȘ, 2020; Garverick, 1997). Follicular cysts in the ovaries are a common source of infertility and financial loss for dairy farms. the extend in calving intervals in cows with ovarian follicular cysts range from 22 days (Lee, Ferguson, & Galligan, 1988) to 64 days (Borsberry & Dobson, 1989); the usual interval is 40 to 50 days (Bartlett et al., 1986). The average time between diagnosis and conception is 50 days (Bierschwal et al., 1975).

COD was previously defined as fluid-filled structures with a diameter of 2.5 cm or greater that remained on the ovarian surface for 10 days or longer without a corpus luteum (CL) (Garverick, 1997; Youngquist & Threlfall, 2007). COD is currently defined as follicle-like structures with a minimum diameter of 17 mm that last longer than 6 days without a corpus luteum and interfere with regular ovarian cyclicity (Silvia, Hatler, Nugent, & Da Fonseca, 2002). Since excessive production was assumed to be the main cause of the problem, most cysts develop during early lactation during the first 60 days of lactation. This disorder does not appear to have a significant hereditary component. Heritability ranges between low and moderate (Stevenson, 2012). Previously, COD was diagnosed by transrectal palpation, which revealed ovarian cysts as follicles that were often larger than normal ovulatory follicles, and also the uterus is flaccid in absence of a corpus luteum (Bierschwal, 1966; Purohit, 2008). Ultrasound and plasma progesterone levels were recently used to make the most accurate diagnosis of the cyst and its type, either follicular or luteal (Kahn, Line, & Aiello, 2010; Rauch, Krueger, Miyamoto, & Bollwein, 2008).

The hormonal therapy for follicular and luteal cysts are different. follicular cysts have been treated with hCG and GnRH analogues since the 1970s. In terms of treatment response and fertility, both appear to be equally successful (Peter, 2004), but the induced estrus would occur 5-21 days later (Kahn et al., 2010). Because of its luteolytic effect, prostaglandin F2 (PGF2α) has been used to treat luteinized cysts, and estrus signs can be seen within 2-3 days after treatment (Kesler & Garverick, 1982). As a result, they are the most effective therapeutic option for luteinized cysts (Kahn et al., 2010).

Administration of progesterone may disturb the endocrine state necessary for the maintenance of follicular cysts, causing them to regress (Hatler, Hayes, Anderson, & Silvia, 2006). It seems to have substantial negative feedback on LH pulse frequency (Kinder, Kojima, Bergfeld, Wehrman, & Fike, 1996), suppressing LH in cows with cysts and permitting normal follicles growth (Calder, Salfen, Bao, Youngquist, & Garverick, 1999). Cows with persistent follicles can be effectively synchronised and time inseminated with progesterone, GnRH, and PGF2, but GnRH plus PGF2 only had a limited response (López-Gatius, Santolaria, Yániz, Rutlant, & López-Béjar, 2001). In beef donor cows with cysts that had been present for a long time, treatment with CIDR was helpful in recovering ovulation and reestablishing normal cyclicity (Douthwaite & Dobson, 2000). In cows with follicular cysts, a CIDR and GnRH injection can cause synchronous follicular wave emergence, similar to that seen in cows with regular estrous cycles (Kim, Suh, Kim, & Kang, 2006). A single dose of GnRH or hCG followed by PG at 7 days later also is a common strategy to treat cysts. Since the standard Ovsynch timed-insemination protocol utilizes GnRH and PG, this program has been used routinely to treat cystic ovarian conditions (Jeengar et al. 2018).

The topic of which treatment is the most cost-effective is frequently asked. Understanding the etiology of this disorder is improving, and treatment

options have improved as well. As a result, the goal of this study was to assess the response of cows with ovarian cysts to three therapies and compare the efficacy of the best treatment regardless of the cyst type.

2. Materials and Methods

2.1. Animals and grouping

This study used 51 lactating multiparous Holstein cows from a commercial dairy farm on the Cairo Alexandria desert road. Individual pens were almost identical in form, size, and quantity of housed cows. Cows were fed two distinct TMR (total mixed ration) diets based on their lactation stage, with an immediate postpartum diet fed between 1 and 21 days in milk (DIM) and a lactating diet fed for the rest of lactation. Maize silage, alfalfa hay, soybean meal, steam-rolled corn, whole cottonseed, calcium salts of palm oil, and a mineral, vitamin, and protein supplement were included in the cows' diets. The two diets were created with NRC in mind (NRC, 2001). Lactating Holstein cows weighing 500 Kg and producing 35 Kg of milk per day with a 3.5 percent fat content. Water was available to cows at all times. As part of a normal reproductive herd health program, all cows were checked for ovarian cysts twice at 40 to 50 DIM using an ultrasound (9 MHz) linear array B-mode veterinary ultrasound transducer (Sonoscape-A5V, Shenzhen, China).,

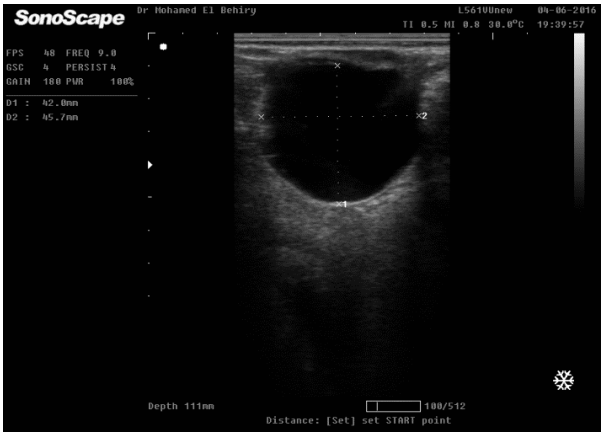

Figure 1. ultrasound image of ovary showing anechoic follicular cyst with a diameter (42X45.7 mm).

Follicular cysts were identified in 51 cows as follicular structures larger than 17 mm in diameter (**Figure 1**) that remained for the two examinations without the presence of a corpus luteum (CL), and the cows were then assigned into four treatment groups at random:

group, 1: CIDR in combination with GnRH and PGF2a

Twelve (n=12) multiparous puerperium cows were diagnosed having cystic ovaries with ultrasound, Received on day, 0: Intravaginal progesterone-releasing insert (CIDR) (**EAZI-BREED™ CIDR®-Zoetis animal production – US)**. Each insert is impregnated with 1.38 g of progesterone and is designed for intravaginal insertion, and 1 mL GnRH (100 µg gonadorelin acetate 100 µg/mL; Ovurelin®, Bayer, NSW, Aust) then an injection of 500µg cloprostenol sodium IM (2 ml of Ovuprost®, Bayer, Aust) on day 7. CIDR was removed on day 8 and a second GnRH injection was given on day 9 (**Figure 2**).

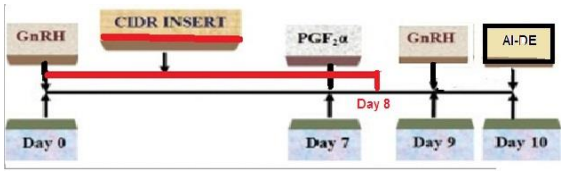

Figure 2. CIDR, GnRH and Prostaglandins for treatment of ovarian cyst

Group 2, GnRH Group

Twelve (n=12) multiparous puerperium cows diagnosed with ultrasound having cystic ovaries were injected with 1 mL GnRH **(100µg gonadorelin acetate 100 µg/mL; Ovurelin®, Bayer, NSW, Aust).**

Group 3: GnRH and prostaglandin:

Twelve (n=12) multiparous puerperium cows diagnosed with ultrasound having cystic ovaries were injected with (GnRH and prostaglandin). Received on day 0, 1 mL GnRH (100 µg gonadorelin acetate 100 µg/mL; Ovurelin®, Bayer, NSW, Aust) then an injection of 500 µg cloprostenol sodium IM (2 ml of Ovuprost®, Bayer, Aust) 7 days later (Figure 3).

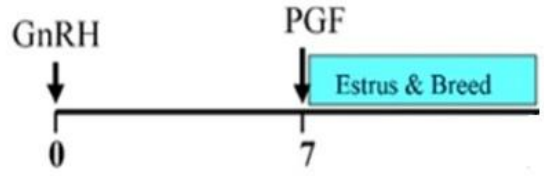

Figure 3. GnRH and Prostaglandin for treatment of ovarian cyst

Group 4 (Control group)

Fifteen (*n*= 15) multiparous puerperium cows diagnosed with ultrasound having cystic ovaries did not receive any treatment and were kept as a control group.

After each treatment, animals were observed for estrus twice per day, 30 minutes each time and checked on SCR. In addition, observed standing estrus during routine handling was recorded. Each animal in estrus was inseminated with proven thawed semen. Resident veterinarian made all inseminations. Trans-rectal ultrasonography on ovaries of all cows was done. Cows that did not return to estrus were examined by ultrasound on day 28 post insemination for pregnancy.

2.2. Ultrasound scanning

A real-time B mode scanner (Sonoscape A5) with a 5L vet rectal linear array auto-adapted frequency transducer range of 6 to 9 MHZ was used for ultrasonography. To avoid air interface, ultrasonic gel was employed to obtain high-quality images with minimal image artefacts. Before transrectal scanning, animals were adequately restrained in headlocks, and the scanning unit was carried by an assistant on the side opposite the operator's arm inserted rectally. The scanner was placed at the level of the operator's eyes, and ambient light was reduced for good observation. The animal rectum was evacuated of all feces before introduction of the handheld transducer. The transducer scan head was covered with coupling ultrasonic gel and was inserted through the rectum with the scan head pressed firmly against the rectal mucosa to prevent air interface. For orientation, the transducer was first moved along the dorsal surface of the reproductive tract to evaluate the uterine horns and body, then laterally to examine the ovaries. The image was saved and kept on the screen. Ultrasonography was advised for diagnosing cystic animals with one or more follicle-like structures that were at least 17 mm in diameter, lasted more than 6 days in the absence of a corpus luteum, and interfered with normal ovarian cyclicity (Silvia et al., 2002). After treatment, animals were observed for estrus, then ultrasonographically evaluated for ovulating follicles measuring 13-17 mm (Ginther, Knopf, & Kastelic, 1989), then inseminated. On day 28 after insemination, each animal that did not return to estrus was checked by ultrasonography for pregnancy.

2.3. **Statistical analysis**

The results are reported as the mean ± the standard deviation of the experiments. Each animal was treated as a separate experimental unit. For statistical analysis, GraphPad Prism 5 software (GraphPad Software Inc., La Jolla, CA) was utilized. Student's t-test (for two groups) or one-way ANOVA followed by Tukey post hoc tests were used to determine statistical significance between groups (for more than two groups). At p 0.05, the results were considered statistically significant. Furthermore, the Chi-square test was employed to determine the degree of heterogeneity in response between the various groups.

3. RESULTS

Table 1 shows the data on estrus exhibition and estrus induction rate: The GP protocol had the highest estrus induction rate (EIR) of 75 %, followed by GnRH with 66.7 % and the CIDR group with the lowest EIR (58.3). Total conception rate (3 cycles after treatment) was 88.9% in the GP protocol, 87.5 % in the GnRH group, and 85.7 % in the CIDR protocol, while pregnancy rates (PR) were highest (66.7 %) in the GP protocol, GnRH (58.3%) and CIDR (49.9 %). **Table 2** shows reproductive performance represented by interval to estrous exhibition from end of treatment in days. There was a statistically significant difference compared to control in the interval recorded in all groups with mean ± SD of (11.3 ± 4.2) in GP Group, (15.5 ± 5.9) in GnRH Group and (10 ± 0.0) in CIDR Group compared to control group (26.7 ± 1.5). **Table 3** There was a statistically significant difference between groups was determined by one-way ANOVA (F (3, 24) =16.8, *P* = 0.00). A Tukey post hoc test confirmed the previous statistically significant difference between each group and the control group as mentioned in **Table 2**. **Table 4** shows reproductive performance represented by interval to conception from end of treatment in

Table 1. Estrus induction, total conception and pregnancy rate following treatment

Treatment	No. of cows within the group	Cows detected in estrus		Conception at 1st AI		Conception at 2nd AI		Conception at 3rd AI		Total conception results		Pregnancy rate
		No.	%	No.	%(a)	No.	%(a)	No.	%(a)	No.	%	
Control	15	4	26.7%	---	---	1	25%	1	25%	2	50%	**13.3%**
GnRH	12	8	66.7%	4	50%	2	25%	1	12.5%	7	87.5%	**58.3%**
CIDR	12	7	58.3%	4	57.1%	1	14.2%	1	14.2%	6	85.7%	**49.9%**
GP	12	9	75%	6	66.7%	1	11.1%	1	11.1%	8	88.9%	**66.7%**

(a)= percent calculated from total detected in estrous within each group

Table 2. Interval to estrus exhibition from end of treatment in days

treatment	Frequency of estrous exhibition from end of treatment in days				Test of significance	
	<10 days	10- <20	20-<30	Mean +/- SD	t-test	p-value
Control	-	-	**4 (100%)** (a)	**26.7 +/- 1.5**	-	-
GnRH	**2 (25%)**	**5 (62.5%)**	**1 (12.5%)**	**15.5 +/- 5.9**	**T= 5.01***	**P= 0.001**
CIDR	-	**7 (100%)**	-	**10 +/- 0.0**	**T= 22.3***	**P= 0.00**
GP	**4 (44.4%)**	**4 (44.4%)**	**1 (11.2%)**	**11.3 +/- 4.2**	**T= 6.9***	**P= 0.00**

(a) = percent calculated from total detected in estrous within each group

Table 3. One-way ANOVA

	F	df1	df2	P- value
Interval to estrous exhibition from end of treatment in days	16.8	3	24	0.000*

Table 4. Interval to conception from end of treatment in days

Treatment	Interval to conception from end of treatment in days	Test of significance	
	Mean ± SD	t-test	p-value
Control	67.5 ± 7.8	-	-
GnRH	29.4 ± 22.6	T=2.25*	***P*= 0.05**
CIDR	29.3 ±30.9	T=1.6	***P*= 0.15**
GP	20.5 ± 16.7	T=3.7*	***P*= 0.00**

Table 5. Interval to conception from end of treatment in days

	F	df1	df2	P- value
Interval to conception from end of treatment in days	2.27	3	19	0.11

days with a mean and SD of (20.5 ± 16.7) with GP, (29.3 ± 30.9) with CIDR and (29.4 ± 22.6) with GNRH while that of control was (67.5 ± 7.8). There was a statistically significant difference in the results of GnRH and GP groups compared with the control group. Results of the one-way ANOVA test (F (3,19) =2.27, P = 0.11) revealed that there was no statistically significant difference between groups, as shown in **Table 5**.

4. DISCUSSION

Ovarian cysts can be classified into follicular and luteal cysts (Garverick, 1997). Both of them decrease the reproductive efficiency leading to prolonged calving interval and subsequent less production. Regaining fertility often requires longer time due to the disturbance in endocrinology and uterine pathology that follows the long standing cases (Purohit, 2008), so we started our diagnosis early (40-50 days post-partum). Protocols of treatments for ovarian cysts are numerous and variable, and have changed considerably over the years (Peter, 2004; Purohit, 2008; Woolums & Peter, 1994). In this study we tried three protocols for treatment and evaluated the response to treatment in form of EIR, conception rate, interval to estrus, interval to insemination and pregnancy rate.

Follicular cysts were identified more frequently (84.6 %) than luteal cysts (15.4 %), regardless of the type of the cyst (GnRH, PGF2α, and CIDR), assuming synergistic effects on the luteinization of follicular cysts and its susequent regression (PGF2α) according to Carroll, Pierson, Hauser, Grummer, and Combs (1990), Douthwaite and Dobson (2000), and Lopez-Gatius and Lopez-Bejar (2002 In previous studies exogenous injection of GnRH increased LH production from the pituitary gland (Hanzen, 1984), GnRH-induced LH secretion in postpartum cows is enhanced (Randel, Lammoglia, Lewis, Neuendorff, & Guthrie, 1996). This could have a positive effect on cyst luteinization and/or ovulation of another follicle via endogenous and/or exogenous GnRH. Furthermore, removing the Eazi-Breed CIDR causes a rapid drop in plasma progesterone levels, which triggers the release of LH to assist follicular growth and eventually ovulation (Colazo & Mapletoft, 2014). Furthermore, progesterone works by promoting the mRNA expression of galanin, a neuropeptide involved in the release of gonadotropins during the preovulatory surge (Brann, Chorich, & Mahesh, 1993). The positive treatment results of the (GP) protocol and CIDR were independent of the kind of cyst, despite the fact that the luteolytic action of the PGF2α application would have predicted higher results for luteal cysts.

Dinsmore, White, and English (1990) found that giving GnRH and PGF2α at the same time had no negative effect on PGF2α's luteolytic effect in luteal cysts. Furthermore, cows given GnRH and PGF2α had superior reproductive performance (EIR, conception rate, and total pregnancy rate) than cows given GnRH alone or GnRH plus CIDR. Because of the autocrine regulating function of PGF2α, we concluded that treatment of all cows with GnRH and PGF2α, regardless of the kind of ovarian cyst, could be advised., In humans, Naor et al. (2007) recommended for the use of GnRH and PGF2α in the treatment of infertility and disorders characterized by imbalanced LH and FSH output, such as polycystic ovarian syndrome, as well as hormone-dependent diseases such prostate cancer and endometriosis. In addition to clinical response, reproductive performance must be considered when evaluating therapeutic efficacy, particularly from an economic standpoint (Lopez-Gatius & Lopez-Bejar, 2002).

The current study showed that the GP group achieved the highest EIR recorded at 75% with mean ±SD of (11.3 ± 4.2) days as the treatment-estrus interval. Using the same protocol, while employing PGF2α, 14 days following GnRH, Gatius and colleagues reported 29.4% EIR (López-Gatius et al., 2001) and 42 % in a later trial (Lopez-Gatius & Lopez-Bejar, 2002). Waheeb and Hatab (2017) claimed 87 % EIR and Saad reported 66.6 % EIR (Saad, 2013). Using the GnRH 7 days-PGF2α regimen, 34.9% EIR was obtained, it is clear from our results that GnRH-7days- PGF2α is the more successful therapeutic program. Exogenous PGF2α is used to induce regression of the luteinized cyst that developed from GnRH treatment 7-14 days later during GP treatment. As a result, the time between treatment and estrus is reduced, and the degree of estrus synchronization is increased. GnRH alone resulted in 66.7 % EIR, which is consistent with the findings

of Probo et al., who reported 71.3 % EIR (Probo et al., 2011), Waheeb & Hatab (70.3 %) (Waheeb & Hatab, 2017), and Bierschwal et al., who reported 64-82 % EIR following GnRH injection at varying doses (Bierschwal et al., 1975). Within 30 days of treatment, Mollo et al reported 64% (Mollo, Stradaioli, Gloria, & Cairoli, 2012) and 48% (Saad, 2013). Within 21 days after therapy, it was 37.1 % (Kim et al., 2006) and 28 % (Dinsmore et al., 1990). GnRH was found to be useful in treating both follicular and luteal cysts in the ovaries. Its mechanism of action can be described in two ways: GnRH either causes the cyst to luteinize or stimulates ovulation. And formation of new corpora lutea. GnRH injection, on the other hand, was demonstrated to cause ovulation in follicles other than the cystic one present at the time of therapy (Ambrose, Schmitt, Lopes, Mattos, & Thatcher, 2004).

Pregnancy rate (PR) was substantially greater in the GP group (66.7%) than in the other treatment protocols (58.3 percent, 49.9% in GnRH, and 49.9% in CIDR, respectively). Taktaz and colleagues obtained a higher PR of 76.6 % using the same GP technique (Taktaz, Kafi, Mokhtari, & Heidari, 2015), which is similar to Waheeb and Hatab's PR of 65.21 % (Waheeb & Hatab, 2017). Other investigations found lower percentages of around 18% (Bartolome et al., 2000), 13 % (Lopez-Gatius & Lopez-Bejar, 2002), and 5.9% (López-Gatius et al., 2001). GnRH alone was able to obtain PR (58.3%), which is within the previously reported ranges (46.42 % -71.42 %) of (Bierschwal et al., 1975). Dinsmore et al. attained a higher percentage of 71.8 % (1990). Using a single injection of GnRH, a PR of roughly 20% was recorded in cystic Friesian cows (Mollo et al., 2012), while a PR of 63 % was reported in cystic Friesian cows (Mollo et al., 2012). (Waheeb & Hatab, 2017). In our study, the CIDR group reported EIR (58.3%). Gatius and coworkers reported (83.3 %) EIR after 9 days of using the progesterone-releasing intravaginal device "PRID" (López-Gatius et al., 2001), and 100 % EIR after 12 days of PRID (Douthwaite & Dobson, 2000), but Waheeb reported (37.36 %) EIR after 12 days of PRID (Waheeb & Hatab, 2017).

Gatius and coworkers reported (83.3 %) EIR after 9 days of using the progesterone-releasing intravaginal device "PRID" (López-Gatius et al., 2001), and 100 % EIR after 12 days of PRID (Douthwaite & Dobson, 2000), but Waheeb reported (37.36 %) EIR after 12 days of PRID (Waheeb & Hatab, 2017). Follicular cyst has been linked to high levels of LH and an increase in its pulse frequency, which enhance the development and persistence of large cysts (Calder et al., 1999). The PR rate for the CIDR group was 49.9%. (6 pregnant out of 12 total treated). Using the same CIDR technique, other investigations showed PR of 41% (Ambrose et al., 2004) and 57.1 percent (Amer & Badr, 2008). Waheeb & Hatab recorded a PR rate of 47.36 % (Waheeb & Hatab, 2017). It was 50% after 12 days of PRID (Douthwaite & Dobson, 2000), 27.8% after 9 days of PRID (López-Gatius et al., 2001), and 20% after 10 days of PRID (Mollo et al., 2012).

Overall, the results of the current study's therapeutic protocols demonstrated that COD may be effectively treated even in the lack of cyst classification diagnostic tools. When ultrasonography and the P4 assay were employed to determine cyst type in other research, the results were identical (Probo et al., 2011; Taktaz et al., 2015).

5. Conclusion

Treatment of cystic cows with GnRH followed 7days later with PGF2α (GP protocol) recorded highest EIR and pregnancy rate (75% and 66.7% respectively); GnRH (66.7% & 58.3%) CIDR (58.3% & 49.45%). The GnRH and PGF2α protocol are an effective therapy in dairy cows diagnosed with COD.

Author contributions

All authors contributed to the conception and realization of the work. All the authors have contributed to the paper redaction and given their approval to the final version of the manuscript.

Conflict of interests

There are no conflicts of interest stated by the authors.

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