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The Effects of $PGF_{2\alpha}$ and CIDR on Ovarian Antral Follicular Development and Plasma IGF-1 Concentration in Goats

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Abstract: The aim of this study was to determine the effects of oestrus synchronization with $PGF_{2\alpha}$ and CIDR on the ovarian antral follicle population and plasma IGF-1 concentration in goats. Daily transrectal ultrasonographic examination was conducted in 24 regularly cycling goats that were divided equally into 3 groups and oestrus synchronized with $PGF_{2\alpha}$ (group A), CIDR (group B) and unsynchronized group (C). The mean number of follicles and IGF-1 concentration was significantly higher in the synchronized and subsequent natural oestrous cycles of group A and B when compared to group C. The total number of 3 mm diameter follicles were significantly higher in groups A and B compared with the control group C while the follicles that were 6 mm and larger were not significantly different ($p>0.05$). There was a significant low positive correlation ($r = 0.14$, $N = 234$) between IGF-1 concentration and the number of 3 mm follicles and between plasma IGF-I concentration and number of follicles ($r = 0.13$, $N = 234$). In conclusion, oestrus synchronization with $PGF_{2\alpha}$ or CIDR was associated with increased plasma IGF-1 concentration and number of follicles compared with naturally cycling goats.

Key words: Oestrus synchronization, ultrasonography, CIDR, $PGF_{2\alpha}$, follicular development, IGF-1, goats

INTRODUCTION

Transrectal ultrasonography is a non-invasive and reliable method of monitoring ovarian follicular development and has considerably increased the understanding of ovarian physiology in ruminants including goats (Adams *et al*., 2008; Ginther and Kot, 1994). Consequently, better methods of manipulating the oestrous cycle in goats were developed (Menchaca and Rubianes, 2004; Rubianes and Menchaca, 2003). Shortening the luteal phase with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or extending the luteal phase with progesterone (or synthetic progestagens) are the most commonly used methods of oestrous synchronization (Whitley and Jackson, 2004).

The process of recruitment of follicles, follicle selection, follicle deviation, dominance and atresia is regulated by hormonal interactions involving the hypothalamic-pituitary axis, the cyclic ovarian structures and the uterus (Adams *et al*., 2008; De Castro *et al*., 1999). In addition, ovarian folliculogenesis is closely associated with the insulin like growth factor-1 (IGF-1), their binding proteins and proteases (Hwa *et al*., 1999; Monget and Bondy, 2000; Monget *et al*., 2002). High positive correlations between IGF-1 concentration and several reproductive traits such as conception rate at first service, shorter interval to commencement of luteal activity and shorter calving to conception interval was reported from studies in cattle and led to suggestions that circulating IGF-1 concentration could be a useful predictor of reproductive success (Velazquez *et al*., 2008). In addition, the relationship between IGF-1 concentration and number of developing follicles in the ovaries may indicate the usefulness of measurement of endocrine IGF-1 concentration and its clinical applications. Thus, this study was conducted to describe the effects of oestrus synchronization with $PGF_{2\alpha}$ or CIDR on follicular populations and to depict the changes in plasma IGF-1

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concentration and relationship with number of follicles during follicular and luteal phases in oestrus synchronized goats.

MATERIALS AND METHODS

Experimental animals and management: A total of 24 multiparous cycling Boer x Australian feral goat crosses of 3-4 years of age were used in this study. The goats were regularly cycling and ovulation occurred in all the goats at the end of each of three consecutive oestrous cycles preceding the commencement of this study. The goats are known to breed throughout the year (non seasonally polyoestrous). Body Condition Score (BCS) of the goats was assessed with score 1 being very thin with prominent ribs and vertebrae, score 3 being moderate condition whereby the vertebrae and rib areas are smooth and even and 5 been very fat (Burkholder, 2000). The mean body weight and median BCS for the experimental animals were 35±2.7 kg and 3, respectively. The goats were housed in roofed pens with slatted floors at a goat farm in Kuang, Malaysia (Lat: 3°15′N and Long: 101°32′60″E). The mean daily ambient temperature and relative humidity during the period of this study was 28°C and 87%, respectively. The does were fed with mixed feed of palm leaf silage and soya bean pulp and supplemented with commercial feed pellets with minimum of 16% crude protein and 10 MJ kg^{-1} metabolizable energy. The does were kept indoor throughout the study and they were in very good health. Water and salt licks were provided *ad libitum*. The goats were randomly allocated into three equal groups of 8 goats each: $PGF_{2\alpha}$ synchronized group (group A), CIDR synchronized group (group B) and unsynchronized or control group (group C). In group A, oestrus was synchronized with a double injection of 125 μg (0.5 mL) of the $PGF_{2\alpha}$ analogue, cloprostenol (Estrumate™, Schering-Plough, Australia) 11 days apart (Kusina *et al*., 2000). For group B, the goats were synchronized with Controlled Internal Drug Release Device (CIDR, EAZI-BREED™, New Zealand) containing 0.3 g progesterone which was inserted into the vagina and left in place for 17 days (Wildeus, 2000). The natural oestrous cycle immediately after synchronization in groups A and B were also studied. None of the CIDR inserts was lost during the period of treatment. Group C (control) were not oestrus synchronized and were naturally cycling goats which were ultrasonographically monitored until ovulation occurred and data collection commenced. The goats in groups A-C were not evaluated for changes in sexual behaviour and the length of the interval between ovulatory periods was used to represent oestrous cycle length (Ginther and Kot, 1994).

Ultrasonography: Daily ultrasonographic scanning of the ovaries was performed to study follicular development using a real-time B-mode ultrasound scanner (Aloka, 500 SSD, Japan) with a transrectal 7.5 MHz linear probe (UST-660-7.5 model). The ultrasound scanning commenced 24 h after the second $PGF_{2\alpha}$ injection in group A and the removal of CIDR in group B to record the day of ovulation (day 0). However for group C, commencement of scanning was timed to coincide with the end of oestrus synchronization treatment of group A, B and the scanning was continued until a complete oestrous cycle of normal length (19-22 days) was attained and recorded. The scanning was performed from 0800-1200 h. Each goat was scanned once daily for two consecutive oestrous cycles in group A and B to record the synchronized oestrous cycle and the natural oestrous cycle immediately subsequent to the synchronized cycle. On the other hand, group C was scanned for one oestrous cycle because the goats were in different phases of the oestrous cycle and were monitored until ovulation (day 0) and commencement of the study.

Ovaries were visualized and the number of antral follicles that were at least 3 mm in diameter were measured using the ultrasound scanner's built-in calipers. Images of ovaries were sketched as they were visualized in real time (Ginther and Kot, 1994; Simoes *et al*., 2006). Ovulation occured when a preovulatory follicle of >5 mm in diameter has collapsed with the subsequent appearance of a corpus luteum on the site of ovulation (Ginther and Kot, 1994).

Blood collection and hormone analysis: About 5 mL of blood samples were collected each day from the day of ovulation and before scanning via the jugular vein into heparinized vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA). Blood samples were centrifuged at 1006×g for 15 min and plasma was aspirated into clean glass tubes and stored at -20°C until assay. Plasma progesterone concentration was measured from samples taken twice a week at interval of 3-4 days only to characterize the oestrous cycle. The luteal phase was considered as when the progesterone concentration rose >1 ng mL^{-1} and the follicular phase was when the concentration declines to below the threshold value of 1 ng mL^{-1}. The plasma progesterone concentration was determined using radioimmunoassay kit (PROG-CTK-4; DiaSorin, Italy). Inter and intra-assay Coefficient of Variation (CV) was 5.9 and 4.0%, respectively. Analytical sensitivity was 0.05 ng mL^{-1}. The phases of the oestrus cycles were determined with ultrasonography and retrospectively confirmed with progesterone assay. Thus, subsequent analyses of plasma IGF-1 concentration were

aligned to the days of the oestrous cycle. Concentration of plasma IGF-1 levels throughout the synchronized and subsequent oestrous cycles of group A, B and control group C were measured from blood samples collected 3-4 days apart.

On the other hand, the concentration of IGF-1 were determined from 3 samples from each of mid follicular and mid luteal phases of synchronized and natural oestrous cycles of group A, B and control group C to compare the plasma IGF-1 concentration during the follicular and luteal phases.

The IGF-1 concentration was measured using DSL-2800 (ACTIVE™ Non-Extraction IGF-1 ELISA, Diagnostic Systems Laboratories, Inc. Webster, Texas, USA) for the quantitative measurement of IGF-1 in plasma. The inter-assay and intra-assay CV was 6.3 and 2.4%, respectively. Analytical sensitivity was 0.01 ng mL^{-1}.

Statistical analysis: Data from one goat in group A was not included in the analysis due to its short interovulatory interval (<15 days). Ultrasonographic data obtained were combined for left and right ovaries and analysis of follicle populations began with the first ovulation that subsequently resulted in a corpus luteum with normal life (at least 13 days). The ultrasonographic and hormonal data were matched with the days of the oestrous cycle for statistical analysis. Levene's test of homogeneity of variances was not significant and assumptions for parametric analysis were met. The 3 and ≥6 mm diameter follicle categories were non normally distributed and were log transformed prior to analysis. Analysis of Variance (ANOVA) was followed-up with Duncan's post hoc test were conducted to examine differences in follicle number and IGF-1 concentration between the treatment and control groups as well as between follicular and luteal phases. ANOVA for repeated measures for daily number of follicles and for IGF-1 concentration among groups was also performed. The Pearson correlation coefficient between follicular development and plasma IGF-1 concentration was calculated. All analyses were conducted using SPSS statistical software (SPSS Inc. Version 17). Analyses were considered to be statistically significant at $p<0.05$.

RESULTS

The mean number of follicles and plasma IGF-1 concentration during the follicular phase were not significantly different ($p>0.05$) among the synchronized and subsequent natural oestrous cycles of $PGF_{2\alpha}$, CIDR synchronized and control groups (Table 1). However, the number of follicles and plasma IGF-1 concentration in the control group during the luteal phase was significantly smaller than in the follicular and luteal phases of the $PGF_{2\alpha}$, CIDR synchronized and subsequent natural oestrous cycles. Furthermore, there was a significant difference in overall mean follicle numbers and plasma IGF-1 concentration when either $PGF_{2\alpha}$ or CIDR synchronized or natural oestrous cycles was compared with group C. The mean plasma progesterone concentration was significantly higher during the luteal compared to follicular phase but was not significantly different between the synchronized and natural oestrous cycles of $PGF_{2\alpha}$ and CIDR synchronized, their subsequent natural and unsynchronized oestrous cycles.

The distribution of follicles that were 3-5 and ≥6 mm in diameter among the follicular and luteal phases of the $PGF_{2\alpha}$ (A), CIDR (B) and control (C) groups are shown in Table 2. The frequency of 3 and 4 mm diameter follicles were not significantly different ($p>0.05$) between the follicular and luteal phases of $PGF_{2\alpha}$ or CIDR synchronized, subsequent natural oestrous cycles and the control group. Similarly, the mean diameter of the 5 mm follicles was not significantly different between the follicular and luteal phases of $PGF_{2\alpha}$ synchronized oestrous cycles (group A) but was higher during the follicular compared with the luteal phase of CIDR

Table 1: Mean number of follicles and plasma IGF-1 concentration during the follicular and luteal phases in the $PGF_{2\alpha}$ and CIDR synchronized and control groups

		No. of follicles		IGF-1 (ng mL^{-1})		Progesterone (ng mL^{-1})	
Oestrous phase	Groups	Synchronized	Natural	Synchronized	Natural	Synchronized	Natural
Follicular	$PGF_{2\alpha}$ (A)	7.2±0.7^{a}	5.9±0.8^{a}	108.6±18.9^{m}	122.2±17.5^{m}	0.4±0.1^{x}	0.6±0.2^{x}
	CIDR (B)	6.8±0.7^{a}	5.7±0.6^{a}	135.9±16.0^{m}	120.8±22.4^{m}	0.4±0.0^{x}	0.8±0.4^{x}
	Control (C)	5.0±1.1^{a}		85.4±11.7^{m}		0.4±0.7^{x}	
Luteal	$PGF_{2\alpha}$ (A)	4.8±0.5^{a}	5.7±0.6^{a}	88.9±11.3^{m}	92.5±14.1^{m}	3.7±0.2^{y}	3.8±0.5^{y}
	CIDR (B)	5.6±0.5^{a}	5.4±0.9^{a}	85.5±6.50^{m}	84.2±7.90^{m}	4.6±0.6^{y}	3.1±0.7^{y}
	Control (C)	3.8±0.4^{b}		64.8±17.8^{n}		2.1±0.7^{y}	
Total	$PGF_{2\alpha}$ (A)	6.3±0.4^{a}	5.2±0.3^{a}	92.8±6.30^{m}	109.8±10.4^{m}	2.0±0.3	
	CIDR (B)	5.9±0.4^{a}	5.5±0.3^{a}	111.6±8.60^{m}	100.4±8.80^{m}	2.2±0.3	
	Control (C)	4.4±0.3^{b}		81.4±6.90^{n}		1.9±0.6	

Values within a column of the same parameter (number of follicles a, b, IGF-1 m, n and progesterone concentration x, y) with common superscripts do not differ ($p<0.05$)

Table 2: Frequency distribution of follicles during the follicular and luteal phases in the $PGF_{2\alpha}$ and CIDR synchronized and control groups

			Diameter of follicles (mm)			
Groups	Types of oestrous cycle	Phases of oestrous cycle	3	4	5	>6
A ($PGF_{2\alpha}$)	Synchronized	Follicular	3.6 ± 0.6^{a}	2.0 ± 0.4^{a}	$0.8\pm0.2^{a,b}$	0.9 ± 0.2^{a}
		Luteal	$2.8\pm0.4^{a,b}$	1.1 ± 0.2^{a}	0.6 ± 0.2^{a}	0.4 ± 0.1^{a}
	Natural	Follicular	$2.9\pm0.8^{a,b}$	1.6 ± 0.4^{a}	$0.7\pm0.2^{a,b}$	0.6 ± 0.2^{a}
		Luteal	3.1 ± 0.5^{a}	0.9 ± 0.3^{a}	$0.9\pm0.4^{a,b}$	0.8 ± 0.2^{a}
		Total	3.1 ± 0.3^{x}	1.5 ± 0.2^{x}	0.8 ± 0.1^{x}	0.8 ± 0.1^{x}
B (CIDR)	Synchronized	Follicular	3.5 ± 0.8^{a}	1.0 ± 0.3^{a}	1.5 ± 0.3^{b}	0.9 ± 0.2^{a}
		Luteal	3.0 ± 0.5^{a}	1.0 ± 0.2^{a}	0.6 ± 0.3^{a}	1.1 ± 0.1^{a}
	Natural	Follicular	$2.6\pm0.9^{a,b}$	1.9 ± 0.5^{a}	0.4 ± 0.1^{a}	0.6 ± 0.1^{a}
		Luteal	$2.1\pm0.5^{a,b}$	1.6 ± 0.6^{a}	0.3 ± 0.2^{a}	0.9 ± 0.2^{a}
		Total	2.8 ± 0.3^{x}	1.4 ± 0.2^{x}	0.8 ± 0.0^{x}	0.9 ± 0.1^{x}
C (Control)	Unsynchronized	Follicular	$1.7\pm1.1^{a,b}$	1.8 ± 0.5^{a}	1.5 ± 0.4^{b}	1.1 ± 0.4^{a}
		Luteal	0.8 ± 0.2^{b}	1.3 ± 0.4^{a}	$0.9\pm0.2^{a,b}$	0.8 ± 0.2^{a}
		Total	1.1 ± 0.4^{y}	1.1 ± 0.1^{x}	1.1 ± 0.1^{y}	0.9 ± 0.1^{x}

Values within a column with different superscripts (a-c and x, y) are significantly different ($p<0.05$)

synchronized oestrous cycle (group B). In addition, the total number of 3 mm diameter follicles was significantly smaller in group C compared with group A and B. On the other hand, the total number of 5 mm follicles was significantly smaller in group A and B compared with group C. The mean number of ≥6 mm diameter follicles was not significantly different among the follicular, luteal phases and group totals of the $PGF_{2\alpha}$ (A), CIDR (B) and control (C) groups. ANOVA for repeated measures showed significant main day effects ($p<0.05$) for mean daily number of follicles and for IGF-1 concentration. However, there was no interaction ($p>0.05$) between method of oestrus synchronization and the daily number of follicles.

Figure 1 shows the distribution of the mean daily number of follicles during the interovulatory interval in the $PGF_{2\alpha}$ and CIDR synchronized groups, their respective subsequent natural oestrous cycles and in the control group.

The day of ovulation (day 0) following the synchronized oestrous cycle and which marked the beginning of the subsequent natural oestrous cycle was also indicted (arrow). The IGF-1 concentration among the $PGF_{2\alpha}$, CIDR and control groups from day of ovulation (day 0) is shown in Fig. 2. The IGF-1 concentration was different among days of sampling in both the treatment and control groups.

There was significant positive correlation between plasma IGF-1 concentration and number of follicles ($r = 0.14$, $p = 0.02$, $N = 234$). Of the different categories of follicles (3 to ≥6 mm) only the 3 mm sized follicles were positively correlated with the plasma IGF-1 levels ($r = 0.13$, $p = 0.03$, $N = 234$). The larger size follicles (4 to ≥6 mm) had low positive non-significant correlation with plasma IGF-1 concentration.

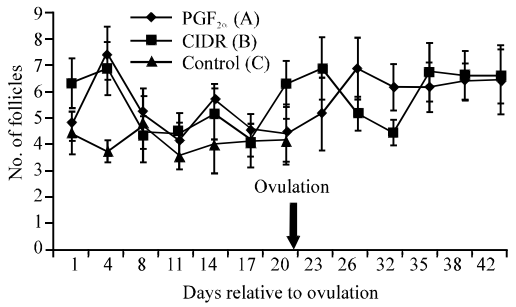

Fig. 1: Mean number of follicles among $PGF_{2\alpha}$ and CIDR synchronized groups, their respective subsequent natural oestrous cycles and the control group. The arrow indicates the time of second ovulation

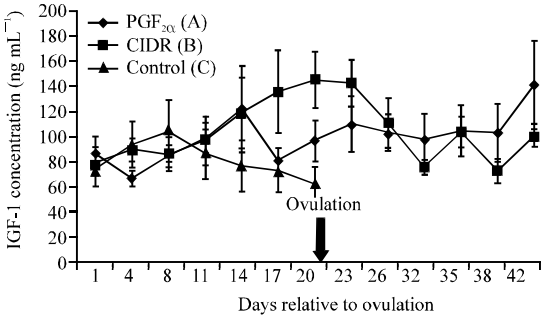

Fig. 2: Mean plasma IGF-1 concentration among $PGF_{2\alpha}$ and CIDR synchronized groups, their respective subsequent natural oestrous cycles and the control group. The arrow indicates the time of second ovulation

DISCUSSION

In the present study, the mean number of follicles and plasma IGF-1 concentration during the $PGF_{2\alpha}$ and CIDR synchronized oestrous cycles and their respective

subsequent natural oestrous cycles were not significantly different. Similarly, in a previous study the presence or absence of a corpus luteum during oestrus synchronization with the synthetic prostaglandin analogue (luprostiol) or the progestagen (fluorogestone acetate) did not alter follicular development from onset of oestrus to 2 days after ovulation in non-lactating crossbred Alpina-Boer goats during the breeding season (Lassala *et al*., 2004). Similar studies in both cows and heifers suggested that $PGF_{2\alpha}$ treatment did not significantly modify the follicular dynamics of the oestrous cycle (Figueiredo *et al*., 1997).

However in the present study, the lower number of follicles indicated in the control group suggests that oestrus synchronization with $PGF_{2\alpha}$ and CIDR resulted in higher number of follicles during the synchronized and natural oestrous cycle. This observation could be explained with a previous report that follicular turnover was higher in $PGF_{2\alpha}$ synchronized Anglo-Nubian goats compared with natural oestrous cycle (Vazquez *et al*., 2010). In the current study, the mean number 3 and 5 mm follicles were higher in the $PGF_{2\alpha}$ and CIDR synchronized oestrous cycles compared with the larger ≥6 mm diameter follicles implying that the oestrus synchronization treatment did not alter the frequency of antral follicles >6 mm in diameter during the interovulatory intervals. In a previous report, small antral follicles (3 mm) were described as part of an underlying dynamic pool of follicles that developed and regressed rather than part of a cohort of follicles, one or more of which might have grown to preovulatory size and ovulated (Ginther and Kot, 1994).

The insulin-like growth factor-1 is a peptide and one of the complex IGF-1 superfamily (Hwa *et al*., 1999). IGF-1 stimulates follicular development through recruitment of follicle cohorts in a process that is gonadotrophin independent although FSH may affect the rate of preantral follicle growth (Hwa *et al*., 1999; Sudo *et al*., 2007). As the follicles grow larger, preovulatory selection and dominance are FSH dependent (Webb *et al*., 2004). In the present study, IGF-1 concentration during the follicular and luteal phase of the treatment and control groups were not significantly different. In contrast, a previous study showed that the endocrine IGF-1 concentrations in non-seasonally polyoestrous miniature Japanese Shiba goats increased during the follicular phase of the oestrous cycle compared with the luteal phase (Hashizume *et al*., 2000).

There were differences in plasma IGF-1 concentration between sampling days as depicted by the significant day effects in the analysis for repeated measures. Generally, the concentration of peripheral IGF-1 concentration is influenced by the activities of the IGF binding proteins and proteases and are very important in regulating peripheral IGF-1 concentration (Mihm and Bleach, 2003). However, the reason for the lower mean plasma concentration of IGF-1 in the control group is unclear. Perhaps, the CIDR and $PGF_{2\alpha}$ stimulated the synthesis and release of IGF-1 from the liver and other tissues. Furthermore, it was reported that the increased plasma IGF-1 concentration in goats which peaked at oestrus originated mainly from the uterus (Sumie *et al*., 2003).

The significant low positive correlation between the number of 3 mm diameter follicles and IGF-1 concentration found in the present study was probably because IGF-I is primarily postulated to stimulate the proliferation of granulosa cells from small (1-3 mm in diameter) but not from large (>5 mm in diameter) follicles (Hwa *et al*., 1999; Sudo *et al*., 2007). A weak relationship was similarly found between IGF-1 concentration and follicular development in cow (Spicer *et al*., 1992).

On the other hand, previous studies showed that IGF-1 concentration in cattle, sheep and goats managed under improved nutrition (Rhoads *et al*., 2007) or administered with insulin or growth hormone (Gong *et al*., 1996; Sarath *et al*., 2008; Scaramuzzi *et al*., 1999) show significantly higher follicular turnover and higher endocrine IGF-1 concentration compared with controls. Thus, the positive correlation between IGF-1 concentration and number of follicles could be attributed to the stimulatory effect of IGF-1 on growth of antral follicles that were <3 mm in diameter.

CONCLUSION

Results from the current study indicated that follicle populations and plasma IGF-1 concentration was not significantly different between $PGF_{2\alpha}$ and CIDR synchronized oestrous cycles and their subsequent natural oestrous cycles but were lower in the unsynchronized (natural) oestrous cycles suggesting that oestrus synchronization with $PGF_{2\alpha}$ and CIDR had a positive effect on the follicle populations and plasma IGF-1 concentration. In addition, the low positive correlation between 3 mm diameter antral follicles and plasma IGF-1 concentration and lack of correlation with the large antral follicles indicated that plasma IGF-1 concentration might not be a meaningful measure of antral follicular development in goats.

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