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Paraoxonase Activities, Total Sialic Acid Concentration and Lipid Profile After Use of Controlled Internal Drug Release (CIDR) in Gurcu Goats

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ABSTRACT

The purpose of this study was to determine the effect of the use of controlled internal drug release (CIDR) in Gurcu goats for estrus synchronization on paraoxonase activity (PON1), total sialic acid (TSA) concentration and lipid profile. In the study, 50 Gurcu goats were examined. On day 9, 400IU pregnant mare serum gonadotropin and 5mg dinoprost tromethamine were injected. On day 11, CIDR was removed. Following estrus detection, goats on estrus mated with fertility proven Gurcu bucks (mating day). Biochemical analyses were conducted with samples taken on day 0, day 11 and mating day. An increase in TSA concentration and a decrease in PON1 activity was detected according to synchronization days (day 0, day 11 and mating day). A decrease was found in total cholesterol (TC), triglycerides and high-density lipoprotein concentrations. On day 11, an increase in TSA concentration and a decrease in PON1 activity was detected compared to control group. According to synchronization days (day 0, day 11, mating day), it was determined that TSA concentration increased in pregnant and non-pregnant goats (P=0.007 and P=0.013, respectively) and PON1 activity decreased (P=0.004). A negative correlation was determined between PON1 and TC (r=-401, P<0.05). In conclusion, CIDR treatment caused changes in PON1 activity, TSA concentration and lipid profile, on the other hand, did not negatively affect fertility.

Key words: CIDR, Gurcu goats, Lipid profile, Paraoxonase activities, Total sialic acid.

INTRODUCTION

Progesterone releasing devices [sponge or controlled internal drug release (CIDR)] can be used as intravaginal for estrus synchronization of small ruminants. Length of use of these devices might vary depending on breeding season (Abecia *et al.,* 2012; Kaçar *et al.,* 2016; Çizmeci *et al.,* 2016). During this season, these devices that remained in vagina can cause tissue damage, inflammation and infection problems (Kuru *et al.,* 2015; Manes *et al.,* 2015). Therefore, this kind of applications is reported to cause changes in oxidative stress parameters (Oral *et al.,* 2015). Especially for goats, intravaginal applications are reported to cause a specific level of stress (Kuru *et al.,* 2016). However, information was not found about the effect of a device placed in vagina of goats, such as CIDR, on serum paraoxonase activity (PON1) and total sialic acid (TSA) concentration, and about the relationship between these parameters and fertility.

Oxidative stress has an important role in many diseases' pathophysiology. As a response to inflammatory stimulus, reactive oxygen species (ROS) or free radicals are released from dendritic cells, neutrophil and macrophages. The produced ROS should be sustained in balance with antioxidant system in the cell. An increase of ROS level in cells can cause oxidative damage in protein, lipid and DNA (Ozcan and Ogun 2015; Kara *et al.,* 2016). Paraoxonase enzyme is an antioxidant enzyme found in serum, liver, kidney and intestine (Deveci *et al.,* 2017). PON1 is found with high-density lipoprotein (HDL) in plasma. PON1 can prevent both HDL and low-density lipoprotein (LDL) against oxidation (Yegin *et al.,* 2013; Kaya *et al.,* 2016). It has been reported that PON1 can act as a negative acute phase protein and hepatic synthesis can decrease in case of infection (James and Deakin 2004).

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and extend their lives and functionalities (Varki and Schauer 2009). Some functions for example binding and transporting of ions and drugs, stabilizing of proteins conformation, including also enzymes, increasing viscosities of musings are caused by sialic acids relatively powerful electronegative charge. One of the general characteristics of sialic acids is their free radical cleansing antioxidative effect which has been recently defined (Varki and Schauer 2009; Ciftci *et al.,* 2010). Additionally, sialic acid is reported to take roles in inflammation, immune response and infection cases (Deveci *et al.,* 2017; Abdoon *et al.,* 2020).

In this study, it was aimed to determine the effect of use of CIDR for estrus synchronization in Gurcu goats on PON1 activity, TSA, triglyceride (TG), total cholesterol (TC), HDL, LDL, very low-density lipoproteins (VLDL), phospholipid (PL) and total lipid (TL) concentrations. Additionally, PON1 activity after CIDR application, and the relationship of PON1 activity and TSA, TC, TG, HDL, LDL concentrations with fertility would be determined as comparing the related parameters in serum samples taken during synchronization process from pregnant and non-pregnant goats.

MATERIALS AND METHODS

This study was conducted with permission of Kafkas University Animal Experiment Local Ethic Committee (KAÜ-HADYEK-2016/20).

Location, animal material and ration

This study was conducted in Kafkas University, Veterinary Faculty, Prof. Dr. Ali Rıza AKSOY Research Farm, in 2016. In this study, 50 Gurcu goats, age of 2-4 years, weight of 40-50kg, that were not in lactation period and clinically healthy were used. Estrus synchronization with CIDR was applied to 40 of the goats. Ten goats were selected as control group and any kind of treatments were not applied. Goats were fed with dry alfalfa herb, dry herb and concentrated feed (12% rude protein, 2600kcal/kg) twice a day. Water and mineral salt lick were available *ad libitum.*

Estrus synchronization protocol and pregnancy diagnosis

Estrus synchronization was applied during breeding season (October-December). CIDR (0.33g progesterone, Eazi-Breed CIDR®, Zoetis, Turkey) was placed in vagina of goats (n=40) and kept in vagina for 11 days. On day 9, 400 IU pregnant mare serum gonadotropin (i.m., PMSG, Chronogest®, MSD-İntervet, Turkey) and prostaglandin F2α (i.m., 5 mg, dinoprost trometamin, Dinolytic®, Zoetis, Turkey) were injected on day 11, CIDR was removed and estrus detection was started. For estrus detection, one buck was left among Gurcu goats in 6-hour intervals. Goats that were detected with estrus were mated with fertility proven Gurcu bucks. Any kind of treatments was not applied to goats in control group (n=10). Estrus detection and mating were not applied.

Pregnancy diagnosis was made with linear probe transrectal ultrasonography (7.5MHz, SonoSite Titan®, SonoSite, USA) 30 days later then mating process. Goats were recorded as pregnant when an embryo was detected.

Blood sampling and biochemical analysis

Blood samples were taken before CIDR was inserted in vagina (day 0), CIDR removal day (day 11), and mating day. Blood samples were taken with sterile holder needles from *vena jugularis* to vacuumed and clot activated 10mL tubes (Vacutest Kima®, Vacutest, Italy). After blood samples were centrifuged at 3000rpm for 10min at 4°C, serum specimens were allocated and stored at -20°C.

TSA was measured using spectrophotometer (Epoch, Biotek®, USA) in accordance with the method explained by Sydow (1985), and results were recorded as mg/dL.

PON1 activity was measured in accordance with the methods of Eckerson *et al.* (1983), and Gülcü and Gürsu (2003). PON1 activity was identified with measurement of absorbance of colored composite caused by 4-nitrophenol which is an enzymatic product of paraoxon-ethyl (Sigma®, London, UK), used as a substrate, with spectrophotometer at 25°C and 412nm. For paraoxonase activity, enzyme activity that could convert 1nmol paraoxon-ethyl of enzyme in 1 mL serum to 4-nitrophenol 1min was identified as unite, and results were recorded as U/L.

Triglyceride, TC and HDL concentrations were measured in auto analyzer (Roche®/Hitachi 917) by using Biotrol® (Biotrol Diagnostic, France) commercial kits, and results were recorded as mg/dL. LDL and VLDL concentrations were calculated using the formula: LDL= TC−HDL−(TG/5), presented by Friedewald *et al.* (1972) [TG (mg/dL) <400mg/dL VLDL (mg/dL) = TG (mg/dL)/5]. Phospholipid concentration was calculated with formula, PL (mg/dL)=0.766TC+0.623, and total lipid concentration was calculated with formula TL (mg/dL)=2.27*TC+0.623 (Phillips *et al.,* 1989).

Statistical analysis

Results were statistically analyzed by using SPSS® (SPSS 18.0, Chicago, IL, USA) software program. Statistical differences between pregnant, non-pregnant and control groups were evaluated with one-way ANOVA and Dunnett's T3 test. Statistical differences between synchronization group and control was compared with Student *t*-test. Statistical differences between days (day 0, day 11 and mating day) were compared with repeated measured of ANOVA and Bonferroni. Pearson correlation co-efficiencies were calculated to define the correlation between variables.

RESULTS

Thirty days after mating, 28 pregnant (70%) were identified in pregnancy diagnose process conducted with transrectal ultrasonography. A statistical change was observed in TSA concentration in terms of estrus synchronization days (day 0, day 11, mating day), (P=0.005). Especially, in day 11, the change was in the highest level (Table 1). The change in PON1 activity in terms of days was statistically significant (P<0.001) and was observed as the lowest level on day 11 (Table 1). A statistically important change was not observed in lipid profile in terms of LDL concentration (P=0.471); while statistical differences were observed in terms of TC (P<0.001), TG (P=0.001), HDL (P<0.001), VLDL (P=0.002),

Table 1: Serum PON1 activity, TSA, TC, TG, HDL, LDL, VLDL, PL and TL concentrations of (S) group that estrus synchronization was made with CIDR and control group (C) on day 0, day 11 and mating day

Parameters	Group	N	Day 0 Mean±SEM	Day 11 Mean±SEM	Mating day Mean±SEM	P value
TSA (mg/dL)	S	40	11.32±0.67[a]	15.38±0.98[bA]	11.74±0.84[ab]	0.005
	C	10	11.06±1.48	10.62±1.54[B]	11.03±1.32	0.978
	-	P value	0.993	0.011	0.697	-
PON1 (µmol/min/L)	S	40	125.16±6.32[a]	95.67±4.66[bA]	117.85±4.43[a]	<0.001
	C	10	126.29±10.26	125.01±8.59[B]	123.60±5.88	0.419
	-	P value	0.931	0.009	0.518	-
TC (mg/dL)	S	40	124.95±3.00[a]	104.47±2.92[bA]	115.03±2.85[c]	<0.001
	C	10	123.90±7.55	124.10±5.20[B]	117.30±4.03	0.716
	-	P value	0.883	0.004	0.710	-
TG (mg/dL)	S	40	48.53±1.72[a]	40.19±0.91[bA]	44.63±1.89[a]	0.001
	C	10	43.70±1.89	48.70±3.29[B]	43.30±2.15	0.303
	-	P value	0.185	0.031	0.738	-
HDL (mg/dL)	S	40	85.59±1.56[a]	62.96±1.76[bA]	74.50±1.05[c]	<0.001
	C	10	83.20±4.34	85.20±6.07[B]	84.30±5.21	0.972
	-	P value	0.531	0.005	0.096	-
LDL (mg/dL)	S	40	30.08±2.25	33.48±3.61	31.60±2.61	0.471
	C	10	31.96±7.19	29.16±6.20	24.34±4.66	0.718
	-	P value	0.744	0.587	0.210	-
VLDL (mg/dL)	S	40	9.71±0.34[a]	8.04±0.18[bA]	8.93±0.38[a]	0.002
	C	10	8.74±0.38	9.74±0.66[B]	8.66±0.43	0.303
	-	P value	0.184	0.031	0.738	-
PL (mg/dL)	S	40	158.01±2.29[a]	142.33±2.24[bA]	150.41±2.19[c]	<0.001
	C	10	157.21±5.79	157.36±3.98[B]	152.15±3.09	0.716
	-	P value	0.681	0.002	0.740	-
TL (mg/dL)	S	40	394.46±7.65[a]	339.65±7.15[bA]	368.03±7.70[c]	<0.001
	C	10	387.25±16.75	392.71±14.49[B]	371.87±8.45	0.631
	-	P value	0.883	0.004	0.710	-

[a,b,c]: The difference between values with different letters on the same line is significant (P<0.05). [A,B]: Different superscripts within column are significant (P<0.05). PON1: Paraoxonase, TSA: Total sialic acid, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low-density lipoproteins, PL: Phospholipid, TL: Total lipid. S: Synchronization group, C: Control group.

PL (P<0.001) and TL (P<0.001) concentrations. Additionally, after synchronization application, a statistically significant increase was observed in TSA concentration compared to control group (P=0.011), and a statistically significant decrease was observed in PON1 activity (P=0.009) and lipid profile indicators (except from LDL) (P<0.05, Table 1).

It was determined that TSA concentration statistically significant changed in pregnant and non-pregnant (P=0.007 and P=0.013 respectively). It was observed that especially TSA concentration was increased on day 11 and decreased down to day 0 levels on mating day (Table 2). Unlike TSA, PON1 activity was observed to decrease on day 11, while there were non-significant changes in LDL concentrations in terms of days (pregnant and non-pregnant), however, significant (P<0.05) changes were observed in other lipid profile indicators (Table 2).

On day 11, TC, PL and TL concentrations were observed to be statistically significant in pregnant and non-pregnant goats. On mating day, TC, LDL, PL and TL concentrations were determined with significant (P<0.001) differences in terms of pregnant and non-pregnant goats (Table 2).

Statistical comparison of group (S) for which estrus synchronization was made with CIDR and control group (C) in terms of PON1 activity, TSA concentration and lipid profile changes are presented in Table 1. Statistical comparisons of pregnant, non-pregnant and control group in terms of PON1 activity, TSA concentration and lipid profile changes are presented in Table 2. Correlations between PON1 activity, TSA concentration and lipid profile indicators in terms of application days (day 0, day 11, mating day) are presented in Table 3.

DISCUSSION

Sponge or CIDR can be used for estrus synchronization in vagina of sheep and goats. The main purpose of use of these devices is to increase serum progesterone concentration (Abecia *et al.,* 2012; Kaçar *et al.,* 2016). Changes in acute inflammation markers and oxidative stress indicators (Kuru *et al.,* 2015, 2016; Oral *et al.,* 2015) were observed after this application that cause especially local tissue damage and inflammation (Suárez *et al.,* 2006; Kuru *et al.,* 2018). In this study, as first time in literature, the effect of a device, such as CIDR that was placed in vagina, on serum PON1 activity, TSA concentration was determined.

Sialic acids can affect fertilization during sperm interaction with female reproduction system surfaces or various fluids. Additionally, agglutinin and sialic acids are recognized in endometrium. It is thought that sialic acids engage directly in fertilization and affect embryogenesis. However, the mechanism is not entirely known (Velásquez *et al.,* 2007; Varki, 2008). In this study, TSA concentration was affected by inflammation caused by CIDR and TSA was increased especially on day 11. TSA was determined as high concentration compared to control group (Table 1). This increase did not affect fertilization and condition of spermatozoon in female genital tracks,

Table 2: Changes in PON1 activity, TSA, TC, TG, HDL, LDL, VLDL, PL and TL concentrations of pregnant, non-pregnant and control group on synchronization days (day 0, day 11 and mating day) in terms of pregnancy diagnosis made 30 later then mating

Parameters	N	Day 0	Day 11	Mating Day	P value	Pregnancy Status*
TSA (mg/dL)	28	11.12±0.90^{a}	16.56±1.40^{bA}	11.58±1.08^{a}	0.007	Pregnant
	12	10.87±1.31^{a}	16.39±1.27^{bA}	12.09±1.29^{a}	0.013	Non-pregnant
	10	11.06±1.48	10.62±1.54^{B}	11.03±1.32	0.978	Control
	P value	0.737	0.041	0.958		
PON (µmol/min/L)	28	127.25±9.30^{a}	96.24±6.08^{bA}	118.68±4.98^{a}	0.004	Pregnant
	12	121.33±5.96^{a}	94.63±7.45^{bA}	116.33±8.94^{a}	0.004	Non-pregnant
	10	126.29±10.26	125.01±8.59^{B}	123.60±5.88	0.419	Control
	P value	0.899	0.019	0.785		
TC (mg/dL)	28	128.03±3.64^{a}	108.82±3.77^{bA}	122.71±2.99^{aA}	<0.001	Pregnant
	12	117.75±4.88^{a}	94.33±2.48^{bB}	97.08±1.70^{bB}	<0.001	Non-pregnant
	10	123.90±7.55	124.10±5.20^{C}	117.30±4.03^{A}	0.716	Control
	P value	0.325	0.001	<0.001		
TG (mg/dL)	28	48.93±2.16^{a}	41.65±1.12^{bA}	46.53±2.53^{ab}	0.037	Pregnant
	12	47.58±2.85^{a}	36.81±1.04^{bA}	40.17±1.68^{ab}	0.019	Non-pregnant
	10	43.70±1.89	48.70±3.29^{B}	43.30±2.15	0.303	Control
	P value	0.39	0.001	0.238		
HDL (mg/dL)	28	85.02±1.06^{a}	62.09±2.13^{bA}	75.85±1.12^{cA}	<0.001	Pregnant
	12	86.91±4.70^{a}	65.00±3.15^{bA}	71.33±2.14^{bA}	<0.001	Non-pregnant
	10	83.20±4.34	85.20±6.07^{B}	84.30±5.21^{B}	0.972	Control
	P value	0.723	<0.001	0.007		
LDL (mg/dL)	28	33.23±2.77	38.41±4.79	37.55±2.77^{A}	0.314	Pregnant
	12	22.73±2.96	21.97±2.44	17.72±3.38^{B}	0.402	Non-pregnant
	10	31.96±7.19	29.16±6.20	24.34±4.66^{B}	0.718	Control
	P value	0.157	0.083	<0.001		
VLDL (mg/dL)	28	9.77±0.43^{a}	8.32±0.22^{bA}	9.31±0.51^{ab}	0.037	Pregnant
	12	9.52±0.57^{a}	7.36±0.21^{bA}	8.03±0.31^{ab}	0.019	Non-pregnant
	10	8.74±0.38	9.74±0.66^{B}	8.66±0.43	0.303	Control
	P value	0.39	0.001	0.238		
PL (mg/dL)	28	160.37±2.79^{a}	145.66±2.89^{bA}	156.30±2.99^{aA}	<0.001	Pregnant
	12	152.50±3.74^{a}	134.56±1.90^{bB}	136.67±1.31^{bB}	<0.001	Non-pregnant
	10	157.21±5.79	157.36±3.98^{C}	152.15±3.09^{A}	0.716	Control
	P value	0.325	0.001	<0.001		
TL (mg/dL)	28	401.87±9.54^{a}	350.97±9.19^{bA}	387.40±8.55^{aA}	<0.001	Pregnant
	12	377.18±11.42^{a}	313.25±5.40^{bB}	322.85±4.06^{bB}	<0.001	Non-pregnant
	10	387.25±16.75	392.71±14.49^{C}	371.87±8.45^{A}	0.631	Control
	P value	0.32	<0.001	<0.001		

* Pregnancy status: 30 days of pregnancy after the mating, ^{A,B,C}: Different superscripts within column are significant (P<0.05). ^{a,b,c}: the difference between values with different letters on the same line is significant (P<0.05). PON1: Paraoxonase, TSA: Total sialic acid, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low-density lipoproteins, PL: Phospholipid, TL: Total lipid.

because there was no statistically significant difference between TSA concentrations of pregnant and non-pregnant goats (Table 2).

In oxidative stress conditions, lipid peroxidation occurs. PON1 can prevent both LDL and HDL against oxidation. It has been argued that PON1 contributes antioxidant effect through HDL (Deveci *et al.,* 2016). Especially introducing infection effect to body or creation of inflammation can cause changes in serum oxidized lipids (Memon *et al.,* 2000). Changes in cholesterol concentrations in infection or inflammations have been detected, however the mechanism could not be entirely explained (Apostolou *et al.,* 2009). In some studies, it was determined that CIDR or similar progesterone releasing devices intravaginal application caused especially oxidative damage or changes in inflammation markers (Kuru *et al.,* 2015; Oral *et al.,* 2015). In our study, we determined that PON1 activity decreases with CIDR application (day 11) and this decrease, which was found significantly different when compared with control group. Additionally, we determined a decrease in TC, TG and HDL concentrations. Moreover, an increase was determined in LDL concentration, which was not statistically significant. These results reflect that stress occurred by CIDR can cause lipid peroxidation and PON1 activity can decrease against the oxidation.

Devices like CIDR are sustained-release devices and give rise to serum progesterone concentrations on application day. Especially, they can be used in ruminants to imitate corpus luteum (Kuru *et al.,* 2015, 2017a, 2017b). Progesterone can be used in humans for contraceptive purposes in long term manner (Yadav *et al.,* 2011). In previous studies, it was determined that progesterone treatment could cause a decrease in HDL and TG while can cause an increase in LDL (Faddah *et al.,* 2005). It was determined that progesterone treatment to rats could cause a decrease in serum TL and TC concentrations (Moorthy *et al.,* 2004). In our study, it was determined that statistically significant decrease was found in HDL, TG and TC concentrations, in PON1 activity while a numerical increase was found in LDL concentration. The obtained findings are in compliance with previous studies in literature. The result has been found as long-term progesterone treatment can cause changes in lipid metabolism and PON1 activity.

Table 3: Dual Pearson correlation co-efficiencies between PON1 activity, TSA, TC, TG, HDL, LDL, VLDL, PL and TL in goats that estrus synchronization was made, on day 0, day 11 and mating day.

Day 0	TSA	PON1	TC	TG	HDL	LDL	VLDL	TL
PON1	-0.220							
TC	-0.284	0.186						
TG	-0.350*	0.351*	0.389*					
HDL	-0.107	0.175	0.565**	0.161				
LDL	-0.189	0.095	0.829**	0.230	0.046			
VLDL	-0.350*	0.351*	0.389*	1.000**	0.161	0.230		
TL	-0.332*	0.245	0.978**	0.571**	0.539**	0.790**	0.571**	
PL	-0.284	0.186	1.000**	0.389*	0.565**	0.829**	0.389*	0.978**
Day 11								
PON1	-0.198							
TC	0.075	-0.401*						
TG	-0.171	-0.306	0.527**					
HDL	0.209	-0.169	-0.197	-0.034				
LDL	-0.033	-0.232	0.877**	0.392*	-0.643**			
VLDL	-0.171	-0.306	0.527**	1.000**	-0.034	0.392*		
TL	0.047	-0.409*	0.994**	0.616**	-0.187	0.862**	0.616**	
PL	0.075	-0.401*	1.000**	0.527**	-0.197	0.877**	0.527**	0.994**
Mating day								
PON1	-0.064							
TC	-0.363*	0.248						
TG	-0.362*	0.183	0.562**					
HDL	-0.202	-0.285	0.274	0.340*				
LDL	-0.263	0.355*	0.902**	0.333*	-0.152			
VLDL	-0.362*	0.183	0.562**	1.000**	0.340*	0.333*		
TL	-0.394*	0.251	0.979**	0.718**	0.314*	0.841**	0.718**	
PL	-0.363*	0.248	1.000**	0.562**	0.274	0.902**	0.562**	0.979**

*: Correlation is significant at the 0.05 level (2-tailed) **: Correlation is significant at the 0.01 level (2-tailed). PON1: Paraoxonase, TSA: Total sialic acid, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low-density lipoproteins, PL: Phospholipid, TL: Total lipid.

Conclusion

Intravaginal CIDR treatment for estrus synchronization in goats could cause changes in PON1 activity, TSA concentration and lipid profile. Since the measured parameters turned to physiological limits on mating day, it was not negatively affecting the fertility.

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