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Relationship of serum adiponectin and IGF-I concentrations with progesterone and their effect on pregnancy rates in cows

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ABSTRACT: The aims of this study were to determine serum adiponectin and insulin-like growth factor-I (IGF-I) concentrations in early and late luteal phases following artificial insemination, to evaluate their relationship with progesterone concentrations, and to detect their effects on the pregnancy rate. We used 45 Holstein cows aged 3-4 years who had given birth at least once and who did not have any problem in the genital system as observed on rectal palpation/ultrasonography examination. Presynch-ovsynch synchronization protocol was applied on cows. Blood samples were collected to determine the concentrations of progesterone, adiponectin, and IGF-I on days 5 and 18 following artificial insemination (AI). Pregnancy examination using real-time ultrasonography was performed on day 30 following AI. Fifteen (33.33%) of the 45 cows were determined as pregnant. The pregnancy rates were increased with increasing progesterone concentration on day 5 following artificial insemination, and the pregnancy rates were the highest (53.84%) among the cows with progesterone concentration of >2.00 ng/mL. Adiponectin and IGF-I concentrations were determined as 26.69±11.84 vs 24.14±9.19 and 17.52±4.19 vs 17.42±2.92, on days 5 and 18 after AI, respectively ($P>0.05$). Negative correlation was observed between adiponectin and progesterone concentrations ($P<0.05$), whereas positive correlation was observed between IGF-I and progesterone on day 5 following AI ($P<0.05$). Progesterone and IGF-I concentrations in pregnant cows were higher than in non pregnant cows on days 5 and 18 following AI ($P<0.05$). In conclusion, the progesterone and IGF-I concentrations in early and late luteal phase following AI had a positive effect on the pregnancy rate. However, although early adiponectin concentration affected progesterone concentrations, it did not affect the pregnancy rate.

Keywords: Adiponectin, conception rate, cow, insulin-like growth factor-I, progesterone.

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INTRODUCTION

Progesterone, synthesized by the corpus luteum, plays an important role in maintenance and establishment of pregnancy in cattle (Bilodeau-Goeseels and Kastelic, 2003). Progesterone orchestrates several molecular, biochemical, and physiological interactions affecting the growth, development, and viability of the embryo in the uterus (Mann and Lamming, 1999). Moreover, progesterone affects the secretions (embryotrophic substances) supplied by the endometrium, the development/prolongation of the conceptus, the ability to produce interferon tau, which is secreted from the trophectoderm cells of the conceptus and suppresses luteolysis, the release of $PGF_{2\alpha}$ from uterine endometrium (Morris and Diskin, 2008; Spencer et al., 2015). It induces a set of genes in the endometrium that establish uterine receptivity, which is the physiological state of the uterus when conceptus growth and implantation is possible (Spencer et al., 2015). In addition, an important inhibitory role of progesterone is to reduce the motility (contractions) of the myometrium. Such a role causes a quieting effect on the myometrium in the cow (Senger, 2005). Thus, it was reported that there was a strong positive association between the post-ovulatory rise in progesterone concentration and embryonic development in cattle. Rise in progesterone concentration is affected by conceptus growth and development (Stronge et al., 2005; Morris and Diskin, 2008; Spencer et al., 2015). However, the low progesterone concentration during the early period post-insemination is closely related with low embryo survival/pregnancy rates (Stronge et al., 2005; Morris and Diskin, 2008). Therefore, insufficient secretion of progesterone causes poor development of the embryo and pregnancy losses (early embryonic deaths) (Morris and Diskin, 2008; Spencer et al., 2015).

Adiponectin is a 30-kDa protein with 244 aminoacids and synthesized by adipocytes. Adiponectin plays an important role in regulating energy homeostasis such as lipid and glucose metabolism (Sauerwein and Häußler, 2016). It was reported that there is a negative correlation between adiponectin and the body condition score and it was positively associated with insulin responsiveness of the glucose and fatty acid metabolism in dairy cows (de Koster et al., 2017). Moreover, the potential effects of adiponectin on reproduction have been addressed in various studies (Kafi et al., 2015; Heinz et al., 2015; Dobrzyn et al., 2017) and it was reported that adiponectin had a direct peripheral role in regulation of reproductive functions (dos Santos et al., 2012). Adiponectin may affect the female reproductive system at different levels, through hypothalamic-pituitary axis, ovary, uterus and embryo (Campos et al., 2008; Heinz et al., 2015).In addition, adiponectin is involved in many reproductive processes such as oocyte maturation, steroidogenesis, embryo development and implantation (Lagaly et al., 2008; Maillard et al., 2010).

Recently, it has been found that adiponectin has an effect on progesterone production at different animals (Campos et al., 2008; Kafi et al., 2015; Dobrzyn et al., 2017; Gupta et al., 2019). In addition to its direct effects on steroidogenesis in the ovary, adiponectin could also indirectly affect gonadal function by controlling the secretory activity of the hypothalamus and pituitary (Maleszka et al., 2014). Adiponectin can inhibit GnRH secretion in GT1-7 hypothalamic GnRH neurons through the activation of AMP-activated protein kinase (AMPK) signaling pathway (Wen et al., 2008). Adiponectin alone or in combination with hormones such as FSH, LH, insulin, and insulin-like growth factor-I (IGF-I) stimulates steroid synthesis (Campos et al., 2008). Furthermore, a significant interaction among adiponectin, insulin and IGF-I was reported by dos Santos et al. (2012). Moreover, Combs et al. (2004) and Campos et al. (2008) reported that the high expression of adiponectin in circulation negatively affected fertility in mice. Although adiponectin deficiency had no effect on fertility, it is noted that the concentration of adiponectin is lower at subfertile pigs (Campos et al., 2008). Kalamaras (2012) suggested that dairy cows with high adiponectin and normal progesterone concentrations may have a high probability of pregnancy. Since the effect of adiponectin on fertility in different species is controversial, further studies are needed to determine the relationship between adiponectin and other factors.

IGF-I, produced in the liver, plays an important endocrine role in the reproductive system by stimulating steroidogenesis and cell proliferation in both follicular and luteal cells (Zulu et al., 2002; Taylor et al., 2004). It has been reported that factors such as negative energy balance, metabolic diseases, body condition score, lactation number and period, milk yield and days in milk affect the IGF-I level (Taylor et al., 2004; Kul and Erdem, 2018). Moreover, there is also a positive correlation between serum IGF-I and follicular development as well as ovulation and corpus luteum function (Zulu et al., 2002). Spicer et al. (1993) reported that IGF-I stimulates the proliferation of *in vitro* bovine granulosa cells, and FSH, insulin and IGF-I increase the production of progesterone and estradiol in granulosa cells. In vivo, low serum IGF-I concentration was closely related with ovarian dysfunction and reproductive performance was poor in cows with low serum IGF-I concentration (Zulu et al., 2002). As a result, it has been reported that adiponectin and IGF-I may have a relationship with progesterone and these hormones may have an effect on fertility. Thus, the aims of this study were as follows: 1) the determination of the relationship between serum adiponectin and IGF-I concentrations and progesterone concentration during the early and late luteal phase after artificial insemination (AI); 2) the evaluation of the concentrations of these hormones during the early and late luteal phase; and 3) the detection of their effects on pregnancy rates in cows.

MATERIAL AND METHODS

The present study was conducted with the approval and permission of the Ethics Committee of Selcuk University, Faculty of Veterinary Medicine, Experimental Animals Production and Research Center (Approval Number: 2020/8).

Location

The study was conducted at Koçaş Agricultural Enterprise, where 4000 Holstein cattle are bred and 1800 of them were at lactation period. In the enterprise, cows were hosted in groups in free-movement paddocks of 150 animals. Rations of the animals were prepared with total mix ration and feeding was conducted twice a day. The ration included concentrate feed (7.75 kg), corn silage (28 kg), alfalfa silage (1 kg), dry alfalfa (1.25 kg), vetch (2.5 kg), triticale (1.5 kg), straw (2.2 kg), vitamin, and mineral supplementation (10 g).

Animals

The animals were first selected through the Dairy Plan (GEA Farm Technologies, USA) that was already being used by the farm management. Cows with problems during or after labor, such as dystocia, retained fetal membranes and metritis, were not selected in the study.

Forty-five Holstein cows aged 3-4 years, at their 2ndor 3rd lactation, with mean milk yields per day 26.33±5.13 kg, on 60-90 day postpartum that gave birth at least once and did not have any problem in the genital system as observed upon rectal and ultrasonographic examinations (6.0 MHz linear probe, Falcovet, Pie Medical, Netherlands) were used in this study. During rectal and ultrasonographic examinations, the anatomical location of the genital tract, ovaries, uterus and cervix were checked for pathological condition. Only cows with a corpus luteum were included in the study. However, cows with problems in their genital organs, such as adhesions, ovarian cysts, and metritis/pyometra or with the presence of fluid (≥2 mm) in the uterine lumen during ultrasonographic examination, were not included in the study. Additionally, only cows with a body condition score of 3-3.25 were included in the study to eliminate hormonal differences (especially adiponectin) related to the body mass.

Synchronization protocol

The presynch-ovsynch synchronization protocol was applied to the cows. For this purpose, the cows received 2 doses of $PGF_{2\alpha}$i.m. (25 mg, Dinoprost, Dinolytic®, Zoetis, USA) 14 days apart. GnRH (10 µg Buserelin, Receptal®, Intervet, Netherlands) was injected 12 days following the second dose of $PGF_{2\alpha}$, and 7 days later a 3rd dose of $PGF_{2\alpha}$ was injected. 48 h after $PGF_{2\alpha}$ administration, the second GnRH injection was administered, and fixed time AI was performed 12-16 h later. All AIs were conducted by an experienced technician.

Blood sample collection

Blood samples were taken from *v. coccygea* into 10 mL vacuum tubes of all cows to determine progesterone, adiponectin, and IGF-I concentrations on days 5 and 18 following AI. Serum was separated from the blood samples by being centrifuged at 3000 rpm for 15 min and stored at −20°C until further analyses.

Hormone analyses

Adiponectin (Bovine Adiponectin kit, Bioassay Technology Laboratory, China), IGF-I (Bovine IGF-I kit, Bioassay Technology Laboratory, China), and progesterone (Bovine Progesterone kit, Cusabio Technology, USA) concentrations were determined by ELISA according to instructions of manufacturing company.

Pregnancy diagnosis

Pregnancy diagnosis was performed on day 30 following AI by using real-time ultrasonography (6.0 MHz transrectal linear probe, Falcovet, Pie Medical, Netherlands). In this examination, the appearance of an echogenic embryo in a non-echogenous region in the uterus was recorded as positive for pregnancy.

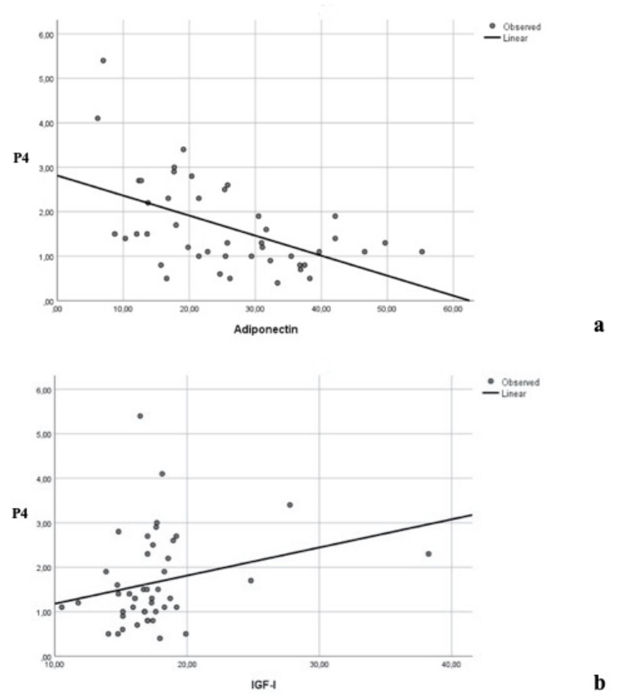

Figure 1. Correlation between adiponectin (a), IGF-1 (b), and progesterone concentrations on day5 following artificial insemination

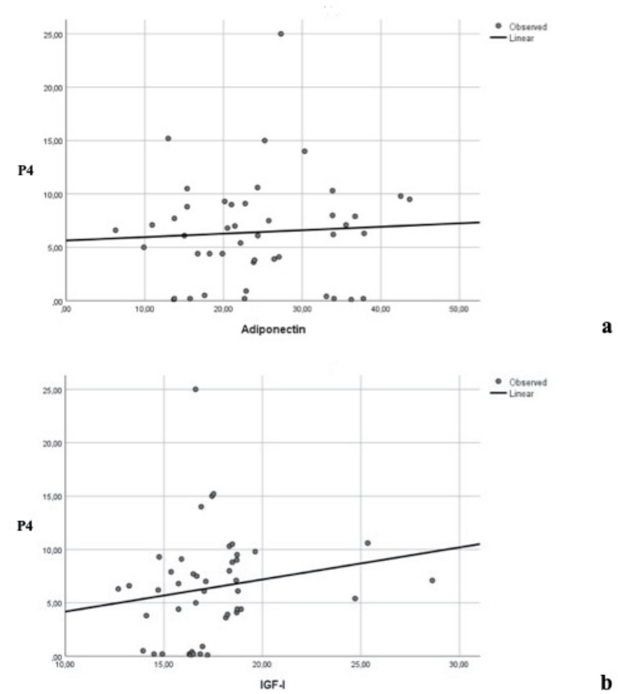

Figure 2. Correlation between adiponectin (a), IGF-1 (b), and progesterone concentrations on day 18 following artificial insemination

Statistical analysis

SPPS 25 (IBM Corp. Released 2017; IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) program was used for statistical analyses. The results expressed as mean ± standard deviation. Variables were evaluated after preconditions of normal distribution and homogeneity of variance was checked (Shapiro-Wilk and Levene Tests). The suitability of the data to repeated measurements of variance analysis was evaluated using Mauchly's Sphericity test and Box's M variance homogeneity test. Repeated measurements variance analysis in the factorial order was used for the comparison of means. If one of the factors did not meet the preconditions of the parametric tests (repeated measurements variance analysis in the factorial order), one of the Greenhouse and Geisser or Huynh and Feldt tests were used in the correction of the degree of freedom. Multiple comparisons were performed using Bonferroni correction test. Variables were evaluated (Shapiro-Wilk and Levene tests) after the preconditions of normality and homogeneity of variances were checked. For data analysis, independent two group t-test (Student's t-test) was used for the comparison of two groups (pregnant vs not pregnant or day 5 vs 18), and Mann-Whitney's U-test was used when preconditions were not met; for the comparison of three or more groups when one-way variance analysis and Tukey's HSD test of multiple comparison tests were not met, Kruskal-Wallis and Bonferroni Dunn test of multiple comparison tests were used. The relationship between two continuous variables was evaluated using Spearman's correlation coefficient if the Pearson's correlation coefficient did not meet the parametric test prerequisites. Binary logistic regression analysis was used to demonstrate the model of the relationship between independent and dependent variables. Statistical significance level was accepted as $P < 0.05$ and $P < 0.01$.

RESULTS

In this study, 15 of 45 Holstein cows were determined as pregnant on day 30 following AI. According to the serum progesterone concentrations on day 5 after AI, the cows were divided into three subgroups (≤1.00, 1.01-2.00, and >2.00 ng/mL). The pregnancy rates were increased with increasing progesterone concentration on day 5 after AI, and the pregnancy rate was the highest in cows with a progesterone concentration of>2.00 ng/mL (Table 1).

The concentrations of adiponectin, progesterone, and IGF-I on days 5 and 18 following AI are presented in Table 2. Although progesterone concentration was significantly higher on day 18, no estrus cycle-dependent difference was observed in adiponectin and IGF-I concentrations. The correlation between the concentration of adiponectin or IGF-I and progesterone on day 5 and 18 following AI are presented in Table 3. On day 5 following AI, a negative correlation was observed between adiponectin and progesterone concentration ($P<0.05$), whereas a non-significant positive correlation was observed between IGF-I and progesterone concentrations (Figure 1). On day 18, there was a significant positive correlation only between IGF-I and progesterone concentrations ($P < 0.05$, Figure 2b).

According to the pregnancy status (pregnant and not pregnant) on day 30 following AI, the adiponectin, IGF-I and progesterone concentrations on days 5 and 18 after AI are presented in Table 4. On day 5 and on day 18 following AI, the progesterone and IGF-I concentrations of pregnant cows were higher than in non pregnant cows ($P<0.05$).

DISCUSSION

In this study, we found that the pregnancy rate increased as the progesterone concentration increased; thus, the progesterone concentration on day 5 following AI had an effect on the pregnancy rate. It was reported that the progesterone concentration during the early post-ovulatory period was very important and early pregnancy losses were high among cows with low progesterone concentration (Mann and Lamming, 1999; McNeill et al., 2006). In addition, higher progesterone concentration regulates the elongation of the conceptus and endometrial gene expression, which stimulates interferon tau production during the early postovulatory period (O'Hara et al., 2014).

In this study, a negative correlation ($r=-0.516$) was observed between adiponectin and progesterone concentrations on day 5 following AI. Kalamaras (2012) reported a negative relationship between adiponectin and progesterone concentrations in dairy cows. In *in*

Table 1. Pregnancy rates according to progesterone concentrations on day 5 following artificial insemination and odds ratio

Progesterone concentration (ng/mL)	Pregnant	Non-pregnant	Total	Pregnancy rate (%)	Odds ratio	95% confidence interval	P
≤1.00	2	12	14	14.28[a]	Reference		
1.01-2.00	6	12	18	33.33[a,b]	2.33	0.59-10.10	<0.05
>2.00	7	6	13	53.84[b]	7.00	1.09-24.60	

Table 2. Serum progesterone, adiponectin, and IGF-1 concentrations (±SD) on days 5 and 18 following artificial insemination

	Progesterone (ng/mL)	Adiponectin (µg/mL)	IGF-1 (ng/mL)
Day 5	1.69 ± 0.83	26.69 ± 11.84	17.52 ± 4.19
Day 18	6.41 ± 2.94	24.14 ± 9.19	17.42 ± 2.92
P	<0.05	>0.05	>0.05

Table 3. Correlation between adiponectin and IGF-1 with progesterone concentrations on day 5 following artificial insemination

		Day 5		Day 18	
		Progesterone	IGF-1	Progesterone	IGF-1
Adiponectin	r	−0.516**	−0.128	0.060	0.109
IGF-1	r	0.294*	-	0.309*	-

**Correlation is significant at the 0.01 level

*Correlation is significant at the 0.05 level

Table 4. Progesterone, adiponectin, and IGF-1 concentrations (±SD) on days 5 and 18 following artificial insemination of pregnant and non-pregnant cows

Pregnancy	Day 5			Day 18		
	Progesterone (ng/mL)	Adiponectin (µg/mL)	IGF-1 (ng/mL)	Progesterone (ng/mL)	Adiponectin (µg/mL)	IGF-1 (ng/ml)
Pregnant (n = 15)	2.09 ± 0.69	24.98 ± 7.42	20.37 ± 5.87	8.94 ± 2.05	24.78 ± 10.47	19.60±3.67
Not pregnant (n = 30)	1.52 ± 0.54	28.05 ± 10.57	16.1 ± 1.93	5.14 ± 2.26	23.82 ± 8.65	16.33±1.66
P	<0.05	>0.05	<0.05	<0.05	>0.05	<0.05

vitro study, it was found that adiponectin (3 μg/mL) significantly inhibits progesterone and androstenedione production induced by LH and insulin in bovine theca cells (Lagaly et al.2008). Additionally, it was reported that in the presence of adiponectin, progesterone and androstenedione concentrations significantly decreased by 40% and 26%, respectively. Moreover, Heinz et al. (2015) suggested that there might be a negative relationship between progesterone and adiponectin concentrations in the estrus cycle. Tabandeh et al. (2010) reported that in dairy cows, adiponectin mRNA expression was low in an active corpus luteum, and expression of adiponectin was the highest in a regressed corpus luteum.

It was reported that IGF- Iplays an important role in steroidogenesis in cattle (Spicer et al., 1993). *In vitro* studies found that IGF-I acted as a stimulator for steroidogenesis in bovine granulosa and luteal cells (Spicer et al., 2002). The IGF-I stimulates the aromatase system, which implies its steroidogenic effect (Zulu et al., 2002). Spicer et al. (1993) reported that IGF-I increased progesterone production a several-fold in granulosa cells on day 4 of their *in vitro* culture. In the present study, there was a significant positive correlation (r=0.294) between progesterone and IGF-I concentrations on day 5 following AI. Spicer et al. (1990) reported a positive correlation between serum IGF-I and progesterone concentrations in dairy cows (r=0.315). Samardžija et al. (2006) found high progesterone and IGF-I concentrations in postpartum cyclic cows. A significant positive correlation was also observed between progesterone and IGF-I concentrations during early puerperial period in cows with normal ovarian cyclicity. It was suggested that the serum IGF-I concentration may affect progesterone production (Samardžija et al., 2006).

It was reported that different types and receptors of adiponectin were expressed in the endometrium, uterus, trophoblast, and conceptus (Smolinska et al., 2014). There was an interaction between adiponectin and steroid secretion during maternal recognition of pregnancy and implantation periods in pigs (Smolinska et al., 2017; Dobrzyn et al., 2017). Dobrzyn et al. (2017) reported that in porcine, progesterone and adiponectin systems were critical in the maternal recognition and implantation processes of pregnancy, and progesterone modulated the adiponectin sensitivity of endometrial cells. Moreover, dos Santos et al. (2012) reported that the low expression of adiponectin receptors in the uterus caused repeated implantation losses in women. In addition, Takemura et al. (2005) demonstrated that serum adiponectin concentration in women with high implantation loss was lower than healthy women. Smolinska et al. (2017) reported that the plasma adiponectin concentration in sows was the highest on days 15-16 of the cycle (pre-implantation period). The endometrial physiology in cattle is regulated by the concentration of circulating progesterone and the expression of transient receptors in endometrial cells. Therefore, progesterone activity in endometrial cells was necessary for the establishment and maintenance of pregnancy (Spencer et al., 2015; Ribeiro et al., 2018). In the present study, the relationship between adiponectin and progesterone concentrations was tried to be determined before maternal recognition of pregnancy. However, unlike other species, a weak positive correlation between adiponectin and progesterone was observed.

Maillard et al. (2010) reported that adiponectin supplementation decreased progesterone and estradiol concentrations in granulosa cells but did not have any effect on early embryonic development. In the present study, although there was a negative relationship between adiponectin and progesterone concentrations, serum adiponectin concentration did not have any effect on the pregnancy rates. These results suggest that serum adiponectin concentration may not have an effect on pregnancy rates. However, as there are many factors affecting pregnancy rates in cattle, the effect of only serum adiponectin concentration currently remains controversial.

Locally or systematically secreted IGFs positively affect early embryo development by directly affecting the embryo or indirectly regulating oviduct secretion and muscular activity (Pushpakumara et al., 2002). Moreover, Ribeiro et al. (2016) reported that IGF-I plays a role in the elongation of conceptus and stimulates proliferation and survival of embryonic cells in cattle. Taylor et al. (2004) reported that as IGF-I concentration increases, the possibility of pregnancy increases at first postpartum insemination. Gobikrushanth et al. (2018) also found that the pregnancy rate of cows with high IGF-I concentration was greater. Moreover, IGF-I has been reported to have beneficial effects on bovine embryo development *in vitro*. Addition of IGF-I to embryo culture can increase pregnancy rates in lactating dairy cows (Block, 2007; Block and Hansen, 2007). Thus, IGF-I has an effect on pregnancy rates in cattle. In the present study, serum IGF-I concentration on days 5 and 18 following artificial insemination was higher in pregnant cows than in non-pregnant animals ($P<0.05$). Based on these results, it was thought that IGF-I concentration may have a positive effect on pregnancy rates.

CONCLUSION

As a result, on day 5 following AI, a negative correlation was observed between adiponectin and progesterone concentrations, whereas a positive correlation was observed between IGF-I and progesterone concentrations. It was concluded that serum IGF-I concentration in cows may be associated with pregnancy rate; however, there may not be a relationship between adiponectin concentration and pregnancy rate.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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