Progesterone and insulin - like growth factor 1 in serum of Shami goats during the early breeding season

Solieman A. Salhab[1†], Adnan Al-Assad [2], D. Keisler[3] and Moutaz Zarkawi [4]

[1]Dep. Anim. Prod., Fac. Agric, Univ. Damascus, Syria, Visiting Scholar, Div. Anim. Sci., Univ. Missouri, USA; [2]PhD Student, Anim. Prod., Fac. Agric., Univ. Damascus, Syria; [3]Div. Anim. Sci., Univ. Missouri, Columbia, MO 65211, USA; [4]Div. Anim. Prod., Atomic Energy Commission, Damascus, Syria

SUMMARY

The study aimed to determine the level and characterize the plasma IGF-1 profiles with relationship to progesterone profiles during the early breeding season in Shami goats. 10 multiparous- non pregnant Shami does, kept indoors at night and outside for most of the day were offered diets based on barley and wheat straws with free access to natural grazing, water and minerals ad libitum. Daily prefeeding- blood samples (10 ml) for 46 days were collected in heparinized tubes by jugular venipuncture and centrifuged at 3000 rpm for 20 min. Serum was harvested and stored at -20°C until assayed for hormonal analysis using radioimmunoassay technique. Data were analyzed as a repeated measure design using PROC GLIIMMIX Procedures in SAS 9.4. Differences in least square means for IGF-1 and progesterone were tested using Fisher's protected least significant differences ($p \leq 0.05$). Results showed only 20% of Shami goats showed ovarian activity based on P4 serum concentration during the early breeding period. No significant effect for the studied groups (cyclic vs. non cycilc) was observed, but significant effects ($p<0.03$) for the seasonal days and interaction with the animal groups ($p< 0.02$) on the concentration of IGF-1 were observed. A negative and significant relationship ($r = - 0.39$, $p<0.01$) were obtained between levels of IGF-1 and progesterone and the peak of IGF-1 preceded the p4 peak by 12 days in cycling does. Determination the concentrations of these two hormones can help in assessing the reproductive status of Shami goats and facilitate the ability to select females most suited higher reproductive efficiency.

Keywords: Shami goats, breeding season, cyclicity, IGF-1, progesterone.

† Corresponding author e-mail address: ssalhab2@gmail.com

INTRODUCTION

Reproductive seasonality limits the reproductive efficiency in goat production systems (Shelton, 1991). The yearly reproductive cycle of the goat is primarily controlled by an endogenous reproductive rhythm, which is synchronized by the day length (i.e. photoperiod) (Delgadillo et al., 2004).The duration of anestrus can also be modulated by nutritional and socio-sexual factors in sheep and goats (Martin et al., 1999; Forcada and Abecia, 2006).

Better understanding of the relationship between nutrition and ovarian function is a fundamental cue to optimizing the reproductive parameters. In goats, as with other ruminants, the nutritional effect on ovulation and follicular recruitment was mainly explained by short period influence of energetic status on gonadotropin secretion (Mani et al., 1996). Rondina et al. (2005) indicated that opposite dietary intakes for a medium period can regulate the early onset of follicle growth of local goats. Undernutrition for short (Mani et al., 1992; 1996), medium (Tanaka et al., 2004) or long period (Paula et al., 2005) has been extensively reported to exert a negative influence on ovarian activity in goats and level of progesterone secretion.

Some investigators have reported the concentrations of plasma progesterone during the estrous cycle in goats for different breeds (Bauernfeind and Holtz, 1991; El-Hommosy et al., 1991; Pathiraja et al., 1991), while Mavrogenis (1988), Shalaby et al. (2002), Khadiga et al., (2005) and Zarkawi and Soukouti (2001) studied changes in the plasma progesterone concentration during different stages of the estrous cycle in Shami goats.

Many studies have highlighted the role of the insulin-like growth factor I (IGF-I) system in the control of follicular growth (Giudice, 1992; Armstrong and Webb, 1997; Armstrong et al., 1998; Woad et al., 2000). The responsiveness of ovarian follicles to IGF-I has been demonstrated in numerous studies. When added during the *in vitro* culture of preantral follicles, IGF-I has been shown to stimulate follicular growth in various species (rat: Zhou et al., 2003; cow: Gutierrez et al., 2000; human: Louhio et al., 2000). In addition, IGF-I increases follicular diameter, DNA content, promote functional integrity and stimulated steroidogenesis during rat preantral follicle culture (Demeestere et al., 2004). However, much less is known about the involvement of IGF-I in the regulation of goat preantral follicular development.

It is reported that plasma concentration of IGF-1 increases during estrus in ruminants (Spicer and Zavy, 1992; Hashizume et al., 2000) and thought to function primarily as a circulating hormone secreted by the liver in response to GH in domestic animals (Hossner, et al., 1997), in the ovine ovary (Perks et al., 1995), in oviduct of bovine (Schmidt et al., 1994) and

ovine (Stevenson and Wathes, 1996), in ruminants and rat uterus (Wathes et al., 1998) and from the uterus in goats (Nonaka et al., 2003). It has been speculated that most of IGF-1 in blood during estrus in ruminants might be derived from the uterus (Wathes et al., 1998; Stevenson et al., 1994; Geisert et al., 1991; Ko et al., 1991).

Shami (Damascus) goat is a native breed to Syria and requires an improvement management and feeding environment to express its all genetic potential (Mavrogenis et al., 2006). It is a highly adaptive and prolific animal that is recognized as the ultimate goat in either dual or single purpose production systems. It can be used in pure bred or cross-bred milk or meat production systems, surpassing the production figures of equivalent animals in intensive, semi-intensive or extensive systems (Constantinou, 1989). Shami goats are considered as the most important goat breed in the Arab and West Asian countries, due to its high milk yield (450-850 kg\260 days) and meat production potential (1.8 litter size) (Abdullah et al., 2012). It is a seasonal breed, and the occurrence of the first seasonal estrus is somewhat irregular. Does exhibit a short (August–October) and sometimes long breeding season (July–November), rarely demonstrating estrus during winter (December and January) in Syria (Al Khouri, 1996). The main breeding season starts in late August and extends through mid-December in Cyprus (Abdullah et al., 2012).

Certain reproductive parameters in Damascus does have been studied such as oestrous cycle (Zarkawi and Soukouti 2001), duration of pregnancy (Zarkawi and Al-Masri 2002), early pregnancy diagnosis and monitoring corpora lutea (Zarkawi et al., 2003) and the response to some veterinary agents (Zarkawi, 2007).

The hypothesis of the present research is that alteration in the IGF-1 level might reflex the nutrition status and its influence on reestablishment ovarian cyclicity during the early breeding season in Shami goats and might facilitate the ability of producers to select females most suited for particular nutritional environments and higher reproductive efficiency. This work, therefore, aimed to determine the level and characterize the plasma IGF-1 profiles with relationship to progesterone profiles during the early breeding season in Shami goats.

Material and Methods

Ten multiparous, not pregnant Shami does with a live weight of 55.6 ± 5.06 kg (Mean ± SEM) reared at Der Al-Hajar Shami Goat Production Research Station, 33 km southeast of Damascus were used. This is considered a dry area with an annual rainfall of about 100 mm occurring mainly in December and January. The does were kept separated from the rest of the herd and kept indoors at night and outside for most of the day.

Indoors, the animals were offered diets based on barley and wheat straw and outdoors, they had free access to natural grazing with major fluctuation and feed availability throughout of the year. Water and minerals were available *ad libitum*. Parasite treatment and estrus detection by introducing a buck two times daily (09:00, 16:00 h) were practiced.

Once a day (9:00 h) and for 46 days (August 11 to September 25), pre feeding- blood samples (10 ml) were collected in heparinized tubes by jugular venipuncture and centrifuged at 3000 rpm for 20 min, serum was harvested and stored at -20°C until assayed. Frozen serum was replaced into a well-three folded box containing 12 kg of frozen gel to keep the samples frozen during the air transportation to the reproductive lab at the Animal Science Research Center (ASRC) at the University of Missouri for hormonal analysis. Insulin-like growth factor 1 (IGF1) and Progesterone were analyzed via double antibody radioimmunoassay previously validated within our laboratory (Morrison et al., 2002; Lalman et al., 2000, Pohler et al., 2015) and inter- and intra-assay CV were < 5%.

The data were analyzed as a repeated measure design outlined by Littell et.al. (1998). The main plot contained the main effect of group (cyclic and Non-cyclic), the subplot contained the effects of day and the interaction of group*day. The denominator of F for main plot was animal identification (group) and for the subplot effects was the residual mean square. The data were analyzed using PROC GLIIMMIX Procedure in SAS 9.4. Differences in least square means were tested using Fisher's protected least significant differences (LSD). ($p \leq 0.05$). Correlation was also applied to determine the relationship between the concentration of IGF-1 and progesterone over times in the same animal and between does.

RESULTS

The serum profiles of IGF-1 and progesterone (P4) in Shami goats, measured by RIA during the early breeding season for cyclic and non-cyclic does are presented in Figure 1. Only 2 out of 10 Shami goats showed ovarian activity based on P4 serum concentration during the early breeding period (Fig. 1). In the ANOVA, no significant effect for the studied groups (cyclic vs. non cyclic) was observed, but there were significant effects ($p<0.03$) for the seasonal days and interaction with the animal groups ($p< 0.02$) on the concentration of IGF-1. Correlation analysis showed a negative and significant relationship ($r = - 0.39$, $p<0.01$) between levels of IGF-1 and progesterone in Shami does.

No significant changes in the concentration of serum IGF-1 were observed in non-cycling group (Fig. 1). However, does within this group were highly reproducible from day today and the reproducibility of IGF-1 concentration , pooled across lines among days 1 to 10 , 11 to 16, 17 to 34

and 35 to 46 were 1.1, 0.95, and 1.2, respectively. These changes were highly significant ($p< 0.05$) in cycling group and the IGF-1 curve for the two cycling does was similar and the concentration of IGF-1 started to rise from day 11 in animal 7 and day 13 in animal 9 and reached the highest value on day 16 of seasonal days in both does. The mean maximal IGF-1 concentration observed on day 16 was significantly ($p< 0.01$) higher than any following days in cycling animals and any days during the studied period in non- cycling does ($p< 0.05$).

Concentration of P4 was mostly undetectable or lower than 0.3 ng/ml in non- cycling does (n=8) (Fig. 1) while it increased significantly ($p < 0.01$) in cycling does (n=2) with similar patterns during the study period (Fig. 1).

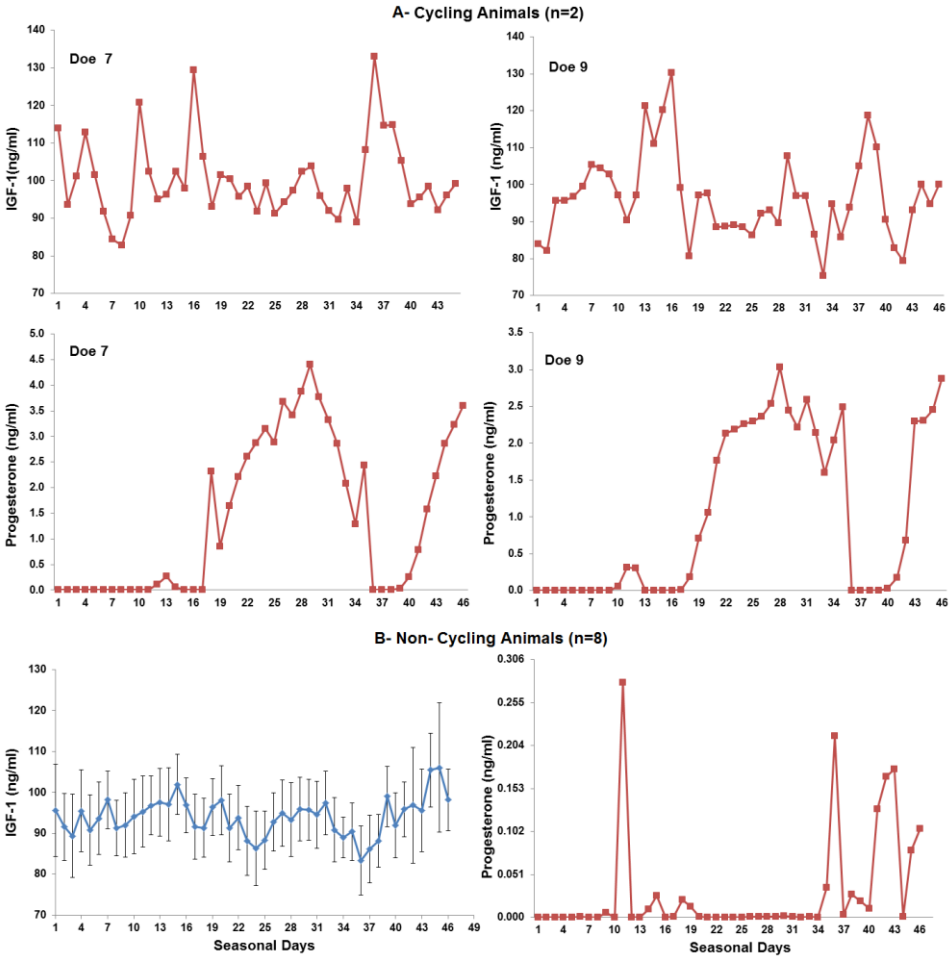

Figure 1. Daily patterns of serum IGF-1 and progesterone in cycling (A, does Nos. 7 and 9) and non –cycling Shame does (n=8, B) during the early breeding season (Aug. 11th - Sept. 26th). Hormone concentrations were measured in samples collected on daily basis using RIA technique.

In cycling does, the P4 concentration started to rise on day 19 and peaked up on day 28 (doe 7) and day 27 (doe 9) then gradually decreased to become undetectable on day 36 and showed new sustainable increase after day 41(2nd cycle) during the study period of breeding season. These changes and the increase in p4 concentrations above 1 ng/ml between day 18 and day 35 and day 20 and day 35 of the studied period in does 7 and 9, respectively indicates to the evidence of ovulation and the presence of active corpus luteum. The mean maximal progesterone concentration (3 to 4.45 ng/ml) occurred from day 20 to day 35 of the study period in these cycling does and simultaneous significant reduction in the level of IGF-1 confirms the negative relationship between the secretions of these two hormones.

DISCUSSION

To our knowledge, this is the first investigation to clarify the profile of serum IGF-1 and its relation to P4 profile during the early breeding season in Shami goats.

The overall mean concentration of IGF-1 in Shami goat was 97.64 ± 14.2 ng/ml in cycling does and 93.77 ±7.11 ng/ml in non- cycling does which is higher than 35 to 80 ng/ml out of breeding season in Boer goats in Croatia (Djuricic et al., 2011) and much less than 150 ng/ml and 250 ng/ml reported by Hashizume et al. (2000) during the luteal and estrus phases, respectively in Japanese goats and also less than 150 to 200 ng/ml during the estrus cycle in sheep (Spicer and Zavy, 1992).

The role of IGF-1 in the reproduction of ruminant has been the subject of intensive studies during the last two decades (Wathes et al., 1998; Tamadon et al., 2010) and its role is very complex, as it occurs on different levels, e.g. at the central hypothalamic level (Todd et al., 2010) and its local level through its influence on ovary activity (Yu et al., 2003; Hunter et al., 2004) and owing to its systemic secretion, mostly by the liver, and simultaneous to local production in different tissues of reproductive tract (Millard et al., 2010). Plasma IGF-1 concentrations increase during the estrus in rats (Carlsson et al., 1989), in Sheep (Spicer and Zavy, 1992; Leeuwenberg et al., 1995) and goats (Hashizume et al., 2000; Nonaka et al., 2003). Hashizume et al. (2000) confirmed that IGF-1 releases from the ovaries during cyclic activity could increase systemic IGF-1 concentrations. Richards et al. (1991) reported that ovariectomy causes a decrease in serum IGF-1 in cattle and the exogenous estradiol causes a significant increase in serum IGF-1 in ovariectomized cows. The consistent and large increase in plasma IGF-1 observed after injection of PGF2α in goats (Hashizume et al., 2000) and shortly after sponge withdrawal and reaching a maximum about day after the onset of estrus in ewes (Spicer et al., 1993)

suggests that follicular estrogen may regulate IGF-1 secretion in goats and sheep as also suggested in cattle (Simpson et al., 1997).

The present study clearly demonstrated that there is no more 20% of the Shami does resume their cycling activities in August, the early period of breeding season and serum p4 is a reliable and convenient means of monitoring ovarian activity in Shami goats, like in other goat breeds (Shami goats, Zarkawi and Soukouti, 2001; Alpine goat, Thibier et al., 1981; Dwarf goats, Khanum, et al., 2008).

The P4 concentrations at the luteal phase was 1 to 4.5 ng/ml which is comparable to 2.33- 2.94 ng/ml in Dwarf goats (Khanum, et al. (2008) in Pakistan, to 2.6 to 5.4 ng/ml (Khadeja et al., 2005) in Shami goats in Sudan and 1.025 to 8.8 ng/ml (Zarkawi and Soukouti, 2001) in Damascus goats in Syria. However, these variations might be due to genetic, time of breeding season, number of corpora lutea (Jones and Knifton, 1972) and /or body condition (Cortés et al., 2009).

Based on the data presented in this study, the maximal serum IGF-1 concentration (130 ng/ml) proceeded the transition elevation in p4 concentration ≥ 1ng/ml by 3 to 4 days is a good evidence of resumption of cyclic activity occurring estrus and ovulation in Shami goats. This is in agreement with several investigations confirmed that plasma IGF-1 levels increase during the estrus cycle in sheep (Leeuwenberg et al., 1996; Spicer and Zavy, 1992) and goats (Hashizume et al., 2000). In Shipa goats, plasma IGF-1 increases 2 days prior to estrus and reaches its maximal level during the preovulatory LH surge and is coincident with estrus behavior, before decreasing around ovulation time (Hashizume et al., 2000). In agreement with these data, an increase in IGF-1 concentrations in blood serum of pluriparous goats and the tendency to increase in Boer goats during the first ovarian activity after kidding were observed (Djuricic et al., 2011). Maximal IGF-1 concentration presented in this study in serum of Shami goats preceded the maximal p4 concentration by approximately 12 days (Fig.1) and by 8 days in Boer goats (Djuricic et al., 2011). These observations are in agreement with the systemic and local role of IGF-1 in ovarian cycle. Todd et al. (2010) approved that, in estrogen- positive feedback conditions, IGF-1 signaling in the hypothalamus is necessary for secretion of LH surge. Estrogens increase the IGF-1 mRNA in the uterus (Wathes et al., 1998; Carlsson et al.,1991) and the expression in the uterus is independent of GH but, dependent on estrogen (Jones and Clemmons, 1995; Norstedt et al., 1989) and the uterus is the largest of the female reproductive organs. In which the estrogen receptor is present. *In vitro* it was confirmed that IGF-1 also stimulates angiogenesis in the early corpus luteum (Schams et al., 2002). Moreover, the highest mRNA expression for IGF-1 was observed in the early luteal phase and decreased during the middle and late luteal phase (Schams, 1987). Hence, it was postulated that

the IGF-1 system is essential for the development of the early corpus luteum through the stimulation of angiogenesis, luteinization of granulosa –lutein cells and of progesterone production (Berisha and Schams, 2005).

In this study, the presence of non-significant differences in the IGF-1 concentrations between non -cycling Shami goats and significant differences with a long plateau seen especially during the luteal phase in cycling does might be due to the body weights and considerable individual variation in the level of energetic body reserve (Rondina et al., 2005) specially these animals were raised in conditions with major fluctuations in feed availability throughout of the year which can result in the quantity and quality of food intake and, therefore affect body condition. Feed intake influences IGF-1 synthesis in the liver, playing an important role as a metabolic signal in the regulation of the first ovulation (Braw-tal et al., 2004) and the influence of poor energetic status on cyclic activity has been well established (Spicer et al., 1990: Lucy, 2000).

CONCLUSIONS

In conclusion, it was established that serum IGF-1 concentrations in serum of Shami goats follow the cycling activity during the early breeding season period and it is correlated negatively and significantly with the p4 concentrations. The peak of IGF-1 preceded the p4 peak by 12 days in cycling does. Determination the concentrations of these two hormones can help in assessing the reproductive status of Shami goats and facilitate the ability of producers to select females most suited for particular nutritional environments and higher reproductive efficiency.

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