POSTPARTUM PROGESTERONE PROFILE AND SOME PERIPARTUM BLOOD PARAMETERS RELATED TO LIPID METABOLISM AND LIVER FUNCTION IN EWES

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Abstract. In order to determine whether the postpartum progesterone profile varies according to cholesterol and other blood parameters related to lipid metabolism and liver function during the peripartum period, a study was conducted on 13 clinically healthy ewes of "Ouled Djellal" breed. A total of 144 blood samples were collected during the fifth month of pregnancy and between day 7 and day 57 postpartum. Blood plasma was used to assess total cholesterol, triglycerides, albumin, total bilirubin and direct bilirubin concentrations via a quantitative colorimetric enzymatic method, and to establish the postpartum progesterone profile using radioimmunoassay. The parameters recorded were within reference ranges which could suggest that the ewes were healthy in regard to lipid metabolism and liver function. The prepartum compounds did not significantly affect the postpartum progesterone pattern ($P>0.05$). All biochemical parameters measured during peripartum did not significantly differ ($P>0.05$) between ewes expressing a progesterone basal level lower than 1 ng/ml and those showing higher values indicating luteal activity (≥1 ng/ml). Although, only total cholesterol on days 27 and 32 postpartum had shown a significant linear model ($P<0.01$), suggesting a moderate variability of progesterone concentrations ($r2= 0.49$ and 0.57, respectively), the relationship between blood parameters and plasma progesterone appeared to not follow a simple linear function ($P>0.05$). It appears that, in healthy ewes, the peripartum changes in concentrations of plasma cholesterol and other blood tests did not predict significantly the postpartum progesterone kinetic.

Keywords: Cholesterol, Ewes, Liver function, Postpartum, Progesterone

Introduction. The postpartum period is a critical reproductive stage; it includes uterine involution and ovarian activity resumption. If lambing occurs during the short days period, the first postpartum ovulation will mainly depend on the nutritional status (Lindsay et al., 1993). Important factors, other than nutrition and season (reviewed by Rosa and Bryant, 2003) may also have an impact (Lassoued, 2011). The reestablishment of regular postpartum ovarian cycles can be affected by a failure of luteolysis that can happen when ovulation occurs too early after lambing. This state may be aggravated by the metabolic demand due to lactation and the changes in circulating concentrations of steroid hormones (Mitchell et al., 2003). Progesterone, as the predominating steroid hormone during most of the estrous cycle length, appears as a regulatory factor for the occurrence of normal postpartum estrous cycles (Schirar et al., 1989) and as a determinant factor of the steroidogenic capacity of developing follicles (Atkinson et al., 1998). It is produced from cholesterol which is synthetized and catabolized mainly in liver (Kaneko et al., 2008). Cholesterol used for steroidogenesis is obtained from the circulating blood in the form of LDL or HDL (Niswender et al., 2000). It has been found that increased levels of cholesterol can cause a greater synthesis of progesterone in early lactating ewes fed diets based on protected fat (Bianchi et al., 2014). This lipid and other biochemical indicators such as triglycerides, albumin and some liver tests such as bilirubin were usually used to assess nutritional status, lipid metabolism and liver function in ruminant (Van Saun, 2000; Nazifi et al., 2002).

The aim of this study was to determine whether the postpartum progesterone profile is dependent on plasma cholesterol and other blood markers of lipid metabolism and liver function measured during late pregnancy and up to two months postpartum in ewes lambing during the breeding season.

Materials and Methods

Animals and flock management

The study was conducted in a semiarid province located in eastern Algeria (Constantine) during autumn lambing. Thirteen clinically healthy ewes of "Ouled Djellal breed", aged two to five, in an adequate body condition (BCS mean: 3.42±0.39) and in their fifth month of pregnancy were selected from a flock of a "model farm" managed under a semi intensive livestock system. Pregnancy followed synchronization of estrus via fluorogestone acetate treatment (FGA) impregnated intravaginal sponges and eCG. Ewes' feeding was based on the alternation of stall feeding and grazing. During rainfall days, the ewes were fed hay and straw and supplemented continuously with concentrate.

Sampling

Blood samples were collected from jugular vein into heparinized vacuum tubes, at 7:30 am before the morning feeding once during the last month of pregnancy and at a five day interval post lambing, beginning on day 7 and ending on day 57. Plasma was separated by blood centrifugation and stored in Eppendorf vials at -20°C until assay.

Progesterone assay

Postpartum concentrations of progesterone (P4) were obtained by radioimmunoassay using the radioimmunological competitive analysis commercial kits (Immunotech Sa, Beckman Coulter Company, Marseille Cedex, France). A progesterone level above 1 ng/ml was considered as an indication of luteal activity (Mitchell et al., 2003). The threshold concentration of 1 ng/ml was used for comparison of blood parameters in relation to progesterone kinetic, basal (P4<1 ng/ml) and luteal (P4≥1 ng/ml) levels.

Blood parameters

Separated plasma collected during prepartum and early lactation (two first postpartum months) was used to measure concentrations of total cholesterol (Chol), triglycerides (TG), albumin (Alb), total bilirubin (TB) and direct bilirubin (DB) via a quantitative colorimetric enzymatic method using commercial kits (Spinreact, SA, Spain) and an automatic analyzer (Technicon® equipment, model RAXT).

Statistical analyses

Biochemical data (Albumin, cholesterol, triglycerides, total and direct bilirubin) were compared using one-way ANOVA in SPSS Statistics 17.0 to look for any statistical significant difference of the studied parameters between prepartum and postpartum periods and between ewes showing basal and luteal progesterone levels. The results are expressed as the means ± standard error of the mean. The effect of prepartum blood parameters values on the postpartum progesterone level was evaluated by Pearson linear correlation. The linear regression was also used to predict the value of postpartum progesterone concentration (dependent variable) based on its linear relationship with every biochemical value (independent variable) recorded during the same sampling times. Statistically significance was considered when P<0.05.

Results

Blood parameters during late pregnancy and post-lambing period

Blood parameters values measured in late pregnancy and the two first months after parturition and up to day 7 and day 57 postpartum were largely within reference ranges. However, concentrations of cholesterol during prepartum and albumin during prepartum and the first month postpartum were significantly higher than the upper limit of reference ranges (Table 1).

A clear diminution of monitored parameters concentration from late pregnancy to the two first months of lactation has been recorded.

Table 1. **Concentration of blood parameters during late pregnancy and postpartum in monitored ewes**

	Alb (g/dl)	Chol (mg/dl)	TG (mg/dl)	DB (mg/dl)	TB (mg/dl)
Reference range	2.4 - 3.0[1]	52 - 76[1]	17.7 - 88.5[2]	0 - 0.27[1]	0.1 - 0.5[1]
Prepartum	4.65±0.21[b]	99.46±6.15[b]	72.62±15.09	0.09±0.02	0.16±0.02
Day 7	3.75±0.10[ab]	79.15±3.44[a]	41.31±2.81[a]	0.07±0.01	0.06±0.01[a]
Day 12	4.08±0.15[b]	89.31±8.52	38.15±3.89[a]	0.11±0.02	0.15±0.03
Day 17	3.65±0.12[ab]	86.23±4.83[a]	30.46±2.98[a]	0.12±0.02	0.16±0.02
Day 22	3.67±0.18[ab]	78.46±6.08[a]	30.77±3.24[a]	0.12±0.02	0.17±0.02
Day 27	3.45±0.25[a]	82.77±7.05	40.38±5.07	0.08±0.02	0.13±0.01
Day 32	3.61±0.16[ab]	80.15±5.45[a]	29.77±2.21[a]	0.12±0.02	0.23±0.05
Day 37	3.78±0.35[b]	82.69±4.54[a]	32.15±2.98[a]	0.08±0.02	0.17±0.03
Day 42	3.32±0.20[a]	69.00±4.40[a]	32.46±5.14[a]	0.09±0.03	0.12±0.03
Day 47	3.17±0.15[a]	68.77±5.35[a]	33.23±6.73[a]	0.05±0.01[a]	0.10±0.02[a]
Day 52	3.11±0.19[a]	67.00±5.23[a]	33.08±3.94[a]	0.05±0.01	0.06±0.01[a]
Day 57	3.18±0.16[a]	62.33±6.68[a]	36.42±4.73[a]	0.05±0.01[a]	0.09±0.02[a]
- a: by column, significant difference (P<0.05) between prepartum and postpartum values ; - b: Recorded values are significantly higher than maximal value of reference range ; 1: Kaneko et al. (2008), 2: Aitken (2007)					

Variation of biochemical parameters and progesterone profile

All ewes have shown a resumption of luteal activity (P4> 1 ng/ml) by the first month postpartum. Postpartum progesterone concentrations seem to be not related to prepartum biochemical parameters values (Table 2).

During postpartum, the concentrations of all biochemical parameters did not significantly differ (P>0.05) between ewes showing a progesterone basal level (P4 < 1ng/ml) and those displaying a luteal activity, apart from direct bilirubin on day 27 postpartum whose level was lower during the basal secretion phase although lying within reference values (Table 3).

The results of linear regression shown in Table 4 could indicate that the relationship between blood parameters and plasma progesterone was not a simple linear function (P>0.05). However, the linear regression model which showed that a relationship existed between the postpartum progesterone (P4) concentration and cholesterol (Chol) level was seen only on days 27 and 32 postpartum at a moderate coefficient of correlation:

P4 (day 27) = -2.67 + 0.057*Chol (day 27), (r2=0.49, P<0.01) and P4 (day 32) = -6.59 + 0.12*Chol (day 32), (r2=0.57, P<0.01)

Table 2. **Pearson correlation "r", between prepartum blood parameters levels and postpartum daily sampling progesterone concentration**

Prepartum blood parameters concentrations		Postpartum progesterone concentrations										
		Day 7	Day 12	Day 17	Day 22	Day 27	Day 32	Day 37	Day 42	Day 47	Day 52	Day 57
Alb	r	0.36	0.32	0.33	0.40	0.40	0.24	0.15	0.53	0.39	0.43	0.21
	P-value	0.22	0.28	0.26	0.17	0.18	0.42	0.63	0.06	0.19	0.16	0.51
Chol	r	0.09	0.22	0.17	0.25	0.15	0.12	-0.06	0.06	-0.14	0.16	-0.25
	P-value	0.76	0.48	0.59	0.40	0.63	0.70	0.84	0.84	0.64	0.61	0.44
TG	r	-0.19	-0.03	-0.14	0.10	-0.07	-0.09	-0.20	-0.24	-0.11	-0.03	-0.16
	P-value	0.53	0.92	0.65	0.75	0.81	0.76	0.51	0.43	0.71	0.93	0.61
BD	r	-0.41	-0.27	-0.34	-0.51	-0.06	0.00	-0.10	-0.36	-0.53	-0.18	-0.52
	P-value	0.17	0.37	0.26	0.08	0.84	1.00	0.75	0.23	0.06	0.57	0.08
BT	r	-0.37	-0.30	-0.43	-0.33	0.11	0.06	-0.24	-0.30	-0.37	-0.31	-0.43
	P-value	0.22	0.32	0.14	0.28	0.71	0.84	0.43	0.32	0.21	0.32	0.16

Table 3. **Comparison of postpartum blood parameters in relation to postpartum profile, basal and luteal levels**

	P4 levels	Alb	P-value	Chol	P-value	TG	P-value	DB	P-value	TB	P-value
Day 7	Luteal	3.84±0.10	0.06	80.27±3.71	0.47	40.27±3.17	0.41	0.07±0.05	0.22	0.06±0.01	0.90
	Basal	3.30±0.10		73.00±11.00		47.00±5.00		0.03±0.02		0.07±0.06	
Day 12	Luteal	4.11±0.21	0.75	95.00±8.08	0.34	41.22±4.96	0.25	0.11±0.02	0.99	0.16±0.04	0.68
	Basal	4.00±0.17		76.50±21.77		31.25±5.11		0.11±0.04		0.13±0.07	
Day 17	Luteal	3.68±0.13	0.78	85.50±4.35	0.88	33.13±4.27	0.28	0.14±0.02	0.19	0.18±0.03	0.23
	Basal	3.60±0.27		87.40±11.33		26.20±3.29		0.09±0.02		0.12±0.02	
Day 22	Luteal	3.67±0.22	0.99	81.00±7.76	0.67	30.86±5.01	0.98	0.12±0.03	0.87	0.17±0.02	0.93
	Basal	3.67±0.31		75.50±10.23		30.67±4.42		0.13±0.04		0.17±0.04	
Day 27	Luteal	3.59±0.15	0.61	91.00±8.97	0.15	42.88±6.39	0.56	0.10±0.02	0.04	0.15±0.02	0.18
	Basal	3.22±0.65		69.60±9.59		36.40±8.95		0.04±0.01		0.11±0.03	
Day 32	Luteal	3.53±0.21	0.54	87.50±6.17	0.09	30.00±3.22	0.90	0.12±0.02	0.78	0.24±0.09	0.86
	Basal	3.74±0.28		68.40±8.30		29.40±3.01		0.13±0.03		0.22±0.04	
Day 37	Luteal	3.77±0.38	ND	82.92±4.93	ND	31.75±3.21	ND	0.08±0.02	ND	0.18±0.03	ND
	Basal	4.00		80.00		37.00		0.08		0.10	
Day 42	Luteal	3.20±0.22	0.46	72.88±4.06	0.28	32.00±4.65	0.92	0.11±0.05	0.48	0.13±0.02	0.61
	Basal	3.52±0.40		62.80±9.44		33.20±12.06		0.05 ±0.03		0.10±0.06	
Day 47	Luteal	3.26±0.21	0.42	70.00±7.51	0.75	34.56±9.63	0.78	0.05±0.01	0.97	0.11±0.02	0.49
	Basal	2.98±0.13		66.00±5.49		30.25±5.25		0.05±0.01		0.08±0.02	
Day 52	Luteal	3.02±0.12	0.74	68.60±5.52	0.52	32.20±3.45	0.85	0.05±0.02	0.63	0.06±0.02	0.41
	Basal	3.55±1.25		59.00±19.00		37.50±21.50		0.07±0.02		0.03±0.00	
Day 57	Luteal	3.42±0.25	0.21	74.80±8.69	0.12	35.60±8.42	0.89	0.04±0.01	0.57	0.10±0.03	0.59
	Basal	3.00±0.22		53.43±8.52		37.00±6.03		0.05±0.02		0.08±0.02	
ND : Not determined											

Discussion

In the present study, blood parameters values recorded in prepartum and two months post lambing (Table 1) were mostly within reference ranges set up by Aitken (2007) and Kaneko et al. (2008).

Total cholesterol and triglycerides concentration during late pregnancy showed to be higher than during early lactation which is similar to what has been recorded by other authors (Nazifi et al., 2002; Balikci et al., 2007; Mohammadi et al., 2016). This variation could be an expression due to a physiological adaptation of ewes to the energetic requirements at theses stages as reported by Nazifi et al. (2002).

A significant increase in cholesterol concentration has also been reported by Schlumbohm et al. (1997), which they suggested as being due to a diminution of adipose tissue sensitivity to insulin before lambing. The increase in plasma triglycerides concentrations recorded only during late pregnancy (ewes fed on an adequate diet) was as well noted by Mazur et al. (2009). These last authors

have suggested that strong lipomobilisation during late pregnancy in ewes fed restricted diet leads to a reduced hepatic triglyceride secretion.

Table 4. **Regression model of temporal linear relationship of progesterone to blood markers predictor**

	Alb (g/dl)		Chol (mg/dl)		TG (mg/dl)		DB		TB	
Progesterone	r2	P-value	r2	P-value	r2	P-value	r2	P-value	r2	P-value
Day 7	0.20	0.13	0.12	0.25	0.00	0.96	0.03	0.56	0.15	0.20
Day 12	0.00	0.90	0.14	0.22	0.06	0.43	0.06	0.44	0.01	0.71
Day 17	0.00	0.98	0.03	0.61	0.00	0.95	0.17	0.16	0.24	0.09
Day 22	0.12	0.24	0.17	0.16	0.01	0.78	0.02	0.62	0.00	0.88
Day 27	0.02	0.63	0.49	0.01	0.02	0.64	0.00	0.86	0.12	0.25
Day 32	0.00	0.86	0.57	0.00	0.01	0.75	0.02	0.61	0.05	0.45
Day 37	0.01	0.73	0.13	0.23	0.07	0.37	0.07	0.39	0.00	0.88
Day 42	0.02	0.67	0.02	0.62	0.00	0.82	0.01	0.71	0.00	0.83
Day 47	0.29	0.06	0.13	0.23	0.00	0.94	0.00	0.96	0.12	0.25
Day 52	0.00	0.87	0.23	0.11	0.00	0.94	0.02	0.64	0.00	0.98
Day 57	0.01	0.80	0.00	0.96	0.01	0.82	0.00	0.87	0.07	0.40

Albumin plasma concentrations recorded in the present study tended to diminish from prepartum to the first week postpartum, probably as a consequence of its binding capacity to plasmatic NEFA released during triglycerides hydrolysis (lipolysis) in transition period; albumin being known as the plasma transport protein of circulating lipids (NEFA) from adipose tissue to other tissues such as liver (Kaneko et al., 2008). Our results were close to those recorded by Mohammadi et al. (2016) who noted the lowest concentration of serum albumin after parturition.

Bilirubin values are specific to hepatobiliary disturbance and should be monitored and interpreted conjointly with total cholesterol and NEFA values during the establishment of metabolic profile (Van Saun, 2000). Bilirubin (total and direct) concentrations recorded during peripartum did not differ from reference values and does not indicate any liver dysfunction. This parameter, together with total cholesterol concentrations, could be expressing a healthy metabolic status of females during a transition period as suggested by Van Saun (2000) in dairy cows. In the present study, higher levels of TB found in pregnant ewes than in first week lambing ones have also been observed by Ramos et al. (1994) as a consequence of higher liver metabolic activity and by Balikci et al. (2007) as a result of additional bilirubin derived from degradation of fetal hemoglobin. Direct Bilirubin values during prepartum and postpartum were not different apart from those recorded on day 47 and day 57.

Prepartum blood parameters at normal concentrations (Table 2) could express an adequate energetic nutritional status before lambing as shown through a good body condition score (3.5/5). Postpartum ovarian activity of monitored ewes in accordance with their progesterone kinetic appeared to not depending of their prepartum nutritional status. Some authors suggested that prepartum nutritional level had low effect on the date of first post-partum ovulation (Sides et al., 1986).

The results of comparison test (Table 3) confirmed by those of regression test (Table 4) showed an absence of a linear relationship among progesterone level between sampling days and corresponding concentrations of blood parameters. One can suggest that progesterone synthesis is not related to cholesterol concentration in blood stream but it may be dependent on changes in steroidogenic enzymes level as reviewed by Niswender et al. (1994) since they allow cholesterol conversion in follicles and luteal cells depending on gonadotrophin hormones (FSH and LH). This could explain the weak significance value of cholesterol and its related blood parameters in order to predict the rate of progesterone synthesis in the present study.

Furthermore, the absence of relationship between cholesterol and progesterone synthesis was also found by Akbarinejad et al. (2012) and Khotijah et al. (2015) despite a supplementation with polyunsaturated fatty acids. In our study the absence of this relationship could be due to the fact that most of the amount of cholesterol used for steroidogenesis derives from the bloodstream in the form of LDL or HDL under normal condition and from acetate under condition of lipid deprivation as reviewed by Niswender et al. (2000). In experimental condition, an in vitro study on ovine luteal cells has revealed that maximal stimulation of progesterone secretion by lipoprotein correlates quite well with normal levels of HDL or LDL in serum and cholesterol and bovine serum albumin treatment had no effect ($P>0.05$) on progesterone synthesis (Wiltbank et al., 1990). Similarly, recorded levels of albumin, the main protein transport hormone as well as cholesterol and triglycerides concentrations, appeared to be not related to progesterone kinetic in monitored ewes.

The exceptional linear models that appeared on days 27 and 32 postpartum (Table 4) with a moderate correlation, tend not to exclude a possible relationship between cholesterol and progesterone as described by Özpınar and Fırat (2003), who found such a relation during the luteal phase in multiple lambing Sakız Ewes. Furthermore, an increase of plasma concentrations of cholesterol, triglycerides and progesterone was reported

in ewes fed supplemental fat (Ghoreishi et al., 2007; El-Nour et al., 2012; Bianchi et al., 2014).

In the present study, blood bilirubin levels as well as cholesterol and triglycerides appeared within reference ranges and did not express any liver dysfunction. These findings could explain the absence of a linear model via which it would be possible to explain the relationship between the variation in concentrations of postpartum progesterone and the blood parameters recorded ($P>0.05$). The circulating progesterone concentration was determined as a balance between progesterone synthesis, primarily by corpus luteum, and progesterone metabolism, primarily by the liver by Wiltbank et al. (2012). These last authors have suggested that the rate of progesterone metabolism is generally determined by liver blood flow and can be of critical importance in determining circulating progesterone concentrations, particularly in dairy cattle. In this species, it is clearance, more than luteal synthesis that determines peripheral progesterone concentration in pregnant lactating dairy cows (Rhinehart et al., 2009).

Conclusions

The present study had been conducted in periparturient healthy ewes under normal conditions of lipid metabolism and liver function as expressed by normal concentrations of monitored compounds. In these conditions, the profile of progesterone appeared mostly not linearly related to cholesterol and other parameters investigated. Therefore, these blood tests had not a substantial predictive value of the postpartum interval length.

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