



Assessment of Relationship Between IGF-I Concentration Before Parturition and Postpartum Endometritis and Ovarian Cysts in Dairy Cattle

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Abstract

This study was carried out to assess the IGF-I, non-esterified fatty acids (NEFA), beta hydroxybutyrate (BHB) and glucose concentrations during the peripartum period of dairy cows in normal condition, and cows with endometritis puerperalis and cystic ovarian disease. The study was conducted on 87 lactating Holstein cows (parity: 1-7) in the 9th month of pregnancy in Shiraz, Iran. Blood samples were collected every 2 weeks from 2 weeks before until 6 weeks after calving. Two, four and six weeks after calving, palpation of the reproductive tract was performed. Cows were first inspected for the presence of fresh abnormal discharge on the vulva, perineum, or tail then those were examined intra-vaginally. Following inspection, ultrasonographic assessment of uterus and ovaries was also performed and ovarian structures (palpable follicle, CL and cyst) were scanned. Prepartum IGF-I concentration was significantly lower in cows that developed cystic ovaries than non-cystic (35.89±9.09 versus 41.99±3.65 µg/L) and cows with clinical endometritis early postpartum than normal cows (36.65±5.38 versus 43.64±4.32 µg/L). Calving-first service interval and ovarian cycle resumption after calving was significantly shorter for cows without clinical endometritis than cows with clinical endometritis. In conclusion, prepartum IGF-I concentration was the main factor associated with occurrence of endometritis and cystic ovarian disease after calving and it was a notable feature of the current study.

Özet

Sütçü İneklere Doğum Öncesi ve Postpartum Endometritis ve Yumurtalık Kistlerinde IGF-I Düzeylerindeki İlişkinin Değerlendirilmesi

Bu çalışma peripartum dönem sırasında normal durumdaki sütçü inekler ile puerperal endometritis ve yumurtalık kisti olan ineklerdeki IGF-1, esterleşmemiş yağ asitleri (NEFA), beta hidroksibutirat (BHB) ve glukoz düzeylerinin değerlendirilmesi için gerçekleştirilmiştir. Çalışma İran, Şiraz'da gebeliklerinin 9. ayında bulunan 87 adet laktasyondaki Siyah Alaca (doğum sayısı: 1-7) inekte yürütülmüştür. Buzağı doğumlarından 2 hafta öncesinden başlayarak doğumdan 6 hafta sonrasına kadar her 2 haftada bir kan örnekleri alınmıştır. Buzağı doğumlarından iki, dört ve altı hafta sonra ineklerin genital organlarının durumları rektal palpasyon ile değerlendirilmiştir. İneklerin vulva, perineum ya da kuyruk bölgesinde taze anormal akıntı varlığı yönünden incelendikten sonra intravajinal incelemesi de yapılmıştır. İnceleme sonrası, rahim ve yumurtalıkların ultrasonografik değerlendirilmesi yapılmış ve yumurtalık yapıları (palpe edilebilen folikül, CL ve kist) taranmıştır. Prepartum IGF-I düzeyleri kistik yumurtalıkları oluşan ineklerde kistik olmayanlara göre (35,89±9,09'a karşı 41,99±3,65 µg/L) ve erken postpartum dönemde klinik endometritli ineklerde sağlıklı ineklere göre (36,65±5,38'a karşı 43,64±4,32 µg/L) anlamlı olarak daha düşük bulunmuştur. Klinik yönden endometritli olmayan ineklerde doğum sonrası ilk tohumlama aralığı ve doğum sonrası östrus siklusunun yeniden başlama sürelerinin klinik yönden endometritli ineklere göre anlamlı olarak daha kısa bulunmuştur. Sonuç olarak, prepartum IGF-I düzeyi doğum sonrası endometritis ve kistik ovaryumun oluşumu ile ilişkili temel faktördür ve ortaya konulan bu sonuç çalışmanın önemli bir özelliğidir.

Introduction

Endometritis is characterized by inflammation of the superficial layer of uterine lumen with various consequences as a result of delayed uterine involution. It has negative effects on reproductive performance in dairy cows because it increases services per conception, calving to first service interval and calving to conception interval, reduces the chance of pregnancy, decreases the conception rate, and results in more culls due to conception failure (Heuwieser et al., 2000). The continued bacterial contamination and endometritis in postpartum uterus causes inflammation, pathological changes of the endometrium, and so, delayed uterine involution (Sheldon et al., 2003; Williams et al., 2005). Therefore, uterine diseases must be identified and treated efficient and timely manner in order to decrease their negative effects on fertility (Sheldon, 2004). Cystic ovarian disease (COD) is also one of the most common causes of reproductive failure in cattle and the incidence in dairy cows has been reported to range from 5.6% to 18.8% (Peter, 2004).

Most cows acquire uterine bacterial contamination at calving. This is normally cleared within 2–3 weeks, but about 15% of animals develop persistent endometritis in the 3–6 week postpartum period (Sheldon et al., 2009). Subclinical endometritis is associated with longer intervals to conception (Gilbert et al., 2005). Severe negative energy balance in early postpartum dairy cows is associated with poor subsequent fertility. The risk of uterine disease also increases in cows with a high liver fat content, with differences becoming apparent around 7–10 days postpartum (Zerbe et al., 2000). Therefore some changes in metabolic processes during the genetic progress toward improved potential for productivity might be the possible mediator for the negative effects on the reproductive system of the modern dairy cow.

One of the most important metabolic factors affecting the reproductive activity is insulin-like growth factor-I (IGF-I). Insulin like growth factor-I has been identified as a hormonal mediator of reproduction in cattle. For example, multiparous cows that did not ovulate until 45 days after calving had significantly lower concentrations of IGF-I (Kadivar et al., 2012). Multiparous cows with a low nadir in circulating IGF-I in the first 2 weeks postpartum subsequently failed to conceive (Taylor et al., 2004). Uterine health is an important factor involved in reproductive efficiency during the postpartum period in cattle (Roche, 2006). This is not surprising as it is well documented that IGF-I

can significantly influence the immune system in several species, including cattle (Heemskerk et al., 1999). But few previous studies have investigated the relationship among systemic IGF-I and the occurrence of postpartum reproductive diseases in dairy cows.

This study was carried out to assess IGF-I and other metabolites [non-esterified fatty acids (NEFA), beta hydroxybutyrate (BHB) and glucose] in normal condition, endometritis and cystic ovarian disease during the peripartum period in dairy cows.

Materials and Methods

Animals and herd

The study was conducted on 87 lactating Holstein cows (parity: 1-7) in the 9th month of pregnancy in a large commercial dairy herd in Shiraz, Iran (longitude 052°36'E and latitude 29°33'N). All cows had dystocia, RFM or pyometra excluded from our study. Throughout the year, cows were housed in a tie-stall barn. Cows were group fed a total mixed ration to meet production requirements. The cows were machine-milked three times daily. The mean 305-day fat-corrected milk (FCM) yield was calculated according to the formula (Ptak et al., 2004):

$$\text{FCM} = (15 \times \text{fat weight}) + (0.4 \times \text{milk weight}).$$

Body condition score of selected cows (based on scale 1–5 with 0.25 increments) was between 3 to 4 at parturition (Edmonson et al., 1989).

Sampling and biochemical analysis in serum

Blood samples were collected (2 weeks prepartum and 2, 4 and 6 weeks after parturition) from coccygeal vessels into a glass tube, kept in a cool box and transported to the laboratory. Within 4 h after collection, serum was separated by centrifugation (1700 × g for 15 min), and subsequently stored at -20 °C until analysis. Serum IGF-I was measured using ELISA kits (UK Immunodiagnostic Systems Ltd, IDS). The inter- and intra- assay coefficients of variation were 6.5 and 7.2%, respectively, and the sensitivity was 3.1 ng/mL. The serum was analysed for glucose using the glucose oxidase method. The BHB and NEFA were measured by kinetic enzymatic and colorimetric methods, respectively using BHB and NEFA kits (Randox Laboratories, Crumlin, Antrim, UK).

Reproductive management and clinical examinations

A voluntary waiting period of 50 days was generally maintained, and cows detected in estrus after this period were artificially inseminated. Estrus detection

was performed by visual observation by the herdsmen. Pregnancy diagnosis was performed by ultrasound examination 30–35 days after artificial insemination (AI). Calving and AI dates and the results of pregnancy tests were recorded.

Examination of the reproductive tract postpartum was carried out from 2 to 6 weeks postpartum, at 2-week intervals by palpation per rectum of the ovaries and uterus. Cows were examined at 26–32 days in milk (DIM) for diagnosis of clinical endometritis. During examination, the cow's vulva was thoroughly cleaned with a dry paper towel and a clean, lubricated, gloved hand was inserted through the vulva and the mucus contents of the cranial vagina were withdrawn manually for examination. Cows with abnormal uterine discharge were diagnosed with clinical endometritis (LeBlanc et al., 2002). Transrectal ultrasonography using a rectal linear probe (real time B-mode linear array scanner with a 5 MHz transducer, 500 V, Ami, Canada) was also performed to confirm palpation per rectum findings. Ultrasonographic assessment of uterus and ovaries was also performed and ovarian structures [palpable follicle, CL and cyst] were scanned. Ovarian cysts have been defined as follicles with a diameter of at least 25 mm, present on one or both ovaries in the absence of any active luteal tissue, without contraction in uterine horn and which clearly interfere with normal ovarian cyclicity (Vanholder et al., 2006). At confirmed diagnosis, all cows with ovarian cysts in second exam between 39 and 50 days postpartum.

Statistical analysis

Eighty seven lactating Holstein cows without any other postpartum disease were selected for this study. They are considered to be taken at random from a reference population (commercial dairy cattle). The following mixed model was used:

$$Y = m + u + p + o + ux + uo + px + ux + o + c + e$$

Where *m* is the general mean, *u* the effect of 'uterine health status' (fixed), *p* is peripartum period (fixed), *o* is the ovarian health status (fixed), *c* is the effect of dairy cow (random) and *e* the residual. Least square means were computed for each dependent variable in each group using a mixed model with animal as a random effect. The proc mixed procedure of the SAS (2005) software was used. The different groups were compared using Duncan's multiple range test. Calving to first AI, calving to conception interval, days open and ovarian cycle resumption after parturition between cows with and without clinical endometritis

were compared using t-test. Significance was established at $P < 0.05$.

Results

Concentration of IGF-I and other metabolites in cows with different uterine health status

Table 1 shows overall (over peripartum days) concentration of IGF-I, BHB, NEFA, glucose and 305 day milk yield in cows with clinical endometritis and normal cows. Cows with clinical endometritis had significantly lower concentrations of IGF-I and NEFA ($P < 0.05$). Other metabolites and 305 day milk yield did not show any significant difference between groups ($P > 0.05$). As is shown in Figure 1, the significant difference in IGF-I concentration between two groups of cows (with or without clinical endometritis) was in prepartum IGF-I, and cows with clinical endometritis had significantly lower concentrations of IGF-I before parturition (70.31 ± 22.07 versus 86.44 ± 16.75). The pattern of fluctuations in serum IGF-I concentration was similar in the two groups of cows during the dry and early lactation periods. Serum IGF-I concentration was highest late in the dry period and progressively decreased towards parturition, reaching the lowest levels 25 to 30 days after calving. The IGF-I level then progressively increased with the increase in the number of days postpartum (Figure 1). Changes in concentration of IGF-I, BHB, NEFA and glucose during peripartum period are shown in Table 2. As seen, the concentration of NEFA and glucose IGF-I decreased significantly ($P < 0.05$) during the peripartum period in the two groups of cows.

As is expected cows without clinical endometritis had significantly ($P < 0.05$) fewer days to their first AI, and ovarian cycle resumption was significantly ($P < 0.05$) earlier in cows without clinical endometritis than cows with endometritis (Table 3). Although the calving to conception interval was greater in cows with clinical endometritis, but no significant difference was seen. ($P > 0.05$).

Concentration of IGF-I and other metabolites in cystic and non-cystic cows

Cows that developed cystic ovaries early postpartum had significantly ($P < 0.05$) lower concentrations of IGF-I than non cystic cows (Table 4). Figure 2 shows the significant difference in IGF-I concentration between cystic and non cystic cows was in prepartum IGF-I and cystic cows had significantly lower concentrations of IGF-I before parturition (65.82 ± 21.19 versus 82.81 ± 19.32). The pattern of IGF-I

concentration changes was similar in cystic and non cystic cows (Figure 2). Also, serum BHB concentration was significantly ($P<0.05$) higher in cystic cows (Table 4). Cystic and non cystic cows had no significant difference in NEFA and glucose concentrations and 305 day milk yield ($P>0.05$). Table 5 shows IGF-I, BHB, NEFA

and glucose changes during peripartum period in cystic and non cystic cows. NEFA and glucose decreased significantly during the peripartum period ($P<0.05$). Ovarian health status and peripartum period showed significant interaction only for IGF-I ($P<0.05$).

Table 1. IGF-I and Blood metabolites concentrations and 305 day milk yield (LSM±SE) in clinical endometritis and normal cows.

Table 1. Klinik yönden endometritisli ve normal ineklerdeki IGF-I ve kan metabolitleri düzeyleri ile 305 günlük süt verimleri (LSM±SE).

Parameter	Uterine Health Status	
	Cows with Clinical Endometritis [n=28]	Normal Cows [n=59]
IGF-I, µg/L	36.65±5.38*	43.64±4.32
BHB, mmol/lit	0.25±0.01	0.23±0.01
NEFA, mmol/lit	0.86±0.09*	1.01±0.06
Glucose, mmol/lit	1.94±0.12	1.88±0.09
305 day milk yield, lit	8417.40±260.05	8149.48±164.31

*Asterisk indicates means differ from each other ($P<0.05$).

Table 2. Metabolites concentrations (LSM±SE) of cows with and without clinical endometritis, during the peripartum period.

Table 2. Peripartum dönemde klinik yönden endometritis olan ve olmayan ineklerin metabolit düzeyleri (LSM±SE).

Parameter	Uterine Health Status	
	Cows with Clinical Endometritis [n=28]	Normal Cows [n=59]
IGF-I, µg/L		
2 weeks prepartum	70.31±4.17 ^a	86.44±2.18 ^a
4 weeks postpartum	15.08±0.70 ^b	16.26±0.53 ^b
6 weeks postpartum	23.12±1.78 ^c	26.07±1.37 ^c
BHB, mmol/lit		
2 weeks prepartum	0.27±0.01	0.23±0.06
2 weeks postpartum	0.25±0.01	0.24±0.01
4 weeks postpartum	0.26±0.02	0.24±0.01
6 weeks postpartum	0.21±0.01	0.22±0.01
NEFA, mmol/lit		
2 weeks prepartum	1.00±0.1 ^a	1.15±.06 ^a
2 weeks postpartum	0.73±0.08 ^b	0.80±0.05 ^b
Glucose, mmol/lit		
2 weeks prepartum	2.64±0.11 ^a	2.67±0.06 ^a
2 weeks postpartum	1.79±0.1 ^b	1.80±0.07 ^b
4 weeks postpartum	1.77±0.1 ^b	1.61±0.07 ^b
6 weeks postpartum	1.48±0.07 ^c	1.42±0.05 ^c

^{a, b, c} : Values in the same column with different superscripts are significantly different ($P<0.05$).

Table 3. Calving to first AI, calving to conception interval, days open and ovarian cycle resumption (LSM±SE) in cows with and without clinical endometritis.

Tablo 3. Klinik yönden endometritisi olan ve olmayan ineklerde buzağılama sonrası ilk suni tohumlama, buzağılama ile gebe kalma zamanı arasındaki aralık, boştta kaldığı gün sayısı ve östrus siklusunun yeniden başladığı gün (LSM±SE).

Reproductive Parameter	Uterine Health Status	
	Cows with Clinical Endometritis (n=28)	Normal Cows (n=59)
Calving to first AI, day	81.64±8.20*	59.52±2.83
Calving to conception interval, day	131.25±10.91	124.83±8.65
Days open	174.25±24.00	137.06±10.72
Ovarian cycle resumption, day	33.64±1.78*	28.27±1.06

* Asterisk indicates means differ from each other (P<0.05).

Table 4. IGF-I, blood metabolites concentrations and 305 day milk yield (LSM±SE) in cystic and non cystic cows.

Tablo 4. Kistik ve kistik olmayan ineklerdeki IGF-I, kan metabolitleri düzeyleri ve 305 günlük süt verimi (LSM±SE).

Parameter	Cystic ovaries development	
	Cystic cows (n=8)	Non cystic cow (n=79)
IGF-I, µg/L	35.89±9.09*	41.99±3.65
BHB, mmol/lit	0.28±0.03*	0.23±0.01
NEFA, mmol/lit	1.04±0.18	0.96±0.05
Glucose, mmol/lit	1.88±0.23	1.89±0.07
305 day milk yield, lit	8294.9±703.82	8229.7±138.05

* Asterisk indicates means differ from each other (P<0.05).

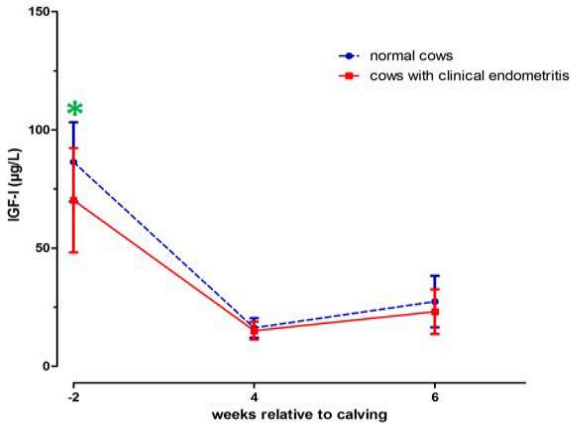


Figure 1. LSM±SE over time obtained for IGF-I in cows with and without clinical endometritis (Asterisk indicates means differ from each other).

Şekil 1. Klinik yönden endometritli ve endometriti olmayan ineklerde IGF-I için elde edilen zamana karşı LSM±SE (Asterisk ortalamaların birbirinden farklı olduğunu göstermektedir).

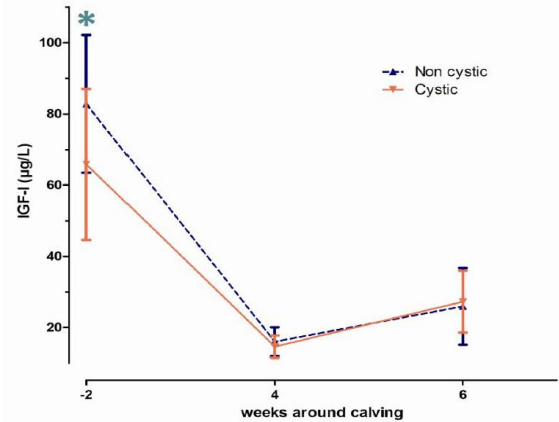


Figure 2. LSM±SE over time obtained for IGF-I in cystic and non cystic cows during the sampling period (Asterisk indicates means differ from each other).

Şekil 2. Klinik yönden kistikli ve kistik olmayan ineklerde IGF-I için elde edilen zamana karşı LSM±SE (Asterisk ortalamaların birbirinden farklı olduğunu göstermektedir).

Table 5. Metabolites concentrations (LSM±SE) of cystic and non cystic cows during the peripartum period.**Tablo 5.** Peripartum döneminde kistik olan ve kistik olmayan ineklerin metabolit düzeyleri (LSM±SE).

Parameter	Cystic Ovaries Development	
	Cystic Cows (n=8)	Non Cystic Cows (n=79)
IGF-I, µg/L		
2 weeks prepartum	65.82±7.51 ^a	82.81±2.17 ^a
4 weeks postpartum	14.62±1.10 ^b	16.01±0.45 ^b
6 weeks postpartum	27.23±3.08 ^c	25.94±1.21 ^c
BHB, mmol/lit		
2 weeks prepartum	0.25±0.01	0.24±0.00
2 weeks postpartum	0.34±0.03	0.24±0.01
4 weeks postpartum	0.33±0.05	0.24±0.01
6 weeks postpartum	0.22±0.02	0.2±0.01
NEFA, mmol/lit		
2 weeks prepartum	1.08±0.17 ^a	1.16±0.53 ^a
2 weeks postpartum	0.99±0.19 ^b	0.76±0.39 ^b
Glucose, mmol/lit		
2 weeks prepartum	2.59±0.12 ^a	2.67±0.05 ^a
2 weeks postpartum	1.74±0.1 ^b	1.80±0.06 ^b
4 weeks postpartum	1.79±0.24 ^c	1.60±0.06 ^c
6 weeks postpartum	1.39±0.18 ^d	1.45±0.04 ^d

^{a, b, c}: Values in the same column with different superscripts are significantly different (P<0.05).

Discussion

It was found in this study that the serum IGF-I concentration was lowest during the fourth week postpartum in all groups of cows and was similar among the groups. Early lactation in dairy cattle is characterized by elevated blood concentrations of growth hormone (GH) when concentrations of IGF-I in serum are low (Radcliff et al., 2006). Low serum IGF-I in early lactation is associated with essential changes in the growth hormone (GH)-IGF axis such as down regulation of liver GH receptors and GH resistance of hepatic tissue (Fenwick et al., 2008). During NEB, however, the GH-IGF axis uncouples due to a down-regulation in liver GH receptors and this is associated with a reduction in circulating IGF-I and elevated GH concentrations (Lucy et al., 2001).

It is well documented that IGF-I can significantly influence the immune system in several species (Clark, 1997; Heemskerk et al., 1999). Thus we hypothesized that serum IGF-I concentration can be associated with postpartum endometritis. Information regarding the concentration of IGF-I and the prevalence of

endometritis, however, is limited. It was revealed in this study that the lower concentration of IGF-I is associated with postpartum clinical endometritis. Similarly, it was shown that concentrations of IGF-I in cows and heifers that developed postpartum reproductive diseases decreased for a short time and barely recovered to normal values after cessation of lactation (Nakada, 2006). In bovine, circulating IGF-I levels are low following parturition and gradually increase during subsequent lactation to obtain maximal concentrations around the period of uterine involution. These IGF-I kinetics markedly coincide with lower PMN viability (Mehrzhad et al., 2001) and higher PMN apoptosis (Vangroenweghe et al., 2001) during the periparturient period. Besides, the presence of IGF-I primes the secretion of various important inflammatory cytokines, namely IL-2, IL-6, IL-8 and tumor necrosis factor-α (TNF-α). During the periparturient period, the level of IGF-I decreases considerably following parturition, concomitantly with the increase in IGFBP-5 and a decreased circulation of IGFBP-3, resulting in lower bio-availability of IGF-I (Moreira da Silva et al., 1998). As a result, susceptible

dairy cows suffering from endometritis are less capable of producing pro-inflammatory cytokines, which are necessary in the resolution of the inflammatory status, mainly through up-regulation of PMN functionality and rapid recruitment of PMN to the infected uterus.

Postpartum ovarian cycle resumption was earlier in cows without clinical endometritis as well. Hypothalamic and pituitary function is critical for directing ovarian cycles. Follicle stimulating hormone concentrations are not affected in animals with uterine disease, so follicle waves emerge in diseased animals as in normal animals (Sheldon et al., 2002). However, lipopolysaccharide (a pathogen associated molecule) suppresses the hypothalamic release of gonadotropin releasing hormone (GnRH), pituitary secretion of luteinizing hormone (LH), and the sensitivity of the pituitary to GnRH in sheep (Battaglia et al., 2000). The consequences of these changes would be that animals are less likely to ovulate.

The results of our study demonstrated prepartum higher concentration of IGF-I in cows which did not develop cystic ovaries within 45 days postpartum compared with cystic cows. Zulu et al. found that cows with low circulating IGF-I concentrations in early postpartum were likely to have poor reproductive function, as seen in the development of cystic ovaries (Zulu et al., 2002). Cairoli et al. (2008) also showed that postpartum IGF-I plasma levels were, on average, always higher in cystic as compared to cycling cows. In beef cows it was observed that plasma concentrations of IGF-I during the postpartum period increased linearly up to the day of first ovulation (Stagg et al., 1998). Likewise, dairy cows with normal ovulatory follicles during the first weeks postpartum usually show a higher IGF-I blood concentration during this period compared with animals that develop inactive ovaries, cystic follicles and persistent corpus luteum (Kawashima et al., 2007). Therefore, normal follicular development may be associated with an early rise in IGF-I postpartum. This is partially associated to the greater steroidogenic output of ovulatory first wave dominant follicles, as shown by the high correlation between plasma estradiol and IGF-I observed in cows that ovulated earlier (Beam and Butler, 1998). In this regard, Vanholder et al. reported that high yielding dairy cows have low concentrations of IGF-I, and there is circumstantial evidence that this may contribute to the development of cystic ovarian disease through an impairment of follicular cell proliferation and steroidogenesis (Vanholder et al., 2005).

Although a postpartum higher concentration of BHB was revealed in cows that developed cystic ovaries, but significance difference in NEFA and glucose concentration was not shown in the present study. Treatment of bovine granulosa cell with BHB resulted in a higher number of granulosa cells with reduction in Granulosa cell steroidogenesis (Vanholder et al., 2006). Consequent reduced steroidogenesis may insufficiently stimulate GnRH/LH release from the hypothalamus-pituitary, and the dominant follicle may develop into a cyst due to the inability to elicit an LH-surge or to elicit one of sufficient magnitude. These data support the notion that IGF-I plays a role in the regulation of folliculogenesis, and may participate in the pathogenesis of cystic ovarian disease in cattle (Ortega et al., 2008).

Therefore, based on this study, having a higher concentration of IGF-I before parturition is an important factor in the prediction of non cystic ovaries and having no uterine endometritis after calving. The association between low IGF-I concentration before parturition and occurrence of some reproductive diseases after calving (endometritis and cystic ovarian disease) was a notable feature of the current study. It was mentioned that genetic selection alters circulating concentrations of IGF-I, therefore, selection for cows with greater concentrations of IGF-I or measuring peripheral IGF-I, helps in the prediction of better reproductive health after calving.

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