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RESEARCH ARTICLE

Immunomodulatory Effects of Inactive Parapoxvirus Ovis Administration to Pregnant Heifers on Colostrum and Calf Health

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ABSTRACT

The aim of this study was to evaluate the effect of inactive Parapoxvirus ovis (IPPVO) immunomodulation protocol administration to pregnant heifers in the third trimester of pregnancy on colostrum quality, passive transfer success and calf health. Animal material of the study included 40 Holstein breed pregnant heifers and their calves, 20 of them was IPPVO group and rest 20 was control group. Totally 3 doses of 2 ml IPPVO (Zylexis, Zoetis, USA) was administered intramuscularly to study group in 25, 23 and 21 days before estimated birth date. Also control group was injected the same amount of isotonic NaCI %0.9 with IPPVO in the same days. Colostrum samples from heifers after birth and blood samples from calves 24-48 hours after birth were taken and sera were extracted. Immunoglobulin G (Ig G) concentrations of colostrum and serum samples were measured by using enzyme linked immunoassay (ELISA) method. Calves' health status were observed during first 30 days. There was no adverse effect was detected in heifers administered IPPVO during study procedure. IgG concentrations of heifers that received IPPVO was 59.64 mg/ml; that of control group was 59.62 mg/ml and the difference between groups was statistically insignificant ($p>0.05$). Average serum IgG concentration of calves born from heifers that received IPPVO was 32.6 mg/ml; that of control group was 28.7 mg/ml. When the yielded results of daily health status controls of two claves groups evaluated, no statistically significant difference was detected in terms of developing any disease and calf deaths ($p>0.05$).

Keywords: Colostrogenesis, Holstein Pregnant Heifer, IgG, Immunomodulation, Inactive Parapoxvirus Ovis

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Gebe Düvelerde İnaktif Parapoxvirus Ovis Uygulamasının Kolostrum ve Buzağı Sağlığı Üzerine İmmunmodulatorik Etkileri

ÖZ

Sunulan bu çalışmanın amacı sığırlarda gebeliğin son döneminde uygulanan inaktif Parapoxvirus Ovis (İPPVO) immunmodulasyon protokolünün kolostrum kalitesi, pasif transfer başarısı ve buzağı sağlığı üzerine etkilerinin araştırılmasıdır. Çalışmanın hayvan materyalini 20 kontrol ve 20 İPPVO grubu olmak üzere 40 adet Holstein ırkı gebe düve ve buzağıları oluşturdu. İPPVO grubuna muhtemel doğum tarihlerine 25, 23 ve 21 gün kala, toplamda 3 doz, 2 ml lik İPPVO preparatı, intramusküler (Zylexis, Zoetis, USA), kontrol grubuna ise aynı planda ve hacimde izotonik NaCI %0.9 enjeksiyonu yapılmıştır. Doğumla birlikte annelerden kolostrum örnekleri, buzağılardan ise doğumdan 24 – 48 saat sonra kan alınarak serumları çıkartılmıştır. Kolostrum ve serum örneklerinde ELISA yöntemi kullanılarak IgG konsantrasyonları ölçülmüştür. Buzağılar ilk 30 günlük dönemde sağlık yönünden takip edilmiştir. Çalışma kapsamında İPPVO preperatı kullanılan düvelerde herhangi bir yan etki gözlenmemiştir. İPPVO uygulanan düvelerin kolostrum IgG konsantrasyonları 59.64 mg/ml, kontrol grubunda ise 59.62 mg/ml olarak ölçülmüş ve aradaki fark istatistik yönden anlamsız bulunmuştur ($p>0.05$). İPPVO uygulanan düvelerden doğan buzağıların ortalama kan serumu IgG konsantrasyonu 32.6 mg/ml, kontrol grubunda 28.7 mg/ml olarak ölçülmüştür. Çalışma kapsamında iki grup buzağıları arasında yapılan günlük sağlık kontrolleri sonucunda toplanılan veriler değerlendirildiğinde hastalığa yakalanma ve buzağı ölümleri yönünden de anlamlı bir farklılık tespit edilmemiştir ($p>0.05$).

Anahtar Kelimeler: Kolostrogenezis, Gebe Holstein Düve, IgG, İmmunmodülasyon, İnaktif Parapoxvirus Ovis

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INTRODUCTION

Passive transfer (PT) is a process based on absorption and transfer to systemic circulation of immune components with nutritional substances in colostrum of cow that in puerperium through digestive system of calf (Zarcula 2008; Aydoğdu et al 2019). Calves with passive transfer deficiency (PTD) have 1,6 fold increased risk of developing any disease and their average daily live weight gain 0,06 kg less than normal calves until weaning (Kara and Ceylan 2021). While death rate of calves having less than or equal to 2 mg/ml blood IgG concentrations is over than 50%, mortality of claves having more than 18mg/ml blood IgG concentrations is less than 5% (Besser and Gay 1994). Three Q formula (Quantity, Quality, Quickly) is important for succeeding passive transfer (Jaster 2005). Also, PT success can be affected by administration method of colostrum, presence of cow, metabolic diseases of cow, various physiologic behaviors of calves and cows and calving season (Gökçe and Erdoğan 2013).

Because it is known that IgG concentrations in colostrum and calf blood is correlated, only adequate quality of colostrum use is required (Quigley 2007). PTD risk is 15,422 fold increased in calves fed with poor quality colostrum (Kara and Ceylan 2021). Colostrum quality can be affected by age, breed, vaccination status, (dry period) nutrition, health status, body condition score of the cow, the duration of dry period, calving season, milk leakage from breast in prepartum period, the time between calving and colostrum milking (Kaygısız and Köse 2007; Godden 2008; Gulliksen et al 2008; Cortese 2009; Conneely et al 2013; Phipps et al 2017; Kara et al 2020; Kara and Ceylan 2021; Kurtdede et al 2022). It is known that IgG concentrations in colostrum is directly related to that of mother's blood serum, immunomodulation and immunosuppression applications during colostrogenesis affect IgG concentrations in colostrum. Long acting corticosteroid use in the period of colostrogenesis reduces the IgG concentrations in colostrum (Gökçe ve Erdoğan 2013). Some of the immonumodulatory applications to mother in dry period in order to increase the colostrum quality are levamizol, natural zeolite, Saccharomyces cerevisiae, Corynebacterium cutis, Propionobacter acnes, mannan oligosaccharide, clinoptilolite, vitamin E and some minerals as selenium (Se) (Heinrichs et al 2003; Şentürk er al 2003; Zarcula et al 2008; Waldner and Rosengren 2009; Hall et al 2014; Çalık 2016).

Immunomodulatory term is used for substances that have stimulatory, suppressive and regulatory effects on the immune system (Kart et al 2010). Applications that immunostimulants used for is named as immunostimulation (Thacker 2010). Immunomodulation is classified in two groups as "specific" that is special for a certain pathogen and "non-specific" that is not directed against a specific pathogen (Galeotti 1998; Dhama et al 2015). While vaccines prepared for a certain agent constitute specific immunomodulators, various microorganisms or their metabolites, animal and herbal extracts, complex carbohydrates, nutritional factors, cytokines and various chemicals are some of non-specific immunomodulators (Galeotti 1998; Pirofski and Casadevall 2006; Yanar and Aktaş 2021; Atlı and Şimşek 2022). Immunomodulation is applied for generating immunity against infective agents, maintaining that the immunity is faster, more effective and longer lasting; alleviating the stress with immunosuppressive effects (Dhama et al 2015). Non-specific immunomodulators that are applied in veterinary clinical practice are used especially for supporting immune system additional to therapy, augmentation of effect of vaccines or protection and treatment of cancer cases (Kart et al 2010; Mohamed et al 2013). The most used non-specific immunomodulators applied in veterinary practice are vitamin C, vitamin D, vitamin E, vitamin A and its precursor βeta carotene, various amino acids, selenium, zinc, beta glucan, levamizol, inactive parapoxvirüs ovis (IPPVO), lysate of Corynebacterium cutis and Propionibacterium acnes and echinacea (Kim et al 2007; Cao et al 2015; Aydın and Aktaş 2021).

PPVO, in other words Orf virus (OV, ORFV), is the pathogen of a zoonotic disease named as "ecthyma disease of sheep" that is so contagious and characterized of crusted papulles especially in mucous membranes in goats and sheep (Nandi et al 2007). Results of in vivo and in vitro studies reveal that PPVO proteins induce immunomodulatory activity when used as combination with inactive vaccine virus particules (Fleming and Mercer 2007). As a strong immunomodulatory, PPVO activates most of the cells of the natural immune system via mediating rapidly the responses of humoral and cellular immunity (Orta et al 2020). By way of these activations, secretion of various chemokines and cytokines are induced. Whitin in immunoreaction, neutrophyles, natural killer (NK) cells and dentritic cells (DC) migrate to infection area (Wang and Luo 2018). IPPVO preparates derived from chemically inactivated PPVO are licensed as paraimmunity activator and widely used as immunomodulatory in veterinary field (Fachinger et al 2000; Adams and Horohov 2013). It was reported that the immunomodulatory effect was observed in the controls performed 4 days after IPPO injection in cattle (Erbasan and Mamak 2023).

The aim of this study was to evaluate the effect of inactive Parapoxvirus ovis (IPPVO) immunomodulation protocol administration to pregnant heifers in the third trimester of pregnancy on colostrum quality, passive transfer success and calf health.

MATERIALS and METHODS

Ethical approval

The study was conducted upon the approval of Ankara University Local Ethics Committee of animal experiments with approval number of 2019-5-44.

Animal Material

The animal material of the study consisted of 40 Holstein heifers and their offspring reared in a private farm in Ankara. In order to eliminate the effects of breed, age and nutrition on colostrum quality, heifers at the same age, breed, fed in the paddock with the same ration included in the study. Heifers were applied immunomodulation three month period including February-April dates. Animals were selected as control and study group respectively. Heifers detected any disease (like lameness) during the pre-study examination excluded from the study. Animals having body condition score 3.5±0.5 included in the study. Newborn calves were fed with amount of 12% of their live weight colostrum via bottle in the first 4 hours.

Study plan

Artificial insemination records and estimated birth days of animals which included in the study were determined and noted. Pregnancy period was accepted as 280 days. Totally 3 doses of 2 ml Zylexis (Zoetis, USA) that includes IPPVO D1701 strain were administered intramuscularly to heifers in the study group in 25, 23 and 21 days before estimated birth date. Also, heifers in the control group was injected intramuscularly the same amount of isotonic NaCI %0,9 with IPPVO as placebo in 25, 23 and 21 days before estimated birth date. Heifers were milked with portable single automatic milking machines within the first 2 hours following calving. A sample of 50 ml colostrum was taken into tubes before feeding and stored in a -20 °C freezer. Blood samples from calves were taken between 24-48 hours of age (Figure 1). Colostrum and blood sera were stored at -20 °C freezer.

until IgG analysis. IgG analysis was conducted with commercial enzyme linked immunoassay (ELISA) kits (Bovine Immunglobulin ELISA kit/Bio-X, Belgium-Lot No: IG19B04) according to the company's directions.

Statistical analysis

The data were summarized in tables and expressed as descriptive statistics; scatter plots were used. Independent samples t test was used for comparing blood IgG concentrations of IPPVO and control groups and Mann-Whitney U test was used for comparing morbidity (diarrhea, respiratory system infections, omphalitis and joint infections) rates of calves and colostral IgG concentrations between groups. While Pearson correlation analysis was being used for determining the relation between evaluated parameters, Chi-square test was used for comparison of groups in terms of death and morbidity rates of calves. All mentioned statistical analysis was conducted by using IBM SPSS 25 package program and significance level was accepted as $p<0,05$.

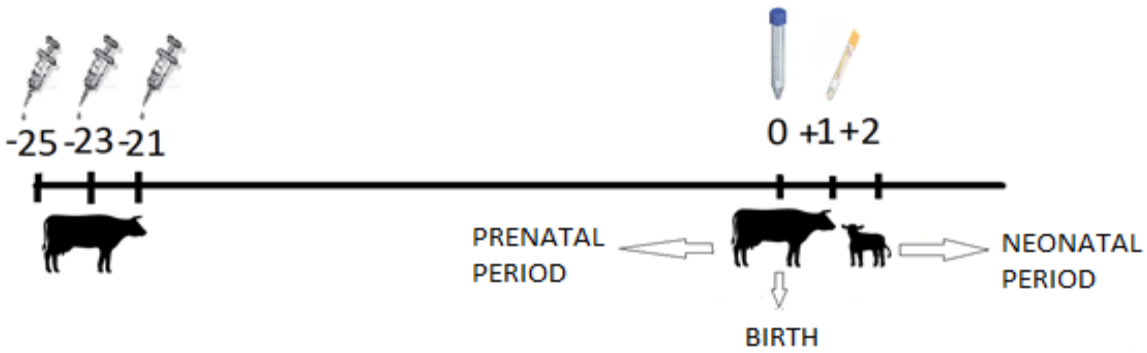

Figure 1: The days when the treatment was applied to the heifers and the days when blood and milk samples were collected from the heifers and calves.

RESULTS

There was no adverse effect reported in pregnant heifers that applied IPPVO commercial preparate (Zylexis, Zoetis / USA) via intramuscular injection 25, 23 and 21 days before birth.

Within the scope of the study, colostrum samples were taken from a total of 40 heifers, 20 in the control and 20 in the study group (IPPVO). While mean colostral IgG concentration of control group was measured as 59.62 mg/ml, it was found as 59.64 mg/ml in study group (Table 1). There was no statistically significant difference between groups ($p>0.05$).

Although each group contained 20 heifers, as a result of a heifer's twin birth, 21 calves was attained from IPPVO group. Within the scope of the study, blood samples were taken from newborn calves 24-48 hours after birth and blood samples of calves died within

first 24 hours after birth excluded from the study. One calf from control group and 4 calves from IPPVOP group died within first 24 hours after birth. Mean blood IgG concentration of calves in control group (n:19) was 29,9 mg/ml; that of calves in IPPVO group (n:17) was 32.6 mg/ml (Table2) and). the difference was statistically insignificant (p>0.05
Totally 41 calves were born, 20 of them was in the control group and 21 of them was in IPPVO group. In the first 30 days period, 7 of 41 calves died (17.1%); 3 of them (15%) were from control group, 4 of them were (19%) from IPPVO group. While all of deaths was occurred within firs 24 hours in IPPVO group, 1calf died within first 24 hours and 2 calves died 30 days period after 24 hours in control group (Table 3). When calf deaths evaluated in the farm, there was no statistically significant difference defined between groups (p>0.05)

Table 1. Colostral IgG concentrations (mg/ml) of heifers by groups

	Group	N	Mean	Median	SD	SE	p
Colostrum IgG (mg/ml)	Control	20	59,62	42,7	35	7,84	**0,947**
	IPPVO	20	59,64	51,7	34,1	7,63	

*N: Animal count in the group, SD: standard deviation, SE: standart error.

Table 2. Blood IgG concentarions (mg/ml) of calves 24-48 hours after birth

Independent Sample T-Test

	Group	N	Mean	Median	SD	SE	p
Blood IgG (mg/ml)	Control	19	29,9	28,7	12,1	2,77	**0,486**
	IPPVO	17	32,6	33,3	10,8	2,63	

*N: Animal count in the group, SD: standard deviation, SE: standart error.

Table 3. Number of dead and alive calves in the first 24 hours and between 1 and 30 days.

	Groups			
Deaths	**Control 20 calves**	**IPPVO 21 calves**	**Total**	**p**
First 24 hours	1 (%5)	4 (%19)	5 (%12,2)	
1 – 30 days	2 (%10)	0 (%0)	2 (%4,9)	**0,192**
Total	3 (%15)	4 (%19)	7 (%17,1)	
Alive	17 (%85)	17 (%81)	34 (%82,9)	

When calves that can be followed after receiving passive transfer compared, no statistically significant difference was detected between groups (p>0.05) (Table 4).
Within the scope of study, daily health checks were carried out on newborn calves for 30 days. Calves that died in the first 24 hours were excluded from evaluation during health checks, as their passive transfer success could not be evaluated. After evaluation of calves that had treatment at least for one of the following diseases: diarrhea, respiratory infections, fever, omphalitis and arthritis in first 30 days, it was found out that 11 of 17 calves (57.9%) in control group and 11 of 19 calves (64.7) in IPPVO group and totally 22 of the 36 calves (61.1%) had at least one of the mentioned diseases signs (Table 5). When evaluated in terms of the occurrence of at least one of the diseases, the statistical difference between the groups was found to be insignificant (p>0.05).
Nine calves (47.4%) from control group and 6 (35.3%) calves from IPPVO group and totally 15 calves (41.6%) had diarrhea in the first 30 days period (Table 5). No statistically significant difference was detected between groups in terms of newborn calf diarrhea (p>0.05).

Table 4. Comparison of alive and dead calves in terms of passive transfer success

	Groups			
Passive Transfer	**Control 19 calves**	**IPPVO 17 calves**	**Total**	**p**
Died after 24 hours	2 (%10)	0 (%0)	2 (%4,9)	**0,487**
Alive	17 (%89,5)	17 (%100)	34 (%94,4)	

Table 5. Disease occurrence status in calves in the first 30-day period

	Groups			p
Disease types	***Control***	***Ippvo***	***Total***	
Diarrhea	*9(47,4%)*	*6(35,3%)*	*15(41,6%)*	***0,192***
Respiratory disease	*2(10,5%)*	*5(29,4%)*	*7(19,4%)*	***0,153***
Occurrence status of at least one disease	*11(57,9%)*	*11(64,2%)*	*22(61,1%)*	***0,144***

Additionally, 2 calves (10.5%) from control group and 5 calves (29.4%) from IPPVO group and totally 7 calves (19.4%) represented respiratory infection signs in the first 30 days period (Table 5). Also, any statistically significant difference wasn't found between groups (p>0.05).

When the effect of prolonging the pregnancy period on colostrum quality both in the control and IPPVO group was evaluated in the work plan prepared with reference to 280 days in heifers; it was determined that the relationship between these continuous variables showed a negative trend (r=-0.115) (r=-0.254), but the correlation between both values was not statistically significant (p=0.613) (p=0.267) (Figure 2).

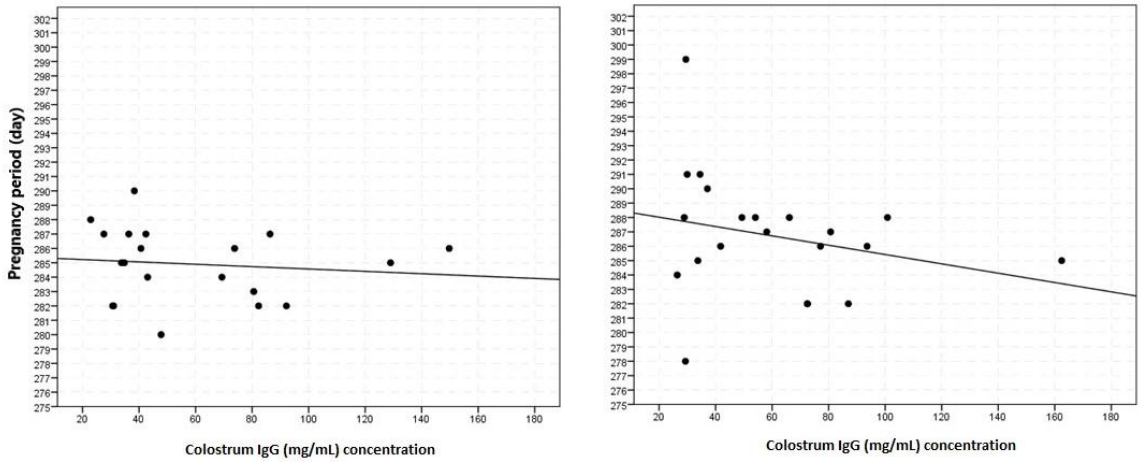

Figure 2. Evaluation of pregnancy period and colostrum IgG (mg/ml) concentration in control group (left) and IPPVO group (right) heifers.

DISCUSSION

Although the success of PT and the importance of colostrum are well known, the prevalence of PTD is still quite high (Gökçe and Erdoğan 2013; Güzelbekteş and Aydoğdu 2024). When the factors affecting the success of PT are considered, among many variables, the amount, quality, and timing of colostrum given to the calf (3 Q rule) stand out (Zarcula et al 2008).

Colostrum quality has a diverse place among all these variables. Also; it can be affected by variables such as the cow's age, breed, vaccination applications in dry period, nutrition, season, health status, dry period, and the time between colostrum milking and birth (Gökçe and Erdoğan 2013). It was reported that colostral IgG concentration of Holstein cows varies between 99 mg/ml and 186 mg/ml and average of 76 mg/ml (Swan et al 2007). According to the results of different studies, it has been revealed that the colostrum average IgG concentrations of first-born Holstein heifers are between 69.66 mg/ml and 119 mg/ml (Saucedo-Quintero et al 2004; Kehoe et al 2011; Aydoğdu and Güzelbekteş 2018; Kara and Ceylan 2021). In the presented study, the average colostrum IgG concentrations were measured as

59.62 mg/ml in the control group and 59.64 mg/ml in the IPPVO group. Although the average IgG concentration measured for both groups was above the 50 mg/ml, which is the threshold value of quality colostrum, it was found to be low compared to other studies on first-born Holstein heifers (Gökçe and Erdoğan 2013). For this reason, it would be beneficial to carry out additional practices to increase the overall colostrum quality in the farm where the study was conducted.

It is known that there is a linear relationship between colostrum quality, that is, the IgG concentration in its content, and the IgG level in the cow's blood serum. Because of this, studies have been carried out for many years to increase the colostrum quality and therefore the success of PT by targeting the colostrogenesis period and strengthening the immune systems of cows (Gökçe and Erdoğan 2013). According to results of the studies conducted by Şentürk et al. (2003) on pregnant heifers and Krakowski et al. (1999) on pregnant mares revealed that levamisole protocols targeting colostrogenesis increased colostrum quality and PT success (Krakowski et al 1999; Şentürk and Polat 2003).

In two different studies, it was reported that IgG levels in colostrum and calf blood serum increased with vaccinations against calf diarrhea at the end of pregnancy (Güngör and Baştan 2004; Sancak and Gül 2021). Çalık (2016) applied commercially available Corynebacterium cutis lysate to pregnant heifers and Turna Yılmaz et al. (2011) targeted colostrogenesis in pregnant sheep, and they reported that colostrum quality and PT success increased (Turna Yılmaz et al 2011; Çalık 2016). In this study, a commercially available IPPVO preparation was administered for 3 doses at the end of pregnancy, similarly targeting colostrogenesis, but it was determined that the IgG concentrations in colostrum and calf blood serum were not different from the control group. When other immunomodulation studies targeting colostrogenesis in order to increase colostrum quality and therefore PT success in calves are examined; It has been interpreted that the reason why the findings of this study differ from other immunomodulators that significantly increase colostrum quality may be related to the mechanism of action of the applied immune stimulant and the immune stimulation protocols.

In a research passive transfer success and calf health in different dairy farms were evaluated and it was reported that the average blood serum IgG level of calves were 19±10 mg/ml (Johnson et al 2017). The rate of calves suffering from diarrhea in the period until weaning varied between 24.1% and 74.4% among farms with the average recorded as 48.2%. In the same period, the rates of respiratory system diseases in calves were found to be between 20.4% and 77.8%, with the average as 45.9%. It has been determined that the rate of calves suffering from diarrhea is especially widespread in the first 2 weeks, while respiratory system diseases appear in the 4–9-week period. In the same study, calf mortality rates were recorded as 3.1% in the first month.

Lombard et al. (2020), in their evaluation of 2360 heifer calves on 103 farms; They reported PTY as 12%, the rate of having at least one disease as 34.3, and mortality as 3.2% (Lombard et al 2020). Urie et al. (2018), in their study involving 13 states and 104 enterprises across the USA, reported calf deaths as 5% until the weaning period in 2545 calves. They reported that at least one morbidity case was detected in 33.8% of 2545 calves, diarrhea was detected in 17.2% of the calves, and pneumonia was detected in 27% (Urie et al 2018). There is no large population study examining calf deaths in Turkey. Şahal et al. (2018) state that neonatal calf death rates in Turkey are estimated to be around 15%, that calf death rates in European countries are around 10 - 15%, and that this rate can be reduced to 5% in farms with good manegement (Şahal et al 2018). Akyüz et al. (2017) report that calf deaths are 10% in state farms (General Directorate of Agricultural Enterprises) and more than 50% in commercial farms (Akyüz et al 2017). Yüceer and Özbeyaz (2008) reported that 81 calves from 90 cows were born alive, and 5 calves (6.17%) died due to diarrhea and respiratory system infections in the first month of life (Yüceer and Özbeyaz 2010). In the evaluation made by subtracting the deaths occurring in the first 24 hours within the scope of this study, the calf mortality rate was recorded as 10% (2/19) in the control group and (0) in the IPPVO group. When all calves included in the study were evaluated, the mortality rate in the farm was found to be 4.9% (2/36). The results obtained in the study in terms of calf deaths were found to be well below the country average and were found to be compatible with good management averages. It was understood that the calf mortality rate in the farm was below 5% and that it met the targeted success criteria. Based on colostrum IgG averages, PT success was found to be compatible with literature information (Şahal et al 2018). When the diseases that occurred in the calves included in the study during the research were evaluated; In the control group, 47.4% had diarrhea, 10% had respiratory system infection, and 57% had at least one disease of different organ system. In the IPPVO group, diarrhea was observed in 35%, respiratory system infection was observed in 29.4%, and at least one disease was observed in 64.7%. Considering the entire population together, during the 30-day monitoring period, 41.6% of the 36 calves had diarrhea, 19.4% had respiratory system infection, and 61.1% had at least one disease. When the results obtained are evaluated; It was understood that the cases of diarrhea in calves were compatible with the literature information and the rate of respiratory system infection was lower than some of the literature data. This is because; It has been understood that diarrhea is more intense in the first month of life in calves, and respiratory system

infection is more common in calves, according to the literature, especially in the second month and during the weaning period. When the case of at least 1 disease in calves was evaluated, it was determined that the disease rate increased due to other diseases, especially omphalitis and trauma, but the results obtained were compatible with the literature information (Yüceer and Özbeyaz 2010; Sancak and Gülhan 2021; Şimşek and Akkan 2021).

In previous studies conducted in the same region, it was reported that the average gestation period for Holstein heifers ranged between 277.6 - 281.5 days (Koçak et al 2007; Koçak et al 2008; Şahin and Ulutaş 2010). In the presented study, it was determined that the pregnancy of 1 heifer lasted less than 280 days, the pregnancy of 1 heifer lasted 280 days, and the pregnancy of 38 heifers lasted longer than 280 days. The average gestation period in the IPPVO group was recorded as 286.85 days, and in the control group the average pregnancy period was 284.9 days. Hurley and Theil (2011) mention that IgG has a half-life (Hurley and Theil 2011). Although the half-life of IgG varies between 1-3 weeks, the half-life of IgG1, which is the predominant IgG subtype in colostrum, is reported to be shorter than IgG2 (Cervenak and Kacskovics 2009). Husband et al. (1972) reported that the average half-life of IgGs was approximately 16 days (Husband et al 1972). It was thought that the prolongation in the birth dates of most heifers within the scope of the study could be effective in the formation of the targeted IgG concentrations in the trial group. Even though there was a negative trend between those two parameters, it was not statistically significant because of the small number of trial animals.

CONCLUSION

As a result, it was observed that the IPPVO protocol applied to heifers at the end of pregnancy did not have any side effects related to pregnancy, and the immunomodulation protocol applied did not have a positive effect on colostrum quality and blood passive transfer success of calves. In addition, it was determined that the applications did not have any effect on calf sickness rates and calf mortality. However, it was observed that prolonged gestation period had a negative effect on colostrum quality and this effect was not statistically significant in the studied population.

Author's Contributions: HK and MŞ contributed to the project idea, design and execution of the study. HK contributed to the acquisition of data. HK and MŞ analysed the data. HK and MŞ drafted and wrote the manuscript. HK and MŞ reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical approval: The study was conducted upon the approval of Ankara University Local Ethics Committee of animal experiments with approval number of 2019-5-44

Conflict of interest: The authors have no conflicts of interest to report

Acknowledgement: This research article is summarized from the doctoral thesis of the same name and has not been published anywhere before. No person/organization financially supported the study and the authors have no relevant interests. The authors contributed equally to the design of the study, collection of data, and writing of the article.

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