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Placental Traits, and Plasma Concentration and Placental mRNA Expression of IGF-I in Bafra Sheep Breed with Different Birth Type

Farklı Doğum Tipine Sahip Bafra Irkı Koyunlarda Plasental Özellikleri ve IGF-I'in Plazma Konsantrasyonu ve Plasental mRNA Ekspresyonu

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PLACENTAL TRAITS, AND PLASMA CONCENTRATION AND PLACENTAL MRNA EXPRESSION OF IGF-I IN BAFRA SHEEP BREED WITH DIFFERENT BIRTH TYPE

ABSTRACT:

Insulin-like growth factors (IGF) promote follicle development, ovulation, and embryonic development and affect placental and fetal growth and development in many mammalian species. Therefore, this study aims to determine the relationship between birth type, plasma concentration, and placental mRNA expression of IGF-I in Bafra ewes. A total of 30 ewes with single (n=15) or twin (n=15) gestation and at least 2 offspring were used as experimental animals. Before mating, blood samples were collected from the jugular vena of all ewes. Following lambing, birth type, live weight, and sex of lambs and placental traits have been recorded. A commercial ELISA kit was used to measure plasma IGF-I concentration levels. IGF-I gene expression level has been determined by real-time quantitative polymerase chain reaction. No difference was observed between single and twin-bearing sheep in terms of placental weight and various cotyledon characteristics in the study. In contrast, total cotyledon weights were lower in singleton gestation those in twins ($P<0.05$). Similarly, the total and medium cotyledon number and cotyledon efficiency of Bafra ewes with single deliveries were lower than Bafra sheep with twin births ($P<0.05$). Although the birth type had no affect on both placental gene expression level and plasma concentration of IGF-I, sheep that gave birth to twins exhibited 0.908 times more gene expression than those which gave single births. The study results showed that birth type did not affect plasma IGF-I concentration and placental IGF-I gene expression level in Bafra sheep breed but changed placental characteristics.

Keywords: *IGF-I, Gene Expression, Placenta, Birth Type, Fetal Development.*

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FARKLI DOĞUM TİPİNE SAHİP BAFRA IRKI KOYUNLARDA PLASENTAL ÖZELLİKLERİ VE IGF-I'İN PLAZMA KONSANTRASYONU VE PLASENTAL MRNA EKSPRESYONU

ÖZ:

İnsülin benzeri büyüme faktörleri (IGF), birçok memeli türünde folikül gelişimini, ovülasyonu ve embriyonik gelişimi destekler ve plasental ve fetal büyüme ve gelişmeyi etkiler. Bu nedenle, bu çalışmada Bafra koyunlarında doğum tipi, plazma konsantrasyonu ve IGF-I'in plasental mRNA ekspresyonu arasındaki ilişkinin belirlenmesi amaçlanmıştır. Deney hayvanı olarak tekiz (n=15) veya ikiz (n=15) gebeliği olan ve en az 2. doğumunu yapmış toplam 30

baş koyun kullanılmıştır. Çiftleşmeden önce tüm koyunların jugular vena'sından kan örnekleri alınmıştır. Kuzulamadan hemen sonra doğum tipi, canlı ağırlık, cinsiyet ve plasenta özellikleri belirlenmiştir. Plazma IGF-I konsantrasyonu, ticari bir ELISA kiti kullanılarak belirlenmiştir. IGF-I gen ekspresyon seviyesi, gerçek zamanlı kantitatif polimeraz zincir reaksiyonu ile belirlenmiştir. Çalışmada plasenta ağırlığı ve çeşitli kotiledon özellikleri açısından tekiz ve ikiz koyunlar arasında bir farklılık tespit edilmemiştir. Ancak, toplam kotiledon ağırlıkları tekiz gebelerde ikizlere göre daha düşüktü ($P<0.05$). Benzer şekilde, tekiz doğum yapan Bafra koyunlarının toplam ve orta kotiledon sayısı ve kotiledon verimi, ikiz doğum yapan Bafra koyunlarından daha düşüktü ($P<0.05$). Doğum tipi, hem plasental gen ekspresyon seviyesini hem de IGF-I'nin plazma konsantrasyonunu etkilemese de, ikiz doğuran koyunlar, tekizlere göre 0.908 kat daha fazla gen ekspresyonu sergiledi. Sonuç olarak, Bafra koyun ırkında doğum tipinin plazma IGF-I konsantrasyonunu ve plasental IGF-I gen ekspresyon düzeyini etkilemediğini, ancak plasenta özelliklerini değiştirdiği tespit edilmiştir.

Anahtar Kelimeler: *IGF-I, Gen Ekspresyonu, Plasenta, Doğum Tipi, Fötal Gelişim.*

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1. INTRODUCTION

Bafra sheep is a crossbreed of Chios (75%) and Karayaka (25%) sheep breeds (Yakan and Unal, 2010). Body-color is white and covered with fleece. Black spots are seen around the mouth, eyes, and ears. They are generally raised in the middle of the Black Sea Region and are well suited to the harsh climate, poor pasture, and severe climatic conditions. Lambs of Bafra breeds are grown for meat production (Yakan, 2008; Yakan and Unal, 2010). Average live weight is 62 kg, height at withers 68 cm, body length 71 cm (Yakan, 2008).

Except for their role in cell metabolism, proliferation, and differentiation, Insulin-Like Growth Factors I (IGF-I) has the greatest impact on reproductive processes. IGF-I is particularly important in fetal and postnatal development (Igwebuike, 2010). Previous studies have found the presence of the IGF family in the uterus and placenta of sheep (Stevenson et al., 1994; Reynolds et al., 1997). Watson et al. (1994) reported the presence of mRNAs for IGF-I in sheep embryos throughout preimplantation development from the post-fertilization zygote stage to the blastocyst stage. Similarly, Stevenson and Wathes (1996) showed that the expression of mRNA for IGF-I was maximal in the mucosal layer of the oviduct within which early embryonic development takes place.

IGF-I plays an important role in the division and proliferation of IGF-I granulosa cells and increases the capacity of FSH and LH to bind to their receptors in granulosa cells (Behl and Kaul 2002; Mazerbourg and Monget, 2018). It also

shows that IGFs have a synergistic effect on the induction of granulose cells by providing FSH regulation (Behl and Kaul 2002; Mazerbourg and Monget, 2018). IGF- I is the most thoroughly evaluated amongst the various growth factors being investigated for their role in ovarian follicular dynamics in the mammalians (Hastie and Haresign, 2006). Previous studies have shown that IGF-I regulates its effects on ovarian activity or follicular development either alone or in harmony with gonadotropins secreted from the pituitary gland (Behl and Kaul, 2002; Mazerbourg and Monget, 2018). In addition, IGF-I increases the activity of gonadotropin hormones by affecting granulosa and teka cells in the ovarian follicles (Taketani et al., 2008).

IGF-I is an important factor that promotes follicle and oocyte development, ovulation and embryonic development in many mammalian species (Behl and Kaul 2002; Mazerbourg and Monget, 2018). Additionally, the gene expression level of IGF-I, which is associated with cell proliferation in placental tissue, may affect placental and fetal growth and development (Igwebuike, 2010). Therefore, the aim of this study is to determine the relationship between birth type, placental characteristics, plasma concentration and placental mRNA expression of IGF-I in Bafra ewes.

2. MATERIAL AND METHODS

The experimental procedures were approved by the Local Animal Care and Ethics Committee of Ondokuz Mayıs University, Samsun, Turkey, ensuring compliance with EC Directive 86/609/EEC for animal experiments (Date: July 10, 2018, Approve number: 68489742-604-E.15277). A total of 30 Bafra ewes, which have single (n=15) or twin (n=15) gestation and at least 2 offspring, have been used as experimental animals in the present study.

Approximately 10 ml of blood was taken from the jugular vein using a vacutainer in sterile heparin tubes 1 day before mating from all ewes used in the experiment. Collected blood was centrifuged at 3400 rpm for 10 minutes at 4 °C and plasma samples were stored at -20 °C until analysis of Insulin-Like Growth Factor I (IGF-I). All ewes were submitted to natural mating and housed under the same conditions. Following lambing, birth type, live weight and sex of lambs were recorded within 12 h after parturition. Each ewe was left to deliver the placenta naturally and placentas were collected from single or twin gestations immediately after delivery; care was taken to ensure that any placental weight (PW) taken were of the total placenta with any fluid being removed before weighting. The cotyledon samples to be used in RNA isolation from the collected placenta were isolated, weighed and stored at -80 °C until analysis of the placental IGF-I gene expression. Furthermore, the total cotyledon numbers (TCN) and total cotyledon weights (TCW) of placental cotyledons dissected from the chorioallantois were also counted and determined. The diameter of cotyledon were measured with a

digital compass and divided into three categories as small (<20 mm diameter), medium (20-30 mm diameter) and large (>30 mm diameter). The total cotyledon surface area (TCSA) was calculated after the measurements of all the cotyledons in each placenta as cm^2 with the following formula: radius squared of cotyledon $[((CWi + CL) / 4)^2] \times 3.14 (\pi) \times TCN$. PE was calculated as the ratio of kid BW to PW for each doe (Sen and Onder 2016). Additionally, placental efficiency (PE; lamb BW / PW), cotyledon efficiency (CE; lamb BW / TCSA) and cotyledon density (CD; TCN / PW) were calculated for each ewe.

Pre-mating plasma IGF-I concentrations of sheep with different birth types were determined using the commercial ELISA kit (SunRed, sheep IGF-I ELISA kit) in accordance with the test procedure recommended in the kit. IGF-I concentrations in plasma samples were determined by using an ELISA reader (ThermoScientific) device adjusted to 450 nm wavelength. In the reading process, the device was zeroed according to the control (blind) wells and then the measurement process was performed. The concentration of IGF-I in plasma samples was calculated according to the concentration of the standards and their respective OD (optical density) values using the standard linear regression curve equation (Figure 1).

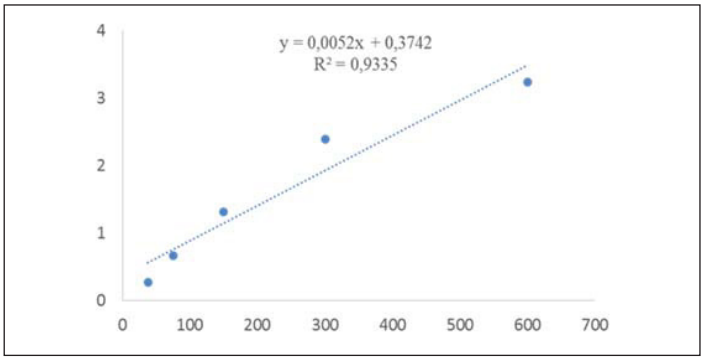

Figure 1. Standard linear regression curve for calculation of the plasma IGF-I concentration

A commercial RNA kit (NucleoSpin® RNA kit) was used for RNA isolation in cotyledon samples and the process was carried out as recommended by the manufacturer of the commercial kit. After genomic DNA was eliminated by digestion with DNase I (Thermo Scientific, Waltham, USA), the RNA quality and quantity were determined using NanoDrop 2000 (Thermo Scientific, Waltham, USA), all RNA samples showed A260/A280 values within the range of 2.01 to 2.08 and A260/ A230 values above 2. Commercial cDNA kit (BIORAD iScript cDNA, 1708890) and Thermal Cycler (BIORAD) device were used for cDNA synthesis and the analysis was done as recommended by the manufacturer of the commercial kit. Primer and reference gene base sequences in the 5 'and 3'

directions used in Real-Time PCR are shown in Table 1.

Serial No	Oligonucleotide Name	Base Sequence 5'-3'
20191003-79	Primerpair 1-F	ATGGGCATTTCCCCAATGA
20191003-80	Primerpair 1-R	GCAATCTACCAACTCCAGGGT
20191003-81	Primerpair 1-exon 2-F	TCATCTTCCTCCTGGGTCCTT
20191003-82	Primerpair 1-exon 2-R	GTCACTCACACACCTTGTTGC
20191003-83	GAPDH-F	GCAAGTTCCACGGCACAG
20191003-84	GAPDH-R	TCAGCACCAGCATCACCC

Table 1. Primer and reference gene base sequences in the 5 'and 3' directions used in Real-Time PCR

In detail, the PCR was carried out in a reaction system of the total volume of 50 µL containing 25 µL premix TaqTM, 17.5 µL 0.1% 114 DEPC water, 2.5 µL forward primers (10 µmol/L), 2.5 µL reverse primers (10 µmol/L) and 2.5 µL cDNA template. PCR procedure was carried out as follows: 98 °C for 4 min, followed by 32 cycles of 98 °C for 40 s, 60 °C for 40 s, 65°C for 30 s, and then 90 °C extension for 10 min, finally 4 °C to terminate the reaction. Relative quantification of all transcripts was performed by qRT-PCR using the real-time PCR system. Real-time quantitative PCRs were run with SYBR Premix Ex TaqTM II. The reaction system was in a total volume of 10 µL containing 5 µL 2 × SYBR Premix Ex Taq II, 0.4 µL forward primer (10 µmol/L), 0.4 µL reverse primer (10 µmol/L), 0.2 µL 50 × ROX Reference Dye, 3 µL 0.1% DEPC water and 1 µL template cDNA. PCR amplification was carried out as follows: a denaturation of 98 °C for 30 s, followed by 40 cycles of 98 °C for 5 s, specific annealing temperature 60°C for 30 s. The $2^{-\Delta\Delta Ct}$ method was used to analyze the mRNA expression levels.

The effects of birth type on placental characteristics and plasma concentration and placental mRNA expression of IGF-I were analyzed using a completely randomized design by the General Linear Model (GLM) procedure of the SPSS package program. Significant differences between means were tested using Duncan's test and results were computed as mean ± s.e.m. Statistical significance was considered at $P<0.05$.

3. RESULTS AND DISCUSSION

The sheep placenta has multiple cotyledonal structures that consist of maternal and fetal tissues and provide the circulation between dam and offspring (Igwebuike, 2010). The cotyledons on the sheep placenta are structures randomly distributed on the placental surface and positioned separately from each other (Igwebuike, 2010; Sen, 2021). The structures formed by the fetal-induced cotyledons on the sheep placenta by settling on the carancula of the uterus endometrium are called placentomes (Redmer et al., 2004). This structure carries out all circulation activities between dam and offspring. Therefore, the determination of cotyledon numbers on the placenta after birth is an indication of the number of placenta occurring

during gestation, but also an indicator of the circulation rate between offspring and dam. The binding of fetal originated cotyledons to the uterus in sheep is 25-30 weeks of pregnancy (Redmer et al., 2004). Growth restrictions (insufficient nutrition, abnormal environmental conditions and abnormal endocrinal activity, etc.) that occur between the days may affect the final cotyledon number of the placenta (Wathes et al., 1998; Redmer et al., 2004; Sen et al., 2013). Restrictive interventions in the last period of pregnancy may affect the morphology and size of cotyledons rather than the number of cotyledons (Vatnick et al., 1991). In the current study, there were no significant differences between singleton and twin gestation ewes in terms of mating weight, but lamb birth weight of ewes giving birth to singletons is higher than those giving birth to twins (Table 2). Also, some differences were detected between the placental characteristics of Bafra sheep that gave birth to single and twins (Table 2). Total cotyledon number and medium cotyledon number were found to be statistically significant between the birth type groups, and the total and middle cotyledon number of single-birth Bafra sheep was found to be lower than that of twin-birth Bafra sheep ($P<0.05$). However, there was no statistical difference between the two experimental groups in terms of placental weight, large cotyledon number and small cotyledon number. Additionally, there was a difference in terms of various efficiency features of placenta and cotyledon of Bafra lambs with single or twin birth type (Table 3). The cotyledon efficiency of single bearing sheep was found to be lower than the cotyledon activity of twin sheep ($P<0.05$). However, no significant differences were detected in terms of placental efficiency and cotyledon activity density. The results obtained show that lambs born single and twin in Bafra sheep have different placental features, so it is thought that this difference may be due to the type of birth.

Table 2. The weight characteristics and placental components of Bafra lambs with single or twin birth

	Birth type	
Traits	Single	Twin
MW (kg)	48.05±2.11	48.17±2.15
BW (g)	4207.02±324.23^{a}	3676.42±151.14^{b}
PW (g)	320.53±40.09	326.00±55.00
TCW (g)	94.75±8.61^{a}	135.60±15.30^{b}
TCN	30.86±3.74^{b}	41.78±7.50^{a}
SCN	16.00±3.54	19.00±4.33
MCN	8.00±0.62^{b}	14.56±3.70^{a}
LCN	7.57±1.02	8.33±1.61

^{a,b} Different superscript letters in the same line indicate a significant difference ($p < 0.05$).
BW= birth weight, PW = plasental weight, TCW = total cotyledon weight, TCW = total average cotyledon number, SCN = small cotyledon number, MCN = medium cotyledon number, LCN = large cotyledon number.

Table 3. Various efficiency features of placenta and cotyledon of Bafra lambs with single or twin birth

Traits	Birth type	
	Single	Twin
PE	14.03 ± 1.75	30.70 ± 7.75
CE	17.84 ± 1.35[b]	30.86 ± 4.66[a]
CD	0.107 ± 0.017	0.154 ± 0.029

a.b Different superscript letters in the same line indicate a significant difference ($p < 0.05$). PE = placental efficiency. CE = cotyledon efficiency. CD = cotyledon density

Previous studies have shown that the nutritional level of the mother affects the placental development and lamb birth weight in the middle period of pregnancy when placental development and growth occur in sheep (Sen et al, 2013). This situation shows how important placental functions are in order to continue fetal growth in the last period of pregnancy. It has been reported to be one of the main factors regulating fetal and placental growth due to the effects of IGF-I on cell proliferation and activity in mammals (Igwebuike, 2010). Some studies have reported that the regional production centre of insulin-like growth factor family and its member IGF-I in sheep are placenta and uterus (Stevenson et al., 1994, Reynolds et al., 1997). Watson et al. (1994) reported that IGF-I gene expression level can be effective in embryonic development and placentation. Although it has been stated that IGF-I plays an important role in the regulation of fetal growth, there is not much information about the importance of this factor in many births and postnatal periods. In the current study, the relationship between the differences in the type of delivery in the Bafra breed sheep with the placental features and IGF-I gene expression level was investigated. Although the IGF-I gene expression levels in the placental tissue of Bafra breed sheep with different birth types showed similarity (single; 4.01 ± 0.89 and twin 4.19 ± 0.87, Figure 2), twin-bearing sheep showed 0.908 times more gene expression than those of single-bearing sheep (Figure 3). Although the Bafra breed sheep used in the experiment were exposed to single or twin births in the previous breeding season, in the same enterprise and under similar breeding conditions (care, feeding, etc.), the differences in birth patterns are thought to be due to differences in placental characteristics.

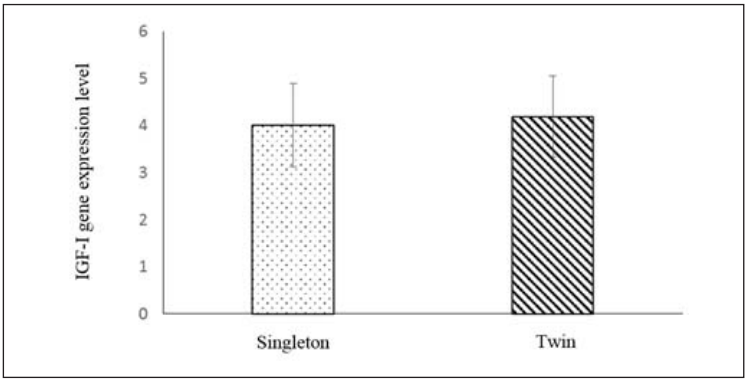

Figure 2. Placental tissue gene expression levels of IGF-I in Bafra ewes with singleton or twin bearing

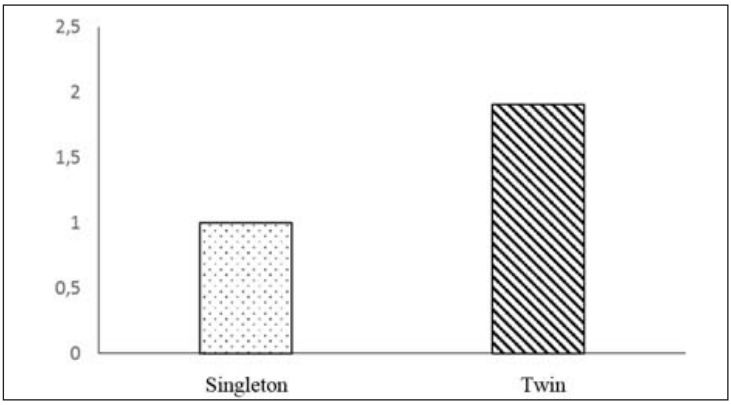

Figure 3. Placental mRNA expression fold change of IGF-I gene in Bafra ewes with singleton or twin bearing.

IGF-I is a potential regulator in the stimulation of protein metabolism, metabolic processes such as glucose transport, glycogen and triglyceride synthesis, and mitogenic activity, myogenesis, cell differentiation, physical injuries, muscle and bone formation (Besnard et al., 1996). Apart from its roles in cell metabolism, proliferation and differentiation, IGF-I exerts its most important effects in reproduction processes (Behl and Kaul, 2002). Although IGF-I is one of the most important growth factors affecting ovarian activity and follicular development, studies have reported that IGF-I is significantly expressed in mammalian ovaries (Hastie and Haresign, 2006). Moreover, many in vitro and in vivo studies show

that IGF-I is a stimulator of ovarian follicle development (Baker et al., 1993; Zhou et al., 1997; Mazerbourg et al., 2003). Studies reveal that there is an IGF system in ovarian development and activity (Behl and Kaul 2002; Hastie and Haresign, 2006; Mazerbourg and Monget, 2018). The role of IGF-I in the ovaries is to ensure the proliferation of granulosa cells in the ovarian follicles and to increase the effect of follicle stimulating hormone (FSH) through steroidogenesis by granulosa cells. The presence of follicular IGF-I, which controls the sensitivity of granulosa cells to gonadotropins, is regulated by the synthesis and proteolysis of IGF-I binding proteins under the control of FSH (Mazerbourg and Monget, 2018). IGF-I plays a controlling role in the actions of growth hormone as well as gonadotropin hormones (FSH and LH) in ovarian activities (Behl and Kaul 2002). In the current study, the effect of IGF-I on ovarian activity was tried to be clarified and it was hypothesized that plasma IGF-I concentration before mating could affect ovarian activity, increasing the number of ovulations and increasing the multiple birth rate. In the study, the plasma IGF-I concentration did not affect birth type in Bafra ewes and the plasma IGF-I concentrations of singleton and twin Bafra sheep were determined as 146.1±36.1 ng/ml and 143.9±36.9 ng/ml, respectively (Figure 4). The similarity in plasma IGF-I concentration in Bafra sheep with different birth types may be due to the fact that the sheep were subjected to a similar feeding regimen. Nutritional status is a key regulator of the circulating and tissue insulin-like growth factor (IGF) system. Previous studies reported that plasma IGF-I level is regulated by the nutritional state, and serum concentration of IGF-I falls in malnutrition and responds immediately to refeeding (Wathes et al., 1998; Reynolds et al., 1997).

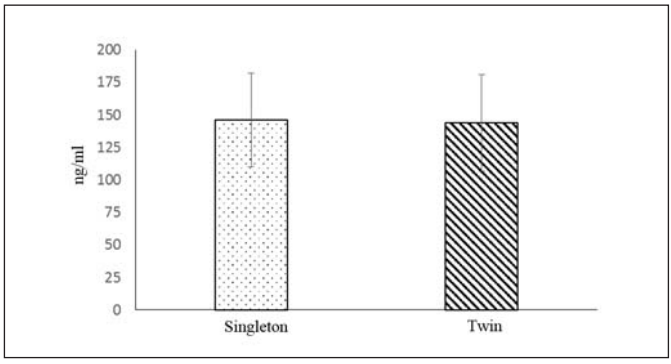

Figure 4. Concentration of plasma insulin-like growth factor I (IGF-I) in Bafra ewes with singleton or twin bearing.

4. CONCLUSION

Although the results of the present study showed that the gene expression level of IGF-I in the placental tissue is similar in Bafra ewes with different birth types, the gene expression fold change in gene expression of IGF-I was higher in twins than in singletons. This indicates that there may be a relationship between the changing level of IGF-I gene expression in the placental tissue and the birth type. Moreover, placental characteristics were affected by the birth type and lamb birth weight. It is the most significant indicator of how much the placental growth and development realized at the optimum level during pregnancy can affect lamb birth weight. Although the lambs used in this study were obtained from Bafra ewes that gave birth at similar parity and age and were raised on the same farm, it is thought that the differences in placental characteristics are entirely due to the differences in birth type.

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Author Contribution Rates

Design of study (Çalışmanın Tasarlanması): UŞ (% 80), ÖK (% 20)

Data acquisition (Veri Toplanması): UŞ (% 30), ÖK (% 70)

Data analysis (Veri Analizi): UŞ (% 80), ÖK (% 20)

Writing up (Makalenin Yazımı): UŞ (% 90), ÖK (% 10)

Submission and revision (Makalenin Gönderimi ve Revizyonu): UŞ (% 90), ÖK (% 10)

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