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Research Article

The Meta-Analysis of Conception Rates of Dairy Cattle Treated with the Ovsynch Protocol in Türkiye

Aytaç AKÇAY [1,a (*)] Murat ABAY [2,b] Elif ÇELİK [3,c]

[1] Ankara University, Faculty of Veterinary Medicine, Department of Biostatistics, TR-06110 Ankara - TÜRKİYE
[2] Erciyes University, Faculty of Veterinary Medicine Department of Obstetrics and Gynecology, TR-38039 Kayseri - TÜRKİYE
[3] Erciyes University, Faculty of Veterinary Medicine, Department of Biometrics, TR-38039 Kayseri - TÜRKİYE
ORCIDs: a 0000-0001-6263-5181; b 0000-0003-2457-1919; c 0000-0002-5073-1907

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Abstract: This study was aimed at the meta-analysis of the conception rates to the first insemination of dairy cattle treated with the Ovsynch protocol, and the determination of the sources of heterogeneity between the studies included in the analysis. The study material comprised of 46 primary studies conducted between 1999-2019 on the use of the Ovsynch protocol in Türkiye. The heterogeneity between these studies was assessed by meta-analysis using the random-effects model and the Der Simonian-Laird method. Accordingly, the common conception rate to the first insemination calculated for the primary studies, in which dairy cattle were treated with the Ovsynch protocol, was 0.412 (95% CI: 0.384-0.442) (P<0.001). The source of heterogeneity between the primary studies was determined by subgroup analyses. Conception rates were calculated for subgroups, which were established for geographical region, cattle breed, year of publication and parity. While the conception rates significantly differed for geographical region, the differences observed for cattle breed, year of publication and parity were statistically insignificant. When assessed for geographical region, the lowest common conception rate was determined in the Eastern Anatolia region (26%), whilst the highest common conception rate was determined in the Black Sea region (51.6%). The common conception rates calculated for cattle breed were 41.3% for Holstein cattle and 43.6% for Brown Swiss cattle. It was observed that the conception rates had decreased by 10% in the last 20 years to a level of 40.2% in the period between 2015 and 2019. The common conception rates calculated for parity were 39.4% for heifers and 41.9% for multiparous cows. It is considered that the results obtained in this study will contribute to the development of new strategies for a rational production in the dairy sector.

Keywords: *Conception rate, Dairy cattle, Meta-analysis, Ovsynch protocol, Synchronization*

Türkiye'de Ovsynch Protokolü Uygulanan Sütçü Sığırlarda Konsepsiyon Oranlarının Meta-Analizi

Öz: Bu çalışmada Ovsynch protokolü uygulanmış olan sürülerdeki ilk tohumlamadaki konsepsiyon oranlarının meta-analizi ile değerlendirilmesi ve çalışmalar arasındaki heterojenliğin kaynaklarının belirlenmesi amaçlanmıştır. Çalışma materyalini, 1999-2019 yılları arasında Türkiye'de yürütülmüş ve Ovsynch protokolü ile yapılmış 46 primitif çalışma oluşturmuştur. Çalışmalar arasında belirlenen heterojenlikten dolayı uygulanan meta-analizinde rastgele etki modeli altında Der Simonian-Laird yöntemi kullanılmıştır. Bu yöntem sonucunda Türkiye'de sütçü sığırlarda ovulasyon senkronizasyon için ovsynch protokolü uygulanmış tüm çalışmalarda ilk tohumlama sonucunda elde edilen ortak konsepsiyon oranı 0.412 (%95 CI: 0.384-0.442) hesaplanmıştır (P<0.001). Çalışmalar arası heterojenliğin kaynağını belirlemek için alt grup analizi yapılmıştır. Oluşturulan alt gruplara göre (coğrafi bölgeler, ırk, yıl ve parity) konsepsiyon oranları hesaplanmıştır. Konsepsiyon oranları arasındaki farklılık coğrafi bölgelere göre önemli bulunurken; ırk, yıl ve pariteye göre önemli bulunmamıştır. Coğrafi bölgelere göre Türkiye'de ortak konsepsiyon oranı en düşük Doğu Anadolu Bölgesinde (%26), en yüksek Karadeniz Bölgesinde (%51.6) belirlenmiştir. Irklara göre ortak konsepsiyon oranları Holştayn'larda %41.3, İsviçre Esmer'lerinde %43.6 olarak hesaplanmıştır. Yayının yapıldığı yıllara göre konsepsiyon oranı son yirmi yılda %10'luk düşüş göstererek son yıllarda (2015-2019) %40.2 'ye gerilemiştir. Pariteye göre ortak konsepsiyon oranı düvelerde %39.4, multipar ineklerde %41.9 hesaplanmıştır. Bu çalışmada elde edilen sonuçların süt sığırcılığında rasyonel üretim için gerekli olan yeni stratejilerin geliştirilmesine katkı sağlayacağı düşünülmektedir.

Anahtar sözcükler: *Konsepsiyon oranı, Meta analizi, Ovsynch protokolü, Senkronizasyon, Sütçü sığır*

Introduction

Recently, dairy holdings are faced with the problem of significantly reduced fertility in parallel with increased milk yields. Due to the difficulty of detecting estrus behavior after parturition or the development of postpartum anestrus

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(*) Corresponding Author

Tel: +90 312 3170315/4475 Cellular phone: +90 5055025853 Fax: +90 3123164472
E-mail: aytacakcay@gmail.com (A. Akçay)

problems in high-producing dairy cattle, performing artificial insemination within the economically viable time interval has become even harder. In 80% of dairy cattle, the first postpartum ovulation occurs within 50 days after parturition, and of these animals, only 54-68% maintain cyclicity. Both estrus detection and timely insemination directly affect the reproductive performance of animals [1].

In dairy cattle, estrus or ovulation synchronization techniques are used to increase reproductive yields, detect estrus, perform timely artificial insemination and avoid postpartum anestrus problems. Synchronization also allows for ease of application, reducing human errors and decreasing labor costs. When applying estrus synchronization techniques, estruses and/or ovulations not being able to be induced timely in all animals, and factors such as ovulations spreading over a one-week period prevent the achievement of the intended conception rates [2,3]. Ovulation synchronization methods synchronize follicular development and corpus luteum regression, such that fixed-time artificial insemination can be performed without the need for observing estrus signs. Cattle with a known ovulation time can be inseminated within the targeted time period to achieve the conception rate required for the intended reproductive yield. These protocols, which mimic the natural estrus cycle, involve the use of several hormones including progestogens, prostaglandin (PG) F2α, gonadotropin-releasing hormone (GnRH), luteinizing hormone, follicle-stimulating hormone and estrogen [4,5].

A fixed-time artificial insemination program has been developed, based on ovulation synchronization (Ovsynch) through the combined use of GnRH and PGF2α. The Ovsynch protocol involves injections of GnRH (on days 0 and 9) and PGF2α (on day 7) and the performance of artificial insemination 16-24 h after the last GnRH injection. This protocol is aimed at achieving follicular development in parallel with luteal regression, and thereby, synchronizing ovulations [6]. The Ovsynch protocol has found common use in dairy holdings, yet the conception rates achieved with this protocol have been reported to be lower than those achieved with inseminations based on estrus detection [7,8]. Furthermore, significant differences have been observed between the conception rates achieved with the use of the Ovsynch protocol in different studies [9].

The conception rates achieved in lactating dairy cattle with the use of the Ovsynch protocol have been reported to range from 32% to 76.9% [6,10-12].

While literature reviews bring together different results obtained from studies conducted on a particular subject, the meta-analysis method has been developed with an aim to combine different results for the generation of a common result. Meta-analysis is a statistical method used to combine and synthesize independent individual studies conducted on a particular subject with an aim to provide interpretation through the conversion of their results into a common measurement unit [13,14].

The present study was designed to perform a meta-analytical assessment of the conception rates achieved with the use of the Ovsynch protocol for ovulation synchronization in dairy cattle raised in Türkiye. For this purpose, firstly the heterogeneities between the primary studies were determined and pooled conception rates were calculated for these studies included in the meta-analysis. Next, subgroups were established for the year of publication, geographical region, cattle breed, and parity (heifers and cows) to perform meta-regression analyses with an aim to determine the sources of heterogeneity between the studies.

Material and Methods

The study material comprised of 46 primary studies, which were selected in view of predetermined inclusion criteria, among 266 studies listed by a database scan *(Table 1)*. Literature searches were performed using "Ovsynch" and "cattle" search strategy in PubMed and Web of Science databases. The inclusion criteria were the study having been conducted in Türkiye, having been published between 1999-2019, having investigated the use of the Ovsynch protocol in dairy cattle for ovulation synchronization, and having reported conception rates achieved with the use of the Ovsynch protocol. Considering the PICO criteria, the problem was determined as the rate of conception with the Ovsynch protocol, intervention was the application of the Ovsynch protocol, the comparison criterion was the comparison of the rates of conception by years and regions, and the result was the effect of the Ovsynch protocol on the conception rates. The PRISMA Statement guidelines were followed in determining the studies to be included in the meta-analysis and the flow chart diagram is presented in *Fig. 1* [15].

Begg and Mazumdar's rank correlation test was used to determine the publication bias of the included studies, and a funnel plot was built as a graphic representation of the effect size and sample size. The funnel plot, where the "x" axis showed the conception rates and the "y" axis showed the standard error of the effect size, was drawn in the reverse scale (zero at the top with downward increasing values). An assessment was made of the heterogeneity between the primary studies for effect size, with an aim to select the meta-analysis method (fixed-effects or random-effects models) to be used for combining the results of the primary studies and calculating the common rates. The degree of heterogeneity was assessed visually using a forest graph and by means of some statistical measures. An increased distance between the point estimates and a

Table 1. Characteristics of studies included in the meta-analysis

No	Study	Number of Animal	Number of Conception	Conception Rate	Breed	Region	Animal Parity
1	**Kaya A, Çoyan K, Semacan A:** GnRH ve PGF2a kombinasyonunun ineklerde östrüs senkronizasyonu ve gebelik üzerine etkisi. *Vet Bil Derg* 15 (1): 121, 1999	10	6	0.600	Brown Swiss	Central Anatolia	Cow
2	**Çoyan K, Ataman MB, Erdem H, Kaya A, Kasıkcı G:** Synchronization of estrus in cows using DoublePGF2α, GnRH-PGF2α and hCG-PGF2α combination. *Revue Méd Vét* 154 (2): 91-96, 2003	10	6	0.600	Brown Swiss	Central Anatolia	Cow
3	**Aral F, Çolak M:** Reproductive performance and synchronization of the ovulation and estrus in brown Swiss Cows and heifers using the protocol GnRH- PGF2 alpha-GnRH and PGF2 alpha. *Turk J Vet Anim Sci*, 28 (1): 179-184, 2004	13	5	0.385	Brown Swiss	Central Anatolia	Cow
4	**Aral F, Çolak M:** Esmer ırk inek ve düvelerde GnRH- PGF 2 alfa-GnRH ve PGF 2 alfa ile östrus ve ovulasyon senkronizasyonu ve döl verim performansı. *Turk J Vet Anim Sci*, 28: 179-184, 2004	13	6	0.462	Brown Swiss	Central Anatolia	Heifer
5	**Nak Y, Nak D, İntaş KS, Tek HB, Keskin A, Tuna B:** Ovsynch, PRD + PGF2α + PMSG ve norgestomet içeren kulak implantı + PGF2α + PMSG ile sağıtılan siklik ve asiklik anöstrüslü sütçü ineklerde kızgınlık ve gebelik oranlarının karşılaştırılması. *Uludag Univ J Fac Vet Med*, 24 (1-2-3-4): 33-39, 2005	109	46	0.422	Holstein	Marmara	Cow
6	**Nak Y, Nak D, İntaş KS, Tek HB, Keskin A, Tuna B:** Ovsynch, PRD + PGF2α + PMSG ve Norgestomet içeren kulak implantı + PGF2α + PMSG ile sağıtılan siklik ve asiklik anöstrüslü sütçü ineklerde kızgınlık ve gebelik oranlarının karşılaştırılması. *Uludag Univ J Fac Vet Med*, 24 (1-2-3-4): 33-39, 2005	34	20	0.588	Holstein	Marmara	Heifer
7	**Adataş TY:** İneklerde Ovsynch ve Co-synch yöntemleri ile ovulasyonun senkronizasyonu. Yüksek lisans tezi, Ankara Üniversitesi Sağlık Bilimleri Enstitüsü, 2006	20	9	0.450	Holstein	Central Anatolia	Cow
8	**Kacar C, Yildiz S, Pancarci SM, Kaya M, Oral H, Gurbulak K, Gungor O:** Administration of GnRH treatment prior to Ovsynch protocol to stimulate ovarian cycle in cows with functional anoestrus. *Bull Vet Inst Pulawy*, 50 (4): 497-501, 2006	24	5	0.208	Crossbred	Eastern Anatolia	Cow
9	**Cirit U, AK K, Ileri IK:** New strategies to improve the efficiency of the Ovsynch protocol in primiparous dairy cows. *Bulletin of the Veterinary Institute in Pulawy*, 51 (1): 47-51, 2007	18	9	0.500	Holstein	Marmara	Cow
10	**Gumen A, Keskin A, Tek HB, Yilmazbas G, Seyrek İntaş K;** Sütçü ineklerde Ovsynch yönteminde yapılan modifikasyonla gebelik oranının artırılması. *II. Veteriner Jinekoloji Kongresi*,122-123, Antalya, 2006	38	17	0.447	Holstein	Marmara	Cow
11	**Kaçar C, Kamiloğlu NN, Uçar Ö, Arı UÇ, Pancarcı ŞM, Güngör Ö:** İneklerde β-karoten + E vitamini uygulamasıyla kombine edilen Ovsynch ve Cosynch senkronizasyon programlarının gebelik oranı üzerine etkisi. *Kafkas Üniv Vet Fak Derg*, 14 (1): 45-50, 2008.	57	10	0.175	Crossbred	Eastern Anatolia	Cow
12	**Bülbül B, Kırbaş M, Köse M, Dursun Ş, Çolak M:** İneklerde östrüs siklusunun farklı dönemlerinde başlatılan Ovsynch protokolünün östrüs senkronizasyonuna etkileri, *İstanbul Üniv Vet Fak Derg*, 35 (1): 7-17, 2009	41	20	0.488	Brown Swiss	Central Anatolia	Cow
13	**Çelik HA, Avcı G, Aydın İ, Bülbül A, Bülbül T**: Effect of β-carotene on ovarium functions and Ovsynch success in repeat breeder cows. *Kafkas* Üniv *Vet Fak Derg*, 15 (1): 87-94, 2009	11	3	0.273	Holstein	Aegean	Cow
14	**Elibol E, Uçar M, Yılmaz O:** Ovsynch uygulanan ineklerde sun'i tohumlama sonrası 12. günde yapılan GnRH enjeksiyonunun gebelik oranına etkisi. *Kocatepe Vet J*, 2 (1): 13-18, 2009	20	11	0.550	Holstein	Aegean	Cow
15	**Aksu EH, Bozkurt T, Türk G:** Farklı senkronizasyon uygulamaları ile senkronize edilen ineklerde üreme performansı üzerine vitamin E'nin etkisi. *FÜ Sağ Bil Vet Derg*, 24 (2): 71-76, 2010	13	3	0.231	Holstein	Eastern Anatolia	Cow
16	**Abay M, Bekyürek T, Demiral O, Atabay Ö**: Holştayn ırkı primipar ineklerde post partum dönemde Cosynch ve Ovsynch uygulamalarının gebelik oranları üzerine etkisi, *III: Veteriner Jinekoloji Kongresi*, Antalya, 2008	16	6	0.375	Holstein	Central Anatolia	Cow
17	**Çevik M, Selçuk M, Doğan S:** Comparison of pregnancy rates after timed artificial insemination in Ovsynch, Heatsynchand CIDR-based synchronization protocolin dairy cows. *Kafkas Univ Vet Fak Derg*, 16 (1): 85-89, 2010	13	10	0.769	Holstein	Black Sea	Cow
18	**Doğruer G, Sarıbay MK, Karaca F:** Laktasyondaki sütçü ineklerde ovsynch ve çift doz PGf2 alfa+ GnRH uygulamaları sonrası elde edilen gebelik oranlarının kıyaslanması. *IV. Veteriner Jinekoloji Kongresi*, 162-163, Antalya, 2010	42	15	0.357	Holstein	Mediterranean	Cow
19	**Keskin A, Mecitoğlu GY, Karakay E, Taşdemir U, Alkan A, Okut H, Gümen A**: Siklik ve siklik olmayan sütçü ineklerde Ovsynch protokolüne verilen yanıtın karşılaştırılması. *Uludag Univ J Fac Vet Med*, 29 (2): 27-34, 2010	250	94	0.376	Holstein	Marmara	Cow
20	**Nak Y, Tuna B, Nak D, Karakaş E:** Kızgınlıkları gözlenemeyen inek ve düvelerde Ovsynch, Ovsynch+Progestin ve Ovsynch+Progestin+çift suni tohumlamanın gebelikler üzerine etkisi. *IV. Veteriner Jinekoloji Kongresi*, 18-19, Antalya, 2010	173	69	0.399	Holstein	Central Anatolia	Heifer
21	**Pancarcı ŞM, Güngör Ö, Lehimcioğlu NC, Kaçar C, Öztürkler Y:** Sağmal ineklerde Ovsynch protokolü sırasında farklı CIDR uygulamarının follikül dalgaları ve aksesuar CL oluşumuna etkileri. *IV. Veteriner Jinekoloji Kongresi*, 242-243, Antalya, 2010	6	2	0.333	Brown Swiss	Eastern Anatolia	Cow
22	**Yıldız A:** Effect of administering Ovsynch protocol plus postbreeding infusion on first service pregnancy outcome in cows. *J Anim Vet Adv*, 9 (9): 1345-1350, 2010	12	3	0.250	Holstein	Eastern Anatolia	Cow

Table 1. Characteristics of studies included in the meta-analysis (continued)

No	Study	Number of Animal	Number of Conception	Conception Rate	Breed	Region	Animal Parity
23	**Kara U, Ayaşan T, Hızlı H, Gök K:** Ovsynch protokolünün inek ve düvelerin gebelik oranı üzerine etkisi. *Erciyes Üniv Vet Fak Derg*, 8 (1): 1-8, 2011	24	12	0.500	Holstein	Mediterranean	Cow
24	**Kara U, Ayaşan T, Hızlı H, Gök K:** Ovsynch protokolünün inek ve düvelerin gebelik oranı üzerine etkisi. *Erciyes Üniv Vet Fak Derg*, 8 (1): 1-8, 2011	24	7	0.292	Holstein	Mediterranean	Heifer
25	**Abay M:** Holştayn ırkı düvelerde uygulanan ovulasyon senkronizasyonunda iki farklı GnRH analoğu ve beta karoten + E vitaminin etkinliği. Doktora tezi, Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü, 2010	40	18	0.450	Holstein	Central Anatolia	Heifer
26	**Keskin A, Mecitoğlu GY, Karakay E, Taşdemir U, Alkan A, Okut H, Gümen A:** Siklik ve siklik olmayan sütçü ineklerde ovsynch protokolüne verilen yanıtın karşılaştırılması, *Uludag Univ J Fac Vet Med*, 29 (2): 27-34, 2010.	347	178	0.513	Holstein	Marmara	Cow
27	**Yılmaz C, Yılmaz O, Ucar M:** Effect of PGF2α and GnRH injections applied before Ovsynch on pregnancy rates in cows and heifers. *Kafkas Univ Vet Fak Derg*, 17 (4): 641-644, 2011	37	14	0.378	Holstein	Aegean	Cow
28	**Yılmaz C, Yılmaz O, Ucar M:** Effect of PGF2α and GnRH injections applied before Ovsynch on pregnancy rates in cows and heifers. *Kafkas Univ Vet Fak Derg*, 17 (4): 641-644, 2011	80	26	0.325	Holstein	Aegean	Heifer
29	**Abay M, Akçay A, Bekyürek T, Gürbulak K, Canooğlu E:** Sütçü ineklerde Ovsynch protokolünde iki farklı GNRH analogunun epidural ve intramuskuler uygulamalarının gebelik oranı üzerine etkisi. Erciyes Üniversitesi Bilimsel Araştırma Projesi Sonuç Raporu (TSA-12-4057), Kayseri, 2012	400	148	0.370	Holstein	Central Anatolia	Cow
30	**Çınar M, Güzeloğlu A, Erdem H:** Effect of presence of corpus luteum at the beginning of Ovsynch protocol on pregnancy rates in lactating dairy cows. *Kafkas Univ Vet Fak Derg*, 18 (3): 513-516, 2012	140	44	0.314	Holstein	Central Anatolia	Cow
31	**Emre B, Zonturlu AK, Korkmaz Ö:** Sütçü ineklerde Ovsycnh protokolünü takiben uygulanan Fluniksin Meglumin'in gebelik oranı üzerine etkisi. *Harran* Üniv *Vet Fak Derg*, 1 (2): 88- 91, 2012	26	14	0.538	Holstein	Southeastern Anatolia	Cow
32	**Gumen A, Keskin A, Mecitoglu GY, Karakaya E, Alkan A, Okut H, Wiltbank MC:** Effect of presynchronization strategy before ovsynch on fertility at first service in lactating dairy cows. *Theriogenology*, 78 (8): 1830–1838, 2012.	126	59	0.468	Holstein	Marmara	Cow
33	**Emre B, Korkmaz Ö, Zonturlu AK:** Sütçü İneklerde Ovsynch protokolünde ikinci GnR uygulamasının geciktirilmesinin gebelik oranı üzerine etkisi. *Atatürk* Üniversitesi *Vet Bil Derg*, 9(3): 187-193, 2014	40	22	0.550	South Anatolian Red	Southeastern Anatolia	Cow
34	**Karakaya E, Yilmazbas-Mecitoglu G, Keskin A, Alkan A, Tasdemir U, Santos J, Gumen A:** Fertility in dairy cows after artificial insemination using sex-sorted sperm or conventional semen. *Reprod Dom Anim*, 49 (2): 333-337, 2014	156	63	0.404	Holstein	Marmara	Cow
35	**Karyağdı SS, Demiral ÖO, Abay M:** Sütçü ineklerde klasik ovulasyon senkronizasyonu protokolünde progesteron ve östrojen uygulamalarının gebelik oranlarına etkisi. *Erciyes* Üniv *Vet Fak Derg*, 11 (3): 175-182, 2014	43	19	0.442	Holstein	Black Sea	Cow
36	**Köse M, Tekeli T:** İsviçre Esmeri düve ve laktasyonda olmayan ineklerde ovaryum fonksiyonlarının östrüs senkronizasyonu ve gebelik oranı üzerine etkisi. *Eurasian J Vet Sci*, 30 (2): 53-58, 2014	20	8	0.400	Brown Swiss	Central Anatolia	Cow
37	**Köse M, Bülbül B, Dursun Ş, Kırbaş M:** Düvelerde östrüs siklusunun folliküler ya da luteal evresinde başlatılan Ovsynch protokolünün folliküler ve luteal senkronizasyon üzerine etkisi. *YYU Vet Fak Derg*, 25 (1): 7-10, 2014	28	8	0.286	Brown Swiss	Central Anatolia	Heifer
38	**Yilmazbas-Mecitoglu G, Karakaya E, Keskin A, Gumen A, Koc V, Okut H:** Comparison of synchronisation and fertility after different modifications of the ovsynch protocol in cyclic dairy cows. *Acta Veterinaria Hungarica*, 62 (1): 64-73, 2014	105	51	0.486	Holstein	Marmara	Cow
39	**Abay M, Bekyürek T, Akçay A, Ata S:** Sütçü ineklerde farklı senkronizasyon protokollerinin gebelik oranı üzerine etkisi. *VI. Türk Veteriner Jinekoloji Derneği Ulusal Kongresi*, 132-133, Muğla, 2015	185	76	0.411	Holstein	Central Anatolia	Cow
40	**Salar S, Baştan A:** Erken postpartum dönemde subklinik ketozisli ineklerin ovsynch protokolüne yanıtlarının incelenmesi. Ankara Üniversitesi Bilimsel Araştırma Projesi Sonuç Raporu (14L0239002), Ankara, 2016	156	48	0.308	Holstein	Central Anatolia	Cow
41	**Çakırcalı R, Gümen A, Karakaya Bilen E, Orman A, Mecitoğlu Z, Keskin A:** Sütçü ineklerde Ovsynch protokolü süresince uygulanan Propilen Glikol'ün fertilite üzerine etkisi. *VII. Ulusal II. Uluslararası Türk Veteriner Jinekoloji Derneği Kongresi,* 170-176, Antalya, 2019	72	22	0.306	Holstein	Marmara	Cow
42	**Karaca F, Dogruer G, Sarıbay MK, Yasar E, Ateş C:** The effect of the reduced dose of GnRH on conception, ovulation and ovarian structures in Ovsynch program of lactating dairy cows. *Animal Review*, 3 (3): 66-72, 2016	20	8	0.400	Holstein	Mediterranean	Cow
43	**Karakaya-Bilen, E, Yilmazbas-Mecitoglu G, Keskin A, Guner B, Serim E, Santos J, Gümen A:** Fertility of lactating dairy cows inseminated with sex-sorted or conventional semen after Ovsynch, Presynch-Ovsynch and Double-Ovsynch protocols. *Reprod Dom Anim*, 5 (2): 309–316, 2019	50	21	0.420	Holstein	Marmara	Cow
44	**Küçük N, Tuna B, Peker C, Uçar EH:** Farklı ovsynch protokolleri ile senkronize edilen Holstein düvelerde ovaryum dinamiklerinin ve gebelik oranlarının araştırılması. *Uluslararası* Çiftlik *Hayvanları Hekimliği Kongresi*, Muğla, 2019	32	19	0.594	Holstein	Aegean	Cow
45	**Shahzad AH, Sattar A, Ahmad N, Ahmad I, Nak D, Nak Y:** Evaluation of Ovsynch and CIDR + Ovsynch protocols to improve reproductive efficiency in lactating dairy cows. *Pakistan J Zool*, 51 (5): 1607-1614, 2019	58	23	0.397	Holstein	Marmara	Cow
46	**Topçu E, Binli F, Ay SS:** Sütçü ineklerde Progesteron (PRID®) ile desteklenen Ovsycnh yönteminin gebelik oranı üzerine etkisi. *Dicle* Üniv *Vet Fak Derg*, 11(2): 71-76, 2018.	30	16	0.533	Holstein	Black Sea	Cow

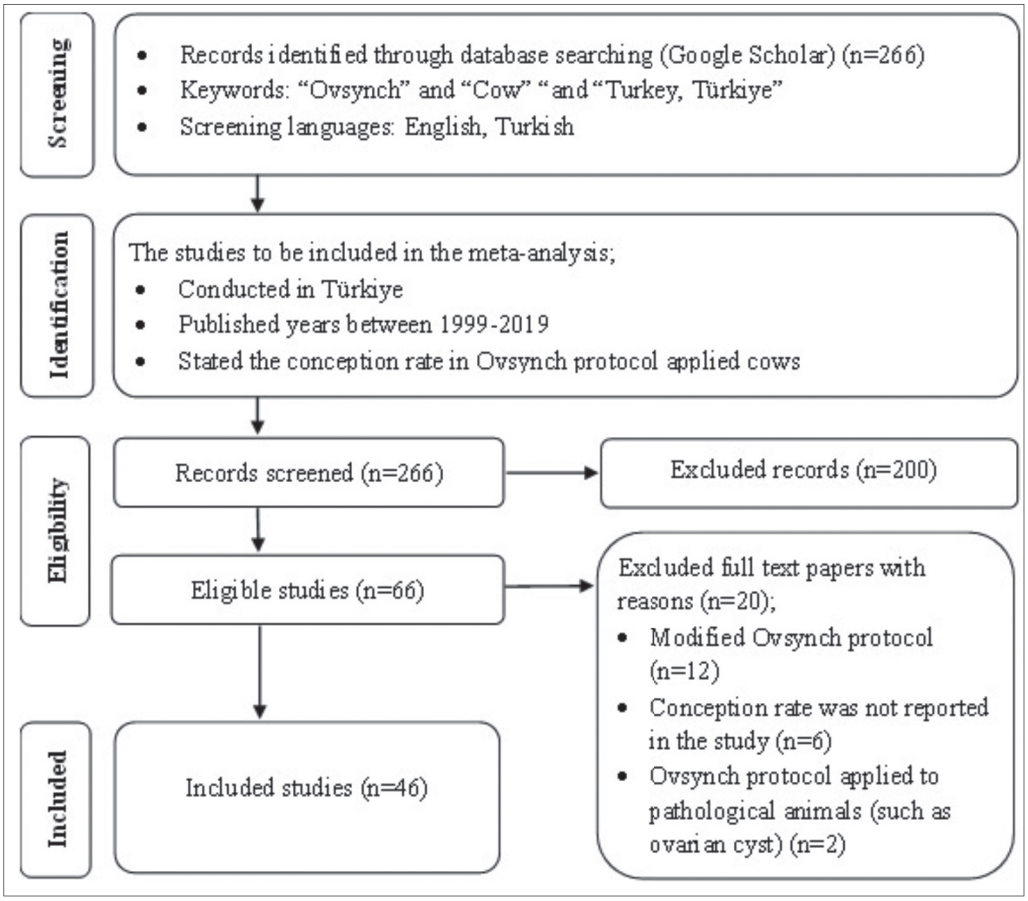

Fig 1. Flow diagram of the literature search selection for studies that Ovsynch protocol applied, and conception rate determined in Türkiye

low intersection of the confidence intervals of studies in a forest graph point out to a high degree of heterogeneity.

Cochran's Q test was used to determine the heterogeneities between the studies, I^2 statistics were used to determine the level of heterogeneity and τ^2 statistics were calculated to determine the true between study variances. As analyses demonstrated a heterogeneity between the primary studies for effect size, the random-effects model (the Der Simonian-Laird method) was chosen. The random-effects model considers variances both within and between the included studies and assumes that there are differences between all studies for effect size.

Subgroup analyses were performed to determine the sources of heterogeneity between the studies. Conception rates were calculated for the subgroups, which were established for geographical region, cattle breed, year of publication and parity. Furthermore, in view of the heterogeneity between the studies, to ensure an effective, reliable and valid parameter estimation with minimum variance, a univariate meta-regression analysis was performed, and a comparison was made of the conception rate alterations observed within the subgroups. The moments method was used for the meta-regression analysis, and models were established according to the random-effects model. A low number of studies being included in the analysis is a major disadvantage for meta-regression analyses. According to the criterion set for the number of studies required for establishing a subgroup, it was not possible to include 4 studies that were conducted in southeastern Anatolia in hybrid and South Anatolian Red cattle. Thus, it was not possible to assess the interaction of multiple factors. Subgroups were established for the geographical region of the study location (Mediterranean, Eastern Anatolia, Aegean, Central Anatolia, Black Sea and Marmara regions), cattle breed (Holstein and Brown Swiss), publication year of the study (1999-2004, 2005-2009, 2010-2014 and 2015-2019) and parity (heifers and multiparous cows). Thereby, common conception rates were calculated for the subgroups and the correlation of these rates were assessed. The statistical significance of the meta-regression models was assessed with the Z test. Meta-analyses were performed using the CMA (Comprehensive Meta Analysis) and R 4.2.1 *(www.r-project.org/)* software and "metaphor" package. The significance level of the Cochran Q heterogeneity statistics was set at $P<0.10$ and the significance level of the effect size and coefficients was set at $P<0.05$.

Results

In the present study, the conception rates of a total of 3182 cattle, which were treated with the Ovsynch protocol in 46 studies conducted between 1999-2019, were included in the meta-analysis. The conception rates reported in these previous studies are shown in the *Table 1*.

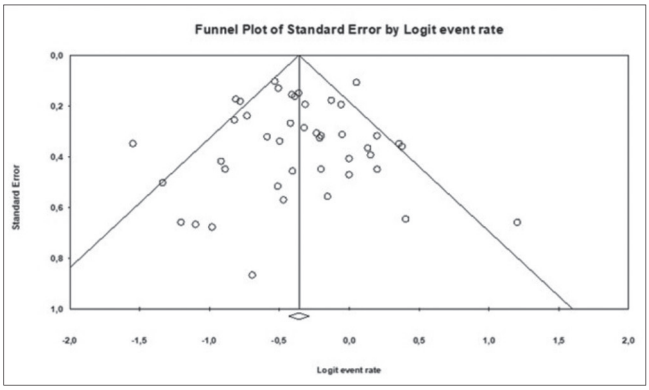

Fig 2. Funnel plot of study sample regarding conception rates with Ovsynch protocol

Begg and Mazumdar's rank correlation test was performed to determine the publication bias of the studies included in the meta-analysis. Kendall's tau b coefficient was calculated. This coefficient is expected to be close to 1 and the p value is expected to be larger than 0.05. Begg and Mazumdar's rank correlation test showed that the study sample was not biased (Kendall's tau=0.04, P=0.670). In the funnel plots, the scattering of the studies included in the meta-analysis within a triangle with a downward-facing base indicated that there was no asymmetry in the study sample *(Fig. 2)*.

The heterogeneity observed between the primary studies for the conception rates was assessed with Cochran's Q, I^2 and τ^2 test statistics (Q=92.392, P<0.001, I^2=51.295, τ^2 =0.067). I^2 (%) calculations showed that there was a moderate level of heterogeneity between the studies for the conception rates. The forest plot, which was built as a graphic representation of this heterogeneity, showed the

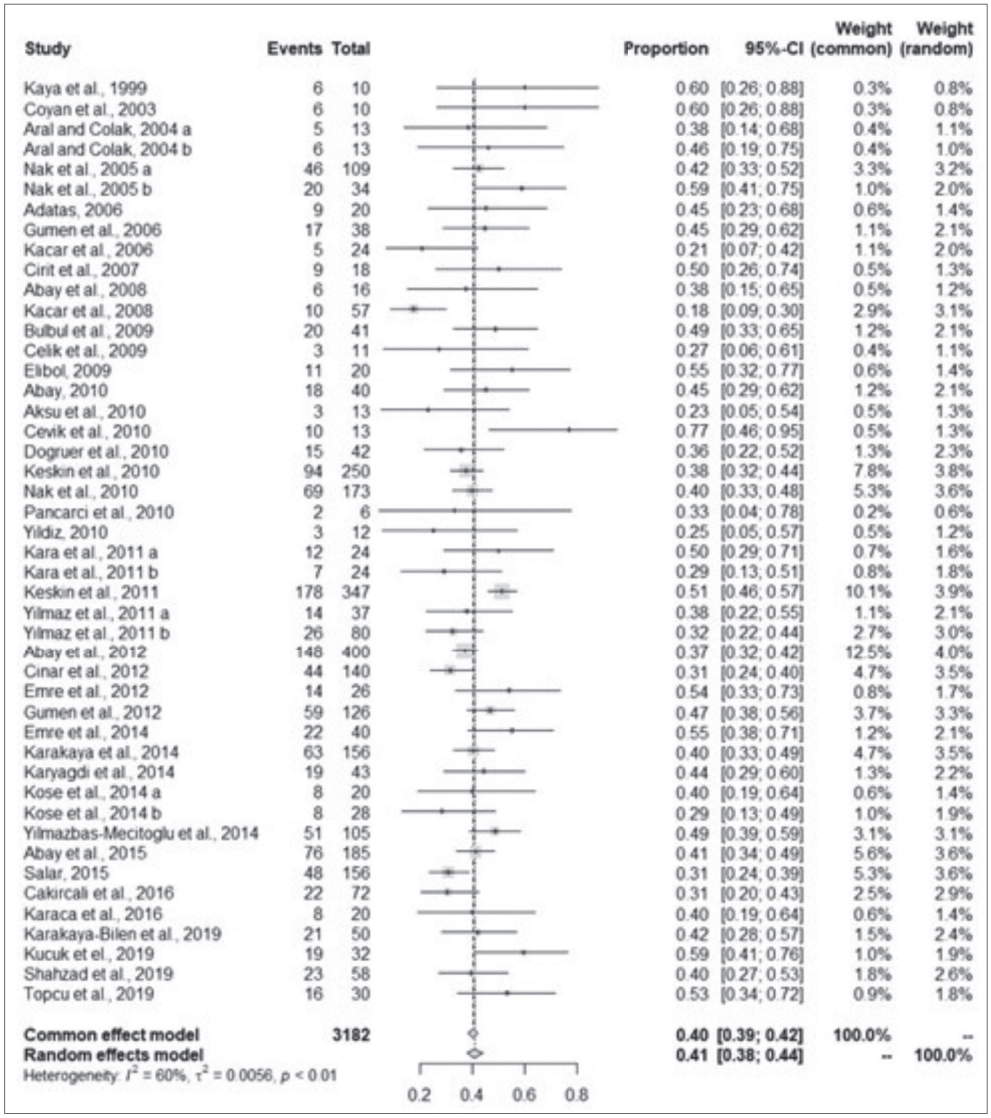

Fig 3. Forest plot regarding conception rates with Ovsynch protocol

Table 2. *Subgroup analysis results by region, breed, year and animal*

Item	Subgroups	Overall Rates of Conception Rates					Heterogeneity		
		Number of Study	Number of Cows	Number of Conception Cows	Conception Rate	95% Confidence Interval of Conception Rate	Cochran's Q	I^2 %	P Values (Cochran's Q)
Region	Mediterranean	4	110	42	0.384	0.297; 0.479	2.342	0.01	Q=10.463, df=5, **P=0.063**
	Aegean	5	180	73	0.425	0.309; 0.549	9.186	56.46	
	Central Anatolia	15	1265	477	0.378	0.352; 0.405	15.653	10.56	
	Black Sea	3	86	45	0.516	0.408; 0.622	3.974	49.68	
	Marmara	12	1363	603	0.438	0.397; 0.480	22.649	51.433	
	Eastern Anatolia	3	31	8	0.260	0.135; 0.440	0.230	0.0	
Breed	Holstein	34	2894	1187	0.413	0.384; 0.443	66.272	50.21	Q=0.244, df=1, **P=0.621**
	Brown Swiss	8	141	61	0.436	0.354; 0.520	5.567	0.0	
Year	1999-2004	4	46	23	0.500	0.357; 0.643	1.546	0.0	Q=4.263, df=3, **P=0.234**
	2005-2009	9	307	141	0.460	0.405; 0.517	5.683	0.0	
	2010-2014	21	2079	851	0.403	0.366; 0.441	44.397	54.95	
	2015-2019	8	603	233	0.402	0.340; 0.466	14.858	52.89	
Animal Parity	Multipar Cow	35	2643	1094	0.419	0.389; 0.449	61.699	44.89	Q=0.326, df=1, **P=0.568**
	Heifer	7	392	154	0.394	0.347; 0.444	9.856	39.12	

Cochrane's Q: Weighted sum of squares of observed effect sizes; I^2 %: The rate of true variance to observed variance; df: Degree of freedom

point estimates and confidence intervals of the studies included in the meta-analysis. Using the Der Simonian-Laird method in association with the random-effects model, the common conception rate for all of the studies, which were included in the meta-analysis and in which dairy cattle raised in Türkiye were treated with the Ovsynch protocol, was calculated as 0.412 (0.384-0.442) (P<0.001) *(Fig. 3)*.

The results of the subgroup analyses performed to determine the source of heterogeneity between the primary studies are shown in *Table 2*. Statistically significant differences were detected between the subgroups established for the geographical regions of the study locations (P<0.10). Accordingly, the lowest conception rate was determined in the Eastern Anatolia Region (26%). No statistically significant difference was determined between the subgroups established for cattle breed (P>0.1). The common conception rates for Holstein and Brown Swiss cattle were calculated as 41.3% and 43.6%, respectively. The subgroups established for the publication year of the studies also showed no statistically significant difference (P>0.1). The lowest common conception rate (40.2%) was determined for the most recently conducted studies (2015-2019). Likewise, the subgroups established for parity did not show any statistically significant difference (P>0.1). The common conception rates for heifers and multiparous cows were calculated as 39.4% and 41.9%, respectively.

The statistical significance of the heterogeneity sources was calculated with univariate meta-regression analyses. In the meta-regression model, the conception rate was the dependent variable and geographical region, cattle breed, year of publication and parity were the independent variables. The use of the hypothesis test with all coefficients as zero in a model assessing conception rates for independent variables of breed, year of publication and parity showed that there was no statistically significant difference (P>0.1). However, it was determined that the geographical regions of Türkiye led to statistically significant differences in the conception rates and was a factor influential on the heterogeneity observed between the primary studies (Q=9.63; P<0.1). In the meta-regression model established for geographical regions, the R^2 analogue value was calculated as 0.34. Therefore, the conception rates for geographical region were determined to account for 34% of the heterogeneity between the studies. Accordingly, the model used for meta-analysis demonstrated that, with reference to the Eastern Anatolia Region, the common conception rate for the Black Sea Region was calculated 1.140 fold higher (P=0.020) *(Table 3)*.

Discussion

In recent years, studies have been conducted on the assessment of the effects of different synchronization methods on the conception/pregnancy rates of dairy cattle by meta-analysis [16-20].

Borchardt et al.[17], upon making a meta-analytical comparative assessment of studies reporting conception rates achieved with the use of different synchronization

Table 3. *Univariate meta-regression models regarding conception rates with Ovsynch protocol*

Item	Variables	Coefficient of Meta-regression Model of Conception Rates					Test of the model (Simultaneous Test that All Coefficients are Zero)	Univariate meta-Regression Models and R^2 Analog Values
		Coefficient	%95 Confidence Interval of Coefficient	Standard Error	Z Values	P Values		
Region	Intercept	-1.046	-1.878; -0.213	0.425	-2.46	**0.014**	Q = 9.63 P = 0.086	CR_{Region}= -1.046 + 0.575(MeR) + 0.705(AR) + 0.579(CAR) + 1.140(BSR) + 0.797(MaR) R^2 analog = 0.34
	Mediterranean	0.575	-0.361; 1.511	0.478	1.20	0.229		
	Aegean	0.705	-0.199; 1.609	0.461	1.53	0.127		
	Central Anatolia	0.579	-0.270; 1.429	0.433	1.34	0.181		
	Black Sea	1.140	0.176; 2.105	0.492	2.32	**0.020**		
	Marmara Region	0.797	-0.050; 1.644	0.432	1.84	0.065		
	Eastern Anatolia (Reference)							
Breed	Intercept	-0.260	-0.642; 0.122	0.195	-1.33	0.182	Q = 0.20 P = 0.656	CR_{Breed}= -0.260 + 0.091(HF) R^2 analog = 0.01
	Holstein	0.091	-0.491; 0.309	0.204	-0.45	0.656		
	Brown Swiss (Reference)							
Year	Intercept	-0.412	-0.649; -0.174	0.121	-3.40	**0.001**	Q = 3.86 P = 0.277	CR_{Year}= -0.412+0.417(Y_1) + 0.268(Y_2) + 0.020(Y_3) R^2 analog = 0.01
	1999-2004	0.417	-0.252; 1.085	0.341	1.22	0.222		
	2005-2009	0.268	-0.100; 0.637	0.188	1.43	0.153		
	2010-2014	0.020	-0.259; 0.299	0.143	0.14	0.888		
	2015-2019 (Reference)							
Animal Parity	Intercept	-0.423	-0.709; -0.137	0.146	-2.90	**0.004**	Q = 0.35 P = 0.552	CR_{Animal}= -0.423 + 0.095(C) R^2 analog = 0.01
	Multipar Cow	0.095	-0.217; 0.407	0.159	0.60	0.552		
	Heifer (Reference)							

Q: *Cochrane's Q (Weighted sum of squares of observed effect sizes),* ***CR:*** *Conception Rates,* ***MeR:*** *Mediterranean Region,* ***AR:*** *Aegean Region,* ***CAR:*** *Central Anatolia Region,* ***BSR:*** *Black Sea Region,* ***MaR:*** *Marmara Region,* ***HF:*** *Holstein-Friesian,* Y_1***:*** *1999-2004,* Y_2***:*** *2005-2009,* Y_3***:*** *2010-2019,* ***C:*** *Cow*

protocols, calculated common conception rates of 41.7% for the Presynch + Ovsynch protocol and 46.2% for the double Ovsynch protocol. The common conception rate calculated in the present study for the use of the Ovsynch protocol in dairy cattle from Türkiye is similar to the common conception rate previously reported for the Presynch + Ovsynch protocol, and lower than that reported for the Double Ovsynch protocol [17].

Rabiee et al.[19] assessed conception rates reported to have been achieved with the use of the Ovsynch, Presynch and Selectsynch protocols by meta-analysis, whilst Borchart et al.[18] assessed conception rates reported to have been achieved with the use of the Ovsynch protocol and the modified Ovsynch protocol by meta-analysis [18,19].

In the present study, with an aim to produce meta-analysis results closer to the population parameter, conception rates achieved with the use of the prostaglandin-based Ovsynch protocol, which is known to have common use in Türkiye, were assessed. In the past 20 years, many individual studies have been conducted in Türkiye for the investigation of the effects of the Ovsynch protocol, applied to dairy cattle for ovulation synchronization, on conception rates. Conception rates ranging from 17.5% to 76.9% were reported in the 46 primary studies included in the meta-analysis performed in the present study. The heterogeneity observed between these primary studies for conception rate are considered to arise, to a large extent, from the results of the studies conducted by Çevik et al.[10], Kaçar et al.[21], Kaçar et al.[22] and however, heterogeneity cannot be simply attributed to consistent differences observed between individual studies.

The heterogeneity between the primary studies included in the meta-analysis was determined by Cochran's Q, I^2 and τ^2 test statistics. In view of the high level of heterogeneity between the studies, the random-effects model, and due to it being least affected by the outlier, the Der Simonian-Laird method were used for the calculation of the common rates. The common conception rate calculated for the studies, which were included in the meta-analysis and involved the application of the Ovsynch protocol to dairy cattle raised in Türkiye, was 41.2% (%95 CI: 38.4-44.2). Out of the 46 primary studies included in the meta-analysis, 10 had reported conception rates that fell within the 95% confidence interval of the common conception rate (38.4-44.2), whilst 17 studies had reported rates below and 19 had reported rates above the CI of the common conception rate. Common conception rates were calculated for the subgroups (geographical region, breed, year of publication and parity) that were established to determine the source of heterogeneity between the studies included in the meta-analysis.

According to meta-regression analyses, among the subgroups established for geographical region, the lowest conception rate was determined for the Eastern Anatolia Region (26%), whilst the highest conception rate was determined for the Black Sea Region (51.6%). The conception rates calculated for the other geographical regions were similar and fell within the confidence interval of the common conception rate. The conception rate calculated for the Eastern Anatolia Region being 1.140 fold higher than that calculated for the Black Sea Region was attributed to the harsh climatic conditions of Eastern Anatolia. Literature reports have also pointed out to the significant effect of geographical region, month/season, and geographical region-month/season interaction on conception rates in different countries [23-25].

Although it has been reported that cattle, which are of different genetic structure and are raised in different geographical regions, would differ for fertility [26,27], the common conception rates calculated for the two breed subgroups in the present study demonstrated similar values for Holstein (41.3%) and Brown Swiss (43.6%) cattle. This result agrees with previous studies suggesting similar fertility characteristics for the Holstein and Brown Swiss breeds, compared to some dual-purpose cattle breeds [28,29].

In parallel with the improvement of management systems in the dairy industry in recent years, better nutrition and extensive genetic selections have resulted in a steady increase in milk yields per cow. However, increased milk yields have brought about decreased reproductive yields [30,31].

In the present study, no statistically significant difference was observed between the subgroups established for the year of publication of the studies with respect to the conception rates of dairy cattle raised in Türkiye (P>0.10). However, it was determined that conception rates had decreased by 10% in the last 20 years.

The present study showed that heifers and multiparous cows included in the subgroups established for parity showed no statistically significant difference for conception rates. It has been reported that the conception rate to the first insemination is either higher [32,33] or similar [21,22,34] in heifers, compared to multiparous cows.

In conclusion, with the meta-analysis conducted in this study results close to the population parameter were obtained for the use of the prostaglandin based Ovsynch protocol, which is known to have common use in Türkiye. It is considered that the results of the present study will contribute to the development of new strategies for rational production in the dairy cattle sector. The main limitation of this study is prostaglandin-based synchronization protocols other than Ovsynch, and progesterone-based synchronization protocols having not been included and assessed. The conduct of a network meta-analysis for the overall assessment and relative comparison of all available synchronization methods in the future would provide more detailed results. The generation of reliable results with a meta-analysis depends on the careful selection of the primary studies to be included in the analysis, the careful assessment of the included studies, the selection of the proper statistical model for use, and the accurate interpretation of the results of the analysis.

The meta-analysis method may produce more reliable and valid results than the individual studies included in the analysis if utmost attention is shown at each phase of the process, from the selection of the studies to be included in the analysis to the interpretation of the results of the analysis. Combining the results of small-sample studies with an aim to make valid, consistent and adequate parameter estimations with minimum variance requires adherence to certain rules as well as planned and disciplined conduct. Thus, in view of the vast amount of data required to be dealt with in meta-analyses, these assessments should be performed by a team of relevant experts with extensive knowledge.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author (A. Akçay) on reasonable request.

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Conflict of Interest

The authors report no conflicts of interest.

Author Contributions

AA and MA conceived the study. AA, MA and EC collected and analyzed data. AA, MA and EC have approved and read the final version of the manuscript.

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