Comparison of impact of synchronization protocols applied to ewes on pregnancy rate in Turkey with bayesian meta-analysis

Research Article

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ABSTRACT

The present study carried a meta-analysis of the pregnancy rates of different synchronization protocols implemented in ewes in Turkey. A common pregnancy rate was estimated by coalescing pregnancy rates, and the heterogeneity between the studies was explored. All studies were carried out independently. This article compiled 28 studies that determined the pregnancy rate for 2,437 ewes in the synchronization studies between the years 1995–2020. The overall effect size of the meta-analysis was found to be 0.66 (95% confidence interval; 0.58–0.74) ($p<0.001$). This meta-analysis indicates that fertility parameters were improved with the highest effect size in the synchronization protocol used in ewes during the breeding season by combining various doses of PMSG at the end of intravaginal sponge application as a source of progesterone. In terms of subgroups, 40 mg FGA + 300 IU PMSG (95% confidence interval; 0.50–0.61), 40 mg FGA + 500 IU PMSG (95% confidence interval; 0.44–0.52), and 40 mg FGA + 700 IU PMSG (95% confidence interval; 0.41–0.61) protocol effect size was estimated to be higher than other protocols during the season. Thus, it is possible to control the reproductive performance in enterprises with estrus synchronization protocols and mating of ewes. However, it is important to validate which of these methods are optimum in terms of economy and efficiency in enterprise conditions. Considering the effects of synchronization protocols on pregnancy, it is predicted that Bayes meta-analysis will guide enterprises as a decision support system in achieving optimum pregnancy rates.

Keywords: Ewes, meta-analysis, pregnancy rate, synchronization, Turkey

INTRODUCTION

In ewes breeding, lamb yield is more important than milk production. The most critical factor affecting the profitability in ewes breeding enterprises is the number of lambs born and the conversion of these lambs into profit (Arıkan, 2021). The main goal in ewes breeding is to increase lamb production and, accordingly, profitability. This is directly proportional to the reduction of lambing interval and the increase of fertility (Doğruer et al., 2015). The seasonal estrus of ewes and goats, especially in ovine breeding enterprises, makes reproductive management vital. The anoestrus period of ewes and goats, which are seasonal polyestrous animals, is considered as out of season period. During the anoestrus period, the enterprises are deprived of brood and milk production. This period of increasing costs, coupled with decreased production, adversely affects the profitability of enterprises. Different synchronization methods are exploited to channelize the anoestrus period in a reproductive manner in ovine breeding enterprises. A significant contribution to enterprises, in terms of reducing costs and increasing profitability, could be obtained by applying these methods.

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With synchronization in the enterprises, conception in a short time throughout the herd, reducing the number of excesses per pregnancy, births at the desired time, more efficient use of labor, feed consumption, and enterprise capacity are enabled. Furthermore, synchronization facilitates planning when the prices of animal products produced and marketed by the enterprise are the highest (Whitley & Jackson, 2004).

The synchronization protocols in ewes employ hormones such as melatonin, gonadotropin-releasing hormone (GnRH), PGF2α and their analogs, estrogens, human chorionic gonadotropin (hCG), pregnant mare serum gonadotropin (eCG/PMSG), progestogens, and their combinations (Aköz et al., 2015; Özyurtlu et al., 2010;).

Many studies have been conducted on the effect of various synchronization applications on the pregnancy rate in ewes. However, the wide distribution of pregnancy rates from different studies indicates the need for a more precise conclusion. One of the most effective methods to draw such a conclusion is meta-analysis. Meta-analysis is a method of compiling the results of many independent studies conducted on a specific subject and reinterpreting them with the aid of suitable statistical analysis of the findings (Lipsey & Wilson, 2001). Meta-analysis improves the precision and power of the parameter estimates and, in turn, the statistical significance by increasing the sample size. For this reason, meta-analysis, in ewes (Palacin et al., 2011) and cattle (Borchardt et al., 2017; Borchardt et al., 2018), is a frequently used tool in the literature to ascertain the effectiveness of different synchronization methods.

In this study, the effect of different synchronization protocols pregnancy rates applied to ewes seasonal and out of season in Turkey considering Bayesian meta-analysis of studies examined with high pregnancy rates was determined. It was then calculated which protocol was lower cost. This method for ewe enterprises; As a decision support system, it is aimed to guide in catching the high pregnancy rate and low protocol cost point.

MATERIAL and METHOD

The present study extracted pregnancy rates from 28 independent studies. These studies determined the pregnancy rates using different synchronization methods in Turkey between the years 1995–2020. Based on the literature review, 371 studies were enlisted within the scope of the analysis. Among these studies, the abstracts of 343 articles that remained after excluding duplicate articles were read in accordance with research strategies, exclusion, and inclusion criteria. Thereafter, 294 articles were excluded, and 49 studies were included for the present meta-analysis. According to the research literature search strategy, 21 studies that failed to provide the necessary statistical data were excluded, and 28 studies were analyzed in terms of content and transferred to the coding form. The literature search method is outlined in the flow chart in Figure 1.

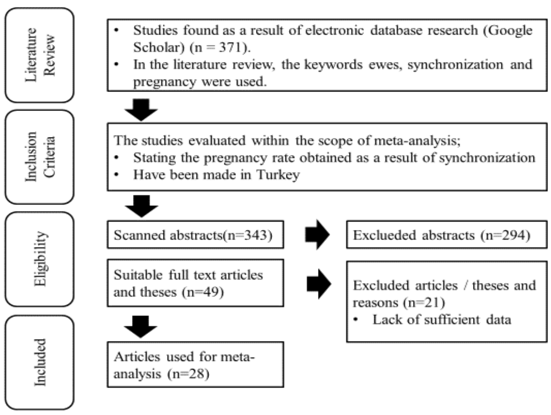

Figure 1. Flowchart about the literature search methodology employed in the meta-analysis

A total of 2,437 ewes from different studies were included in the meta-analysis. The information on the pregnancy rates obtained by the synchronisation method in ewes in Turkey and studies included in the meta-analysis is detailed in Table 1.

The linearity of the study effect sizes and standard errors of the studies included in the meta-analysis were determined by Egger's Linear Regression test. A funnel plot was employed to identify publication bias, and the Trim and Fill method of Duval and Tweedie (2000) were applied to eliminate the bias, and the common exposure value was re-calculated (Duval & Tweedie, 2000). A random-effect model (DerSimonian-Laird method) was used to estimate the variance between studies as well as within-study variance (Sutton et al., 2001).

Table 1. Characteristics of the studies conducted about synchronization in ewes in Turkey between the years 1995–2020, incorporated in the meta-analysis

Studies, Year	Total Number of Ewes	Number of Pregnant Ewes	Pregnancy Rate (%)
Duymaz (2020)	120	103	85.83
Karakaya (2019)	50	32	64.00
Kaya (2019)	70	16	22.86
Özbilek (2019)	238	166	69.75
Akbaş (2016)	75	52	69.33
Doğanay (2011)	90	53	58.89
Solak (2009)	78	12	15.38
Ocak (2007)	89	72	80.00
Topcu (2004)	88	54	61.36
Özyurtlu (2010b)	62	32	51.61
Uçar (2002)	59	46	77.97
Ataman (2009)	75	49	65.33
Kulaksız (2011)	29	24	82.76
Baştan and Kuplülü (1995)	50	33	66.00
Emrelli (2003)	30	16	53.33
Kaya (2003)	80	69	86.25
Algan (2014)	217	92	42.40
Koyuncu (2001)	95	92	96.84
Timurkan and Yıldız (2005)	130	118	90.77
Köse (2016)	124	95	76.61
Öztürkler (2003)	40	34	85.00
Doğan and Nur (2006)	69	36	52.17
Aköz (2006)	88	84	95.45
Kuru (2017a)	148	61	41.22
Kaçar (2008)	29	12	41.38
Kaya (2013)	60	26	43.33
Doğruer (2015)	76	50	65.79
Esen and Bozkurt (2001)	78	71	91.03

Cochrane's Q statistics with degrees of freedom was used to evaluate the heterogeneity of the effect sizes of the studies (k-1). Further, to determine the level of heterogeneity I^2 statistics and to determine the true variance between studies τ^2 statistics were used. I^2 value was assessed by using three categories (low if below 25%, medium between 25–50%, high heterogeneity above 50%) (Patsopoulous et al., 2008).

A priori distributions were classified into two groups as "informative" and "non-informative". In the case of the non-informative prior distribution, the data containing the sample information were weighted more in the posterior distribution, while the data containing the sample information were less weighted in the informative prior distribution (Bolstad, 2007). As the values of parameters, a and b, of the beta distribution changed, the informative and non-informative prior distributions were formed. If a and b are given a value of 1, respectively (equivalent to Uniform (0, 1) distribution), it gives a non-informative a priori distribution so that θ takes any value in the interval (0,1) with equal probability. In this case, the values of a and b are considered 0.5; it is called low informative a priori distribution because θ indicates that the probability of taking extreme values is higher as compared to the probability of taking middle values. Finally, the values of a and b being greater than and equal to 1 and 0.5 provides stronger information about θ. In this case, it emphasizes that θ takes the middle values in the interval (0,1) with a higher probability and that the probability of realization and non-realization is equal.

As a result of the comparison, it was affirmed that the Bayesian meta-analysis obtained by using different a priori distributions gives a narrower estimation range than the classical method. One of the most important advantages of the Bayesian approach over the classical method is that it can compute for all uncertain sources of change. The simulation algorithms developed in recent years have reduced the hurdle of calculating the complex integral operations required for the Bayesian approach.

RESULTS

The list of synchronization studies in ewes that were meta-analyzed in this article, the name of the researchers, the year of publication of the study, the number of synchronized ewes, the number of pregnant ewes, and the pregnancy rate (%) are compiled in Table 1. The heterogeneity test results in the study are summarized in Table 2.

Table 2. Publication bias summary statistics

Fail-Safe N Analysis (File Drawer Analysis)		Rank Correlation Test for Funnel Plot Asymmetry		Regression Test for Funnel Plot Asymmetry		Heterogeneity Statistics						
Fail-safe N	p	Kendall's tau	p	Z	p	Tau	Tau²	I²	H²	df	Q	p
2.328.000	<.001	0.587	<.001	-8.996	<.001	0.381	0.1452 (SE = 0.0425)	48.18%	54.940	27.000	465.999	<.001

Note Fail-safe N Calculation Using the Rosenberg Approach

When Table 2 was evaluated based on the heterogeneity test, the meta-analysis of the studies included in the study was found to be heterogeneous since the p-value was less than 0.05, and the Q value was greater than the value corresponding to the df value. Since the statistical value of I^2 was used to determine the level of heterogeneity, which was calculated to be 48.18, there was a moderate bias in our study, and the random effects model was opted.

The funnel plot obtained in the study to determine the publication bias is illustrated in Figure 2.

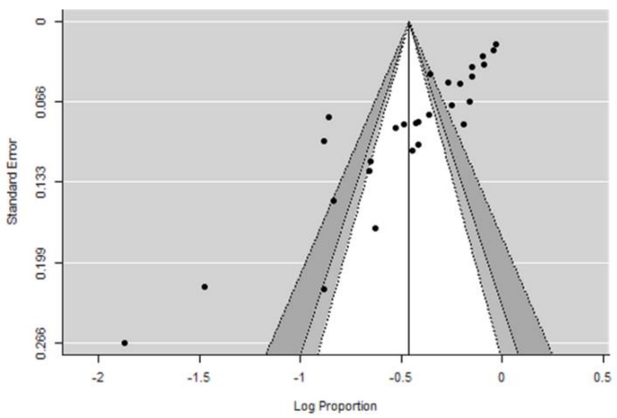

Figure 2. The funnel (Funnel Plot) chart of studies included in the meta-analysis of synchronization studies in ewes published between the years 1995–2020

It is quite evident from the funnel scatter plot in Figure 2 that most of the pregnancy rates of 28 studies included in the study were located near the vertical line designating the combined effect size and at the top of the graph.

The homogeneous distribution value, the average effect size, and confidence intervals of the random effect model are outlined in Table 3.

Table 3. Statistical Values of Random Effect Model

Random-Effects Model (k = 28)						
	Estimate	**se**	**Z**	**p**	**Lower Bound**	**Upper Bound**
Intercept	0.658	0.0407	16.02	<.001	0.571	0.744

Note Tau² Estimator: Empirical Bayes

The effect size value (Estimate) was 0.658, the lower limit of the 95% confidence interval was 0.571, and the upper limit was 0.744 ($p<0.01$). Thus, it can be inferred that there was a significant effect of synchronization operation performed in ewes in Turkey of pregnancy rates in the period we determined (1995–2020). It was also observed that hormone applications to increase pregnancy rates significantly augmented this value statistically. The fit statistics and information criteria for the model are summarized in Table-4.

Table 4. Model Fit Statistics and Information Criteria

	Log likelihood	**Deviance**	**AIC**	**BIC**	**AICc**
Maximum-Likelihood	3.754	113.037	3.508	0.844	-3.028
Restricted Maximum-Likelihood	3.138	-6.275	-2.275	0.317	-1.775

Considering the fit of the model with the information criteria in Table 4, it is predicted that the model is moderately compatible and can provide guidance for further studies.

The forest graph obtained as a result of the meta-analysis applied is shown in Figure 3.

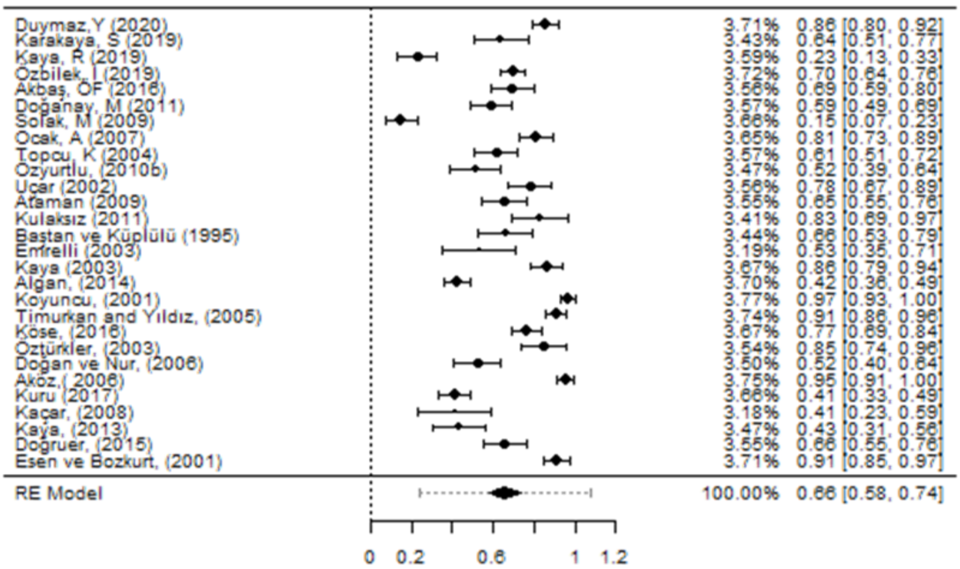

Figure 3. Forest plot of the synchronization studies effective on pregnancy rate in ewes

Figure 3 summarizes the effect sizes and relative weights of each study with the findings of the forest plot. Relative weight is calculated as the percentage of the working weight and it is observed that the study of Aköz et al. (2006) and Koyuncu et al. (2001) revealed the highest weight and effect size. In the forest plot, on the left, the squares represent the effect size of each study, the dimensions of the squares designate the study sizes, and the bars extending to the right and left symbolize the lower and upper limit of the 95% confidence interval of each study's effect size. The diamond on the x-axis in the graph reflects the overall effect size and it is documented that the overall effect size is 0.66 (95% confidence interval; 0.58–0.74) (p<0.001). The squares representing the studies delineate summary information about the proximity or distance to the diamond, which portrays the general effect.

Table 5. Statistical values of the fixed effect model in subgroups in the study of Aköz et al. (2006)

Fixed-Effects Model (k = 6)						
	Estimate	**se**	**Z**	**p**	**Lower Bound**	**Upper Bound**
Intercept	0.431	0.0205	21.0	<.001	0.391	0.471

When Table 5 is examined, the effect size value (Estimate) was determined as 0.431, the lower limit of the 95% confidence interval was 0.391, and the upper limit was 0.471 (p<0.001). The forest chart created for subgroups is illustrated in Figure 4.

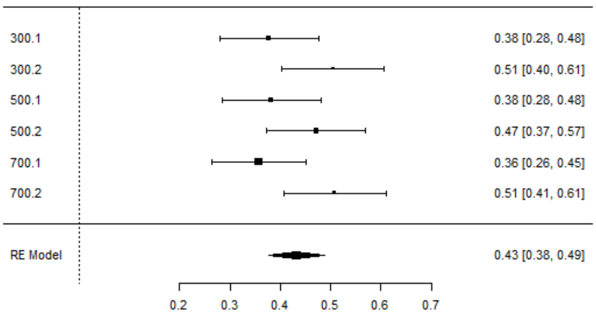

Figure 4. The forest graph obtained from the meta-analysis applied to the subgroups of the study of Aköz et al. (2006)

Scrutinizing Figure 4 in terms of subgroups in the study of Aköz et al. revealed that the protocol where the highest effect size was obtained was 40 mg FGA+300 IU PMSG (95% confidence interval; 0.50–0.61) and 40 mg FGA+700IU PMSG (95% confidence interval; 0.41–0.61).

When Table 6 is investigated; the effect size value (Estimate) was 0.484, the lower limit of the 95% confidence interval was 0.443, and the upper limit was 0.524 (p<0.001). The forest chart created for subgroups is presented in Figure 5.

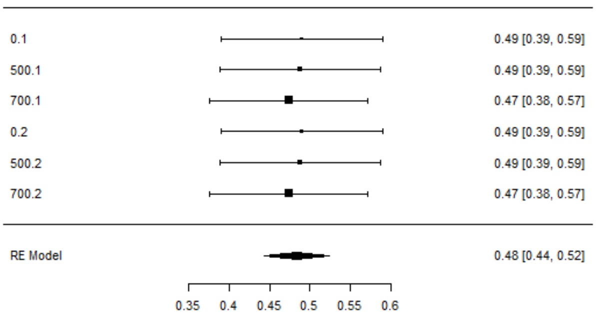

Figure 5. The forest plot acquired from the meta-analysis applied to its subgroups in the study of Koyuncu et al. (2001)

Figure 5, when evaluated in terms of subgroups in the study conducted by Koyuncu et al. (2001), claimed that the protocol with the highest effect rate was 40 mg FGA+500 IU PMSG (95% confidence interval; 0.39–0.59).

DISCUSSION

Although meta-analysis is a method that combines and reviews independent and comparable studies, it summarizes the effect sizes obtained from each study with a single statistic. By eliminating inconsistencies in individual studies, stronger and more precise estimates can be made for the effect size of the population with the analysis. These estimates also found their relevance in the field of veterinary medicine and became widespread in field applications.

Table 6. Statistical values of the random effects model in subgroups in the study of Koyuncu et al. (2001)

Random-Effects Model (k = 6)						
	Estimate	**se**	**Z**	**p**	**Lower Bound**	**Upper Bound**
Intercept	0.484	0.0207	23.4	<.001	0.443	0.524

As far as the effect of synchronization methods on fertility parameters is concerned, meta-analysis has found its use as a valid method in recent studies. The consequences of melatonin implants on pregnancy rates and the number of lambs born in ewes were deciphered by meta-analysis (Palcini et al., 2011). Two different synchronization protocols in dairy cattle, effect on the rate of conception (Borchardt et al., 2017; Borchardt et al., 2018), the effect on pregnancy rate per insemination (Bisinotto et al., 2015), the effect on pregnancy rate (Rabiee et al., 2005) have been elucidated by meta-analysis method. Nonetheless, since these studies are generally limited to paired comparisons, it was beyond the scope of this article to evaluate the advantages of the protocols with a holistic approach.

As with primary research, meta-analysis studies begin with determining the purpose and developing relevant research questions. The data obtained from the studies are synthesized in common size, and the relationships between the characteristics of the studies and the calculated common size are examined. For this common size, the effect size is generally preferred. The most important reason why the effect size, which is a measure of practical significance, is preferred over the p-value, which gives an idea of whether the results are statistically significant. This value is independent of the sample size. In the study, the effect size (Estimate) was determined as 0.658 (0.571-0.744) p <0.01. We can say that the exposures made in Turkey or the methods applied between the periods we have determined (1995-2020) have a significant effect. We can say that interventional or non-invasive methods on pregnancy rates increase the birth rate statistically significantly.

The application of the intravaginal sponge progestagen for the aggregation of heat in ewes breeding attracts all ewes to the luteal stage but accelerates the entry of PMSG into the follicular stage of ewes after the elimination of the sponges. Other studies have reported that PMSG administration reduces the duration of oestrus but has an equal effect on fertility parameters (Zonturlu et al., 2011).

In this study, it was aimed to achieve a common result with the Bayesian meta-analysis by combining the outcomes of the studies comparing the synchronization protocols with the pregnancy rates in ewes and with the control groups.

In this meta-analysis, it was found that two studies had the highest effect size during the breeding season (Aköz et al., 2006; Koyuncu et al., 2001) with the synchronization protocol used in ewes; the fertility parameters were ameliorated by combining with various doses of PMSG at the end of intravaginal sponge application as a source of progesterone. These findings validated the effectiveness of progestagen and PMSG application used for synchronization of pregnancy in ewes, among other protocols. The effect size was 0.66.

In the evaluation made in terms of subgroups in the study conducted by Aköz et al. (2006), the effect size of the 40 mg FGA + 300 IU PMSG (5.99 US$) and 40 mg FGA + 700 IU PMSG (6.05 US$) protocol was calculated higher as compared to the other protocols. It would be more rational to opt for the method whereby costs, ease of application, and success rates are optimum in the selection of the protocol to be applied in large ewes herds. According to Koyuncu et al. (2001) reported that the effect size of the 40 mg FGA + 500 IU PMSG (6.02 US$) protocol was higher than the other groups. Considering the two studies with high effect sizes as a result of meta-analysis in our study, it can be concluded that 40 mg FGA + PMSG (300–700 IU) applications are more effective on pregnancy rate compared to other synchronization protocols.

CONCLUSION

Estrus synchronization in ewes is employed to control pregnancy in the enterprises. Planning the pregnancy under enterprise conditions ensures optimum yield by propagating the lamb or milk yield to the whole year in line with the purpose of the enterprise. It is possible to regulate the reproductive performance in enterprises with estrus synchronization protocols and mating of ewes. However, it is essential to hunt for the optimal method in terms of economy and efficiency in enterprise conditions. Combining this study with the results of studies on the effects of synchronization protocols on pregnancy, it is predicted that Bayes meta-analysis will guide enterprises as a decision support system in achieving the optimum.

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Conflict of interest: There is no conflict of interest.

KAYNAKLAR

Akbaş, Ö. F. (2016). The effect of different synchronization programs on some reproductive parameters during breeding season in awassi ewes. Mustafa Kemal University Graduate School of Health Sciences, MSc Thesis, Hatay-Turkey.

Aköz, M., Bülbül, B., Bozkurt A. M., & Dere, S. (2006). Induction of multiple births in Akkaraman cross-bred sheep synchronized with short duration and different doses of progesterone treatment combined with PMSG outside the breeding season. *Bulletin-Veterinary Institute in Pulawy*, *50*(1), 97–100.

Aköz, M., Bodu M., &Acibaeva B. (2015). Current Methods in estrus synchronization of ewes and does. *Turkiye Klinikleri Reproduction and Artificial Insemination-Special Topics*, *1*(2), 1-8.

Algan, M. N. (2014). *The effects of fluorogeston acetate and eCG on some reproductive parameters in lactating Pirlak sheep*. Afyon Kocatepe University Graduate School of Health Sciences, MSc Thesis, Afyonkarahisar-Turkey.

Arıkan M. S. (2021). Koyun ve Keçi Hekimliği. In: Yarsan, E. (Ed.), İşletme Ekonomisi, Chapter 21, pp.821-822,. ISBN 9789752778238

Ataman, M. B., Aköz, M., Fındık, M., & Saban, E. (2009). Induction of synchronized oestrus in Akkaraman cross-bred ewes treated with prostaglandine F2 alpha, norgestomet and sponges impregnated with different doses of fluorogestene acetate at the beginning transitional period. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*, *15*(5), 801–805. DOI: 10.9775/kvfd.2009.429

Baştan, A., & Küpülü, Ş. (1995). The effects of melatonin and progestagen on reproductive performance in Akkaraman ewes. *Ankara Üniversitesi Veteriner Fakültesi Dergisi*, *4*(2), 263–270.

Bisinotto, R. S., Lean, I. J., Thatcher, W. W., & Santos, J. E. P. (2015). Meta-analysis of progesterone supplementation during timed artificial insemination programs in dairy cows. *Journal of Dairy Science*, *98*(4), 2472–2487. doi: https://doi.org/10.3168/jds.2014-8954

Bolstad, W. M. (2007). Introduction to Bayesian Statistics, Wiley-Interscience, UK.

Borchardt, S., Haimerl, P., Pohl, A., & Heuwieser, W. (2017). Evaluation of prostaglandin F2α versus prostaglandin F2α plus gonadotropin-releasing hormone as Presynch methods preceding an Ovsynch in lactating dairy cows: A meta-analysis. *Journal of Dairy Science*, *100*(5), 4065–4077. doi: 10.3168/jds.2016-11956

Borchardt, S., Pohl, A., Carvalho, P. D., Fricke, P. M., & Heuwieser, W. (2018). Short communication: effect of adding a second prostaglandin F2a injection during the Ovsynch protocol on luteal regression and fertility in lactating dairy cows: a meta-analysis. *Journal of Dairy Science*, *101*, 1–6. doi: 10.3168/jds.2017-14191

Crosby, T. F., Boland, M. P., & Gordon, I. (1991). Effect of progestagen treatments on the incidence of oestrus and pregnancy rates in ewes. *Animal reproduction science*, *24*(1–2), 109–118. doi: https://doi.org/10.1016/0378-4320(91)90086-F

Doğan, I., & Nur, Z. (2006). Different estrous induction methods during the non-breeding season in Kivircik ewes. *Veterinarni Medicina*, *51*(4), 133–138. doi: 10.17221/5532-VETMED.

Doğanay, M. (2011). *The impact of different dosage usage of progestagen+PMSG on the stimulation of ovarian activity, synchronization of sexual cycles and subsequent fertility rate of merino ewes during the anoestros season*. Ankara University Graduate School of Health Sciences, MSc Thesis, Ankara-Turkey.

Doğruer, G., Ergun, Y., Karaca, F., Sarıbay, M. K., Ateş, C. T., Aköz, M., & Aydin, I. (2015). The effect of applications of eCG and PGF2α at different times with FGA containing vaginal sponges on reproductive parameters in ewes at anestrous season. *Eurasian Journal of Veterinaty Science*, *31*, 3, 158–162. doi: 10.15312/EurasianJVetSci.2015310973

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*(2), 455–463. doi: 10.1111/j.0006-341x.2000.00455.x

Duymaz, Y. (2020). The effect of different synchronization methods on fertility in kivircik sheep in anoestrus period. Bursa Uludag University Graduate School of Natural and Applied Sciences, MSc Thesis, Bursa-Turkey.

Emrelli, A., Horoz, H., & Tek, Ç. (2003). The effect of melatonin and progestagen treatments on stimulation of oestrus cycle and reproductive patterns in Merino ewes out of the breeding season. Journal of Faculty of Veterinary Medicine Istanbul University, *29*(2), 267–275.

Esen, F., & Bozkurt, T. (2001). Effect of flushing and oestrus synchronization application on fertility in Akkaraman sheep. *Turkish JournaL of Veterinary And Animal Sciences*, *25*(3), 365–8.

Kacar, C., Kamiloglu, N. N., Gurbulak, K., Pancarci, S. M., Gungor, O., Guevenc, K., & Saban, E. (2008). The effect of administration of testosterone antibody, beta-Carotene and vitamin E on multiple pregnancy and MDA (Malondialdehyde) in Tuj breed sheep in non-breeding season. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*, *14*(1), 51–56. DOI: 10.9775/kvfd.2008.03-A

Karakaya, S. (2019). *The use of darkness apllication in the out-season heat synchronization in akkaram sheep*. Kırşehir Ahi Evran University Graduate School of Natural and Applied Sciences, MSc Thesis, Kırşehir-Turkey.

Kaya, H. H., Kaşıkçı, G., Ak, K., Alkan, S., & Sönmez, C. (2003). Controlling the breeding season using melatonin and progestagen in kıvırcık ewes. *Turkish JournaL of Veterinary And Animal Sciences*, *27*(2), 301–305.

Kaya, R. (2019). *Effects of melatonin and melatonin + progesterone on estrus synchronization and fertility parameters in tuj sheep outside of the breeding season*. Kafkas University Graduate School of Health Sciences, MSc Thesis, Kars-Turkey.

Kaya, S., Kaçar, C., Kaya, D., & Aslan, S. (2013). The effectiveness of supplemental administration of progesterone with GnRH, hCG and PGF2α on the fertility of Tuj sheep during the non-breeding season. *Small ruminant research*, *113*(2–3), 365–370. doi: https://doi.org/10.1016/j.smallrumres.2013.03.018

Koyuncu, M., Uzun, Ş. K., & Şengül, L. (2001). Synchronization of oestrus and the possibilities of improving reproductive performance by using progestagen and different doses of PMSG in Kıvırcık Ewes. *Turkish JournaL of Veterinary And Animal Sciences*, *25*(6), 971–974.

Köse, M., Kırbaş, M., Bülbül, B., Dursun, Ş., & Demİrci, U. (2016). Investigation of possibility of increasing lamb production with Flushing plus Ram effect or the administration of various pregnant mare serum gonadotropin doses in Akkaraman ewes. *Atatürk Üniversity Journal of Veterinary Sciences*., *11*(1), 54–59.

Kulaksız, R., Daşkın, A., & Dalcı, T. (2011). Some reproductive traits of ewes from different breeds following oestrus synchronisation by Flugeston Acetate-eCG during the breeding season. *Atatürk Üniversity Journal of Veterinary Sciences*., *6*(1), 9–15.

Kuru, M., Sogukpinar, O., Makav, M., & Cetin, N. (2017). Effect of barium selenate injections on fertility of Pirlak ewes subjected to estrus synchronization during non-breeding season. *Med Weter*, *73*(8), 479–482. doi: 10.21521/mw.5758

Lipsey, M. W., & Wilson, D. B. (2001). Practical meta-analysis. SAGE publications, Inc.

Ocak, A. (2007). Oestrus synchronization by short term administrations in chios strain cross ewes in the breeding season. Selçuk University Graduate School of Health Sciences, PhD Thesis, Konya-Turkey.

Ozyurtlu, N., Kucukaslan, I., & Cetin, Y. (2010). Characterization of oestrous induction response, oestrous duration, fecundity and fertility in Awassi ewes during the non-breeding season utilizing both CIDR and intravaginal sponge treatments. *Reprodtion of Domestic Animals*, *45*(3), 464–467. doi: 10.1111/j.1439-0531.2008.01246.x

Özbilek, İ. (2019). *The effect of sexual syncronization by reduced dose PGF2α on some reproductive parameters in sheep*. Mustafa Kemal University Graduate School of Health Sciences, MSc Thesis, Hatay-Turkey.

Öztürkler, Y., Çolak, A., Baykal, A., & Güven, B. (2003). Combined effect of a prostaglandin analogue and a progestagen treatment for five days on oestrus synchronisation in Tushin ewes. *Indian Veterinary Journal*, *80*, 917–920.

Palacin, I., Miranda, F. F., & Martínez, J. A. A. (2011). Meta-analysis of the efficacy of melatonin implants for improving reproductive performance in sheep. *Spanish Journal of Agricultural Research*, (3), 730–743. doi: 10.5424/sjar/20110903-348-10

Patsopoulous, N., Evangelou, E., & Ioannidis, J. P. A. (2008). Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *International Journal of Epidemiology*, *37*(5): 1148–1157. doi: 10.1093/ije/dyn065

Rabiee, A. R., Lean, I. J., & Stevenson, M. A. (2005). Efficacy of Ovsynch program on reproductive performance in dairy cattle: A meta-analysis. *Journal of Dairy Science*, *88*(8), 2754–2770. doi: 10.3168/jds.S0022-0302(05)72955-6

Solak, M. (2009). *The effect of timed artificial insemination (in out of breeding season) on pregnancy rates in ovulation and oestrus synchronization protocols appled akkaraman breed ewes*. Erciyes University Graduate School of Health Sciences, MSc Thesis, Kayseri-Turkey.

Sutton, A. J., Abrams, K. R., & Jones, D. R. (2001). An illustrated guide to the methods of meta-analysis. *Journal of Evaluation in clinical practice*, *7*(2), 135–148. doi: 10.1046/j.1365-2753.2001.00281.x

Timurkan, H., & Yildiz, H. (2005). Synchronization of oestrus in Hamdani ewes: The use of different PMSG doses. *Bulletin-Veterinary Institute in Pulawy*, *49*(3), 311–314.

Topçu, K. (2004). *The effects of hCG and GNRH on the pregnancy rate and litter size in the Estrus synchronization of ewes out of the breeding season.* İstanbul University Graduate School of Health Sciences, PhD Thesis, İstanbul-Turkey.

Uçar, M., Gündoğan, M., Özdemir, M., Tekerli, M., Eryavuz, A., Saban, E., & Özenç, E. (2002). Synchronization of oestrus in different sheep breeds by progesterone+CG and investigation of cholesterol and progesterone levels. *Eurasian Journal of Veterinary Sciences*, *18*(3–4), 79 - 85.

Whitley, N. C., & Jackson, D. J. (2004). An update on estrus synchronization in goats: a minor species. *Journal of Animal Science*, *82*(suppl_13), E270-E276. DOI: 10.2527/2004.8213_supplE270x

Zonturlu, A.K., Özyurtlu, N., & Kaçar, C. (2011). Effect of different doses PMSG on estrus synchronization and fertility in Awassi ewes synchronized with progesterone during the transition period. *Kafkas Universitesi Veteriner Fakültesi Dergisi*, *17* (1), 125–129, 2011. DOI:10.9775/kvfd.2010.2572