ORIGINAL RESEARCH

DOI: 10.5336/jcog.2021-86043

Dual Trigger with Gonadotropin-releasing Hormone Agonist and Human Chorionic Gonadotropin Improves Live Birth Rate for Women with Expected Normal Ovarian Response in Gonadotropin Releasing Hormone Antagonist Cycles: Retrospective Study

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ABSTRACT Objective: To evaluate and compare cycle outcomes following triggering final oocyte maturation with dual trigger of concomitant gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (hCG) administration versus hCG alone for women with expected normal ovarian response that underwent antagonist cycles with intracytoplasmic sperm injection (ICSI). **Material and Methods:** Women with expected normal ovarian response that underwent GnRH antagonist cycles with ICSI between January 2010 and April 2020 were evaluated in this retrospective cohort study. A total of 2,443 patients were included. Dual trigger was used for oocyte maturation in 637 cycles whereas hCG alone was used for triggering in 1,806 women. Cycles with dual trigger were assigned to study group and cycles with hCG alone are taken as controls. **Results:** Number of retrieved oocytes (14.08±3.58 vs. 13.15±3.61), number of metaphase 2 oocytes (9.77±3.08 vs. 8.06±3.14), fertilization rate (0.75±0.19 vs. 0.69±0.19), implantation rate (0.43±0.48 vs. 0.35±0.50) and clinical pregnancy rate (49.9% vs. 40.6%) were significantly higher in dual trigger group in comparison to hCG alone group. Higher number of good quality embryos were obtained in dual trigger group (85.7% vs. 76.3%). Live birth rate was significantly increased in dual trigger group in comparison to hCG only trigger group (45.1% vs. 36.7%). Multivariate logistic regression analysis showed dual trigger is a significant factor in predicting live birth deliveries (odds ratio 1.426, 95% confidence interval 1.185-1.716). **Conclusion:** Dual-triggering appears to improve embryo quality, increase implantation rates, clinical pregnancy rates and live birth rates in women with expected normal ovarian response that underwent GnRH antagonist cycles.

Keywords: Live birth; fertilization in vitro; gonadotropin-releasing hormone; infertility, female; antagonists-inhibitors

Human chorionic gonadotropin (hCG) is used as an oocyte triggering agent in in-vitro fertilization (IVF) cycles as a substitute for luteinizing hormone (LH) to trigger granulosa cell luteinization, resumption of meiosis and final oocyte maturation. However, hCG administration is associated with risk of ovarian hyperstimulation syndrome (OHSS) development. Preventive measures like withholding oocyte triggering or cycle cancellation are both grueling and financially costly hence creates frustration on patients.[1] Therefore, alternative methods to prevent OHSS without compromising IVF success have been investigated. Introduction of gonadotropin-releasing hormone (GnRH) antagonist cycles allows the use of GnRH agonists for final oocyte maturation triggering. Triggering of oocyte maturation with a GnRH agonist agent was first proposed by Gonen et al. in 1990 and suggested as a measure to prevent OHSS.[2]

GnRH agonists induce release of gonadotropins form pituitary gland with a flare up effect. Although hCG and LH bind to same LH receptor, these 2 molecules create different effects on downstream signal-

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Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 01 Sep 2021 ***Received in revised form:*** 05 Oct 2021 ***Accepted:*** 18 Oct 2021 ***Available online:*** 22 Oct 2021

ing pathways.[3] Moreover, GnRH agonists are known to induce both LH and follicle stimulating hormone (FSH) surges with their flare-up effects with a shorter duration in comparison to hCG.[4] This pattern of gonadotropin surge more closely mimic the ovulatory changes in natural menstrual cycles.[5] Thus GnRH agonist triggering effectively reduces the rate of OHSS and proposed as a measure to prevent OHSS in high-risk patients.[6] Besides preventing OHSS, GnRH agonist administration has been shown to increase endometrial receptivity probably by direct effects on endometrial cells, increase oocyte maturation rates and increase embryo quality.[7-11] All these advantages makes GnRH agonist triggering seem like an appealing choice to increase IVF success rates not only in patients with high risk of OHSS but also in all women with infertility. However due to the shorter duration and smaller amplitude of gonadotropin surge, GnRH agonist triggering alone, fails to sufficiently support corpus luteum functions and leads to higher rates of early pregnancy losses and lower rates of ongoing pregnancies in fresh embryo transfer cycles.[6] Intensive luteal support and supplementing GnRH agonist with hCG were proposed to overcome this disadvantage.[12,13] To benefit from advantages of both GnRH agonist and hCG, triggering of final oocyte maturation with concomitant administration of GnRH agonist and hCG was described by Shapiro et al. and termed as dual-triggering.[13] There are meagre number of studies in literature evaluating the effects of dual triggering on IVF outcomes in various subgroups of patients such as hyper-responder, normo-responder or poor-responder women.[5,6,11,14-25] Furthermore, studies reporting live birth rates, the ultimate goal of infertility treatment, in dually triggered women with expected normal ovarian response are even scarcer.[5,6,11,21,23,25] Therefore, current amount of evidence is not adequate to recommend or argue against the use of dual triggering particularly in women with predicted normal ovarian response.[26]

In an intention to standardize studies and to provide more functional data to guide the establishment of clinical management strategies, POSEIDON study group re-identified and stratified "low prognosis" women due to various drawbacks of former classification systems.[27]

Here we conducted this study to evaluate the effects of dual-triggering on IVF outcomes of women classified as normal prognosis or expected normal ovarian response, based on POSEIDON classification system.

MATERIAL AND METHODS

This retrospective cohort study was conducted at a university-affiliated infertility center (Memorial Ataşehir Hospital affiliated with Üsküdar University) in İstanbul. Records of patients that underwent intracytoplasmic sperm injection (ICSI) following a GnRH antagonist cycle between January 2010 and April 2020 were analyzed. Data were compiled from electronic medical records. Ethics approval for this study was received from Ethics Committee of Üsküdar University at 28.06.2021 (Approval number: 61351342/June 2021-63). Study protocol is in accordance with the "Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects" and the need for consent was omitted by ethics committee due to the retrospective design. Patients with high (>30 kg/m^2) or low (<18 kg/m^2) body mass index (BMI), patients with additional endocrine co-morbidities namely, diabetes mellitus, thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Addison disease, Cushing syndrome, patients with corrected or present uterine anomalies, patients with infertility due to azoospermia and women with low prognosis due to POSEIDON classification at the initiation of treatment were excluded from the study. Freeze-all cycles were also excluded. Women that antral follicle count ≥5, anti-Mullerian hormone ≥1.2 ng/mL, either have no other previous IVF attempts or that at least 10 oocytes were retrieved in all other previous IVF cycles were included in the study. Among these women that underwent GnRH antagonist cycles, cycle outcomes of dual-triggering and hCG-only triggering were compared. By this way all of the expected or unexpected poor ovarian responders defined by POSEIDON group 1, 2, 3, or 4 were excluded from the study.

Controlled ovarian stimulation was initiated on the 2nd day of menstrual cycle. Recombinant FSH (rFSH) (Gonal F; Serono, Istanbul, Turkey), human menopausal gonadotropin (Merional, IBSA, Istanbul,

Turkey; Menopur, Ferring, Istanbul, Turkey) or combination of recombinant LH and rFSH (Pergoveris; Serono, Istanbul, Turkey) is used for ovarian stimulation on practitioner's choice. Patients are monitored during stimulation for follicular growth with serial transvaginal ultrasounds. Serum estradiol and progesterone levels were assessed at the day of oocyte maturation triggering. Gonadotropin doses are titrated in accordance with each patient's follicular growth. Once the leading follicle is observed to reach a diameter of 12-14 mm, GnRH antagonist (Cetrotide 0.25 mg, Merck-Serono, Istanbul, Turkey) injections commenced to suppress premature LH peak and continued to the day of oocyte maturation triggering. Oocyte maturation is induced when follicles have reached a diameter of 18 mm. In dual-triggering group, concomitant injections of GnRH agonist of 0.2 mg triptorelin acetate, (Gonapeptyl 0.1 mg, Ferring, Istanbul, Turkey) and 250 mcg recombinant hCG (Ovitrelle, Serono, Istanbul, Turkey) were used for final oocyte maturation. In hCG-only group, 250 mcg recombinant hCG (Ovitrelle, Serono, Istanbul, Turkey) injections were used alone to induce final oocyte maturation. Oocytes are retrieved under transvaginal ultrasound guidance 35-36 hours after oocyte maturation triggering. Fertilization was carried out by ICSI. Embryo quality was graded according to the Society for Assisted Reproductive Technology (SART) grading system.[28] In accordance with the SART grading system, Grade 1 embryos are referred as good quality embryos, Grade 2 embryos are referred as fair quality embryos and Grade 3 embryos are referred as poor quality embryos in this study. Day 3 or day 5 embryos are transferred by using an embryo transfer catheter under guidance of abdominal ultrasonography, by phsicians' preference due to individual condition of each patient and embryo cohort. A maximum of 2 embryos were transferred in each attempt. Luteal phase support with intravaginal progesterone is initiated in every patient with either 200 mg Lutinus twice a day or with 200 mg Progestan 3 times a day (Lutınus vaginal tablets, Ferring Pharmaceuticals, Istanbul,Turkey; Progestan Soft Capsules, Kocak Farma, Istanbul,Turkey) and continued through 8^{th}-10^{th} gestational weeks.

Women with expected normal ovarian response that underwent ICSI following a GnRH antagonist cycle with dual-triggering within the selected period of time are assigned to the study group. Women with expected normal ovarian response that underwent ICSI following a GnRH antagonist cycle with hCG-only triggering within the selected period of time are constituted the control group.

Primary outcome of this study was determined as live birth rates. Secondary outcomes are number of oocytes retrieved, number of metaphase 2 (M2) oocytes, oocyte maturation rates (number of M2 oocytes/number of retrieved oocytes), number of 2 pronuclear (2PN) embryos, fertilization rates (number of 2PN embryos/number of M2 oocytes), quality of embryos, progression to blastocyst rates, implantation rates (gestational sacs observed/transferred embryos), clinical pregnancy rates, cycle cancellation rates and miscarriage rates. In terms of outcomes associated with implantation and pregnancy, only results of fresh embryo transfers were included in this study. Outcome parameters were defined in accordance with a previously published consensus.[29]

Statistical analysis was conducted by IBM SPSS 23 (evaluation version). Descriptive statistics were expressed as mean±standard deviations for normally distributed data. Categorical variables were expressed as numbers and percentages (%). Significance of differences between means were assessed with Student's t test. Categorical variables were assessed with Pearson's chi-squared test or Fisher's exact test. p values <0.05 are considered as significant. Multivariate linear regression analysis with backward elimination was performed to identify independent variables effecting implantation rates. Multivariate logistic regression analysis was performed to predict live births.

RESULTS

Following exclusion of ineligible subjects, a total of 637 women with expected normal ovarian response were found to underwent GnRH antagonist cycles that final oocyte maturation was induced by concomitant injections of GnRH agonist and hCG. Whereas 1,806 women were found to underwent GnRH antagonist cycles that oocyte maturation was induced by hCG administration alone within the selected period of time. Dual-triggering and hCG-only

groups were found similar in terms of mean age and mean BMI (p=0.053 and p=0.372 respectively). Infertility causes in study population were as follows with decreasing prevalence: mild male factor infertility, anovulation, unexplained infertility, tubal factor infertility, endometriosis and combined infertility. In dual triggering group, 15.2% of embryo transfers were day 3 transfers and 84.8% of them were day 5 embryo transfers. In hCG-only group, 18.7% of embryo transfers were day 3 embryo transfers and 81.3% were day 5 transfers. No significant differences were found in terms of day of embryo transfers. Of women in dual triggering group, 74.1% were received 3×200 mg oral progesterone for lueat l phase support and 25.8% of them received 2×200 mg intravaginal progesterone. In hCG-only group, 73.2% of patients received 3×200 mg oral progesterone and 26.8% of them received 2×200 mg intravaginal progesterone. No significant differences were found in terms of luteal phase support methods received by patients. No significant differences were found between 2 groups in distribution of prevalence of etiologic factors within patients (p=0.995). Baseline characteristics of dual-triggering group and hCG-only group were given in Table 1.

Required gonadotropin doses, length of ovarian stimulation, peak estradiol levels, peak progesterone levels and cycle cancellation rates were similar in dual-triggering and hCG-only triggering groups. Mean endometrial thickness at the day of embryo transfer, number of retrieved oocytes, oocyte maturation rates, fertilization rates, quality of obtained embryos, implantation rates and clinical pregnancy rates were all found significantly higher in dual-triggering group in comparison to hCG-only group. Multiple pregnancy rate was not significantly different among dual-triggering and hCG-only groups. Although a trend towards lower miscarriage rates in dual-triggering group was observed, the difference was not statistically significant compared to hCG-only group. A significant increase in live birth rate is found in dual-triggering group in comparison to controls. Comparison of IVF cycle outcomes in women that oocyte maturation is induced by dual-triggering or by hCG triggering alone were summarized in Table 2.

TABLE 1: Baseline characteristics of dual-triggering and hCG-only groups.

	Dual-triggering group	hCG-only group	p value
Number of cycles	637	1,806	
Age (years)	32.34±4.52	31.98±4.84	0.053
BMI	24.92±2.99	25.04±3.05	0.372
Infertility etiology			
• Mild male factor	191 (30%)	541 (30%)	
• Anovulation	151 (23.7%)	425 (23.5%)	
• Tubal factor	88 (13.8%)	251 (13.9%)	
• Endometriosis	47 (7.4%)	132 (7.3%)	
• Combined	41 (6.4%)	106 (5.9%)	
• Unexplained	119 (18.7%)	351 (19.4%)	0.995

hCG: Human chorionic gonadotropin; BMI: Body mass index.

Multivariate linear regression analysis with backward elimination was performed to identify independent variables effecting implantation rates. Before applying multivariate logistic regression analysis, univariate analysis were performed and parameters with a p<0.20 were interpreted as candidates for multivariate analysis and tested with backward method to evaluate significance of differences. Factors found as candidates in univariate regression analysis and included in the multivariate logistic regression analysis were age, endometrial thickness, number of retrieved oocytes, number of M2 oocytes, number of 2PN embryos, embryo quality and triggering method. Age (p<0.001), number of 2PN embryos (p<0.001), embryo quality (p<0.001) were found as independent determinants of implantation rate (Table 3). Multivariate logistic regression analysis was performed to predict live births. Following a univariate analysis, parameters with a p<0.20 were interpreted as candidates for multivariate analysis and tested with backward method to evaluate significance of differences. Factors included in the model were age, BMI, endometrial thickness, fertilization rate, number of retrieved oocytes, maturation rate, number of transferred embryos and progression to blastocyst rate and dual triggering. Among these parameters, age [odds ratio (OR) 0.953, 95% confidence interval (CI): 0.936-0.970], fertilization rate (OR: 3.237, 2.074-5.053), maturation rate (OR: 1.786, 95% CI: 1.115-2.860), and dual trigger (OR: 1.426, 95% CI: 1.185-1.716) were found as significant predictors of live birth deliveries (Table 4).

TABLE 2: Comparison of IVF cycle outcomes in dual-triggering and hCG-only triggering groups.

	Dual-triggering group	hCG-only group	p value
Number of cycles	637	1,806	
Required gonadotropin doses (IU)	2529.96±744.67	2480.98±715.74	0.105
Lenght of stimulation (days)	9.67±1.59	9.52±1.35	0.064
Estradiol level (pg/mL)	1965.83±716.92	1933.69±603.42	0.490
Progesterone level (ng/mL)	0.64±0.31	0.68±0.31	0.108
Endometrial thickness (mm)	10.80±1.96	10.50±1.89	**0.001**
Number of retrieved oocytes per cycle	14.08±3.58	13.15±3.61	**<0.001**
Number of metaphase 2 oocytes per cycle	9.77±3.08	8.06±3.14	**<0.001**
Maturation rate per cycle	0.70±0.16	0.62±0.18	**<0.001**
Number of 2 pronuclear embryos per cycle	7.39±4.0	5.60±2.76	**<0.001**
Fertilization rate per cycle	0.75±0.19	0.69±0.19	**<0.001**
Blastocyst progression rate	0.45±0.20	0.45±0.21	0.237
Quality of obtained embryos			
• Good	1991 (85.7%)	3346 (76.3%)	
• Fair	252 (10.9%)	706 (16.1%)	
• Poor	79 (3.4%)	333 (7.6%)	**<0.001**
Number of transferred embryos	1.45±0.52	1.47±0.51	0.405
Quality of transferred embryos			
• Good	778 (84.2%)	1925 (75.4%)	
• Fair	117 (12.7%)	430 (16.8%)	
• Poor	29 (3.1%)	199 (7.8%)	**<0.001**
Number of cryopreserved embryos	2.21±1.50	1.02±1.53	**<0.001**
Quality of cryopreserved embryos			
• Good	1213 (86.8%)	1421 (77.6%)	
• Fair	135 (9.7%)	276 (15.1%)	**<0.001**
Cancellation rate	5 (0.8%)	9 (0.5%)	0.376
Implantation rate per cycle	0.43±0.48	0.35±0.50	**<0.001**
Biochemical pregnancies	39 (6.1%)	135 (7.5%)	0.254
Clinical pregnancy rate	318 (49.9%)	733 (40.6%)	**<0.001**
Singleton pregnancies	236 (37%)	532 (29.5%)	**<0.001**
Multiple pregnancies	33 (5.2%)	80 (4.4%)	0.438
Ectopic pregnancies	2 (0.3%)	14 (0.8%)	0.266
Miscarriages	49/318 (15.4%)	121/733 (16.5%)	0.911
Live birth rate	302 (45.1%)	692 (36.7%)	**<0.001**

IVF: In-vitro fertilization; hCG: Human chorionic gonadotropin.

TABLE 3: Independent variables effecting implantation rates revealed by multivariate linear regression analysis with backward elimination.

	p value	Beta (%95 confidence interval)
Age	<0.001	-0.016 [(-0.020)-(-0.012)]
Number of 2 pronuclear embryo	<0.001	0.017 (0.011-0.024)
Embryo quality	<0.001	-0.20 [(-0.25)-(-0.15)]

TABLE 4: Multivariate logistic regression analysis for the prediction of live births.

	p value	Odds ratio (%95 confidence interval)
Age	<0.001	0.953 (0.936-0.970)
Dual trigger (+)	0.005	1.426 (1.185-1.716)
Fertilization rate	<0.001	3.237 (2.074-5.053)
Maturation rate	0.016	1.786 (1.115-2.860)

DISCUSSION

In the present study, we found that dual-triggering in GnRH antagonist cycles are associated with a significant increase in clinical pregnancy rates and live birth rates in women with expected normal ovarian response. These results might be consequences of increased oocyte maturation, increased embryo quality and increased endometrial receptivity or a combination of these factors.

GnRH agonists induce a surge of both FSH and LH from pituitary with flare-up effects. In a previous study, Lamb et al. demonstrated FSH administration at the time of hCG triggering improves oocyte's developmental competence, oocyte retrieval and number of 2PN embryos in IVF cycles.[30] Although the role of FSH in oocyte maturation is not yet completely understood. It has been shown that FSH induces LH receptor formation on granulosa cells, along with increasing the expression of amphiregulin and epiregulin that take place in cumulus expansion and resumption of meiosis.[31] Besides the effects of FSH, dual-triggering causes surge of LH while hCG only mimics LH by binding the same LH receptor as previously mentioned. Studies demonstrated that although LH and hCG bind to same LH receptor, they activate different downstream signal transduction pathways.[1,3] LH/LH receptor binding primarily stimulates phosphorylation of AKT and extracellular signal-regulated kinase 1/2 that take part in granulosa cell proliferation, whereas hCG/LH receptor binding causes a higher intracellular cyclic adenosine monophosphate accumulation that induce steroidogenesis.[1,3] Furthermore, presence of GnRH receptors are demonstrated on human granulosa cells in antral follicles and GnRH/GnRH receptor interaction is found associated with follicular development and corpus luteum functions.[32] Increased number of M2 oocytes retrieved in normal responder women underwent cycles with dual triggering has been demonstrated in some previous studies.[21,23,33] Griffin et al. showed that dual-triggering is associated with increased oocyte maturation rates.[9] Although, some authors found increased number of M2 oocytes retrieved in dual triggered normo-responder women in their studies, differences have not reached statistical significance probably due to smaller sample size of these studies.[5,10,17,24] Parallel with literature, we found higher number of retrieved oocytes, higher number of M2 oocytes and higher rate of oocyte maturation in our study.

GnRH receptor cells have also been demonstrated to exist on human endometrial cells and evidence indicate that these receptors have a possible role in endometrial receptivity.[32] A study conducted by Rackow et al. revealed a dose dependent reduction in endometrial HOXA10 expression in GnRH antagonist cycles. HOXA10 is a crucial regulator of endometrial receptivity and they suggested that administration of GnRH antagonists could be associated with decreased endometrial receptivity.[34] Supporting this suggestion, some other studies demonstrated increased expression of HOXA10 and HOXA11 along with improved endometrial receptivity with GnRH agonist administration.[7,8] We found increased endometrial thickness and higher implantation rates in women to whom GnRH agonist along with hCG was administered for oocyte maturation. However multivariate linear regression analysis in our study identified age, number of 2PN embryos and embryo quality as independent determinants of implantation, whereas triggering method was not found independently associated with implantation rate. These findings imply that dual trigger primarily increase implantation rates via increasing number of 2PN embryos and embryo quality. It seems dubious that a single dose of 0.2 mg triptorelin acetate administration along with hCG injection 6 days before embryo transfer improves endometrial receptivity to a clinically significant extent in women with expected normal ovarian response.

Some previous studies mentioned a negative impact of hCG on embryo quality and GnRH agonist administration is suggested to improve embryo quality.[6,35] In this study, we found increased total obtained embryo quality in dual-triggering group as substantiated with higher rate of clinical pregnancies and live birth deliveries in this group. Aligning with our findings, some recent studies indicated that dual-triggering was associated with higher embryo quality in normo-responders that underwent GnRH antagonist cycles.[5,10,25]

Among the currently available studies conducted about dual-triggering in normo-reponder women that

reported early pregnancy losses, none of them have shown a significant difference in miscarriage rates.[10,21,23,25] Similarly, we found equivalent rates of miscarriages in women with expected normal ovarian response underwent GnRH antagonist cycles with dual-triggering in comparison to hCG-only triggering.

Although growing number of studies in literature indicate better IVF outcomes in normal responder women underwent GnRH antagonist cycles with dual-triggering, current level of evidence is not adequate to clearly recommend dual-triggering over hCG-only triggering in this group of patients.[23,26] In this retrospective cohort study, we demonstrated clinical pregnancy rates and live birth rates are significantly higher in dual-triggering group in comparison to hCG-only group among women with expected normal ovarian response probably due to accumulative effects of increased oocyte maturation and higher embryo quality.

In our study, mean numbers of cryopreserved embryos per cycle in dual-triggering group and hCG-only group were 2.21±1.5 and 1.02±1.53, respectively. The difference was statistically significant. We also found that the quality of cryopreserved embryos were significantly increased in dual-triggering group compared to hCG-only group in patients with expected normal ovarian response. Although we only evaluated the results of fresh embryo transfers, considering the higher number and quality of surplus embryos that were cryopreserved, dual-triggering could expected to cause an even greater increase in cumulative rates of clinical pregnancies and live birth deliveries whenever frozen embryo transfers are required in these patients due to initial failures in achieving pregnancy following fresh embryo transfers.

CONCLUSION

In conclusion, dual triggering appears to improve embryo quality, increase implantation rates, clinical pregnancies and live birth deliveries in women with expected normal ovarian response that underwent GnRH antagonist cycles.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Fırat Tülek;* ***Design:*** *Alper Kahraman;* ***Control/Supervision:*** *Fırat Tülek, Alper Kahraman;* ***Data Collection and/or Processing:*** *Fırat Tülek;* ***Analysis and/or Interpretation:*** *Fırat Tülek, Alper Kahraman;* ***Literature Review:*** *Alper Kahraman;* ***Writing the Article:*** *Alper Kahraman, Fırat Tülek;* ***Critical Review:*** *Fırat Tülek;* ***Materials:*** *Fırat Tülek*

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