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ARAŞTIRMA / RESEARCH

Evaluation of pregnancy rates in infertile women after application of ovulation induction and intrauterine insemination

Ovulasyon indüksiyonu ve intrauterin inseminasyon sonrası infertil kadınlarda gebelik hızlarının değerlendirilmesi

Sabri Berkem Ökten[1], Zehra Nihal Dolgun[2], Vedat Uğurel[2], Koray Elter[2]

[1]Baskent University Istanbul Health Practice and Research Center, Department of Obstetrics and Gynecology, İstanbul, Turkey
[2]Trakya University Faculty of Medicine, Department of Obstetrics and Gynecology, Edirne, Turkey

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Abstract

Purpose: The aim of this studywas to investigate the effects of these factors on pregnancy rates in infertile patients following ovulation induction and intrauterine insemination.

Materials and Methods: The study was performed retrospectively that investigated examination reports and laboratory results of 201 infertile patients with unexplained infertility, male factor and anovulation. Women were subdivided into two groups according to the ovary-stimulating agent used as gonadotropin or clomiphene citrate. A semen sample was obtained from all men participants.

Results: There were 239 cycles of unexplained infertility (77.9%), 39 cycles in ovulatory dysfunction (12.7%) and 29 cycles in male factor (9.4%) groups. The clinical pregnancy rates per cycle according to infertility type were found as 18.4% (n:44) for unexplained infertility, 17.9% (n:7) for ovulatory dysfunction and 13.8% (n:4) for malefactor. In regression analyses, follicle (diameter>10mm) count on the day of hCG administration and inseminated total motile sperm count (ITMSC) were independently affected pregnancy rate. ITMSC area value under the curve (0.63) was significantly different from 0.5.

Conclusion: Follicle count on the day of hCG administration and ITMSC independently affect the pregnancy rate. Additionally, the intrauterine insemination method should be attempted in appropriate cases that have an acceptable successful pregnancy rate.

Keywords:. Pregnancy rate, infertile women, ovulation induction, intrauterine insemination

Öz

Amaç: Bu çalışmada ovulasyon indüksiyonu ve intrauterin inseminasyon sonrası infertil hastalarda bu faktörlerin gebelik oranlarına etkilerini araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışma retrospektif olarak incelendi ve açıklanamayan infertilite, erkek faktörü ve anovülasyonu olan 201 infertil hastanın laboratuvar sonuçları ve raporları incelendi. Kadınlar gonadotropin veya klomifen sitrat olarak kullanılan ovulasyon uyarıcı maddeye göre iki gruba ayrıldı. Tüm katılımcılardan alınan semen örnekleri değerlendirildi.

Bulgular: Açıklanamayan infertilite 239 siklus (77.9%), ovulatör disfonksiyonda 39 (12.7%) ve erkek faktör (9.4%) gruplarında 29 siklus vardı. İnfertilite tipine göre siklus başına klinik gebelik oranları açıklanamayan infertilite için 18.4% (n:44), ovulasyon disfonksiyonu için 17.9% (n:7), erkek faktör için13.8% (n:4) olarak bulundu. Regresyon analizlerinde hCG uygulamasının yapıldığı gün folikül (çap>10 mm) sayısı ve insemine toplam hareketli sperm sayısı (ITHSS) gebelik oranını bağımsız olarak etkiledi. ITHSS eğrisi altındaki alan değeri (0.63) 0.5'ten anlamlı olarak farklıydı.

Sonuç: hCG uygulamasının yapıldığı gün folikül sayısının ve ITHSS'nin gebelik oranını bağımsız olarak etkilediğini göstermiştir. Ek olarak, kabul edilebilir başarılı bir gebelik oranına sahip uygun durumlarda intrauterin inseminasyon yöntemi denenmelidir.

Anahtar kelimeler: Gebelik hızı, infertilite, ovulasyon indüksiyonu, intrauterine insemination

Yazışma Adresi/Address for Correspondence: Dr. Sabri Berkem Okten, Baskent University Istanbul Health Practice and Research Center, Department of Obstetrics and Gynecology. Istanbul, Turkey. E-mail: berkemokten@gmail.com
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INTRODUCTION

Infertility is defined as the inability to achieve pregnancy with regular unprotected sexual intercourse for a year or more. It is a health problem involving 10-15% of the world population[1]. In women, it is mainly caused by anatomic obstructions, endometriosis or ovulatory dysfunction. In men, it is a result of abnormalities in sperm production and function. Due to this high incidence of infertility, new assisted reproductive techniques such as intra uterine insemination (IUI) and ovulation induction (OI) provided development in last decade[2].

The intrauterine insemination is the initial step in the assisted reproductive techniques, including male and female infertility. It is the placement of concentrated motile sperm prepared by various methods directly into the uterine cavity[3]. It is commonly offered to couples with different causes of infertility such as relative male factor infertility, anovulation, unexplained infertility and reported to influence pregnancy rates. Sperm quality and numbers also affect these rates. In recent studies, a strong correlation between total motile sperm count and pregnancy rates was reported. In the study of Papillon-Smith comparing 1999 and 2010 World Health Organization semen analysis norms, the semen analysis accepted as having importance in the preliminary workup of the male partner. Any published pregnancy rates by a combination of OI+IUI shows great variety in the literature making the success rate remain controversial[4-7]. These success rates depend on many different parameters yet those parameters show inconsistency between the different studies[8].

The objective of this study was to identify the effects of spermiogram parameters, hormone profile, antral follicle count, follicle count and endometrial thickness on the day of hCG administration and other factors on pregnancy rates in infertile patients.

MATERIALS AND METHODS

The study was performed retrospectively that investigated examination reports and laboratory results of 201 infertile patients with unexplained infertility, male factor and anovulation. All participants admitted to the Trakya University, Faculty of Medicine, Infertility Clinic between 04.01.2012 and 01.06.2015 and underwent IUI and OI for the first time in our clinic. All patient data were evaluated after the ethics approval gained from the ethics committee of the Trakya University (No: 2013/158; 21/02 -Date:25.09.2013).

The first evaluation criteria were to have a history of infertility at least for one year with unprotected regular sexual intercourse and to have all data records including age, body mass index, duration of infertility, type of infertility, history of previous medications and infertility treatment and surgeries, FSH, LH, E_2 levels on the third day of menstruation, E_2 levels on HCG day, total antral follicle count, endometrial thickness value on the day of hCG administration and sperm parameters. Women who had second and third ovulation induction in our clinic (2. and 3. cycles) and who had AFC<5 were the ones that gonadotropins were used as the ovulation induction agent. Women with no previous pregnancy were accepted as primary infertile whereas the others were classified as secondary infertile. After evaluation, patients with normal uterine cavity, ovary and tubal passage were included in the study. Any patients having hypogonadotropic hypogonadism, severe endometriosis, endometrioma, intracavitary uterine lesion, history of ovarian surgery and bilateral tubal occlusion were excluded from the study.

Procedures

Ovarian stimulation

Ovarian reserve was determined by serum FSH, E_2 levels, and antral follicle count. Women were subdivided into two groups according to the ovary-stimulating agent used as gonadotropin (*Gonal-F Merck Serono, Bari, Italy; Puregon, N.V Organon, Oss, Holland; Menopur, Ferring, Kiel, Germany*) or clomiphene citrate (*Klomen, Koçak Farma, İstanbul, Turkey*). Ovarian stimulation with clomiphene citrate was started on the 3rd or 4th day of the menstrual cycle and applied for 5 days. In the gonadotropin group, ovarian and endometrial responses were observed by follicular growth in the 6th day of stimulation by transvaginal ultrasonography and controlled at intervals of 3 days if needed. A low dose step-up stimulation protocol was applied to women with polycystic ovary syndrome.

In this protocol, the starting dose was 50 IU/day and weekly dose increase was 37.5 units if needed depending on the ovarian response. When the average follicular diameter reached 16-18 mm in the gonadotropin group and 19-22 mm in the

clomiphene citrate group, we administered 250 µg recombinant hCG *(Ovitrelle, Merck-Serono, Modugno, Italy)*. 36 hours after the hCG administration, we applied the standard IUI procedure. Administration of hCG and IUI were canceled if there were two or more follicles greater than 16 mm, or three or more follicles greater than 14 mm in diameter. Follicle count on the day of hCG administration refers to follicles having at least 10 mm. Vaginal progesterone gel *(Crinone; Merck Serono, USA)* or progesterone capsule *(Progestan 200 mg; Kocak Farma, Turkey)* were prescribed to use for 2 weeks to maintain luteal phase support. Patients with positive serum β-hCG results were accepted as clinically pregnant if only the gestational sac was detected by ultrasonography.

Semen analysis

All men participants were asked to abstain from any kind of ejaculating for 3 days before semen collection. The semen samples were collected by masturbation and delivered to the laboratory within 45 minutes and its analysis was performed according to the guidelines of the World Health Organization. Its volume was estimated by weighing the container with and without the sample. After liquefaction at 37°C, and within 1 hour of ejaculation, the samples were analyzed for sperm motility and graded as fast progressive, mildly progressive, non-progressive or immotile. The semen volume and sperm concentration were evaluated together.

Statistical analysis

The results were analyzed by SPSS Statistics for Windows, Version 20 *(Armonk, New York, USA)*. In the analysis, Kolmogorov-Smirnov was applied as a distribution determination test. Student's t-test was used to compare the means of two groups and ANOVA *(variance analysis)* was used when there were more than 2 groups.

Logistic regression analysis was used to analyze the effects of various parameters and treatment plans on pregnancy. One of the appropriate Chi-square tests *(Pearson, Yates or Fisher)* was used to compare categorical data between groups. Results were summarized as mean±standard deviation or numbers *(percentage)*. Receiver Operating Characteristic (ROC) analysis was done to evaluate the effectiveness of quantitative data detected as independent factors and sensitivity and specificity for different cut-off points were calculated. A p-value <0.05 was considered statistically significant.

RESULTS

We retrospectively evaluated examination reports and laboratory results of 307 cycles in 201 infertile patients with unexplained infertility, male factor and anovulation, who underwent IUI and OI for the first time in our clinic. Among these, 55 patients were clinical pregnancies. The pregnancy rate per patient and cycle were 27.3% and 17.9% respectively. Among these clinical pregnancies, three of them were twins and it was observed that gonadotropins were used as an ovulation induction agent in these patients with multiple pregnancies. Among the 55 pregnancies, 37 were obtained after the first cycle, 9 of them after the second cycle, 7 of them after the third cycle and the rest 2 of them were obtained after fourth and fifth cycles. Patients' characteristics according to pregnancy outcome are shown in table-1 and cumulative pregnancy rates according to several cycles are shown in Table-2. 4^{th}, 5^{th} and 6^{th} cycle counts are not shown in the table due to their few numbers (11 in total).

According to the indication of treatment, there were 239 cycles of unexplained infertility (77.9%), 39 cycles in ovulatory dysfunction (12.7%) and 29 cycles in male factor (9.4%) groups. Unexplained infertility had the highest rate among infertility types whereas ovulatory dysfunction was the second cause. The clinical pregnancy rates per cycle according to infertility type were found 18.4% (n:44) for unexplained infertility, 17.9%(n:7) for ovulatory dysfunction and 13.8% (n:4) for malefactor. Clomiphene Citrate (CC) was used in 94 cycles (30.6%) whereas gonadotropin was used in 213 cycles (69.4%) as ovulation induction agent among all 201 patients and 307 cycles in total. In CC cycles 6.4% (n:6) and in gonadotropin cycles 23% (n:49) pregnancy rates per cycle were observed (Table 3).

Among patients' parameters of FSH, LH, E_2 levels on the third day of menstruation, total antral follicle count, endometrial thickness and highest follicular diameter values measured on the day of hCG administration and also sperm morphology value according to Kruger Strict Criteria were evaluated between the patients with and without clinical pregnancies and no significant differences were observed (p>0.05). During this analysis, not only first but all cycles' data were used because the pregnancy rates were similar (Table 2). Between patients with and without clinical pregnancy, we observed three factors showing the significant difference which were

follicle (diameter >10 mm) count on the day of hCG administration, inseminated total motile sperm count (ITMSC) and OI agent (CC vs. Gonadotropins) (Table 3 and 4). Assessing regression analyses, only two of these three factors being follicle (diameter>10mm) count on the day of hCG administration and ITMSC were found to affect pregnancy rate independently (p:<0.001 and p:0.01 respectively)

Table 1. Patient demographic characteristics according to pregnancy outcome

Parameters	Pregnancy (+) *(n:55)*	Pregnancy (-) *(n:252)*	p
Age *(year)*	30.15 ± 4	29.7 ± 4.4	0.486
BMI *(kg/m^2)*	25.6 ± 3.56	25.20 ± 4.57	0.543
Gravida *(n)*	0.36 ± 0.802	0.39 ± 0.72	0.784
Duration of Infertility	3.58 ± 3.25	4.29 ± 3.46	0.165

Abbreviations. BMI, Body mass index. A student t-test was performed in the present table.

Table 2. Cumulative pregnancy, dropout, and age distribution according to the cycles

Parameters	1st Cycle *(n:201)*	2nd Cycle *(n:75)*	3rd Cycle *(n:20)*
Age	29.86 ± 4.3	30.01 ± 4.03	30.2 ± 3.63
Pregnancy	37 (18.4%)	9 (12%)	7 (35%)
CPR	37 (18.4%)	46 (22.9%)	53 (26.3%)
Quit	89 (44.3%)	46 (61.3%)	2 (10%)

Abbreviations: CPR, Cumulative Pregnancy Rate

.**Table 3. Features of cycles and pregnancy rates according to ovulation induction agent being used.**

Parameters	Clomiphene Citrate *(n:94)*	Gonadotropin *(n:213)*	P
Age *(year)*	28.71 ± 4.27	30.53 ± 4	<0.001
Antral Follicle Count *(n)*	10.85 ± 4.76	8.98 ± 4.97	0.003
Follicle *(dia >10mm)* counton the day of hCG administration	2.36 ± 1.38	2.87 ± 1.52	0.008
Pregnancy Rates *(%)*	6.4 %(6/94)	23% (49/213)	<0.001

Student t-test was performed to compare the groups of Clomiphene Citrate and Gonadotropin.

Table 4. Parameters of patients according to pregnancy outcome

Parameters	Pregnancy (+) *(n=55)*	Pregnancy (-) *(n= 252)*	p
FSH *(mIU/mL)*	5.6 ± 2.76	5.91 ± 2.56	0.423
LH *(mIU/mL)*	4.45 ± 1.95	4.31 ± 2.53	0.72
Basal E_2 *(pg/mL)*	48.1 ± 36.5	54.03 ± 33	0.25
Antral Follicle Count *(PCO excluded)*	9.84 ± 5.22	9.53 ± 4.93	0.69
Largest diameter of Follicle *(mm)*	18.11 ± 2.35	18.7 ± 2.64	0.93
Follicle *(>10mm)* count at the day of hCG administration	3.69 ± 2.27	2.50 ± 1.18	<0.001
Endometrial Thickness *(mm)*	10.6 ± 2.87	10.04 ± 2.41	0.102
Inseminated Total Motile Sperm Count *($n \times 10^6$)*	49.8 ± 47.3	33.09 ± 36.8	0.01
Morphology *(Kruger Criteria)*	5.55 ± 7.89	4.84 ± 5.34	0.45

Abbreviations: FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; E2, Estradiol. Student t-test was performed to compare the groups of positive and negative pregnancy.

One of the independent variables determinative for pregnancy was ITMSC. The variable's area value under the curve (0.63) was significantly different from 0.5 (p:0.008) when Receiver Operating Characteristic (ROC) analysis was performed for ITMSC (Fig. 1). When the cut-off value for inseminated total motile sperm count (ITMSC) is taken as $5.75x10^6$, no pregnancy was observed under this value of ITMSC in IUI performed patients (100% sensitivity for pregnancy, 20.5% specificity). The other one of the independent variables determinative for pregnancy was follicle (diameter >10mm) count on the day of hCG administration. In these groups with similar age and ovary reserve markers, the pregnancy rates for 1-2 follicle count were 7.5-10% while for 3-6 follicle count the rates rise to 25-35%.

The treatment regimen (CC vs gonadotropin) affects pregnancy rates when separately evaluated but it was not found to be an independent determinant after regression analyses. There was a significant difference between CC+IUI and Gonadotropin+IUI in terms of the follicle (diameter>10mm) count on the day of hCG administration (CC 2.36±1.38, Gonadotropin 2.87±1.52; p:0.008).

DISCUSSION

In the present study, we made an effort to determine the prognostic factors that would determine the success of COH/IUI and pregnancy rates in infertile patients. For this purpose, we evaluated spermiogram parameters, hormone profile, antral follicle count, follicle count and endometrial thickness on the day of hCG administration and other factors. Our result improved the importance of follicle count with a diameter bigger than 10mm on the day of hCG administration and ITMSC.

In the literature, published pregnancy rates by a combination of OI+IUI show great variety making the success rate remain controversial. These success rates depend on many different parameters yet those parameters show inconsistency between the different studies. Looking for pregnancy rates per cycle in the literature, we encountered some reports as 14.87%[9], 14.7%[10], 10.8%[4], 12.91%[11], 9.2%[12] and 8.2%[13] in the different studies, with a consistent similarity as being in our study (17.9%).

Follicle count on the day of hCG administration was found to be a useful factor to predict IUI results in our study. While the pregnancy rate for one follicle was 7.5%, it was 10% for two, 34.6% for three and 23.4% for 4-6 follicles with a significant difference. The increase in follicle number increases the possibility of pregnancy. Thus, similarly in the literature, a multifollicular growth definition shows a great variety of studies with the minimum diameter of a follicle from 11 up to 18 mm[14]. Yavuz et al evaluated 980 IUI cycles and observed the highest pregnancy rate (14.4%) in cycles with three follicles and also that presence of at least three follicles (diameter >15mm) lead to a 7.79 fold increase in pregnancy rate[8]. Marvel et al analyzed 1038 cycles and observed pregnancy rates of 11.2% and 23.2% for one and three follicles (diameter >16mm) on the day of hCG administration respectively[10]. Nuojua-Huttunen et al[15] and Dickey et al[16] reported that the presence of 3 or more dominant follicles instead of one (diameter >15mm) lead to a 2-3 fold increase in IUI success rate, as well. Dickey et al also reported that cycles with follicles as small as 10 mm on the day of HCG administration resulted in implantation and births[17]. In a study where Steures et al. compared the effectiveness of intrauterine insemination and controlled ovarian hyperstimulation with that of expectant management in couples with unexplained subfertility, they analyzed 353 cycles and observed no clear differences in pregnancy rates between the cycles with monofollicular and multifollicular (diameter >10 mm) growth[18]. In our study follicle count on the day of hCG administration refers to follicles having at least 10 mm of diameters. We took the cut-off value as 10 mm to reflect ovarian response better in our study. The development of multiple follicles may provide a better endometrium and luteal phase as well as more fertilizable oocytes and so improve fertilization and implantation rates.

When we analyzed the OI agent that was used, we observed that cycles with gonadotropin use had a significantly higher rate of pregnancy than CC cycles (23% vs 6.4%). In a study by Dinelli et al.[19] total, 2019 cycles were analyzed for OI agent and no significant difference was found between CC and gonadotropin whereas in a Cochrane meta-analysis containing 43 studies conducted by Cantineau et al.[20] gonadotropin cycles showed significantly higher pregnancy rates than CC cycles (OR 1.8; 95% CI, 1.2-2.7). In a study reported by Gomez et al.[21], 5346 OI + IUI cycles were evaluated in terms of gonadotropin versus clomiphene citrate and the pregnancy rates were 14.4% and 7.4% respectively in favor of gonadotropins with a significant difference. The majority of the present data available comparing

gonadotropin and CC suggest that gonadotropins seem more effective than CC. But still, being more cost-effective and easy to use, CC can be offered as the drug of the first choice. In a study, Luco et al.[22] reported with 356 analyzed IUIs that no parameter in either the pre or post-analysis predicted pregnancy. Furthermore, they found that the natural cycle and letrozole treatment had similar pregnancy rates like 3% and 3%. They also observed the same between clomiphene citrate and gonadotropin-stimulated cycles (7.5% and 6%).

In our study, ITMSC was found to be one of the independent factors that affect pregnancy outcomes. All pregnancies were observed above the value of $5.7x10^6$. In many studies, there was a correlation between total motile sperm count and pregnancy rates. In the study of Papillon-Smith comparing 1999 and 2010 World Health Organization semen analysis norms[5], the semen analysis accepted as having importance in the preliminary workup of the male partner. However, they warned that the significant overlap in the seminal profiles of men with varying levels of fertility stresses the need to exercise caution. Hassan et al.[23] performed a study with a total of 981 couples who underwent 2231 IUI cycles. Overall, the pregnancy rate was 20.2%. Pregnancy rates did not differ and remained rather stable for the pre and post-processing semen analysis when stratified for TMSC. Ruiter-Ligeti et al.[24] saw a decrease in TMSC, with an average decrease of 50±124% compared to pre-processed samples. Importantly, the decrease in TMSC did not negatively affect pregnancy rates in this study. Normally in our clinic, patients with a total motile sperm count less than $5x10^6$ are directed to IVF treatment. When we checked our retrospective data we observed 43 cycles that underwent IUI with a total motile sperm count less than $5x10^6$. The reason for that was the inconsistency between sperm values analyzed before IUI decision and the sperm values analyzed on the day of insemination. In literature, another important factor seems to be the sperm morphology. In 411 IUI cycles observed by Francavilla et al.[25], it was reported that the most important factor determining pregnancy is the sperm morphology and if there is an absence of teratozoospermia, IUI should be performed. On the contrary in a study evaluating 2564 cycles, Wainer et al.[11] reported no significant relationship between morphology and pregnancy rates like our study. Xiao et al showed higher pregnancy rates in the group with low TMSC on the day of IUI. Badawy et al. analyzed 714 IUI cycles with morphologically normal spermatozoa and they observed that the pregnancy rate per cycle was 5.55% when the number of motile spermatozoa was $<5x10^6$ and 24.28% with normal motile sperm $>5x10^6$ [26]. The overall pregnancy rate was 5.3%. Luco et al.[22] reported total motile sperm count as a predictor of pregnancy that should be considered when deciding whether to suggest IUI and when selecting a protocol for ovulation induction for couples with male factor infertility. Although our study was performed with fewer participants compared to the literature, the outcomes support similar studies that ITMSC is an important factor that affects pregnancy rates.

The ages of women included in our study were varying from 19 to 40. When we evaluated age, serum FSH, LH, E_2 levels on the third day of menstruation, total antral follicle count parameters between the patients with and without clinical pregnancies, no significant differences were observed. Patients with low ovary reserve and high age are mostly referred to in vitro fertilization and that might explain why both pregnancy negative and positive groups showed similar age results in our study. Age is reported as the most effective factor in pregnancy in many studies [27]. However, in studies of Yavuz et al.[8], Iberico et al.[12], Mathieu et al.[28], Khalil et al.[3], it was reported that maternal age was not an independent factor for predicting pregnancies after IUI. Nuojua Huttunen et al.[15] evaluated 811 cycles and reported a pregnancy rate per cycle as 13.7% for women younger than 40 years old while the rate showed a significant decrease to 4.1% in the group older than 40 years. No pregnancy was observed above the age of 42. Brzechffa et al.[29] reported no effect of age on pregnancy rates in IUI performed patients under the age of 40. In our study, one of the other factors that showed no significant effect on pregnancy rates was the endometrial thickness. Kolibianakis et al.[30] evaluated 168 and Yavuz et al.[8] evaluated 596 cases and parallel to our study they reported no significant effect of endometrial thickness on pregnancy rates.

We had some limitations in the current study. First, the study had a limited sample size to reach a stronger conclusion. Second, we had not had enough supporting data for the average follicle count in patients with the polycystic over. Thus, we could not perform a detailed logistic regression analysis including parameters such as basal FSH, AMH values, previous term deliveries, and miscarriages.

In our study, we found that follicle count on the day of hCG administration and ITMSC were found to

affect pregnancy rate independently. In the literature, numerous studies are evaluating the effects of various factors on pregnancy rates of patients who underwent OI+IUI with different results. IUI is a method that should be attempted in appropriate cases that have an acceptable successful pregnancy rate. We suppose that there is a need for more studies to get the ultimate results.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SBÖ; Veri toplama: SBÖ; Veri analizi ve yorumlama: VU; Yazı taslağı: ZND; İçeriğin eleştirel incelenmesi: SBÖ, ZND; Son onay ve sorumluluk: SBÖ, ZND, VU, KE; Teknik ve malzeme desteği: KE; Süpervizyon: SBÖ; Fon sağlama (mevcut ise): yok.

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