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**The Effect of Applying the Iodized Contrast Materials Used in Hysterosalpingography at Body Temperature or Room Temperature on Visual Analogue Scale Scores****Histerosalpingografide Kullanılan İyotlu Kontrast Maddenin Vücut Sıcaklığında ya da Oda Sıcaklığında Uygulanmasının Vizüel Analog Skala Skorlarına Etkisi**BURAK ERSAK<sup>1</sup>YASEMİN TAŞÇI<sup>2</sup>RAHİME BEDİR FINDIK<sup>1</sup>DUYGU TUGRUL<sup>1</sup>AYTEKİN TOKMAK<sup>1</sup>MAHMUT KUNTAY KOKANALI<sup>1</sup>

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**Amaç:** İnfertil hastalarda soğuk ve sıcak kontrast madde kullanılarak çekimi yapılan histerosalpingografi (HSG) işlemi sırasında ve sonrasında vizüel analog skalası (VAS) kullanarak ağrı skorlarını karşılaştırmak ve sıcak kontrast kullanımının spontan gebelik oranını değiştirip değiştiremeyeceğini araştırmak.

**Gereçler ve Yöntem:** Çalışma prospektif randomize kontrollü tasarlandı ve Mart-Eylül 2017 tarihleri arasında HSG prosedürü uygulanan primer infertil hastalar dahil edildi. Hastaların yaşı, vücut kitle indeksi (VKİ), geçirilmiş cerrahi öyküsü, infertilite süresi ve en ağrılı adet dönemindeki ağrı düzeyleri kaydedildi. İşlem sırasında ve işlem sonrası 30. dakikada ağrı şiddeti VAS ile sorgulandı. Hastaların yaşı, vücut kitle indeksi (VKİ), geçirilmiş cerrahi öyküsü, infertilite süresi ve en ağrılı adet dönemindeki ağrı düzeyleri kaydedildi. İşlem sırasında ve işlem sonrası 30. dakikada ağrı şiddeti VAS ile sorgulandı.

**Bulgular:** Gruplar arasında yaş, VKİ, infertilite süresi, geçirilmiş cerrahi ve menstürasyon sırasındaki VAS açısından istatistiksel olarak anlamlı fark yoktu. Sıcak gruptaki hastaların ortalama HSG süresi anlamlı olarak daha düşüktü ( $p=0,001$ ). Sıcak gruptaki hastaların HSG sırasındaki ve 30 dakika sonraki ortalama VAS skoru, kontrol grubuna göre (sırasıyla  $5,3\pm 4,2$  vs  $7,5\pm 2,0$ ) ( $1,1\pm 0,9$  ve  $2,4\pm 1,4$ ) anlamlı derecede düşüktü. HSG sırasında şiddetli ağrı yüzdesi sıcak grupta %25.5 iken kontrol grubunda %66.7 idi. Lojistik regresyon analizinde, iki grup arasında işlem sırasında hissedilen şiddetli ağrı için yalnızca anlamlı ilişkili faktörler olarak bulundu ( $p<0,001$ , OR=0,19, %95 CI=0,08-0,46).

**Sonuç:** HSG işlemi sırasında vücut sıcaklığında kontrast madde kullanılması işleme bağlı ağrıyı azaltır.

**Anahtar Kelimeler:** Histerosalpingografi, iyotlu kontrast madde, pelvik ağrı, sıcak kontrast madde

**ABSTRACT**

**Aim:** To compare pain scores of infertile patients during and after hysterosalpingography (HSG) procedure using visual analogue scale (VAS) between cold and warm contrast medium and to investigate whether using warm contrast can alter spontaneous pregnancy rate.

**Materials and Methods:** Prospective randomized study between March-September 2017. Primary infertile patients undergoing HSG procedure. Patients' age, body mass index (BMI), history of previous surgery, duration of infertility and pain levels during the most painful menstrual period were recorded. The pain severity was questioned during and at the 30th minute after the procedure using VAS. While patients who underwent HSG using a contrast medium at body temperature 37 °C were defined as warm group (n:55), patients who underwent HSG using a contrast medium at room temperature 23 °C were defined as cold group (n:55).

**Results:** There were no significant differences between the groups in terms of age, BMI, duration of infertility, previous surgery and VAS during menstruation. The mean duration of HSG of warm group patients was significantly lower ( $p=0.001$ ). Warm group patients' mean VAS score during and 30 minutes after HSG were significantly lower than in the control group ( $5.3\pm 4.2$  vs  $7.5\pm 2.0$ ), ( $1.1\pm 0.9$  vs  $2.4\pm 1.4$ ), respectively. While severe pain percentage during HSG in warm group was 25.5%, it was 66.7% in the control group. In logistic regression analysis, warm and cold groups were only found as significant related factors for severe pain felt during procedure ( $p<0.001$ , OR=0.19, 95% CI=0.08-0.46).

**Conclusion:** The use of contrast media at body temperature during HSG procedure reduces the pain associated with the procedure.

**Keywords:** Hysterosalpingography, iodinated contrast media, pelvic pain warm contrast media, visual analogue scale.

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## INTRODUCTION

Hysterosalpingography (HSG) is an important procedure used to evaluate the intrauterine pathology, tubal lumina and patency as an initial workup of infertility (1, 2). Although it is considered as a minimal invasive procedure, it is not easy in terms of applicability to patients. Many side effects of HSG have been reported in the literature (3). However, the major patient complaint of HSG is pain. The studies carried out have shown that up to %85 of patients felt pain while undergoing HSG (4).

Reducing or preventing the pain during the process provides better radiological outcomes and information. For this reason, prophylactic analgesia, pretreatment with corticosteroids, showing preprocedural information video were used to reduce frequency of vasovagal and pain symptoms (5-7). Nevertheless, benefits of all these techniques are controversial; it was reported that there was no evidence of effect for oral opioid or non-steroidal anti-inflammatory drugs (NSAID) analgesia in reducing pain during the procedure or more than 30 minutes after procedure (8). In addition, no difference in terms of pain was shown between oil- and water-soluble contrast media (9).

Warming contrast media is another intervention to reduce pain without significant risk. Studies demonstrating that using warm methods were useful for relieving pain and increasing patient comfort were limited to laparoscopic operations, peritoneal dialysis and histerocontrastsonography (10-12) except one randomized prospective study, which has shown that warm contrast reduced visual analogue scale (VAS) pain scores during the HSG procedure by alleviating peritoneal irritation (13).

HSG procedure may increase the chance to conceive due to mechanical lavage effect on the tubes and peritubal adhesions. However, the effect of using warm contrast in HSG on infertility and spontaneous pregnancy rate is unknown.

In our current study, our primary outcome was to compare pain scores with using VAS between cold and warm contrast medium. Secondary, we aimed to investigate whether using warm contrast can alter spontaneous pregnancy rate in early period.

## MATERIALS AND METHODS

This prospective randomized study was approved by institutional ethic committee (17.03.2017/44) and verbal/written informed consent was obtained from each participant before the enrollment.

Between March 2017 and September 2017, a total of 110 pri-

mary infertile patients without any known cause, between the ages of 19-30, who applied to Department of the Infertility and Gynecological Endocrinology Clinic, University of Health Science Zekai Tahir Burak Women's Health Education and Research Hospital were included in the study.

Patients who had genitourinary tract infection, vaginal bleeding, malignancy and known sensitivity to iodine were excluded. Ultrasonography was performed to evaluate the ovaries in transverse and longitudinal planes. In the presence of less than 5-7 antral follicles or a FSH level >8 IU/L were accepted as abnormal ovarian reserve test. Patients with the diagnosis of abnormal ovarian reserve and the patients referred for male factor infertility were excluded from the study, as well.

For each patient, age, body mass index (BMI), history of previous pelvic infections or surgery, duration of infertility and pain levels during the most painful menstrual period within the last year were recorded. A 10-point visual analogue scale (VAS) in which "0-point" was defined as painless and "10-point" as severe pain was used to assess pain severity.

Patients were randomized into two groups according to their appointment numbers. Odd numbers constituted the 'cold group', while even numbers were included in the 'warm group'. In both groups, HSG was scheduled on days 6 through 11 from last menstrual period to avoid both the menstrual bleeding and pregnancy. HSG procedure was performed by the same gynecologist (B.E) according to Baramki's description (14) using a real-time fluoroscopy system (Zen-5000; Genoray, Korea). During the procedure, all the steps were explained to the patients. The contrast medium was stored in a room at 23°C normally. The cold group was composed of women who underwent HSG using a contrast medium at room temperature 23° C, while the warm group was composed of women who underwent HSG using a contrast medium at body temperature 37° C. The contrast medium was heated up to 37° C using a water bath method. Then, the temperature was confirmed using an electronic thermometer by the nurse before the injection. After the insertion of Rubin's cannula, 10 mL of warm or cold nonionic water-soluble contrast media (Urografin %76 100mL, Bayer Turk Chemistry Corp.) was injected slowly into the uterine cavity while the necessary images were obtained. The gynecologist did not know which patients were given warm or cold contrast media while performing the procedure. None of the patients were given prophylactic NSAID or a spasmolytic drug to reduce pain before or during the procedure.

When the contrast media was seen passing through the fimb-

rial ends of the tubes, the pain severity of the patients was questioned by the gynecologist (B.E). At the 30th minute after the procedure, the presence / severity of the pain that the patient felt about the current condition was again questioned by a different physician (D.T.E) who also did not know which patients were given warm or cold contrast media. VAS was used in all these pain assessments. Patients with VAS score  $\geq 6$  was accepted as severe pain. Due to the possibility of spontaneous pregnancy after HSG procedure, all cases were followed up spontaneously for 4 months and the results were recorded as a secondary objective. Statistical analyses were carried out by using the statistical packages for SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine the data distributions. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables were given as number and percentage. Continuous variables were analyzed using Students' t-test and categorical variables were compared using a  $\chi^2$  test. Pearson's correlation coefficient was used to analyze the correlations between VAS score during HSG and 30 minutes after HSG with other factors. Factors classified as related to severe pain felt during HSG were assessed using logistic regression model. The p values less than 0.05 were considered statistically significant.

## RESULTS

During the study period, 110 patients met the inclusion criteria and participated in the study. However, 4 patients of the control group were excluded due to more than 10cc contrast agent usage. While, 55 patients in the study group (warm group) were applied contrast agent warmed to body temperature, 51 patients were applied contrast agent at room temperature (cold group). There were no significant differences between the groups in terms of age, BMI, duration of infertility, previous surgery, systemic disease and VAS during menstruation. However, the mean duration of HSG of patients who were applied contrast agent warmed to body temperature was significantly lower ( $3.7\pm 1.2$ ) than the mean duration of HSG ( $4.4\pm 1.2$ ) of patients who were applied contrast agent at room temperature ( $p=0.001$ ). Furthermore, warm group patients' mean VAS score during HSG and 30 minutes after HSG were significantly lower than in the control group ( $5.3\pm 4.2$  vs  $7.5\pm 2.0$ ), ( $1.1\pm 0.9$  vs  $2.4\pm 1.4$ ), respectively. And also, while severe pain percentage during HSG in warm group was % 25.5, it was % 66.7 in the control group ( $p<0.001$ ) (Table 1).

**Table 1.** Characteristics and pain scores of the groups

	Warm Group (n=55)	Cold Group (n=51)	p
Age (year)	26.6 $\pm$ 3.0	26.3 $\pm$ 3.3	0.735
BMI (kg/m <sup>2</sup> )	25.4 $\pm$ 4.5	25.5 $\pm$ 5.7	0.934
Duration of infertility (year)	2.8 $\pm$ 2.6	2.3 $\pm$ 1.5	0.941
Previous surgery	6 (10.9)	7 (13.8)	0.885
Systemic disease	4 (7.3)	8 (15.7)	0.225
VAS during menstruation	4.7 $\pm$ 1.9	5.02 $\pm$ 1.4	0.300
Duration of HSG (min)	3.7 $\pm$ 1.2	4.4 $\pm$ 1.2	<b>0.001</b>
Tubal occlusion	1 (1.8)	1 (2.0)	0.957
VAS score during HSG	5.3 $\pm$ 4.2	7.5 $\pm$ 2.0	<b>&lt;0.001</b>
VAS score 30 minutes after HSG	1.1 $\pm$ 0.9	2.4 $\pm$ 1.4	<b>&lt;0.001</b>
Severe pain during HSG	14 (25.5)	34 (66.7)	<b>&lt;0.001</b>
Spontaneous pregnancy	4 (7.3)	0 (0.0)	---

Data are shown as mean  $\pm$  standard deviation and number (%).BMI: Body mass index, VAS: Visual analog scale, HSG: Hysterosalpingography  $p<0.05$  was considered statistically significant

In Table 2, correlations between VAS score during HSG and 30 minutes after HSG with other factors were listed. There were no correlation between patient age, BMI, duration of infertility, pain score during menstruation and VAS score during HSG and 30 minutes after procedure. However, duration of HSG ( $r=0.255$ ,  $p=0.008$ ) and VAS score 30 minutes after HSG ( $r=0.588$ ,  $p<0.001$ ) were positively correlated with VAS score during HSG. On the other hand, no correlation was found between duration of HSG and VAS score 30 minutes after HSG.

**Table 2:** Correlations between VAS score during HSG and 30 minutes after HSG with other factors

	VAS score during HSG			VAS score 30 minutes after HSG	
	r	p		r	p
Age	0.003	0.978	Age	-0.137	0.161
BMI	0.109	0.265	BMI	0.170	0.081
Duration of infertility	-0.170	0.082	Duration of infertility	-0.051	0.600
VAS during menstruation	-0.052	0.595	VAS during menstruation	0.096	0.328
Duration of HSG	0.255	<b>0.008</b>	Duration of HSG	0.137	0.160
VAS score 30 minutes after HSG	0.588	<b>&lt;0.001</b>	VAS score during HSG	0.588	<b>&lt;0.001</b>

r: Pearson's correlation coefficient BMI: Body mass index, VAS: Visual analog scale HSG: Hysterosalpingography

$p < 0.05$  was considered statistically significant

The comparison of related factors between severe and non-severe pain groups are shown in Table 3. The mean duration of HSG was significantly higher in severe pain group compared with control group ( $p=0.034$ ). Nevertheless, the age, BMI, duration of infertility, previous surgery, systemic disease and VAS during menstruation did not differ significantly between the groups. In logistic regression analysis, the variables categorized as related factors for severe pain felt during procedure were evaluated. Warm and cold groups were only found as a significant factor ( $p<0.001$ ,  $OR=0.19$ ,  $95\% CI=0.08-0.46$ ).

**Table 3:** Comparison of related factors between severe and non-severe pain groups

Table 3: Comparison of related factors between severe and non-severe pain groups	Severe pain group (N=48)	Non-severe pain group (N= 58)	P	OR (95% CI)	p
Age (year)	26.48±3.14	26.40±3.10	0.892	---	---
BMI (kg/m <sup>2</sup> )	25.67±5.98	25.23±4.25	0.662	---	---
Duration of infertility (year)	2.33±1.67	2.82±1.45	0.247	---	---
Previous surgery	6 (12.5)	7 (12.1)	0.946	---	---
Systemic disease	4 (8.3)	8 (13.8)	0.377	---	---
VAS during menstruation	4.81±1.59	4.88±1.72	0.838	---	---
Duration of HSG (min)	4.32±1.31	3.80±1.19	<b>0.034</b>	1.19 (0.84-1.69)	0.336
Groups					
<i>Warm</i>	14 (29.2)	41 (70.7)	<b>&lt;0.001</b>	0.19	<b>&lt;0.001</b>
<i>Cold</i>	34 (70.8)	17 (29.3)		(0.08-0.46)	

Data are shown as mean ± standard deviation or n (%) BMI: Body mass index, VAS: Visual analog scale, HSG: Hysterosalpingography, OR: Odds ratio, CI: Confidence Interval p <0.05 was considered statistically significant

## DISCUSSION

In our study for pain that patients feel during and after HSG procedure, we reached some findings that we thought were important. Namely, when we used warm medium we found that patients felt less pain both during and 30 minutes after the procedure and the presence of severe pain was more in the cold medium group. Pain felt during the procedure increased as the duration of the procedure increased and this pain was positively

associated with the pain felt at 30 minutes after the procedure. However, there was no relationship between the duration of the procedure and the pain felt after the procedure. On the other hand, those who had severe pain during the procedure had a longer procedure time and less frequent use of warm medium. However, in the presence of these two factors, only the medium used was a significant factor for the presence of severe pain.

Pain during the HSG procedure is a troublesome situation for the patient and clinician (15). The patient may not want to have this procedure done or completed due to this pain. In addition,

the clinician can be prevented from reaching an accurate result (16). Two important mechanisms proposed in the formation of pain that occurs during the HSG procedure are, increased contractions created in the uterus and peritoneal irritation (17, 18). Increased prostaglandin release in the uterus or the inflammatory response developed due to irritation formed in the peritoneum may cause pain associated with this procedure (19). Cold stimulation is a factor that increases contraction in the uterus and peritoneal sensitivity (20). Therefore, in the presence of a cold stimulus, the patient will be expected to experience more pain. Indeed, in 2008, two meta-analyses by Sammour et al and Sajid et al reported that insufflation with heated CO<sub>2</sub> was more advantageous in terms of postoperative pain and analgesia needs (21, 22). In another more recent meta-analysis by Balayssac et al. It has been reported that warm insufflation is more beneficial for immediate postoperative pain (23). On the other hand, studies on using warm medium during HSG are limited. To our knowledge, our study is the second study comparing warm and cold contrast agent for HSG. First study was published by Zhu et al in 2012 (13). In that study, similar to ours, patients' VAS pain scores during HSG were found to be significantly lower in the warm contrast agent applied group. However, VAS pain scores at 30 minutes after procedure showed no statistical difference. In addition, we found the frequency of severe pain more in the cold group. In our study, the duration of the procedure in the cold group was longer, and the prolongation of this period increased the severity of pain felt during the procedure, and the increased pain during the procedure also increased the pain felt at 30 minutes after the procedure. Extending the duration of the HSG procedure indicates that the procedure is more difficult. This may cause more pain to be felt. As a matter of fact, we found that the duration of the procedure in patients with severe pain was longer than the group without severe pain. Although this can be seen as a factor for the presence of severe pain, we have seen that this negative effect disappears with the use of warm medium in the regression model. We think that this finding shows that the warm medium used during HSG procedure is a very effective factor in reducing HSG-related pain.

A relatively increase in spontaneous pregnancies can be observed after HSG procedure, and a number of theories are proposed as a reason (24). Tubal flushing during HSG may increase the chance of pregnancy (25). Depending on the contrast type used, endometrial receptivity and implantation rate may increase (26). Sperm phagocytosis can be prevented due to the im-

munological response in the peritoneal cavity, and tubal ciliary activity may also increase (27, 28). In our study, 4 spontaneous pregnancies were detected in the warm group, but no pregnancy occurred in the cold group during 4-month follow-up period after HSG. This suggests that warm medium may be more beneficial for pregnancy occurrence. However, this finding is a new information for the literature and it should be supported with additional studies with wider participation.

The fact that it is a randomized study on a subject that has not been studied much and that it contains new findings for the literature is the strong features of our study. In addition, the homogeneous groups and the HSG process being performed by the same person and the feature of the contrast material given are not known by the person performing the procedure, provides a more reliable comparison of the results. On the other hand, the relatively small number of participants and the infertile group with certain characteristics may create limitations in generalizing our findings for all infertile patients. In addition, the psychological state of the individuals before the procedure, for example anxiety levels, may affect the level of HSG related pain. It is a limitation that such factors are not evaluated in our study.

As a result, the use of contrast media at body temperature during HSG procedure reduces the pain associated with the procedure. It may also increase the chance of spontaneous pregnancy after the procedure. Nevertheless, additional prospective randomized trials with more participation are needed to achieve the accuracy of such beneficial results in clinical practice.

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