

The Effects of HSG Media on Fertility in Unexplained Infertility Cases

Ekrem SAPMAZ^{a,1}, Mehmet ŞİMŞEK, Bilgin GÜRATES, Selahattin KUMRU, Hüsnü ÇELİK, Aygen ÇELİK, Zeynep ÖZCAN

Fırat Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, ELAZIĞ

ABSTRACT

Objective: Investigation of the effects of liposoluble / watersoluble contrast media used in hysterosalpingography on fertility in unexplained infertility cases.

Material and Method: Sixty primary or secondary infertile cases diagnosed as unexplained infertility were retrieved from the entire infertility cases admitted between June 1998 –March 2001 and they were analyzed by randomized, prospective, single blinded method and classified as the study group (G1=n:30, Lipiodol) and the control group (G2=n:30, Urovision). Hysterosalpingography was provided two days after the end of menses. The patients who were diagnosed as unexplained infertility and with normal basal clinical and laboratory investigations for infertility have been just monitored for over three months after hysterosalpingography was done. They were suggested to return back when menstruation delay occur. If pregnancy not achieved over 3 months patients directed for ovulation induction with clomiphene citrate + intrauterine insemination. Statistically Student T test, Mann Whitney U test and X² were used for continuous, ordinal and nominal data, respectively. P value<0.05 was found significant and relative risk (%95 CI) was calculated.

Results: Rate of pregnancy was found to be 43.7% in study group whereas 10% in control group (p=0.007, X² test, RR=4, %95 CI=1.3-13). Lipiodol is more efficacious in secondary infertility cases and pregnancy rate was 55% in comparison to 5% (p=0.001, X²test, RR=11, %95 CI=1.5-77). No complication (vasovagal reaction, seizure, anaphylaxis, intravasation, embolus) was encountered during hysterosalpingography. One secondary infertile case who was excluded from the study due to the failure of bilateral tubal passage during lipiodol hysterosalpingography; therefore not considered as an unexplained case .

Conclusion: Liposoluble contrast media used in infertility cases during hysterosalpingography increase the rate of pregnancy significantly in respect to water soluble agents. This effect is much obvious particularly in secondary infertility cases. Use of liposoluble media can be proposed in unexplained cases. ©2004, Fırat Üniversitesi, Tıp Fakültesi

Key words: HSG, lipiodol, secondary infertility, unexplained infertility, urovision.

ÖZET

Açıklanamayan İnfertilite Vakalarında HSG'de Kullanılan Ajanların Fertilité Üzerine Etkileri

Amaç: Açıklanamayan infertilite vakalarında histerosalpingografide kullanılan yağda ve suda çözünür ilaçların etkisinin araştırılması.

Gereç ve Yöntem: Haziran 1998 - Mart 2001 yılları arasında primer veya sekonder infertilite tanısı almış 60 hasta tek kör, prospektif randomize olarak çalışma grubu (G1=n:30, Lipiodol) ve kontrol grubu olarak (G2=n:30, Urovision) sınıflandırıldı. Menstruasyon bitiminden iki gün sonra bütün hastalara histerosalpingografi uygulandı. İnfertilite araştırması nedeniyle yapılan bazal klinik ve labaratuvar tetkikleri normal olan infertil hastalar histerosalpingografi sonrasında 3 ay boyunca takip edildi. Menstruasyon rötarı olanlar gebelik tanısı için çağırıldı. İşlemden 3 ay sonra gebelik elde edilmeyen hastalar klomifen sitrat ile ovulasyon induksiyonu ve intrauterin inseminasyona yönlendirildi. İstatistiksel hesaplamalar Student T test, Mann Whitney U test ve X² testleri kullanılarak yapıldı. p<0.05 anlamlı olarak kabul edildi ve rölatif risk (%95 CI) hesaplandı.

Bulgular: Gebelik oranı çalışma grubunda 43.7% , kontrol grubunda ise 10% olarak bulundu (p=0.007, X² test, RR=4, %95 CI=1.3-13). Sekonder infertilite vakalarında Lipiodol daha etkili bulundu ve gebelik oranı çalışma grubunda %55 kontrol grubunda ise %5 olarak bulundu (p=0.001, X²test, RR=11, %95 CI=1.5-77). Histerosalpingografi sırasında olası herhangi bir komplikasyon (vazovagal reaksiyon, konvülsiyon, anafaksi, emboli gibi,) ile karşılaşılma. Bilateral tubal pasaj tıkanıklığı olan bir vaka açıklanamayan infertilite olmadığından çalışmadan çıkarıldı.

Sonuç: İnfertilite vakalarında yağda çözünür kontrast maddelerle yapılan histerosalpingografi sonrası gebelik oranı suda çözünür maddelerle yapılanlara göre oldukça fazla tespit edildi. Bu etki özellikle sekonder infertilite vakalarında gözükmektedir. Açıklanamayan infertilite vakalarında yağda çözünür kontrast maddeler önerilebilir. ©2004, Fırat Üniversitesi, Tıp Fakültesi

Anahtar kelimeler: HSG, lipiodol, sekonder infertilite, açıklanamayan infertilite, urovision.

Unexplained infertility is encountered approximately 20% of the couples. Clinical assessment, sperm analysis, and tubal passage on hysterosalpingography (HSG) or laparoscopy and mid-luteal blood progesterone levels are measured within physiologic ranges in these cases (1).

Hysterosalpingography is the first standard assessment

method for the fallopian tube related infertility cases (2). In 1910, Rindfleish et al delivered Bismuth solution into uterine cavity, at1925 Heuser was the first man who radiologically achieved to demonstrate the uterine cavity via oil contrast media (3,4). Oil contrast media have been used for HSG over 40-50 years; however due to the development of many complications (pulmonary embolus, cerebral embolus, granuloma formation)

^a Yazışma Adresi: Dr. Ekrem Sapmaz, Fırat Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, 23119 ELAZIĞ

Tel: 0 424 237 00 00 / 3098

Fax: 0 424 237 30 98

e-mail: ekremlangaza@hotmail.com

(5,6) by time aqueous contrast media choiced (7).

Liposoluble and water soluble contrast medias have both advantages and disadvantages. With water soluble media uterus, rugae of ampulla and fallopian tubes visualization can be better, whereas liposoluble medias cause lesser pain, vaginal bleeding, infection and higher rates of pregnancy (8-11). However effects on pregnancy ratio were not obtained by the other authors. (12,13).

Our aim for this study is to investigate the effects of liposoluble and water soluble contrast media used during HSG on unexplained infertility cases.

MATERIALS AND METHODS

Unexplained infertility cases selected from the patients admitted to Firat University, Obstetrics and Gynecology Department between the dates of June 1998- March 2001. They were included in the prospective, randomized (randomization was made using random numbers table) single blinded study program. All cases received Doxycycline 2x100 mg/po and paracetamol 3x1/po at the end of their menstrual cycles and were instructed to continue the medication for 5 more days after HSG.

Lipiodol® ampule applied to the study group (G1=n=30) and Urovizyon® ampule used for control group (G2=n=30). HSGs were done 2 days after the end of menses.

The drugs and the related laboratories are listed as follows: Lipiodol® amp (Guerbet lab, Aulnay-sous-bois, France), Ürovizyon® amp (Schering AG, Alman İlaç, Kartal, Türkiye), Diazem® amp (Deva, İstanbul, Türkiye), Adrenalin® amp (Galen İlaç, İstanbul, Türkiye), Dekort® amp (Deva, İstanbul, Türkiye), Systral® amp (İE Ulugay, İstanbul, Türkiye), Atropin® amp (Galen İlaç, İstanbul, Türkiye). Age (<30years), infertility interval (<3years), height, weight, gravida, parity, abortus, and curettage were noted for each patient. Unexplained infertility was diagnosed after no cause obtained full searching for infertility. For example galactorrhoea, obesity and hirsutism evaluated for anovulation and dysmenorrhoea or premenstrual syndrome also assessed. Hormonal parameters FSH, TSH, Ca-125 and PRL levels at 3-5th cycle days and progesteron level at 21st cycle day obtained. patients with normal results, normal pelvic examination with endovaginal ultrasound and normal spermogram values were included into the study (1). Patients monitered for three months after hysterosalpyngography was done. They were suggested to return back when menstruation delay occur. If pregnancy not achieved over 3 months patients directed for ovulation induction with clomiphene citrate + intrauterine insemination (1). Student T test for continuous data, Mann Whitney U test for ordinal data, χ^2 test for nominal data was used and $p<0.05$ was accepted as statically significant. Relative risk (95% CI) was calculated. SPSS 9.0 software program was used in this study.

RESULTS

Table 2. Detailed documentation of the study and the control groups. Values are represented as no of cases / no of pregnant patients / fertility rate (%) respectively.

Parameter	G1	G2	P value	RR (95 % CI)
Primary infertile	10 / 2 / (20%)	10 / 2 / (20%)	1	1 (0.1-5)
Secondary infertile	20 / 11 / (55%)	20 / 1 / (5%)	0.001*	11 (1.5-77)
Total	30 / 13 / (43.7%)	30 / 3 / (10%)	0.007*	4 (1.3-13)

*= $p<0.05$, χ^2 test and RR= Relative risk.

Sociodemographic features of the patients were similar as demonstrated in Table 1.

Basal clinical and laboratory infertility examinations found normal. Number of infertility was significantly high in the study group as the rates were found to be 43.7% (13 cases), and 10% in the control group (3 cases) ($p=0.007$, Fisher exact test, RR=4, 95% CI 1.3-13). In other words, the risk/advantage rate of fertility in the patients undergoing HSG with lipiodol was 4-fold. No statistical difference was noted in primary infertile group in intergroup comparisons. Of note, lipiodol was particularly efficient in the secondary infertile group. Eleven cases of fertility among the secondary infertile patients were obtained in the study group (55%) whereas one fertility (5%) was encountered in the control group, ($p=0.001$, Fisher exact test, RR=11, 95%CI=1.5-77), which were demonstrated on Figure 1. Detailed documentation was shown in Table 2.

Table 1. Socio-demographic data of the cases. Values are represented as mean \pm SD.

Parameter	G1 (n=30)	G2 (n=30)	P value
Age (year)	28.7 \pm 2.2	28.5 \pm 2.3	Ns
Infertility interval (mo)	19.5 \pm 2.2	19.5 \pm 1.9	Ns
Height (cm)	160 \pm 3	160 \pm 2.4	Ns
Weight (kg)	63.3 \pm 2.8	63.4 \pm 2.4	Ns
Gravida (no)	1 \pm 0.9	1 \pm 1	Ns
Parity (no)	1 \pm 0.9	0.9 \pm 0.8	Ns
Survived (no)	0.9 \pm 0.7	0.8 \pm 0.8	Ns

Ns= $p>0.05$, Student t test or Mann Whitney U test.

*= $p<0.05$, Fisher exact test.

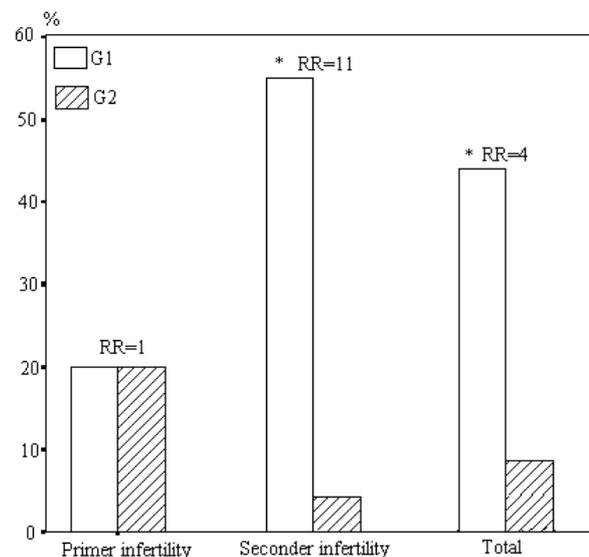


Figure 1. Fertility rates (%) in Groups 1 and 2 are represented by bar graphics with their own RR's. Liposoluble contrast media used in infertility cases during hysterosalpyngography increase the rate of pregnancy significantly in respect to water soluble agents. This effect is much obvious particularly in secondary infertility cases ($p<0.05$, χ^2 test, RR=11, 95% CI:1.5-77).



Figure 2. No bilateral passage is noted. Tubo-cornual spasm or bilateral tubal obstruction are in the differential diagnosis.



Figure 3. HSG with Lipiodol.

Interestingly, one patient who was excluded from the study due to the bilateral tubal obstruction diagnosis after HSG with Lipiodol, however patient return for menses delay 1 month later (Figure 2). Pregnancy diagnosed by β hCG and EVUSG. The case underwent cesarian section for macrosomy a male baby of 4900 g born. Patients investigated with Lipiodol had lesser pain and vaginal bleeding however quality of visualization were better with Urovizyon (Fig 3,4). Control film taken 24 hours later the HSG and can be useful for intraabdominal adhesions when liposoluble media used (Fig. 5).

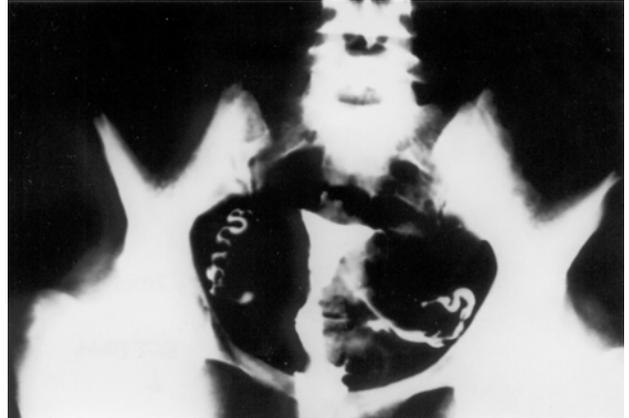


Figure 4. HSG with Urovizyon provides better visualization.

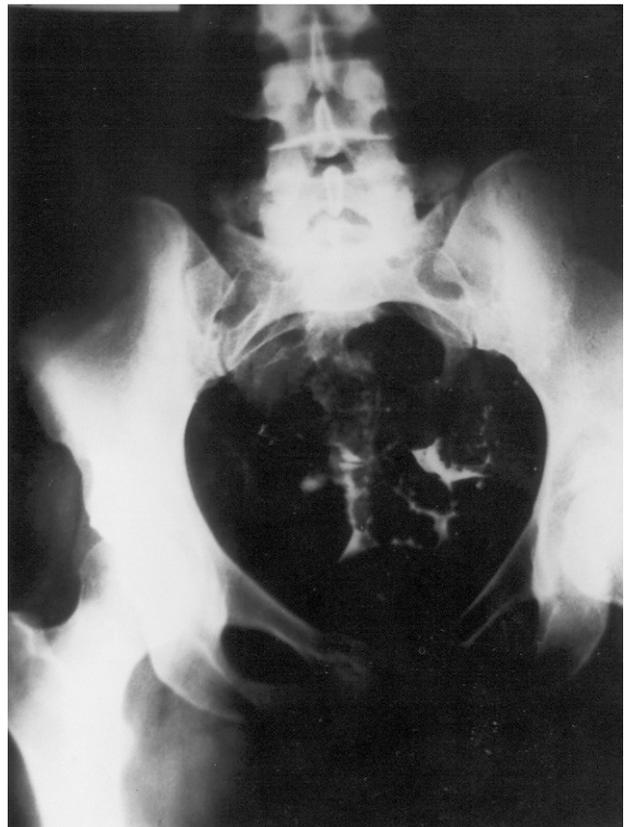


Figure 5. Control X-Ray 24 hours after Lipiodol administration.

One case with the renal colic underwent plain abdominal x-ray and radioopaque medium still visualised in Douglas Pouch 7 days after Lipiodol-HSG investigation (Fig 6). No complication was developed in our cases during HSG procedure (vasovagal reaction, convulsion, anaphylaxis, intravasation, embolus).

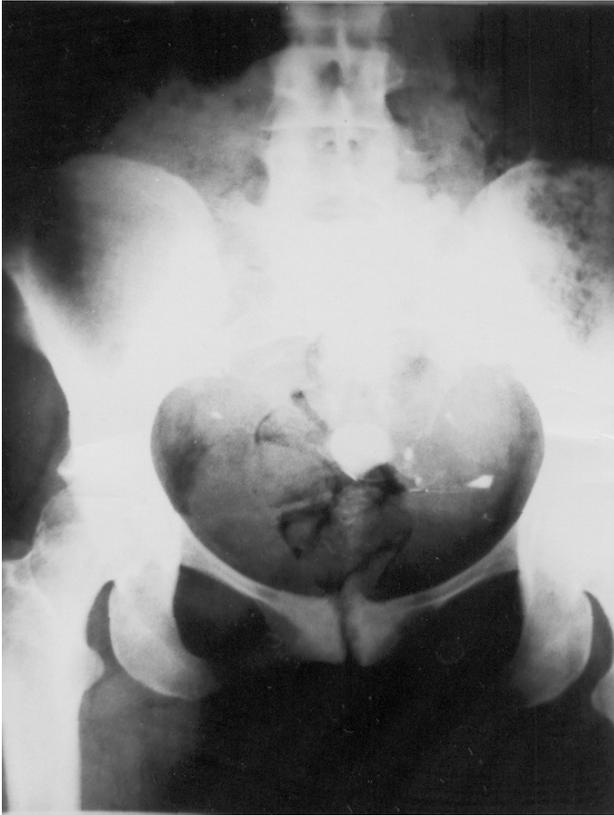


Figure 6. Direct urinary system graphy taken seven days after Lipiodol administration it is still visualised.

DISCUSSION

HSG is one of the basic tool for infertility diagnosis and was performed in all of our cases. Fertility rates were found to be significantly higher particularly at secondary infertility cases whom liposoluble contrast media were used. Our findings were consistent with the literature (8-11). Since removal of speculum is needed in order to evaluate the dimensions of cervix at the time of x-ray exposure, we preferred Collins speculum which provides enough information about the cervix measurements (length, width). Cervical insufficiency, constriction and tuberculosis that is still important in developing countries, are the situations in which length of cervix should be known. In our cases right after the end of menses, Doxycycline 2x100 mg/day was administered before HSG and used for 5 days (14). No infection was noted. In a standard HSG set, parasympatholytic, anticonvulsant, antihistaminic drugs are mandatory. Because all interventions via the cervical canal (D/C, HSG, RIA implantation etc) might lead to life-threatening complications as vasovagal reflex, or convulsion (15). Because the highest conception rate is observed within the first four months after HSG procedure so we prefer to wait for 3 months after HSG and before any ovulation induction and insemination (16). Despite the use of antispasmodic agent, it was of note that one case in whom bilateral tubal passage was absent and therefore excluded from the study, presented with pregnancy one month later; no corresponding publication was available in the literature. Rasmussen et al (11) found out the most unsuccessful cases as being the bilateral occlusion cases, as opposed to the single tubal disease cases in which the fertility rates were similar. We had no complication before and after HSG procedure. Particularly the emboli result from liposoluble contrast media

may be life-threatening. So, careful evaluations must be done for diabetes mellitus, hydrosalpinx, intrauterine adhesion or endometrial damage (17). During HSG with Lipiodol, the initial dose should be administered and monitored under fluoroscopy, if intravasation, hydrosalpinx, and Asherman

Syndrome suspected procedure should be stopped in order to prevent the emboli risk. Furthermore De Cherney et al (9) reported that fertility was accounted 30% of the primary and 56% of the secondary infertile cases, with a total of 40% who underwent HSG investigation with liposoluble agents whereas these ratios were noted 5%, 0%, and 2.6% with water soluble agents. Schawabe et al (8) found 78% fertility in Lipiodol administered cases and 10% in Urovizyon group these findings were consistent with ours. Watson et al declared in their meta analysis that in randomized clinical studies, particularly with unexplained infertilities, liposoluble contrast agents increased the fertility rates as obtained in our study (18). Many speculations have taken place about the causative factors responsible of the increase in fertility. The concentration of macrophages and lymphocytes in peritoneal fluid have found to be increased in unexplained infertility and endometriosis cases (19,20). Boyer et al (21) was the first who claimed that peritoneal macrophages were inhibited in vitro by use of ethiodol. Johnson et al (22) found 1/100 sinographine ineffective on inhibiting the fagocytosis function of macrophages as opposed to ethiodol at the same doses. The decrease in the number and function of peritoneal macrophages/lymphocytes decreases the concentration of reproductive toxic cytokines in peritoneal environment, which in turn contributes to the favorable circumstances for conception and fertility (23). Mechanical effects are accounted as removal of the mucous plaques (11) and adhesions (11,23), promoting the tubal ciliary activity (11,23), and anti infectious effect (11). On the other hand, Alper et al (12) found similar effects of oil and aqueous agents on fertility. However it is of note that he performed this investigation over the entire infertile cases. Referring to Schwabe et al's study (8), similar pregnancy rates were encountered in the rest of infertility cases sparing the unexplained group. The similar results were also valid in the De Cherney et al's study (9) but the lipiodol, which was also efficacious in the male factors. Spring et al (13) also found similar rates for male factors. We believe that De Cherney et al's report was more reliable hypothetically. Because liposoluble media decrease the amount of oxygen radicals, macrophages and lymphocytes in peritoneal fluid which also decrease sperm fagocytosis and contribute to a better environment for conception. Liposoluble media stay in place much longer in the obstructed fallopian tubes or peritoneal cavity (24). In our one case Lipiodol visualised seven days after HSG in Douglas poche. All of our findings were consistent with the literature. Spring et al (13) reported no differences between the effects of liposoluble and water soluble media on fertility. This is not like our results we think that this difference resulted from study group that is composed of all infertility types. We study only the unexplained infertility cases.

CONCLUSION

The use of liposoluble contrast media in HSG in unexplained cases, increases the rate of fertility much more than the water soluble agents do. The use the liposoluble media can be promoted in unexplained infertility cases during HSG procedure.

REFERENCES

1. Ho PC. Unexplained infertility. *Obstet Gyn Comm*1999; 6: 19-25.
2. Siegler AM.. Hysterosalpingography. *Fertil Steril* 1983; 40: 139-158.
3. Rindfleisch W. Darstellung des cavum uteri. *Klin Wochenschr* 1910; 47:780.
4. Heuser C. Lipiodol in the diagnosis of pregnancy. *Lancet* 1925; 2: 1111-1112.
5. Nielsen PH. Injuries caused by hysterosalpingography. *Acta Obstet Gynecol Scand* 1946; 26: 565-597.
6. Faris AM, Mc Murray A. Uterosolpingography: reports of a fatality. *Texas Med* 1947; 45: 592-597.
7. Nunley WC Jr, Bateman BG, Kitchin JD 3rd, Pope TL Jr. Intravasation during hysterosalpingography using oil-base contrast medium--a second look. *Obstet Gynecol* 1987; 70: 309-312.
8. Schwabe MG, Shapiro SS, Haning RV Jr. Hysterosalpingography with oil contrast medium enhances fertility in patients with infertility of unknown etiology. *Fertil Steril*. 1983; 40: 604-606.
9. DeCherney AH, Kort H, Barney JB, DeVore GR. Increased pregnancy rate with oil-soluble hysterosalpingography dye. *Fertil Steril* 1980; 33: 407-410.
10. Lindequist S, Justesen P, Larsen C, Rasmussen F. Diagnostic quality and complications of hysterosalpingography: oil- versus water-soluble contrast media--a randomized prospective study. *Radiology* 1991; 179: 69-74.
11. Rasmussen F, Lindequist S, Larsen C, Justesen P. Therapeutic effect of hysterosalpingography: oil- versus water-soluble contrast media--a randomized prospective study. *Radiology* 1991; 179: 75-78.
12. Alper MM, Garner PR, Spence JE, Quarrington AM. Pregnancy rates after hysterosalpingography with oil- and water-soluble contrast media. *Obstet Gynecol* 1986;68: 6-9.
13. Spring DB, Barkan HE, Pruyn SC. Potential therapeutic effects of contrast materials in hysterosalpingography: a prospective randomized clinical trial. Kaiser Permanente Infertility Work Group. *Radiology* 2000; 214: 53-57.
14. Pittaway DE, Winfield AC, Maxson W, Daniell J, Herbert C, Wentz AC. Prevention of acute pelvic inflammatory disease after hysterosalpingography: efficacy of doxycycline prophylaxis. *Am J Obstet Gynecol* 1983; 147: 623-626.
15. Stubblefield PG. First and second trimester abortion. In: Nichols DH, ed. *Gynecologic and Obstetric Surgery*. St. Louis. Mosby. 1993;1016-1030.
16. Wahby O, Sobrero AJ, Epstein JA. Hysterosalpingography in relation to pregnancy and its outcome in infertile women. *Fertil Steril* 1996; 17: 520-530.
17. Dan U, Oelsner G, Gruberg L, Ezra D, Menczer J. Cerebral embolization and coma after hysterosalpingography with oil-soluble contrast medium. *Fertil Steril* 1990; 53: 939-940.
18. Watson A, Vandekerckhove P, Lilford R, Vail A, Brosens I, Hughes E. A meta-analysis of the therapeutic role of oil soluble contrast media at hysterosalpingography: a surprising result? *Fertil Steril* 1994; 61: 470-477.
19. Haney AF, Muscato JJ, Weinberg JB. Peritoneal fluid cell populations in infertility patients. *Fertil Steril* 1981; 35:696-698.
20. Halme J, Becker S, Haskill S. Altered maturation and function of peritoneal macrophages: possible role in pathogenesis of endometriosis. *Am J Obstet Gynecol* 1987; 156: 783-789.
21. Boyer P, Territo MC, de Ziegler D, Meldrum DR. Ethiodol inhibits phagocytosis by pelvic peritoneal macrophages. *Fertil Steril* 1986; 46: 715-717.
22. Johnson JV, Olive DL. Method for the transportation of peritoneal macrophages. *Fertil Steril* 1992; 58: 1243-1244
23. Goodman SB, Rein MS, Hill JA. Hysterosalpingography contrast media and chromotubation dye inhibit peritoneal lymphocyte and macrophage function in vitro: a potential mechanism for fertility enhancement. *Fertil Steril* 1993; 59: 1022-1027.
24. Soules MR, Spadoni LR. Oil versus aqueous media for hysterosalpingography: a continuing debate based on many opinions and few facts. *Fertil Steril* 1982; 38: 1-11.

Kabul Tarihi:14.06.2004