The Effects of HSG Media on Fertility in Unexplained Infertility Cases

Ekrem SAPMAZ a, Mehmet ŞİMŞEK, Bilgin GÜRATÊŞ, Selahattin KUMRU, Hüsnu ÇELİK, Aygen ÇELİK, Zeynep ÖZCAN

Fırat Üniversitesi Tip 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, X² test, 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, Tip Fakültesi

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

ÖZET
Açıklanmayan İnflertilite Vakalarında HSG’de Kullanılan Ajanların Fertilite Üzerine Etkileri

Amaç: Açıklanmayan infertilite vakalarında histerosalpingografiyle kullanılan yağda ve suda çözünür ilacların etkisini araştırmaktı.

Gereç ve Yöntem: Haziran 1998 - Mart 2001 yılları arasında primer veya sekonder infertilitet tanısal 60 hasta tek kör, prospektif randomize olarak çalışma grubu (G1=n:30, Lipiodol) ve kontrol grubu olarak (G2=n:30, Urovision) sınıflandırıldı. Menstruasyon bitiminden ikinci gün sonrasi tutan hastalar histerosalpingografi uygulandı. Infertilitet araştırması nedeniyle yapılan başlangıç klinik ve labaratuvar testleri normal olan infertil hastalar histerosalpingografi sonrasında 3 ay boyunca takip edildi. Menstruasyon röntgeni olan gebelik tanısı için çıkarmadı. İğnelendik 3 ay sonra gebelik edilemediyse hastalar klomifen sitrat ile ovulasyon indükasyonu ve intrauterin inseminasyonu yöntemlendi. İstatistiksel hesaplama Student T test, Mann Whitney U test ve X² testleri kullanlandı. p=0.05 anlamlı olarak kabul edildiği ve rölatif risk (%95 CI) hesaplandı.

Bulgular: Gebelik oranı çalıştırma grubunda 43.7% , kontrol grubunda ise 10% olarak bulundu (p=0.007, X² test, RR=4, %95 CI=1.3-13). Sekonder infertile vakalarında Lipiodol daha etkili bulundu ve gebelik oranı çalıştırma grubunda %55 kontrol grubunda ise %5 olarak bulundu (p=0.001, X² test, RR=11, %95 CI=1.5-77). Histerosalpingografi sırasında olası herhangi bir komplikasyon (vasovagal reaksiyon, konvülsyon, anafalaksi, embolı gibi) ile karşılaşılmadı. Bilateral tubal pasaj tıkanıklığı olan bir vaka açıklanmayan infertilite olmadığını çıkmadı.


Anahtar kelimeler: HSG, lipiodol, sekonder infertilitet, açıklanmayan infertility, urovision.
Liposoluble and water soluble contrast media have both advantages and disadvantages. With water soluble media, uterus, rugae of ampulla and fallopian tubes visualization can be better, whereas liposoluble media 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®, Urovizyon® and Systral® amp (Guerbet Lab, France), Lipiodol® amp (Schering AG, Alman İlaç, Kartal, Türkiye), Dizasm® amp (Deva, Istanbul, Türkiye), Adrenalim® amp (Galen İlaç, Istanbul, Türkiye), Dekort® amp (Deva, Istanbul, Türkiye), Systral® amp (IE Ulugay, Islambul, Türkiye), Aiprocin® amp (Galen İlaç, İstanbul, Türkiye). Age (<30years), infertility interval (<3years), height, weight, gravidity, parity, abortion, and curettage were noted for each patient. Unexplained infertility was diagnosed after no cause obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation obtained full searching for infertility.

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®, Urovizyon® and Systral® amp (Guerbet Lab, France), Urovizyon® amp (Schering AG, Alman İlaç, Kartal, Türkiye), Dizasm® amp (Deva, Istanbul, Türkiye), Adrenalim® amp (Galen İlaç, Istanbul, Türkiye), Dekort® amp (Deva, Istanbul, Türkiye), Systral® amp (IE Ulugay, Islambul, Türkiye), Aiprocin® amp (Galen İlaç, İstanbul, Türkiye). Age (<30years), infertility interval (<3years), height, weight, gravidity, parity, abortion, and curettage were noted for each patient. Unexplained infertility was diagnosed after no cause obtained full searching for infertility. For example galactorrhea, obesity and hirsutism evaluated for anovulation and dysmenorrhea 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 monitored for 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 clophimine citrate + intrauterine insemination (1). Student T test for continuous data, Mann Whitney U test for ordinal data, χ² 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

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±SD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G1 (n=30)</th>
<th>G2 (n=30)</th>
<th>P value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>28.7±2.2</td>
<td>28.5±2.3</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Infertility interval (mo)</td>
<td>19.5±2.2</td>
<td>19.5±1.9</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160±3</td>
<td>160±2.4</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.3±2.8</td>
<td>63.4±2.4</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Gravidity (no)</td>
<td>1±0.9</td>
<td>1±1</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Parity (no)</td>
<td>1±0.9</td>
<td>0.9±0.8</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Survived (no)</td>
<td>0.9±0.7</td>
<td>0.8±1.0</td>
<td>Ns</td>
<td></td>
</tr>
</tbody>
</table>

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 hysterosalpingography 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, χ² test, RR=11, 95% CI:1.5-77).

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

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

*p<0.05, χ² test and RR= Relative risk.
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).

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


Kabul Tarihi: 14.06.2004