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Why should we check the tubes in IVF patients with ovarian endometriosis before embryo transfer? a retrospective study

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Abstract

Background The endometrioma accompanying hydrosalpinx can affect the success rate of in vitro fertilization (IVF). We aimed to determine the incidence of hydrosalpinx in infertile patients with endometrioma and its effects on in vitro fertilization success.

Methods In our retrospective study, we performed hysterosalpingography (HSG) on patients diagnosed with endometrioma through ultrasound evaluation. Then, we performed diagnostic laparoscopy on patients with suspected tubal pathology and/or hydrosalpinx after HSG assessment. Laparoscopic tubal occlusion was performed for patients with hydrosalpinx.

Results HSG was performed on 760 patients diagnosed with ovarian endometriosis. After the assessment of HSG images, hydrosalpinx was detected in 184 of 760 patients (24.2%) and diagnostic laparoscopy was performed. Unilateral or bilateral hydrosalpinx were detected at 65 of 184 (35.3%) patients. Laparoscopy and proximal tubal occlusion were performed in these patients. Incidence of hydrosalpinx was found to be 8.5% in IVF patients with ovarian endometrioma.

Conclusion Tubal patency screening may be considered for the patients with endometrioma before embryo transfer to prevent IVF failure due to hydrosalpinx.

Keywords IVF, Endometriosis, HSG, Endometrioma, Hydrosalpinx

Introduction

Endometriosis is an inflammatory process that occurs when endometrial tissue settles in an area other than the intrauterine cavity [1]. Endometriosis affects 10% of women of reproductive age and approximately 17–44% of women with endometriosis have endometriomas [2]. Individual immunological factors, and peritoneal clearance mechanisms has been thought to be responsible for the wide range of endometriomas in endometriosis patients [3]. Imaging techniques of endometriosis is evolving constantly. Detection of endometrioma is usually performed with transvaginal ultrasound (TVUSG)

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and magnetic resonance imaging (MRI) almost close to detection rates to the accepted gold standard— surgical visualization of the lesion with histopathological confirmation [4]. Diagnosis of ovarian endometriosis is made by its ground-glass appearance and the absence of blood-flow-containing papillary structures on transvaginal ultrasonography (USG) [5, 6]. Kanti et al. have compared the two techniques- TVUSG and MRI in a meta-analysis including 16 studies and have reported high accuracy for the diagnosis of endometriosis with the two techniques [4].

Hysterosalpingography (HSG) is a potential tool to evaluate the endometrial cavity and the tubes performed by the intracavitary injection of the contrast media under fluoroscopic guidance [7]. The fallopian tubes are accepted as patent on HSG when the peritoneal spillage is free from the distal tubal parts. Tubal factors are the cause of almost 25% of infertility, and the most severe form is hydrosalpinx [8]. Obstruction of the distal part of the tubes is defined as hydrosalpinx (swelling and enlargement of the tubes) and constitutes 10–30% of tubal diseases [9]. In IVF patients, hydrosalpinx reduces implantation and pregnancy rates by affecting the embryo and endometrium through both a mechanical washing and toxic effect [8, 9]. Capmas et al. have analyzed the effects of hydrosalpinx in the era of Assisted Reproductive Technology (ART) in a meta-analysis investigating 19 studies [10]. Their results have revealed decreased implantation rate per embryo transfer (OR of 0.41 [0.32–0.53]) as well as increased rates of ectopic pregnancy (OR = 3.48; [1.60–7.60]) and miscarriage (OR = 1.68; [1.17–2.40]). Therefore, in patients with hydrosalpinx, in order to increase the success of IVF, it is recommended to remove fallopian tube/tubes, perform tubal ligation, or hydrosalpinx aspiration. All the techniques have pros and cons in regards of surgical technique and ovarian reserve. In the same meta-analysis, no difference in ovarian response to stimulation after salpingectomy has been reported except a decrease in antimüllerian hormone compared to no surgery.

When evaluated in terms of IVF success, the IVF outcomes in patients with endometriosis-associated infertility are similar to those treated for other reasons [11]. In two different meta-analyses previously published, the live birth rates (LBR) and the clinical pregnancy rates (CPR) in patients with endometrioma were reported to be similar to those of IVF patients without endometrioma, although the mean number of retrieved oocytes and the cycle cancellation rates were reported to be negatively affected in the study subjects [11, 12]. Although the mean number of retrieved oocytes were lower and the cycle cancellation rates were higher in patients with endometrioma undergoing IVF treatment, these negative effects have not resulted in lower pregnancy success

rates probably due to relatively less affected endometrial receptivity [11, 12]. Also, patients' previous history of surgery leading to diminished ovarian reserve might also be a contributing underlying factor for the explanation of poor response.

Recently, Demirel et al. published an article demonstrating the relationship between severity of endometriosis and hydrosalpinx development and concluded that tubal endometriosis was significantly higher in patients with stage 4 endometriosis (92.9%) [13]. Both the disruption of the tubal flow due to adhesions with possible intratubal endometriosis might play role for the tendency of hydrosalpinx in endometriosis patients.

In this study, we aimed to investigate the incidence of hydrosalpinx in IVF patients with ovarian endometrioma and whether HSG before embryo transfer in this group of patients could be helpful to increase the success rate of IVF in such patients. If the presence of hydrosalpinx would be higher especially in this specific population of endometrioma patients, then the role of monitorization of the tubes would gain much importance during the initial evaluation before embryo transfer.

Methods

This retrospective study was performed at Acibadem Maslak Hospital IVF Center, in Istanbul, Türkiye, in between January 2015 and December 2021. The study protocol was approved by the Institutional Review Board and Ethics Committee of Acibadem Mehmet Ali Aydınlar University (ATADEK-2021/21–19).

The study included all IVF patients between 20 and 40 years of age, with either unilateral or bilateral endometrioma ≥ 1 cm on transvaginal USG, and who had undergone HSG before an IVF procedure in the study period. Women >40 years of age were not recruited in order to rule out a possible embryonic aneuploidy. Also, 1 cm cut-off was selected as the lowest threshold to detect the endometrioma under ultrasound. Women with previous pelvic surgery, pelvic inflammatory disease, and pelvic tuberculosis were excluded from the study. Additionally, patients who met the following criteria which may directly affect IVF success were excluded from the study. Regarding to male infertility, men with azoospermia and cryptozoospermia were excluded. When evaluated in terms of female infertility; 1- women with polycystic ovarian syndrome (PCOS), 2- diminished ovarian reserve, 3- uterine abnormalities (septate, unicornuate, bicornuate, didelphus uterus), 4- Asherman's syndrome, 5- thin endometrium and 6- recurrent IVF failure were excluded from the study.

Diagnosis of endometrioma on transvaginal USG was based on the following criteria: ovarian benign tumor with circular view, thickened enclosure, smooth external rim, and homogenous and little liquid with internal echo

[9]. Endometriomas were measured by three-dimensional configuration on USG. Even though ultrasound diagnosis of endometrioma has some limitations, no statistically significant difference in diagnostic accuracy has been shown in between USG and MRI [4]. Similarly, ultrasonographic diagnosis of endometrioma has been shown to have similar diagnostic rates compared to the gold-standard technique- the surgical technique especially for ovarian, bladder, and bowel endometriosis [14]. When these factors have been considered, USG has been selected as the diagnostic tool in this study.

HSG was performed in all patients with unilateral or bilateral endometrioma as a part of routine institutional protocol applied to all patients. Before HSG, a short anamnesis from each patient about the last menstrual period, existence of any intrauterine device, sign of pelvic infection, allergy, and suspected pregnancy was taken. A speculum was applied to the vagina, and disinfection was conducted with povidone-iodine at the lithotomy position. A 5-F flexible balloon catheter inflated with saline was inserted into the cervical canal. No routine anesthesia was applied. Non-ionic, water-soluble contrast was used because of the low risk of allergic reaction. HSG was carried out by real-time fluoroscopy, and spot x-ray views were taken during the procedure. Hydrosalpinx was identified as the fluid-filled expansion of the tube. The average dose of radiation applied to the ovaries is estimated at 2.7 mGy, with an effective dose of 1.2 mSv. At the end of the procedure, doxycycline 100 mg tablets twice a day for five days were ordered as prophylaxis. A nonsteroid anti-inflammatory pill was suggested, if necessary, for pain relief. HSG images were evaluated by the same IVF specialist. One IVF specialist (BT) evaluated all images in order to ensure consistency and to reduce bias. Findings suggestive of tubal pathology in HSG are listed below [9]:

1-Dilated fallopian tube with complete or partial contrast filling but lack of spill from the tube to pelvic or abdominal cavity.

2-Loculated contrast spill or pooling collections of spilled contrast.

Laparoscopy is the gold standard procedure to evaluate the tubal pathologies therefore, it was performed on patients with suspected hydrosalpinx in HSG [8, 9]. During the procedure, transcervical-intrauterine methylene blue was applied, and a unilateral or bilateral proximal tubal occlusion was performed to the proximal tuba on the sides where hydrosalpinx was confirmed.

Statistical analysis

A statistical analysis was conducted using SPSS software [Version 22.0; SPSS Inc., Chicago, IL, USA]. Continuous variables were expressed as mean \pm standard deviation or median [minimum–maximum]. Categorical variables were expressed as numbers and percentages [%]. The

Kolmogorov–Smirnov test was used to check the distribution of the data. Comparisons between the two groups were made using student's t-test. Adjustments for potential confounding factors were made. Categorical values were analyzed by chi-square test. $P < 0.05$ was considered statistically significant.

Results

A total of 760 IVF patients with unilateral or bilateral ovarian endometrioma ≥ 1 cm and who underwent HSG before starting IVF treatment were included. After the assessment of the HSG images, 184/760 patients (24.2%) had undergone laparoscopy due to suspicion of hydrosalpinx on HSG. All 760 patients were analyzed under three groups: Group I consisted of 119/184 (64.7%) patients in whom hydrosalpinx was suspected but had not been confirmed laparoscopically; Group II consisted of 65/184 (35.3%) patients who had been diagnosed with unilateral or bilateral hydrosalpinx during diagnostic laparoscopy and underwent proximal tubal occlusion; Group III consisted of 576/760 patients in which hydrosalpinx was not detected in HSG. There was no statistically significant difference between the three groups in terms of age, body mass index, duration of infertility, number of ovarian endometriosis and follicle stimulating hormone (FSH) levels. There was also no statistically significant difference in the frequency of unilateral or bilateral endometriomas between the groups (Table 1).

The mean number of previous IVF attempts was significantly higher in Group I, however there was no difference between Group II and Group III. When endometrioma sizes were compared, patients in Group I and II have statistically significantly larger endometriomas than patients in Group III ($p < 0.01$, $p < 0.01$). The mean anti-müllerian hormone (AMH) levels were significantly higher in Group I and Group III when compared to Group II, the highest value in Group I, and the lowest in Group II. Total amount of gonadotropin dose and the duration of use in Group II were higher than those in Group III, but it was not statistically significant.

The mean endometrial thickness on the day of human chorionic gonadotropin (hCG) administration were 10.5 ± 0.3 , 10.6 ± 0.4 and 9.4 ± 0.4 respectively and significantly greater in Group I and Group III, and the less in Group II. The number of retrieved oocytes, number of MII oocytes and estradiol level on the day of trigger were comparable among the three groups (Table 2).

In terms of hCG positivity, there was no statistically significant difference among three groups, however when compared regarding the chemical pregnancy rate, it was statistically significantly highest in Group I and lowest in Group II. Miscarriage rates were significantly higher in Group II. Ectopic pregnancies occurred exclusively in

Table 1 Patient characteristics and cycle parameters of the patients with the diagnosis of endometriosis

	Group I (n = 119)	Group II (n = 65)	Group III (n = 576)	p
Age (years)	35.3 ± 5.2	36.3 ± 5.5	34.7 ± 6.0	ns
Partner's age (years)	36.9 ± 5.6	38.2 ± 6.9	37.6 ± 5.9	ns
BMI (kg/m ²)	25.2 ± 4.9	25.9 ± 5.6	24.9 ± 4.6	ns
Infertility duration (months)	66.5 ± 56.6	53.7 ± 36.4	52.8 ± 54.3	ns
Number of previous IVF attempts (n)	2.11 ± 2.4	1.9 ± 0.7	1.2 ± 1.7	b
Gravida	0.7 ± 1.0	0.7 ± 1.1	0.7 ± 1.2	ns
Endometrioma size (mm)	25.3 ± 12.8	23.6 ± 14.1	19.4 ± 9.5	b,c
Number of endometriomas	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.7	ns
Endometrioma	51/119 (42.9%)	41/65 (63.1%)	214/576 (37.2%)	ns
Unilateral	68/119 (57.1%)	24/65 (36.9%)	362/576 (62.8%)	
Bilateral				
FSH (mIU/mL)	11.8 ± 13.2	14.1 ± 14.9	14.0 ± 16.3	ns
AMH (ng/mL)	2.5 ± 2.8	0.5 ± 1.0	1.5 ± 2.1	a, b,c

p < 0.05: Statistically significant. a: Statistically different in between groups 1 and 2. b: Statistically different in between groups 1 and 3. c: Statistically different in between groups 2 and 3

Table 2 IVF outcomes

	Group 1 (n = 119)	Group 2 (n = 65)	Group 3 (n = 576)	p
Total gonadotropin dose (IU)	4023 ± 1761	3812 ± 1796	3512 ± 1618	b
Gonadotropin duration(days)	8.8 ± 2.3	8.6 ± 2.4	8.3 ± 2.1	b
E2 level (pg/ml) on hCG day	1803 ± 1604	1421 ± 1643	1955 ± 1857	ns
Endometrial thickness on hCG day	10.5 ± 2.8	9.4 ± 2.6	10.6 ± 2.9	a, c
Number of retrieved oocytes	9 ± 7	9 ± 10	10.9 ± 9.8	ns
Number of mature oocytes (M2)	6.4 ± 5.5	6.4 ± 7.5	7.6 ± 6.3	ns
Number of 2 pronuclei embryos	5.5 ± 5.0	6.7 ± 6.6	6.7 ± 5.6	ns
Number of cleavage stage embryos	5.9 ± 4.8	6.7 ± 6.3	6.7 ± 5.5	ns
Number of blastocyst stage embryos	6.3 ± 4.5	5.6 ± 6.2	5.9 ± 4.1	ns

p < 0.05: Statistically significant. a: Statistically different in between groups 1 and 2. b: Statistically different in between groups 1 and 3. c: Statistically different in between groups 2 and 3. hCG: human chorionic gonadotropin. E2: Estradiol

Group I, with a total of three cases. The live birth rate was statistically significantly higher in Group III (Table 3).

Discussion

Tubal factors account for approximately 25% of female infertility [8]. Endometriosis, acute or chronic pelvic infections, tuberculosis, previous pelvic surgery may cause infertility by causing obstruction in the distal or proximal segment of the fallopian tubes. Hydrosalpinx is a condition when the distal part of the fallopian tube is blocked for various reasons and filled up with fluid and, occurs %10–30 of tubal infertility cases [8].

The preliminary screening test in tubal infertility is HSG. It is a non-invasive and cheap procedure. Sensitivity and specificity are 84% and 75% respectively [10, 15]. On the other hand, laparoscopy is the gold standard in diagnosis and treatment [16]. In a study conducted by Tan et al., the results of HSG were checked by laparoscopy and the positive predictive value of HSG in the diagnosis of tubal occlusion was found 87.2% [16]. The negative predictive value for the right and the left tubal occlusions were 92.08% and 95.44%. In our study, we found that the incidence of hydrosalpinx is 8.5% among patients with ovarian endometriosis and HSG performed before IVF treatment could detect about one third of

Table 3 Pregnancy outcomes

	Group 1 (n = 119)	Group 2 (n = 65)	Group 3 (n = 576)	p
Positive hCG test	56/119 (47.1)	32/65 (49.2)	298/576 (51.7)	ns
Biochemical pregnancy	8/56 (14.3)	3/32 (9.4)	15/298 (5.0)	b, c
Miscarriage	4/56 (7.1)	5/32 (15.6)	34/298 (11.4)	a, b
Ectopic pregnancy	3/56 (5.4)	0	0	a, b
Livebirth rate	41/119 (34.5)	24/65 (36.9)	249/576 (43.2)	b, c

p < 0.05: Statistically significant. a: Statistically different in between groups 1 and 2. b: Statistically different in between groups 1 and 3. c: Statistically different in between groups 2 and 3

laparoscopically confirmed hydrosalpinx. To our knowledge, this is the first study to examine the incidence of hydrosalpinx and the efficacy of preprocedural HSG in detecting hydrosalpinx in this patient population.

The relationship between the size of endometrioma and the incidence of hydrosalpinx has not been clearly revealed yet. We found only one study reporting that the risk of hydrosalpinx increases in relation to endometrioma size [17], however there should be a direct relationship between the severity of endometriosis and the likelihood of developing hydrosalpinx. In our study, we did not classify the patients in terms of the stages of the endometriosis. Also, we did not find any statistically significant relationship between the size and the presence (unilateral/bilateral) of endometrioma and the incidence of hydrosalpinx.

Studies have revealed a correlation between low AMH levels and endometriosis however, there is insufficient data regarding the relationship between endometrioma size and AMH value [18, 19]. In a study with Akgul et al., an inverse relationship was found between the AMH level and the presence of the endometrioma, but no relationship was observed between the size of the endometrioma and AMH level [18]. In another study, Zareii et al., observed a moderate decrease in AMH levels as endometrioma size increases, but reported that it was not statistically significant [19]. In our study, we found a statistically significant difference between three groups of patients namely, the mean AMH level is the lowest in Group II, suggesting that the presence of hydrosalpinx may be one of the factors causing low ovarian reserve and low AMH. Muzii et al. have evaluated the AMH levels in the presence of endometrioma in a systematic review and meta-analysis [20]. Their results have revealed reduced AMH levels in patients with ovarian endometriomas compared to patients with healthy ovaries and with patients with other benign ovarian cysts.

In literature, many articles support that the presence of hydrosalpinx decreases the rate of pregnancy in patients receiving IVF treatment [21]. It has been suggested that the fluid leakage into the endometrial cavity affects implantation by modifying the expression of Homeobox A10 (HOXA10) gene. This gene regulates embryonic development and implantation [22]. Additionally, hydrosalpinx may have toxic effect directly on sperm and embryo as well on the endometrium altering the endometrial receptivity [22]. In our study, endometrial thickness in Group II was statistically significantly lower than the other groups. We hypothesize that this could be associated with the presence of hydrosalpinx. We further speculate that this might be related to the washing effect of hydrosalpinx on the endometrium. Infective or inflammatory fluid collection in the tubes might pass through the isthmus part of the tubes towards the endometrial

cavity and might result in a change in the receptive endometrium. Another factor might be the low E2 levels in Group II, although the difference was not statistically significant.

Laparoscopic proximal tubal occlusion before embryo transfer significantly increases the pregnancy rates [23, 24]. Strandell et al. conducted a clinical trial and reported that clinical pregnancy rate was 36.6% in salpingectomy group and 23.9% in non-salpingectomy group [23]. In our study, there is no statistical difference among three groups in terms of hCG positivity, because embryo transfer was performed after laparoscopic tubal occlusion in patients with hydrosalpinx. The biochemical pregnancy rate is the lowest in Group III, compromising patients without the diagnosis of hydrosalpinx. One of the most important factors that may play role in the physiopathology of biochemical pregnancy is hydrosalpinx [25] so it is not surprising to observe the lowest biochemical pregnancy rate in Group III. Also, the frequency of miscarriage was statistically significantly higher in Group II. In a recent meta-analysis by Yang et al., it was suggested that ovarian endometrioma had a negative effect on the number of M2 oocytes and embryos but not on embryo quality and IVF results [11]. Hamdan et al., reported that miscarriages rate, ongoing pregnancy rate and live birth rate were similar between patients with and without endometrioma [12]. The higher miscarriage rates observed in Group II cannot be explained by hydrosalpinx alone. Miscarriages may have resulted as a consequence of other factors, such as embryo euploidy.

There are certain limitations on this study. First, the sample size was limited. Additionally, we were not able to exclude other possible causes of hydrosalpinx, such as previous infection, together with endometrioma. Diagnosis of endometrioma with USG may also be a limiting factor, as it may cause difficulty in differential diagnosis with ovarian hemorrhagic cysts. Lack of endometriosis staging is another limitation of the study, since the difference in AMH levels might also raise the suspicion that it might be due to the different stages of endometriosis.

Conclusion

Although laparoscopy is the gold standard for diagnosing hydrosalpinx, it is not feasible to perform this procedure on all patients; instead, HSG screening may be considered before embryo transfer for each patient with endometrioma to prevent IVF failures caused by hydrosalpinx, which might be a frequent condition in endometrioma patients.

Acknowledgements

None.

Author contributions

C.Y., A.Y., O.K., I.O.A., N.P., Y.C., B.T. designed the study; C.Y., A.Y., O.K., I.O.A., N.P., analysed the data, C.Y., A.Y., O.K., Y.C. wrote the manuscript; Y.C., B.T. edited and revised the manuscript.

Funding

None.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations**Ethics approval**

The study protocol was approved by the Institutional Review Board and Ethics Committee of Acibadem Mehmet Ali Aydinlar University (ATADEK-2021/21 – 19) and adhered the latest legislations of Helsinki Declaration.

Consent to participate

Consent to participate was deemed unnecessary by the Institutional Review Board and Ethics Committee of Acibadem Mehmet Ali Aydinlar University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

Received: 11 February 2025 / Accepted: 18 March 2025

Published online: 08 April 2025

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