Original Article

Effect of Recurrence of Hydrosalpinx after Tubal Ligation on the Outcome of *In vitro* Fertilization Treatment: A Retrospective Cohort Study

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Abstract

Objective: The objective of the study was to evaluate the effects of recurrent hydrosalpinx after proximal tubal ligation and distal salpingostomy on the outcomes of *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment.

Materials and Methods: Seven hundred and twenty-six patients with hydrosalpinx undergoing laparoscopic surgery before IVF were enrolled in the study. Five hundred and sixty-two patients treated with proximal tubal ligation and distal salpingostomy were included in Group A. One hundred and sixty-four cases managed with salpingectomy were grouped into Group B. Group A were further divided into two subgroups. One hundred and forty-six patients in Group A1 had a recurrence of hydrosalpinx. Four hundred and sixteen patients in Group A2 had no repetition of hydrosalpinx. We compared the pregnancy outcomes of their subsequent fresh embryo transfer cycles among the three groups.

Results: There were no significant differences among the three groups in terms of age, body mass index (23.56 ± 3.27 vs. 23.13 ± 3.42 vs. 23.63 ± 3.73, $P = 0.195$), basal hormone level (7.03 ± 1.75 vs. 7.08 ± 2.26 vs. 7.44 ± 2.93, $P = 0.195$), antral follicle count (12.25 ± 5.92 vs. 12.63 ± 5.71 vs. 11.70 ± 4.98, $P = 0.188$), duration of gonadotropin (Gn) (11.19 ± 2.1 vs. 10.93 ± 1.84 vs. 10.79 ± 2.03, $P = 0.182$), consumption of Gn (2136.73 ± 855.65 vs. 1997.15 ± 724.72 vs. 2069.05±765.12 , $P = 0.14$), endometrial thickness (1.1 ± 0.27 vs. 1.1 ± 0.24 vs. 1.1 ± 0.17, $P = 0.352$), base follicle-stimulating hormone (6.21 ± 3.43 vs. 6.52 ± 3.20 vs. 5.89 ± 3.10, $P = 0.1$), number of embryos transferred (1.87 ± 0.36 vs. 1.83 ± 0.42 vs. 1.88 ± 0.37, $P = 0.224$), and number of high-grade embryos (3.77 ± 2.42 vs. 4.01 ± 2.72 vs. 4.17 ± 2.74, $P = 0.41$). No differences were detected in clinical pregnancy rate (50% vs. 54.8% vs. 50%, $P = 0.439$), the live birth rate (86.3% vs. 82.0% vs. 87.8%, $P = 0.398$), fertilization rate (64.1% vs. 64.4% vs. 64.7%, $P = 0.928$), and biochemical pregnancy rate (4% vs. 4.5% vs. 7%, $P = 0.332$) among the three groups.

Conclusion: The recurrence of hydrosalpinx after tubal ligation does not affect the outcomes of IVF/ICSI. It is not necessary to worry about the effect of recurrent hydrosalpinx on pregnancy outcomes of IVF/ICSI that may due to the spread of inflammation through lymphatic circulation or blood circulation.

Keywords: Hydrosalpinx, *in vitro* fertilization, infertility, pregnancy outcome, tubal ligation

Introduction

In vitro fertilization and embryo transfer (IVF/ET) was first used to treat an infertile woman with tubal infertility.[1]

Article History:
Submitted: 2 May 2019
Revised: 11 February 2020
Accepted: 16 March 2020
Published: 1 August 2020

Access this article online

Quick Response Code:

Website: www.e-gmit.com

DOI: 10.4103/GMIT.GMIT_27_19

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How to cite this article: Liu H, Yao Z, Zhang R, Wu S, Lv S, Yan L. Effect of recurrence of hydrosalpinx after tubal ligation on the outcome of *in vitro* fertilization treatment: A retrospective cohort study. Gynecol Minim Invasive Ther 2020;9:118-22.

Hydrosalpinx has a significantly adverse effect on IVF-ET pregnancy outcomes,[2-4] which could be reduced by half.[5] The main mechanism is that hydrosalpinx may flow back into the uterine cavity, which has embryotoxicity and affect endometrial receptivity.[6-8] Salpingectomy, tubal ligation, and proximal tubal occlusion are effective treatments to prevent or reduce reflux of inflammatory secretion into the endometrium.[9-12] However, the recurrence of hydrosalpinx could frequently occur after distal salpingostomy.

Whether the recurrence of hydrosalpinx after tubal ligation could still cause a detrimental effect on the IVF outcomes via the inflammation spread through lymphatic circulation or blood circulation. Till now, there is no literature on this issue. For women with recurrent hydrosalpinx after surgery during IVF, we informed them that previous studies have shown that proximal tubal occlusion and salpingectomy had a similar effect on subsequent IVF outcomes,[12] but we do not know the recurrence of hydrosalpinx whether have an influence on IVF outcomes or not. In this study, we will discuss the effects of recurrence of hydrosalpinx after tubal ligation on the pregnancy outcomes of IVF-ET.

Materials and Methods

We conducted a retrospective cohort study of patients with hydrosalpinx who initiated treatment with proximal tubal ligation and distal salpingostomy (Group A) or salpingectomy (Group B) between January 1, 2012, and December 31, 2016. The protocol of this study was approved by the Institutional Review Board, number 2017-5. We have obtained consent from the patients to use their data. Patients in Group A with a recurrence of hydrosalpinx were classified into two subgroups: Group A1 and Group A2. Group A1 had recurrence of hydrosalpinx diagnosed by transvaginal ultrasound, while Group A2 had no repetition of hydrosalpinx.

The inclusion criteria included (1) women aged ≥21 and ≤43 years and (2) all women were undergoing their first fresh ET cycle of IVF or intracytoplasmic sperm injection (ICSI). The exclusion criteria include (1) women who had ovarian tumor history and (2) the chromosomal examination was abnormal.

Hydrosalpinx could be diagnosed using hysterosalpingography or ultrasonography as the fluid-filled elongated and distended tubes. The diagnosis was further confirmed by laparoscopy before IVF treatment. Definition of postoperative recurrence of hydrosalpinx was that the new appearance of sausages or beaded sample liquid dark spacer on the adnexal area but outside the ovaries according to the vaginal ultrasound imaging during the controlled ovarian hyperstimulation (COH) program.[13]

COH and oocyte retrieval were performed according to the routine protocols of our hospital.[14] Outcomes measured included the fertilization rate, live birth rate, biochemical pregnancy rate, clinical pregnancy rate, abortion rate, and ectopic pregnancy rate (calculated as defined in our previous articles).[15]

Data were expressed as the means ± standard deviation. The normally distributed data were expressed as mean ± standard deviation. The statistical test to analyze the reproductive outcomes was done using Chi-square analysis.SPSS version 22.0 software (SPSS Inc., Chicago, IL) for windows was used for statistical analysis.. $P < 0.05$ was considered statistically significant. CRESS version 1.3 (Huitong medical, nanjing, 2016,China) was used for sample size calculation, and the sample size was calculated setting the Type I and Type II errors at 0.05 and 0.20, respectively. The pregnancy rate in hydrosalpinx patients was usually reduced by half. Based on the literature and combined with the actual situation of our hospital, we supposed the clinical pregnancy rate of patients without hydrosalpinx was 46%.[5] On these bases, we estimated that the number of patients to be enrolled was about 74 women per group.

Results

Seven hundred and twenty-six cases were reviewed. There were 562 patients with tubal ligation in Group A, who were further classified into two subgroups. One forty six patients with recurrence of hydrosalpinx were divided into Group A1 and 416 patients with no recurrence of hydrosalpinx were divided into Group A2. One hundred and sixty-four cases with salpingectomy were included in Group B [Figure 1].

Baseline characteristics of the three groups are shown in Table 1. No significant differences were detected in age (31.82 ± 4.89 vs. 31.90 ± 4.77 vs. 31.85 ± 4.56, $P = 0.985$), body mass index (23.56 ± 3.27 vs. 23.13 ± 3.42 vs. 23.63 ± 3.73, $P = 0.195$), and basal follicle-stimulating hormone (FSH) (7.03 ± 1.75 vs. 7.08 ± 2.26 vs. 7.44 ± 2.93, $P = 0.195$) among the three groups. The number of basal follicular both on the left ovarian and right ovarian and antral follicle count (AFC) in Group A showed a trend toward higher than Group B, but the differences were not statistically significant (12.25 ± 5.92 vs. 12.63 ± 5.71 vs. 11.70 ± 4.98, $P = 0.188$).

The outcomes of the ovarian stimulation and IVF/ICSI outcomes are shown in Table 2. There were no significant differences in any of the listed ovarian response parameters and embryological parameters among the three groups.

Table 3 presents the main outcomes of the IVF/ICSI treatment cycles undertaken by the three groups. There were no

Table 1: Comparison of *in vitro* fertilization/intracytoplasmic sperm injection - embryo transfer general clinical data for three groups of patients

Group	Group A1	Group A2	Group B	*F*	*P*
Age (years)	31.82±4.89	31.90±4.77	31.85±4.56	0.015	0.985
BMI (kg/m^2)	23.56±3.27	23.13±3.42	23.63±3.73	1.638	0.195
Basal FSH (mIU/ml)	7.03±1.75	7.08±2.26	7.44±2.93	1.639	0.195
Number of basal follicular on left ovarian (*n*)	6.03±3.28	6.12±3.43	5.80±3.00	0.518	0.596
Number of basal follicular on right ovarian (*n*)	6.21±3.43	6.52±3.20	5.89±3.10	2.313	0.1
AFC (*n*)	12.25±5.92	12.63±5.71	11.70±4.98	1.675	0.188

Data given as mean±SD. AFC: Antral follicle count, SD: Standard deviation, BMI: Body mass index, FSH: Follicle-stimulating hormone

Table 2: Comparison of controlled ovarian hyperstimulation characteristics among three groups

Group	Group A1	Group A2	Group B	*F*	*P*
The total injection days of Gn (days)	11.19±2.1	10.93±1.84	10.79±2.03	1.711	0.182
The total injection amount of Gn (IU)	2136.73±855.65	1997.15±724.72	2069.05±765.12	1.953	0.143
Endometrial thickness on the day of HCG administration (cm)	1.1±0.27	1.1±0.24	1.1±0.17	1.046	0.352
Retrieved oocytes (*n*)	10.52±5.55	10.62±4.91	10.54±4.67	0.027	0.973
Number of embryos transferred (*n*)	1.87±0.36	1.83±0.42	1.88±0.37	1.501	0.224
Number of follicles ≥14 cm on the day of HCG administration (*n*)	8.75±3.85	9.44±4.40	9.20±4.40	1.3860	0.251
Number of high grade embryos (*n*)	3.77±2.42	4.01±2.72	4.17±2.74	0.892	0.41

Data given as mean±SD. SD: Standard deviation, Gn: Gonadotropin, HCG: Human chorionic Gn

Table 3: Comparison of pregnancy outcomes among three groups

Group	Group A1, *n/N* (%)	Group A2, *n/N* (%)	Group B, *n/N* (%)	*P*
Clinical pregnancy rate	73/146 (50)	228/416 (54.8)	82/164 (50)	0.439
Biochemical pregnancy rate	6/146 (4)	19/416 (4.5)	12/164 (7)	0.332
Abortion rate	7/73 (9.5)	33/228 (14.5)	8/82 (9.7)	0.380
Ectopic pregnancy rate	4/73 (5.4)	7/228 (3.07)	2/82 (3.6)	0.530
Live birth rate	63/73 (86.3)	187/228 (82.0)	72/82 (87.8)	0.398
Fertilization rate	984/1536 (64.1)	2846/4416 (64.4)	1153/1782 (64.7)	0.928

significant differences in clinical pregnancy rate (50% vs. 54.8% vs. 50%, $P = 0.439$), live birth rate (86.3% vs. 82.0% vs. 87.8%, $P = 0.398$), abortion rate (9.5% vs. 14.5% vs. 9.7%, $P = 0.380$), fertilization rate (64.1% vs. 64.4% vs. 64.7%, $P = 0.928$), ectopic pregnancy rate (5.4% vs. 3.07% vs. 3.6%, $P = 0.530$), and biochemical pregnancy rate (4% vs. 4.5% vs. 7%, $P = 0.332$) among the three groups.

Discussion

The aim of the tubal occlusion combined with the opening of the tube distal is to prevent reflux of inflammatory secretion into the uterine cavity, which is believed to be toxic to the embryo and prevent its implantation. Tubal occlusion and opening of the tube distal end can prevent or reduce reflux of inflammatory secretion into the uterine cavity. This study suggests that after proximal tubal ligation and distal salpingostomy, the recurrence of hydrosalpinx after tubal ligation had no adverse effect on the main outcomes of following fresh ET during IVF treatment.

It was reported that proximal tubal ligation and salpingectomy have a similar benefit to the clinical pregnancy rate of IVF-ET.[16] The bilateral proximal tubal occlusion may be preferable in patients with severe pelvic adhesions and easy access to the proximal Fallopian tube.[17] Under the condition of serious complications, bilateral proximal tubal ligation represents a less invasive approach that requires less surgical dissection and operating time while still eliminating retrograde flow of hydrosalpingeal fluid into the endometrial cavity. It also solves the central problem of Fallopian tube water from hydrosalpinx reflux to the uterine cavity. Another advantage is that it does not affect the ovarian blood supply. However, tubal ligation does not entirely remove the lesion, which may lead to the persistence of inflammation, and pelvic pain may occur.

The salpingectomy removes the chronic infection entirely and restoring the anatomical location of the pelvic cavity, making the oocyte retrieval process more safely. However, if the patients had severe pelvic adhesion, the abdominal and pelvic viscera may easily be damaged when performing a salpingectomy. Furthermore, salpingectomy may reduce ovarian function. Gelbaya *et al*. demonstrated

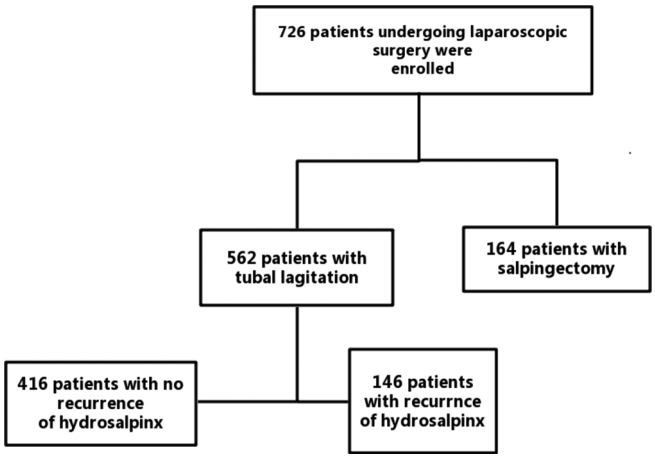

Figure 1: Study flowcharts. Accrual of the study patients. Women were enrolled in the study and divided into three groups

that the retrieved oocytes and basal follicular number in salpingectomy group were reduced compared with the control group.[18] In our study, the basal serum FSH level of salpingectomy group was slightly higher than the tubal ligation group, and the AFC of salpingectomy group was slightly lower than the tubal ligation group. However, these differences were not statistically significant. These slight differences may be due to the affect of ovarian blood supply by salpingectomy. No significant differences were observed in clinical pregnancy rate, biochemical pregnancy rate, abortion rate, live birth rate, and fertilization rate between the three groups.

The direct toxic effect of hydrosalpinx on the embryo and the deficiency receptivity of nutrition affect the development of embryos.[19,20] The regurgitation of fluid to the uterine cavity can change the endometrial receptivity and mechanical scour endometrium.[21] This mechanism may cause a detrimental effect on IVF outcomes when the hydrosalpinx relapses even after tubal ligation. Hysteroscopic tubal occlusion can effectively prevent the fluid flow back to the uterine cavity and benefit subsequent implantation in the course of assisted reproduction without significant complications,[10] although the randomized controlled trial studies have confirmed the efficacy of tubal embolization,[11] but the clinical pregnancy rate was lower than that of laparoscopic ligation group under hysteroscopy.[12] Tubal embolization has the same principle as tubal ligation and blocks hydrops reflux; theoretically, chronic inflammation factors can affect the endometrium receptivity through blood circulation or lymph circulation, increased risk of miscarriage, and ectopic pregnancy. From the results of our study, we only saw a trend toward lower clinical pregnancy rate and higher ectopic pregnancy rate in the recurrence group than the no recurrence group but with no statistical difference. Hence, even if there is a recurrence of hydrosalpinx for patients who have undergone tubal ligation, there are slight adverse effects on IVF outcome and are suspected to be negligible.

Bao reported that patients who underwent proximal tubal occlusion before IVF implantation, the clinical pregnancy and ongoing pregnancy rate significantly increased compared with those with no surgical intervention.[10] The expressions of human endometrial leukemia inhibitory factor (LIF) and integrins αvβ3 on the endometrium of the patients with hydrosalpinx were decreased.[22] However, there is no fundamental research on whether there is still an adverse effect on endometrial tolerance for the hydrosalpinx that has ligated. Further confirmation of our study might also be made by the following basic research. At the same time, no record of acute pelvic inflammatory or severe pelvic pain after tubal ligation was reported, proving that it was a safe, effective, and efficient operation method to carry out proximal tubal ligation and distal salpingostomy for the patients with hydrosalpinx before IVF treatment. Especially for patients with poor ovarian function or severe pelvic adhesion, it is a tough decision to perform salpingectomy. Tubal ligation and distal salpingostomy may be an appropriate choice. However, it requires a continuous and in-depth study to verify the long-term effects, especially the impact on the incidence of ovarian cancer.

Our study has the following strengths. First, the 726 patients make our study one of the largest reported sample sizes. Second, whether the recurrence of hydrosalpinx after tubal ligation could still cause a detrimental effect on IVF outcomes. Till now, there is no literature reporting on this issue. The limitations of our study are as follows. First, this is a retrospective study. The sample selection might exist bias and data were collected from one reproductive center. Second, postoperative recurrence of hydrosalpinx was diagnosed by a vaginal ultrasound scan. However, ultrasound can only indicate irregular and anechoic areas outside of the ovarian and cannot confirm with the recurrence of hydrosalpinx. Transvaginal ultrasound scanning may be helpful, and its sensitivity is up to 85%.[13] The best marker of tubal inflammatory disease was the presence of an incomplete septum of the tubal wall, but there are false-positive examples.[23]

Conclusion

Recurrence of hydrosalpinx after tubal ligation had no adverse effects on the pregnancy outcomes of IVF compared with no recurrence group and salpingectomy group. It is not necessary to worry about the effect of recurrent hydrosalpinx on pregnancy outcomes due to the possible inflammation spread through lymphatic circulation or blood circulation. For the patients with severe pelvic adhesion or decreased

ovarian function, proximal tubal occlusion and distal salpingostomy is an effective way to prevent the adverse effect of hydrosalpinges.

Financial support and sponsorship

This study was supported by the National Key Research and Development Program of China (2017YFC1001000), Medical Science and Technology Development Plans of Shandong Province (2016WS0369), and Projects of Medical and Health Technology Program in Shandong Province (201401).

Conflicts of interest

There are no conflicts of interest.

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