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[原著]Can laparoscopy be omitted for infertile women with bilateral tubal patency assessed by hysterosalpingography?

Can laparoscopy be omitted for infertile women with bilateral tubal patency assessed by hysterosalpingography?

Keiko Mekaru, Chiaki Yagi, Kozue Asato, Hitoshi Masamoto,
Kaoru Sakumoto and Yoichi Aoki

*Department of Obstetrics and Gynecology, Graduate School of Medical Science,
University of the Ryukyus, 207 Uehara Nishihara, Okinawa 903-0215, Japan*

ABSTRACT

Purpose: The aim of this retrospective study was to determine whether laparoscopy is necessary in patients with infertility showing bilateral tubal patency on hysterosalpingography (HSG). **Methods**: One hundred and eight women <40 years of age underwent 4-6 cycles of timed intercourse or intrauterine insemination (IUI) following confirmation of bilateral tubal patency on HSG. Thereafter, 84 women underwent laparoscopy and further cycles of timed intercourse or IUI (laparoscopy group). The remaining 24 women underwent in vitro fertilization-embryo transfer (IVF-ET) without laparoscopy (IVF group). **Results**: Multivariate analysis showed that infertility of ≥ 5 years duration was the only independent factor contributing to the reduced pregnancy rate in the laparoscopy group (HR, 0.64; 95% confidence interval (CI), 0.40-0.96). The cumulative live birth rates were 75.9% for the IVF group and 62.2% for the laparoscopy group (P =0.03). **Conclusions**: In women with bilateral tubal patency observed on HSG, laparoscopy may be omitted if IVF-ET is the subsequent treatment of choice, particularly in women with infertility of ≥ 5 years duration. *Ryukyu Med. J., 30(1〜4)21〜27, 2011*

Key words: Infertility, Laparoscopy, Hysterosalpingography, Bilateral tubal patency, In vitro fertilization-embryo transfer

INTRODUCTION

Laparoscopic evaluation is the definitive diagnostic technique for evaluating female patients with infertility; it is also helpful in treatments such as ablation for endometriosis or peritubal adhesiolysis[1]. Recent improvements in *in vitro* fertilization-embryo transfer (IVF-ET) have resulted in laparoscopy now being primarily used in treatment rather than diagnosis of infertility. In particular, the effectiveness of laparoscopy in the diagnosis and treatment of patients with bilateral tubal patency is unknown[2].

Mol et al. compared tubal findings and subsequent pregnancy rates following hysterosalpingography (HSG) and laparoscopic investigation, and found that in only 2.5% cases, bilateral tubal occlusion was diagnosed by laparoscopy despite bilateral tubal patency being observed on HSG[3]. Therefore, they suggested that there should be a waiting period of at least 10 months before the patient undergoes laparoscopic investigation. In addition, Lavy et al. performed laparoscopy in patients showing bilateral or unilateral tubal patency observed on HSG, and found that bilateral tubal occlusion was present in only 4.8% cases; they concluded that laparoscopy could be omitted in patients showing bilateral tubal patency observed on HSG[4]. On the other hand, laparoscopic cauterization of the lesion is considered effective in improving pregnancy rates for patients with mild endometriosis[5], and laparoscopy is considered useful in the treatment of mild cases of this disorder that are first diagnosed laparoscopically,

even after bilateral tubal patency has been observed on HSG[6-8]. Nevertheless, it is difficult to decide whether laparoscopy or IVF-ET should be chosen for patients with bilateral tubal patency who undergo 4-6 cycles of timed intercourse or intrauterine insemination (IUI).

The objective of this retrospective study was to determine whether laparoscopy is necessary in patients with bilateral tubal patency observed on HSG. This study followed the principles of the Declaration of Helsinki.

MATERIALS and METHODS

Between January 1998 and March 2008, 108 women of <40 years of age underwent 4-6 cycles of timed intercourse or IUI following confirmation of bilateral tubal patency observed on HSG. Thereafter, 84 women underwent laparoscopic evaluation and another 6-10 cycles of timed intercourse or IUI. In these instances, either clomiphene citrate or human menopausal gonadotropin was administered to induce ovulation in women with ovulatory disorders. These women did not undergo IVF-ET during the treatment period (laparoscopy group). The remaining 24 women underwent IVF-ET without laparoscopy (IVF group). Because the women in the IVF group preferred not to undergo diagnostic laparoscopy under general anesthesia, they chose to undergo immediate IVF-ET treatment. Cumulative pregnancy rate and live birth rate were compared between laparoscopy group and IVF group. Fig. 1 shows a flowchart of the treatment course in the laparoscopy and IVF groups. All the patients gave a written informed consent.

The frequency of abnormal intraperitoneal findings during laparoscopy, i.e., tubal occlusion, peritubal adhesions, endometriosis, and the rate of pregnancy following laparoscopy were also investigated. The rates of pregnancy were also compared in relation to the presence of various abnormal intraperitoneal findings. Thereafter, factors that influenced pregnancy outcomes, e.g., age, number of prior pregnancies, duration of infertility, presence or absence of ovulatory disorders, and use of IUI were investigated by univariate and multivariate analyses. The conditions for study exclusion included male infertility and tubal infertility, conditions in which IVF-ET
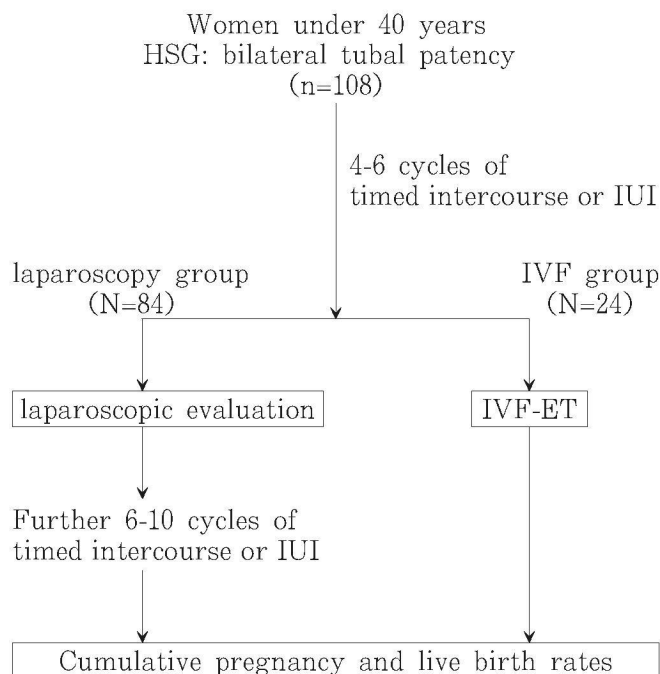

Fig. 1 **Treatment flowcharts of the laparoscopy and IVF groups.**

can be performed. Women with endometriomas observed on diagnostic imaging and suspected endometriosis on physical examination were also excluded.

Endometriosis was evaluated according to the revised American Society of Reproductive Medicine (r-ASRM) classification for endometriosis, and the lesions were cauterized as much as possible. In this classification, endometriotic implants are scored according to their site, diameter, and depth. Adhesions are scored according to their site, density, and the degree of enclosure. A total revised ASRM score (for both implants and adhesions) of 1-5, 6-15, 16-40, and >40 corresponded to stages I, II, III, and IV, respectively.

Peritubal disease was defined as the presence of adhesions, and adhesiolysis was performed upon detection of the disease. To assess tubal patency in all women, chromotubation was performed. Women with tubal occlusion detected by chromotubation underwent selective hysteroscopic tubal cannulation during the procedure for restoration of tubal patency.

In the IVF group patients, controlled ovarian stimulation was carried out using a gonadotropin-releasing hormone agonist. Buserelin acetate (Suprecur®; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) was administered intranasally at a

dosage of 900 μg daily, from the midluteal phase of the pretreatment cycle to the day of human chorionic gonadotropin (hCG) injection. A total of 150 IU of human menopausal gonadotropin (HMG Teizo; Teizo, Tokyo, Japan) was administered daily, and 10,000 IU of hCG (HCG Mochida; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) was administered when 2 ovarian follicles were observed to be $\geq$18 mm in diameter. Clomiphene citrate was not used for controlled ovarian stimulation. Transvaginal oocyte retrieval was performed 35 h after hCG administration. Either 1 or 2 embryos were transferred on day 3 or 5, following oocyte retrieval. For luteal phase support, 5,000 IU of hCG was injected on the day of oocyte retrieval and on days 3 and 7 thereafter.

For statistical analyses, Student's t-test, Mann-Whitney U-test, and x^2 test were used. Cumulative rate of pregnancy was calculated using the Kaplan-Meier method, and the log-rank test was used to test its significance. Receiver operating characteristic curves were produced according to age, gravidity, and duration of infertility. The Cox proportional hazards model was used for multivariate analysis. $P<0.05$ was considered statistically significant.

RESULTS

The mean age of the 84 women in the laparoscopy group was 34.3±3.4 years (range, 23-39 years), and the mean duration of infertility was 4.5±3.2 years (range, 1-14 years); 36 women (42.9%) had primary infertility, 24 (28.6%) had unexplained infertility, and 46 (54.8%) had ovulatory disorders. Ovulation induction was performed in 46 women, using clomiphene citrate in 29 women and human menopausal gonadotropin in 17 women. IUI was performed in 36 women, including 21 women who also underwent ovulation induction.

Following laparoscopy, treatment administered to the 84 women was as follows: the chromotubation procedure during laparoscopy revealed unilateral occlusion in 2 women (2.4%) and bilateral occlusion in another 2 (2.4%); selective hysteroscopic tubation using indigo blue dye was performed to restore tubal patency in these women. The 84 women in the laparoscopy group underwent an additional 6-10 cycles of timed

intercourse or IUI after laparoscopy. Among the women in the laparoscopy group, 39.3% (33/84) of the women conceived, with 90.9% (30/33) of them conceiving within 6 months of the procedure.

Laparoscopy revealed endometriosis in 44 women (52.4%), 32 of whom were classified, as per the r-ASRM classification, as endometriosis stage I, 6 as stage II, and 6 as stage III. Cauterization of endometrial lesions was performed in all cases. Peritubal adhesions were present in 36 women (42.9%), although the adhesions were mild in all cases. Confirmation of dense adhesions by laparoscopy is generally followed by IVF-ET instead of 6-10 additional cycles of timed intercourse or IUI. However, this was not applicable in these women, and hence, none of them underwent IVF-ET because of the mild nature of the adhesions. Both peritubal adhesions and endometriosis were observed in 21 women (25.0%), while 25 others (29.8%) showed no abnormal findings. The cumulative rate of pregnancy was 75.3% for women with endometriosis and 61.9% for those without endometriosis; the difference was not significant. The cumulative rate of pregnancy was 68.7% in women with peritubal adhesions and 63.5% in women without peritubal adhesions; there was no significant difference between the 2 groups.

To clarify the factors that may influence the fertility outcomes including age, number of prior pregnancies, duration of infertility, presence or absence of ovulatory disorders, and use of IUI were examined in the laparoscopy group (Table 1). Univariate analysis of the cumulative pregnancy rate according to age ($\geq$37 or <37 years), number of prior pregnancies (0 or $\geq$1), duration of infertility ($\geq$5 or <5 years), use of IUI, and presence or absence of ovulatory disorders showed that the only significant factor was the duration of infertility ($\geq$5 years). In addition, multivariate analysis showed that infertility lasting $\geq$5 years was the only independent factor contributing to the reduced pregnancy rate (HR, 0.64; 95% CI, 0.40-0.96; P=0.03) (Table 2).

There were no differences in patient characteristics between the laparoscopy and IVF groups except for age (Table 3). The mean number of IVF attempts was 2.3±1.3 (range, 1-4); one IVF attempt for 22 women, two for 9 women, three for 6 women, and four for 1 woman. The mean number of oocytes retrieved and subsequent embryo

Table 1 **Univariate analysis for factors that influenced the fertility outcome in the laparoscopy group**

Variable		No.of patients	Cumulative pregnancy rate	p-value
Age (years)	<37	57	74.5	0.52
	>=37	27	54.6	
Gravidity	0	36	73.5	0.46
	>=1	48	55.3	
Duration of infertility	<5 years	53	88.5	0.019
	>=5 years	31	34.4	
Ovulation dysfunction	—	38	65.2	0.68
	+	46	66.2	
Intrauterine insemination	—	41	75.4	0.23
	+	43	60.9	

Cumulative pregnancy rates were calculated according to the Kaplan-Meier method.
The log-rank test was used for univariate analysis, and receiver operating characteristic (ROC) curves were produced to confirm cutoff value.

Table 2 **Multivariate analyses for factors that influenced the fertility outcome in the laparoscopy group**

Variable		HR	95% CI	p-value
Age (years)	>=37	0.86	0.58-1.22	0.4
Gravidity	0	0.92	0.63-1.31	0.66
Duration of infertility	>=5 years	0.64	0.40-0.96	0.03
Ovulation dysfunction	+	0.84	0.59-1.21	0.36
Intrauterine insemination	+	0.94	0.64-1.34	0.72

The Cox hazard model was used for multivariate analysis.
HR: Hazard ratio, CI: confidence interval

transfers (ETs) performed were 7.6 ± 3.8 (range, 4-18) and 2.3 ± 0.96 (range, 1-3), respectively. The rate of pregnancy with ET was 39.5% (15/38). The pregnancy outcomes in the laparoscopy and IVF groups are shown in Table 4. The cumulative live birth rates were significantly higher in the IVF group (75.9%) than the laparoscopy group (62.2%) (P=0.03; Fig. 2).

DISCUSSION

The application of diagnostic laparoscopy in women with bilateral tubal patency observed on HSG remains debatable. Diagnostic laparoscopy is performed in cases with unexplained infertility, and also to search for peritubal adhesions or mild endometriosis. In a study, peritubal adhesions were found at a high rate in 33%-68% of women with normal HSG results when laparoscopic investigation was carried out[9]. Another study found that a high frequency of peritubal adhesions was found in 49% of HSG-normal women; however, the adhesions were mild in 93% cases[10]. In the present study, a diagnosis of bilateral tubal occlusion was also obtained laparoscopically at a low frequency of 2.4% (2/84). Peritubal adhesions were found at a relatively high frequency of 42.9% (36/84), although they were mild and none of these women required a change in the IVF-ET treatment protocol. Furthermore, since there was no difference in pregnancy rates between patients with and without peritubal adhesions, laparoscopy was considered

Table 3 **Patient characteristics in the laparoscopy group and the IVF group**

	Laparoscopy group (n=84)	IVF group (n=24)	p-value
Mean age (years)	34.3±3.4	36.0±3.8	0.03
Duration of inferility (years)	4.5±3.2	4.0±3.3	0.54
Primary infertility (%)	36 (42.9)	12 (50.0)	0.33
Cause of infertility			
Unexplained infertility	24	5	0.45
Ovulation dysfunction	46	18	0.87
Cervical factor	36	9	0.64
History of laparotomy (%)	13 (15.5)	1 (4.2)	0.27
History of PID (%)	9 (10.7)	1 (4.2)	0.56

PID; pelvic inflammatory disease
Values are expressed as mean ± SD (range).

Table 4 **Comparison of pregnancy outcomes in the IVF and the laparoscopy group**

	IVF group (n=24, 38 cycles)	Laparoscopy group (n=84)	p-value
Cumulative pregnancy rate per patient	89.3%	66.4%	0.012
Cumulative live birth rate per patient	75.9%	62.2%	0.03
Abortion rate	26.7% (4/15)	21.2% (7/33)	0.68
Ectopic pregnancy	13.3% (2/15)	0% (0/33)	0.17

Cumulative pregnancy rates were calculated according to the Kaplan-Meier method, and the log-rank test was used to test the significance.
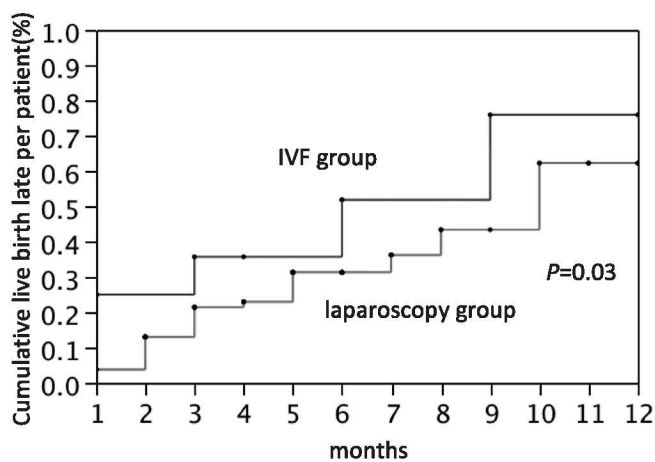x^2 test were used to test the difference of abortion rate and ectopic pregnancy.

Fig. 2 **Comparison of the cumulative live birth rates of the laparoscopy and IVF groups.** Cumulative birth rate was calculated by the Kaplan-Meier method, and the log-rank test was used to test the difference.

to be of low diagnostic significance with respect to tubal occlusion or peritubal adhesions in patients with normal HSG results, and to have little therapeutic effect on adhesiolysis.

Endometriosis is reported 2 times more frequently in infertile than in fertile women[11]. Its severity is difficult to estimate from its symptoms, and laparoscopy is considered necessary to confirm the diagnosis. This study also showed that although suspected endometriosis cases were excluded, findings of endometriosis were observed in about half of the subjects, including 13.6% (6/44) with r-ASRM stage III. Laparoscopic surgery for mild-to-moderate endometriosis is considered useful for diagnostic and therapeutic purposes in infertile women, even in those without symptoms[8]. However, in a randomized comparative clinical trial, the rate of pregnancy in infertile women

was found to be 6.1% per month, and did not reach the rate of 20% per month, as seen in fertile couples[12]. For this reason, laparoscopic surgery is considered non-contributory to increasing the rate of pregnancy in cases of unexplained infertility with asymptomatic endometriosis.

The cumulative pregnancy and live birth rates were higher in the IVF group, suggesting that laparoscopy could be omitted in women with bilateral tubal patency as observed on HSG, for which IVF-ET is a possible alternative. In particular, because duration of infertility ≥ 5 years was found to be an independent risk factor in the laparoscopy group, IVF-ET should be the recommended treatment in this group. However, it has been reported that the risk of congenital abnormalities and intrauterine growth retardation are 2.2 and 1.6 times higher in IVF-ET pregnancies[13]. In addition, the risk of premature birth after IVF-ET is 1.95 times higher even for a single fetus, and neonatal mortality is 2.19 times higher[14]. The safety of IVF-ET must always be taken into account, and a full informed consent is required in such cases. The limitations of this study are its retrospective nature and the limited number of subjects in the IVF group. Larger trials are required to establish the effectiveness of IVF in these women.

In conclusion, in women with bilateral tubal patency observed on HSG, laparoscopy may be omitted if IVF-ET is the subsequent treatment of choice, particularly in women with infertility ≥ 5 years.

ACKNOWLEDGMENTS

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