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The role of laparoscopy in intrauterine insemination: a prospective randomized reallocation study

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BACKGROUND: We questioned whether a laparoscopy should be performed after a normal hysterosalpingography before starting intrauterine inseminations (IUI) in order to detect further pelvic pathology and whether a postponed procedure after six unsuccessful cycles of IUI yields a higher number of abnormal findings. METHODS: In a randomized controlled trial, the accuracy of a standard laparoscopy prior to IUI was compared with a laparoscopy performed after six unsuccessful cycles of IUI. The major end-point was the number of diagnostic laparoscopies revealing pelvic pathology with consequence for further treatment such as laparoscopic surgical intervention, IVF or secondary surgery. Patients were couples with medical grounds for IUI such as idiopathic subfertility, mild male infertility and cervical hostility. RESULTS: Seventy-seven patients were randomized into the diagnostic laparoscopy first (DLSF) group and the same number was randomized into the IUI first (IUIF) group. The laparoscopy was performed on 64 patients in the DLSF group, 10 patients withdrew their consent from participation and three patients (3%) became pregnant prior to laparoscopy. In the IUIF group, 23 patients remained for laparoscopy because pregnancy did not occur after six cycles of IUI. From the original 77 randomized patients, 38 patients became pregnant and 16 patients dropped out. Abnormal findings during laparoscopy with therapeutic consequences were the same in both groups: in the DLSF group, 31 cases (48%) versus 13 cases (56%) in the IUIF group, $P = 0.63$; odds ratio (OR) = 1.4; 95% confidence interval (CI): 0.5–3.6. The ongoing pregnancy rate in the DLSF group was 34 out of 77 patients (44%) versus 38 out of 77 patients (49%) in the IUIF group ($P = 0.63$; OR = 1.2; 95% CI: 0.7–2.3). CONCLUSIONS:Laparoscopy performed after six cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences compared with those performed prior to IUI treatment. Our data suggest that the impact of the detection and the laparoscopic treatment of observed pelvic pathology prior to IUI seems negligible in terms of IUI outcome. Therefore, we seriously question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. Further prospective studies could be performed to determine the effect of laparoscopic interventions on the success rate of IUI treatment in order to rule out completely the laparoscopy from the diagnostic route prior to IUI.

Key words: diagnostic laparoscopy/endometriosis/hysterosalpingogram/infertility work-up/intrauterine insemination

Introduction

Diagnostic laparoscopy is generally accepted as the most accurate procedure to detect tubal pathology and endometriosis. Less invasive diagnostic tests such as patient's history, chlamydia antibody testing (CAT), ultrasonography and hysterosalpingography (HSG) are available, but it is still a matter of debate how the value of these tests compares with laparoscopy in the infertility work-up (Tanahatoe *et al.*, 2003*a*). Several studies describe risk factors for tubal pathology such as previous abdominal surgery and previous pelvic inflammatory disease (PID). However, up to 68% of patients without any of these risk factors can still possess abnormalities as shown by laparoscopy (Donnez *et al.*, 1982; Musich and Behrman, 1982; Corson *et al.*, 2000).

Several studies describe the accuracy of CAT and HSG with diagnostic laparoscopy (DLS) as gold standard. A meta-analysis of studies comparing chlamydia antibody titres and laparoscopy for tubal patency and peritubal adhesions has shown that the discriminative capacity of chlamydia antibody titres in the diagnosis of any tubal pathology is comparable to that of HSG in the diagnosis of tubal occlusion (Mol *et al.*, 1997). Although CAT can be determined at low cost, it fails to provide information about the severity of tubal pathology, which is of importance to fertility prognosis and, subsequently, to infertility treatment. Furthermore, it cannot detect tubal pathology due to other causes or endometriosis.

A meta-analysis of 20 studies comparing HSG and laparoscopy for tubal patency and peritubal adhesions showed that HSG is of limited use for detecting tubal patency because of its low sensitivity, though its high specificity makes it a useful test for confirming the presence of tubal obstruction. For the

evaluation of tubal patency and peritubal adhesions, but especially endometriosis, HSG is not reliable and requires laparoscopy (Swart *et al.*, 1995). Laparoscopy still reveals tubal pathology or endometriosis in 35–68% of cases, even after normal HSG (Wood, 1983; Henig *et al.*, 1991; Opsahl *et al.*, 1993; Cundiff *et al.*, 1995; Belisle *et al.*, 1996; al Badawi *et al.*, 1999; Corson *et al.*, 2000).

According to World Health Organization (WHO) guidelines, DLS is still recommended as a minimal requirement in the investigation of infertility in the female (Rowe *et al.*, 1993). However, it remains questionable whether DLS in general provides more information to further diagnosis and treatment decisions. There is a growing tendency to bypass diagnostic laparoscopy in couples with a normal HSG who will undergo intrauterine insemination (IUI) treatment for idiopathic infertility, mild male subfertility and cervical hostility.

Recently we showed, in a retrospective analysis, that DLS detected tubal pathology and endometriosis in 25% of patients undergoing DLS after a normal HSG (Tanahatoe *et al.*, 2003*b*). Seventy-five percent of the patients had normal findings or minor pathology without expected impact on fertility resulting in subsequent IUI treatment. On the other hand, 21% of the patients had laparoscopic abnormalities treated directly during laparoscopy followed by IUI treatment and 4% had such severe pathology that IVF or secondary surgery was recommended.

In other words, if DLS had not been performed prior to IUI, 25% of the patients were treated incorrectly with IUI—assuming that the change of treatment, laparoscopic intervention, IVF or secondary surgery is effective in terms of IUI outcome. If this scenario is correct, it would probably lead to a lower pregnancy rate or would result in more time to achieve pregnancy and finally more patients resorting to IVF treatment. On the other hand, if DLS was performed routinely it should be realized that it is an invasive procedure to patients and its routine performance implies considerable costs.

Given the invasive and costly nature of the procedure, we considered it clinically relevant to investigate the effectiveness of the DLS as part of the IUI work-up. The purpose of the diagnostic laparoscopy is first to trace abnormalities and secondly to treat them when necessary. We questioned if the laparoscopy should always be performed before starting IUI. Considering treatment efficacy and applying cumulative pregnancy rate findings of the study by Marcoux *et al.* (1997), we expected that the difference in the cumulative pregnancy rate with and without laparoscopic treatment would be no more than 10% in the IUI setting. To demonstrate such a difference, a large study sample of at least 1000 patients would have been necessary.

We decided first to assess whether the laparoscopy as a diagnostic rather than a therapeutic tool yields more abnormal findings when performed after six unsuccessful cycles of IUI instead of before IUI. Theoretically, over the course of six IUI cycles, some concentration may be expected of patients with laparoscopic abnormalities among those who did not become pregnant. This would lead to less laparoscopies and, when DLS is performed, to a higher yield of abnormal findings with clinical implications. Therefore, we compared the value of diagnostic laparoscopy prior to IUI with the value of one performed after six cycles of IUI. The major end-point was the number of diagnostic laparoscopies revealing pelvic pathology with consequence to further treatment.

Methods

Patients

Subjects were patients who were referred to the Reproductive Medicine Department of the Academic Hospital 'VU Medical Centre' in Amsterdam for secondary level investigation and treatment of infertility. The study was conducted according to the principles of the Declaration of Helsinki 1975 as revised in 1983 and in accordance with the research guidelines of our institute. Approval from the institute's review board was given before starting the study. Patients were informed about the purpose and hazards of this study both orally and in writing, and had to give their informed consent. Basal infertility work-up included a basal body temperature chart, a post-coital test (PCT), at least two semen samples and an HSG. Subsequently, a DLS was performed to determine tubal pathology and endometriosis.

Only couples with medical grounds for IUI treatment were included. These included couples affected with male subfertility, cervical hostility and with idiopathic subfertility. Male subfertility was diagnosed when at least three out of five semen samples showed a total number of $<20 \times 10^6$ spermatozoa per ml, or <40% progressively motile spermatozoa, or a positive mixed agglutination reaction (positive defined as >10%) followed by an immunobead test of >60% (Yeh *et al.*, 1995). Cervical hostility was defined as a negative PCT performed at the correct time, in good cervical mucus with intercourse between 6 and 18 h prior to the test, in combination with normal semen samples. Idiopathic subfertility included all patients with normal findings at basal infertility work up and a history of infertility of at least 3 years.

Inclusion criteria concerned a normal HSG with bilateral tubal patency and spill of contrast medium, no suspicion of phimosis, salpingitis isthmica nodosa, hydrosalpinx or adhesions and female of age <39 years of age.

Exclusion criteria were a history of pelvic surgery including DLS in the past, a history of pelvic inflammatory disease, patients with unresolved cycle irregularities as indicated by basal body temperature charts and severe male subfertility showing semen samples of $<1 \times 10^6$ million progressively motile spermatozoa after processing.

Procedures

After clarifying the nature of the study by their gynaecologist and after giving written informed consent, patients eligible for the study were randomized by means of a computer-generated schedule in blocks of 20, administered by numbered masked and sealed envelopes. Patients and gynaecologists were not blinded to the group assignment.

Patients were randomized after they finished the basic infertility investigation but before DLS was performed. One group of patients was randomized to DLS with dye before infertility treatment. The other group started with IUI directly. In this group, diagnostic laparoscopy was performed if pregnancy did not occur after six cycles of IUI to evaluate pelvic pathology.

Follow-up stopped after a maximum of six cycles of IUI in the DLSF group or if ongoing pregnancy occurred. In the other group, follow-up also stopped in case of clinical pregnancy or when six cycles of IUI were finalized by a diagnostic laparoscopy. Ongoing pregnancy was defined as positive fetal heart rate seen with ultrasonography at 12 weeks.

During diagnostic laparoscopy, treatment decisions were made according to laparoscopic findings. The following three scenarios were possible: (i) if no laparoscopic abnormalities were found, the patient was treated with IUI; (ii) if severe laparoscopic abnormalities were found, the patient was treated with IVF or secondary surgery; and (iii) when mild laparoscopic abnormalities were found, direct

surgical treatment was performed, i.e. adhesiolysis or evaporation of endometriosis. In the latter group, the patient was treated with a maximum of six cycles of IUI after laparoscopy.

Severe laparoscopic abnormalities were defined as bilateral tubal occlusion confirmed by no spill of dye, unilateral or bilateral hydrosalpinx, frozen pelvis, bilateral phimosis of the fimbriae, bilateral dense adhesions with enclosure of more than one-third of the tubes and/or ovaries or filmy adhesions with enclosure of more than two-thirds of the tubes and/or ovaries, moderate or severe endometriosis (Revised American Fertility Society stage 3–4).

Mild laparoscopic abnormalities were defined as minimal and mild endometriosis (Revised American Fertility Society stage 1–2), uni- or bilateral peritubal dense adhesions with enclosure of less than one-third of the tubes and/or ovaries, or filmy adhesions with enclosure of less than two-thirds of the tubes and/or ovaries.

Diagnostic laparoscopy was performed following standard procedures and on an outpatient basis. During diagnostic laparoscopy, laser equipment was available and used for adhesiolysis or evaporation of endometriosis.

In both treatment schedules, the first three treatment cycles of IUI were performed in the natural cycle. Baseline pelvic ultrasound was performed on cycle day 2, 3 or 4 in the first and fourth treatment cycle. About cycle day 10, transvaginal ultrasonography was performed to measure the dominant follicle. If a follicle of at least 14 mm was seen, the patient started with urine tests on luteinizing hormone (LH) surge twice daily. A single IUI was performed 20–30 h after the LH surge was detected in urinary samples. A suspension of 0.2–0.5 ml of processed spermatozoa was introduced into the uterine cavity ~1 cm below the fundus. If menstruation did not start on the 15th day after insemination, a pregnancy test was carried out.

If pregnancy did not occur after three cycles of IUI in the natural cycle, then the patient could choose between continuing IUI in the natural cycle or starting IUI with mild ovarian stimulation with a maximum of another 3 cycles. IUI in the natural cycle was performed as described above. IUI with mild ovarian stimulation was performed with recombinant follicle stimulating hormone (FSH) to achieve the growth of a maximum of three dominant follicles before administration of human chorionic gonadotropin (HCG). Pelvic ultrasonography was performed on cycle day 3 to exclude cysts >25 mm. Subsequently, patients injected themselves daily until transvaginal ultrasonography showed at least one follicle of 18 mm. If this occurred, an injection of HCG was given in the evening. A single IUI was performed ~42 h after HCG injection. To prevent ovarian stimulation syndrome and high order multiple pregnancies, IUI was withheld if more than three follicles with a diameter of at least 18 mm or more than five follicles with a diameter of 14 mm were present. If the menstruation started on the 15th day after insemination, a pregnancy test was carried out.

Statistical analysis

The primary end-point of this study was the number of abnormal laparoscopies leading to a change of treatment versus the total number of performed laparoscopies. Our major aim was to be able to observe a clinically relevant increase of 25 to 50% abnormal laparoscopies in case diagnostic laparoscopy would be performed after six cycles of IUI. To demonstrate a difference between 25% and 50%, the minimal sample size for each group should be 56, with α of 0.05 and power of 80%. Taking account a drop-out percentage due to pregnancy in the IUI group of 25% and a drop-out due to other reasons of 5%, then 77 patients per group would be necessary.

Student's *t*-test was used to analyse continuous data and the χ^2 test was used for discrete data on the characteristics of the patients. The number of abnormal laparoscopies leading to a change of treatment decision was expressed as a binomial value and can be tested using a χ^2 test.

Results

Patients

Between March 2001 and April 2003, 154 patients gave their consent to participate in the study. Seventy-seven patients were randomized in the diagnostic laparoscopy first (DLSF) group and the same number was randomized for the IUI first (IUIF) group. Randomization was performed successfully; group characteristics were identical according to the frequency of idiopathic subfertility [44 (57%) versus 43 (56%)], male subfertility [23 (30%) versus 23 (30%)] and cervical hostility [10 (13%) versus 11 (14%); $P = 0.97$], primary infertility [59 (77%) versus 58 (75%); $P = 0.85$], age of the female [32.3 years (95% confidence interval (CI): 31.4–33.1) versus 33.2 years (95% CI: 32.3–34.0); $P = 0.11$] and duration of infertility [2.9 years (95% CI: 2.6–3.2) versus 3.0 years (95% CI: 2.7–3.4); $P = 0.43$].

Diagnostic laparoscopies were performed in 64 patients in the DLSF group and in 23 patients in the IUIF group. In the DLSF group, 13 patients (17%) dropped out of the study. Of these, 10 patients (14%) withdrew their consent from participation and three patients (3%) became pregnant prior to laparoscopy. In the IUIF group, 54 patients dropped out before laparoscopy was performed. In this group, 12 (15%) patients stopped treatment before starting or during IUI treatment and four (6%) stopped IUI treatment for medical reasons. The remaining 38 (50%) patients in the IUIF group did not undergo laparoscopy due to natural pregnancy or pregnancy as result of IUI treatment (Fig. 1). The analysis was carried out according to the principle of intention-to-treat.

The group characteristics in patients who underwent laparoscopy were not different between both groups with regard to primary or secondary infertility, idiopathic subfertility, male subfertility or cervical hostility, female's age and duration of subfertility (Table I).

The mean waiting period between randomization and laparoscopy was 14.8 weeks (95% CI: 11.9–17.8). The mean waiting period between randomization and the start of the first IUI cycle was 14.3 weeks (95% CI: 11.0–17.6). The waiting periods between groups did not differ significantly ($P = 0.8$).

Outcome of treatment

In the DLSF group, abnormalities were found at laparoscopy in 31 cases (48%). These abnormalities included adhesions in three patients and endometriosis in 28 patients. In all these cases, the abnormalities were evaporated or coagulated (Table II).

In the IUIF group, laparoscopy revealed abnormalities in 13 cases (56%). This included endometriosis, which was treated immediately by evaporation or coagulation in 12 patients and bilateral hydrosalpinx in combination with adhesions in one patient (Table II). The number of abnormal findings during laparoscopy that resulted in a laparoscopic intervention was not significantly different between the DLSF group and the IUIF group ($P = 0.63$; odds ratio (OR) = 1.4; 95% CI: 0.5–3.6).

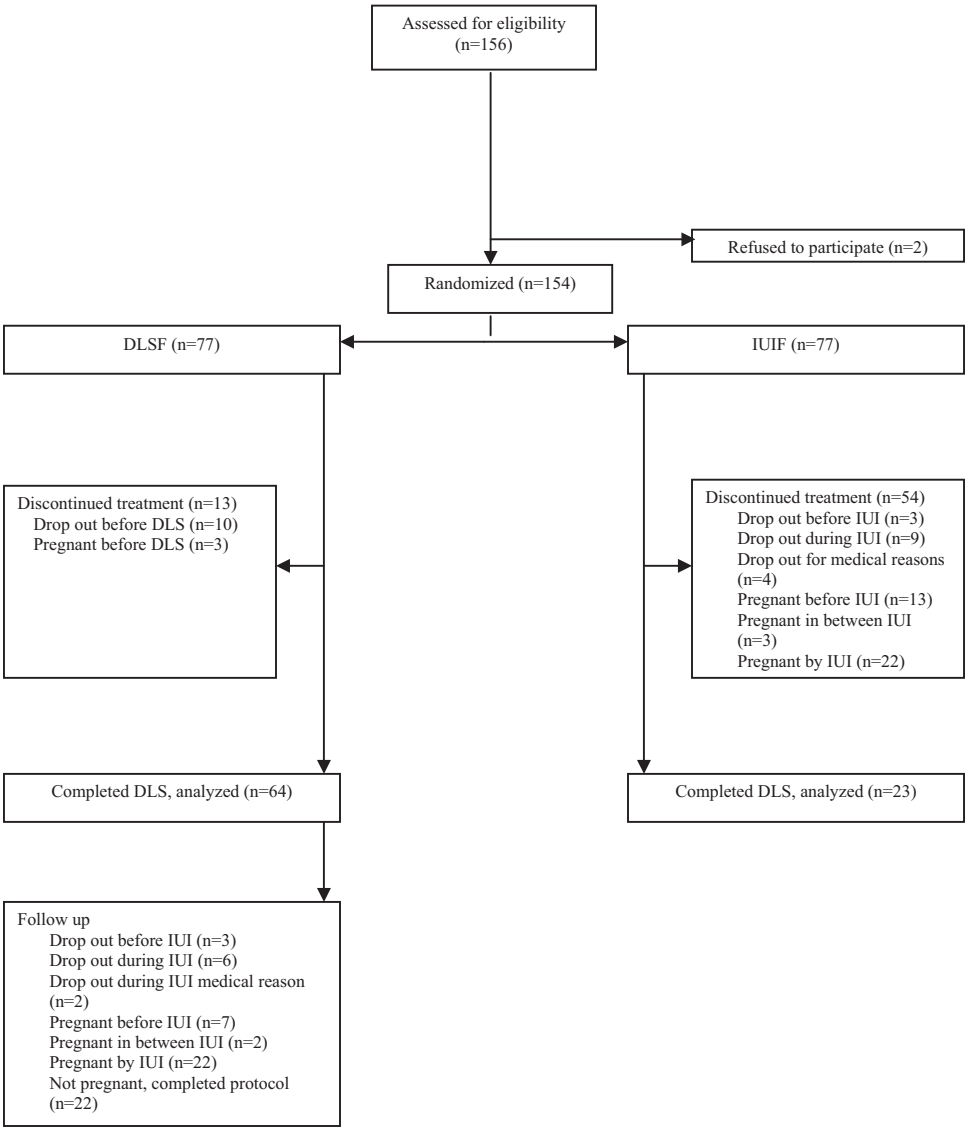

Figure 1. Trial profile.

Table I. Group characteristics

	DLSF (*n* = 64)	IUIF (*n* = 23)	*P*
Infertility factor			0.81
Idiopathic subfertility	37 (58%)	14 (61%)	
Male subfertility	18 (28%)	6 (26%)	
Cervical hostility	9 (14%)	3 (13%)	
Primary infertility	51 (80%)	20 (87%)	0.54
Secondary infertility	13 (20%)	3 (13%)	
Female age in years (95% CI)	32.3 (31.4–33.1)	33.4 (32.3–34.0)	0.22
Duration of infertility in years (95% CI)	2.9 (2.6–3.2)	2.9 (2.7–3.4)	0.93

Table II. Findings and interventions by laparoscopy

	DLSF (*n* = 64)	IUIF (*n* = 23)	*P*	OR (95% CI)
No abnormalities	33 (52%)	10 (44%)	0.63	1.4 (0.5–3.6)
Abnormalities and intervention	31 (48%)	13 (56%)		
Adhesiolysis	3 (4%)*	–		
Evaporation endometriosis	28 (44%)**	12 (52%)***		
Fimbriolysis	–	1 (4%)****		

*Two unilateral adhesions, one bilateral adhesions; **22 stage I, three stage II, two stage III, one stage IV; ***11 stage I, one stage III; ****one bilateral hydrosalpinx and adhesions.

The overall ongoing pregnancy rate in the DLSF group was 34 out of 77 patients (44%) versus 38 out of 77 patients (49%) in the IUIF group ($P = 0.63$; OR = 1.2; 95% CI: 0.7–2.3). In the DLSF group, 12 natural pregnancies occurred including three pregnancies prior to laparoscopy, seven pregnancies after laparoscopy but before IUI treatment, and two natural pregnancies in between IUI treatment cycles. In the DLSF group, 22 patients became pregnant due to IUI treatment (Table III).

Of the 43 patients without an ongoing pregnancy in the DLSF group, 10 patients withdrew from participation prior

Table III. Pregnancy rate

	DLSF (n = 77)	IUIF (n = 77)	P value	OR (95% CI)
Natural pregnancy	12	16		
IUI pregnancy	22	22	0.6	1.2 (0.7–2.3)
Total pregnancy rate	34 (44%)	38 (49%)		

to laparoscopy, three patients underwent laparoscopy but did not start IUI treatment at all and 6 patients stopped before finializing 6 IUI cycles. Finally, 22 patients did not become pregnant after laparoscopy and 6 cycles of IUI. In two cases, IUI treatment was withheld due to deterioration of semen samples.

In the IUIF group, a total number of 16 patients became naturally pregnant, 13 patients prior to any IUI and three in between IUI treatments. In 22 cases, pregnancy occurred by IUI. Treatment by IUI remained unsuccessful after six cycles in 27 patients. Twelve patients stopped IUI treatment before finalizing six cycles. Four patients were advised to stop IUI treatment for medical reasons.

In the DLSF group, 237 IUI cycles had been performed of which 73 cycles of IUI (31%) were performed in combination with ovarian stimulation by gonadotrophins. In the IUIF group, ovarian stimulation during IUI occurred in 77 cycles on a total of 277 (28%) cycles. The number of stimulated cycles was not significantly different between the groups (P = 0.5; OR = 0.87; 95% CI: 0.59–1.27). There were no cases of ovarian stimulation syndrome in both groups and no complications as result of laparoscopy.

Discussion

From our study, it appears that the number of abnormalities requiring laparoscopic intervention was not significantly higher when the laparoscopy was performed after six cycles of IUI compared with the group who underwent immediately laparoscopy prior to IUI. Apparently, reallocation of the laparoscopy after six cycles of IUI did not lead to a considerable concentration of patients for whom intervention was necessary.

This finding is in sharp contrast to the hypothesis that we had formulated, namely that there would be a considerable increase of ~25% in abnormal findings.

To substantiate the found difference of 8% a sample size of about 1200 patients significantly, it would be necessary to take into account an α of 0.05 and power of 80%. But even if the 8% increase could be statistically corroborated in larger studies, its clinical value is debatable.

Our original idea was that, by performing IUI, we would more or less separate patients with and without intra abdominal abnormities by virtue of the occurrence of pregnancy upon IUI. Those that do not become pregnant after six IUI treatments would consequently more often have infertility-related intra abdominal disease. We speculate that this concentration did not occur substantially because there was no profound change in pregnancy rate upon the laparoscopic intervention prior to the IUI procedure. A possible absence of a substantial effect on pregnancy rate of the laparoscopic intervention could be explained in two ways. First, it is possible that most of the observed and treated abnormities play a minor or no role in infertility. Secondly, it could be that the applied intervention is ineffective. But again, group size in the current study was not based on tracing potential differences in pregnancy rate.

However, this seems to be in contrast to existing data. There is evidence that laparoscopic ablation of minimal and mild endometriosis improves the fecundity rate as described by a Cochrane review assessing the efficacy of the treatment of endometriosis by comparing the outcome of laparoscopic surgical treatment of minimal and mild endometriosis with the outcome of expectant management (Jacobson *et al.*, 2002). This analysis showed that surgical treatment rather than instead of expectant management is favourable (OR for ongoing pregnancy rate = 1.64; 95% CI: 1.05–2.57). There is also evidence that medical treatment by GnRH agonist of minimal and mild endometriosis prior to IUI enhances the pregnancy rate of IUI (Kim *et al.*, 1996). In case of adhesions, there is some evidence that laparoscopic adhesiolysis leads to higher natural pregnancy rates (Tulandi *et al.*, 1990).

It has been reported that there is a negative impact of endometriosis on the outcome of IUI (Dodson *et al.*, 1987; Chaffkin *et al.*, 1991; Dickey *et al.*, 1992; Crosignani and Walters, 1994; Hughes, 1997; Nuojua-Huttunen *et al.*, 1999). If it is assumed that endometriosis reduces the outcome of IUI and that laparoscopic surgical treatment of endometriosis and adhesions may improve fecundity rate, then some effect should have been expected in the IUI setting. Our study, however, showed no significant difference in prevalence of endometriosis and adhesions at laparoscopy before IUI as well after six cycles of IUI. Apparently, such minimal and mild endometriosis and adhesions probably impair the IUI outcome to a very limited extent.

Follow-up of our study ended after six cycles of IUI. The subsequent obvious question concerns what the next step should be taken after six unsuccessful IUI cycles when a laparoscopy is not performed. Should this be IVF or is continued IUI still an option? And could performance of a laparoscopy have a role in such a strategy? If so, when should it be performed? Most clinics choose IVF in this situation. In our clinic, this strategy is indeed more or less the routine procedure. But as far as we are aware, there are no published studies on this. Such studies should be performed. They should also evaluate the issue of a diagnostic/therapeutic laparoscopy in such a scenario.

Remarkably, this study showed substantially more abnormal findings during the laparoscopy than in our previous retrospective study (Tanahatoe *et al.*, 2003*b*). Most likely, has resulted from the fact that the surgeons kept strictly to the protocol in this prospective trial. A further explanation for the discrepancy could be that some observational bias yielded higher number abnormalities because the surgeons were aware that the patients were participating in a study. The clinical protocol for systematic classification of laparoscopic findings in our clinic has been part of the routine procedure for many years, and it was the same during our retrospective and current studies. Therefore, we consider the latter type of bias unlikely.

Some comments have to be made on why the desired group size was not achieved in the IUIF group. It appears that more

than expected patients became pregnant and more dropped out. Drop-out rates were similar in both arms and thus were probably not related to the randomization.

In both groups, the natural pregnancy rate while patients were without any treatment was considerable, with 12 patients in the DLSF group versus 16 patients in the IUIF group (16% versus 21%, respectively). In view of this, one could argue that a prolonged period of expectant management prior to any treatment seems a feasible option.

In summary, laparoscopy performed after 6 cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences compared with those performed prior to IUI treatment. Our data suggest that the impact of the detection and the laparoscopic treatment of observed pelvic pathology prior to IUI seems negligible in terms of IUI outcome. Therefore, we seriously question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. Further prospective studies should be performed to determine the effect of laparoscopic interventions on the success rate of IUI treatment in order to completely justify or to rule out the laparoscopy from the diagnostic route prior to IUI.

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