Clinical work-up strategies before IUI

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1

Introduction and aim and outline of the thesis

Introduction

Intrauterine insemination (IUI) as a treatment for subfertility is known for more than two centuries. Nowadays it is still a frequently used treatment whose application in the meantime is studied extensively. Idiopathic subfertility is identified as a proven treatment indication for IUI compared to timed intercourse in terms of pregnancy rate per woman, peto odds ratio (OR) 1.68; 95% confidence interval (CI): 1.13 to 2.50 (Verhulst *et al.*, 2006). In case of mild male subfertility there is evidence that IUI is beneficial over timed intercourse regarding pregnancy rate per completed cycle, OR 3.1; 95% CI: 1.5 to 6.3 (Cohlen, 2005). However, a recent review studying only those papers with pregnancy rate per woman found no difference between IUI compared with timed intercourse due to a lack of power, peto OR 5.3; 95% CI: 0.42 to 67 (Bensdorp *et al.*, 2007).

Whether cervical hostility should be treated with IUI is still unclear, because several studies showed conflicting results probably due to small sample sizes and variations in patient characteristics and interventions (Helmerhorst *et al.*, 2005). A recent well performed randomized study showed that there might be a beneficial effect of IUI over expectant management in couples with cervical hostility (Steures *et al.*, 2007).

The mechanism of action of IUI is based on optimizing the concentration of the inseminated sperm at the site of fertilization and optimizing the timing of insemination i.e. around ovulation. To perform IUI some conditions are required. This includes 1) a certain amount of progressively motile spermatozoa, 2) the presence of ovulation, 3) functional fallopian tubes, 4) the capability of fertilization of the gametes and 5) implantation of the embryo (the latter is beyond the scope of this thesis). Whether all these factors should be completely evaluated and if so, how they could be optimized prior to IUI is an ongoing debate.

This chapter gives an overview of which diagnostic tests are available to analyze the above mentioned factors required to perform IUI and how these factors could be optimized prior to IUI.

Semen quality

In case of male subfertility semen quality is measured to judge whether IUI, in vitro fertilization (IVF) or intracytoplasmatic sperm injection (ICSI) should be advised in order to provide the optimal chances to conceive. Several studies have shown that normal semen quality based on the World Health Organization (WHO) criteria are of little use, because of its poor prognostic value on IUI outcome (Branigan *et al.*, 1999; Dickey *et al.*, 1999). The postwash total motile sperm count (TMC) however seems to be of higher predictive value (Branigan *et al.*, 1999). A meta-analysis, assessing the performance of the postwash TMC as a test to predict IUI outcome, showed that cut-off levels between 0.8 to 5 million motile spermatozoa provided a substantial discriminative performance (van Weert *et al.*, 2004). At these cut-off levels, the specificity of the postwash TMC was 99 to 100%; the specificity was defined as the ability to predict failure to become pregnant. But an optimal cut-off value could not be extracted from the included studies. The sensitivity, the ability to predict pregnancy, on the other hand, turned out to be limited and no optimal cut-off value could be extracted. However, the clinical value of this test is substantial as the test can distinguish significantly those patients who are not likely to benefit from IUI in case of male subfertility. The authors commented appropriately that all the studies that were reviewed used the postwash TMC at the time of the insemination instead of the values from an earlier sample taken for fertility work up. Such studies were lacking. For the time being it seems more practical to use the postwash TMC at fertility work up in counseling patients for IUI, IVF or ICSI.

Before starting fertility treatment it is important to optimize semen quality because of two reasons. First, improved sperm parameters per se lead to higher pregnancy rates of assisted reproductive techniques (ART) (Berg *et al.*, 1997; Donnelly *et al.*, 1998). Second, optimizing sperm quality could be of great importance if it would make more complicated modes of ART such as IVF and ICSI avoidable. These reproductive techniques require strong ovarian stimulation with gonadotropins and ovarian puncture which are a burden to patients and require extensive laboratory effort. Furthermore, although so far no significant disadvantages for the offspring are reported, future health of children born after IVF and ICSI remain a matter of concern (Bonduelle *et al.*, 2002; Sutcliffe *et al.*, 2002; Sutcliffe and Ludwig, 2007; Van Steirteghem *et al.*, 2002b; Van Steirteghem *et al.*, 2002a). Therefore upgrading sperm quality to IVF, IUI or even to normal sperm counts may be of benefit.

Optimizing semen quality can theoretically be obtained by treating the underlying cause of diminished semen quality. The causes of male subfertility can be categorized in to: hormone disorders, anatomic defects and idiopathic subfertility. Hormone disorders include 1) hypergonadotropic hypogonadism caused by germ cell failure, Klinefelter's syndrome (47XXY), or testicular damage, 2) congenital or acquired hypogonadotropic hypogonadism caused by pituitary tumors, anorexia nervosa, excessive exercise, drug use or hyperprolactinemia and 3) androgen resistance or insensitivity. The predominant anatomic defects are varicocele, obstruction and retrograde ejaculation caused by disruption of the innervation of the vas deferentia and bladder neck.

As well in case of hypergonadotropic hypogonadism, independent of its cause, as well in case of androgen receptor defects there are no proven effective treatment options to improve semen quality. On the other hand, semen defects due to hypogonadotropic hypogonadism, accounting for 1-2% of the causes of male subfertility (Collins *et al.*, 1984), is treatable by correction of food deficiency or drug intake or by dopaminergic medical treatment of a hyperprolactinemia. In case of other causes of hypogonadotropic hypogonadism semen defects can be treated by replacement of gonadotropins. Although the available literature concerning the hormonal treatment of male subfertility due to hypogonadotropic hypogonadism concerns small sample sizes, they all showed an overall increased level of sperm concentration and some cases even conceived naturally (Zitzmann and Nieschlag, 2000).

Obstructive azoospermia is approximately in 40% of the cases responsible for azoospermia, which is present in 10% of the subfertile men. The obstruction can be present at several levels of the genitourinal tract which can be congenital or postinflammatory, but the most are caused by vasectomy. Microsurgical vasectomy reversal by vasovasostomy is often successful. Return of sperm to the ejaculate occurs in 70-95% of patients and natural conceptions are seen in 30-70% (Belker *et al.*, 1991). Vasoepididymostomy results in a natural pregnancy rate of 20-40% (The Practice Committee of the American Society for Reproductive Medicine, 2006).The successful outcome of reversal of vasectomy, however, depends on the obstructive interval which is inversely related. A larger obstructive interval leads to less chances of return of sperm in the ejaculate and natural pregnancy (Belker *et al.*, 1991). Another treatment option for obstructive azoospermia due to vasectomy is sperm retrieval from the epidydimus or testis combined with an IVF/ICSI procedure. A study comparing microsurgical reconstruction to sperm retrieval in combination with IVF/ICSI showed that microsurgery is more cost-effective (Kolettis and Thomas, Jr., 1997; Pavlovich and Schlegel, 1997).

Another anatomic disorder related to male subfertility is the varicocele. The reported prevalence of a varicocele in subfertile men is 20-40% compared to 1.9-14.7% in the normal population (Oster, 1971; Steeno *et al.*, 1976; World Health Organization, 1992). It is apparent that varicocele repair results in significant improvement in semen parameters (Agarwal *et al.*, 2007; Schlesinger *et al.*, 1994) but its potential to improve the ability to conceive spontaneously remains controversial. There are only a few randomized controlled trials studying the effect of varicocele repair on spontaneous pregnancy, however, the results are conflicting which are probably due to clinical and statistical heterogeneity and lack of methodological quality (Breznik *et al.*, 1993; Evers *et al.*, 2001; Madgar *et al.*, 1995; Nieschlag *et al.*, 1998; Nilsson *et al.*, 1979; Yamamoto *et al.*, 1996). On the other hand, observational, uncontrolled studies have shown that surgical treatment by varicocelectomy results in such improvement of semen quality that 40-66% of the couples altered candidacy for another mode of ART (Cayan *et al.*, 2002; Matkov *et al.*, 2001). Based on the latter findings it could be justified to repair a varicocele in subfertile male.

In case of idiopathic male subfertility there are no known treatment options to increase sperm quality. There are studies suggesting that lifestyle factors such as smoking, alcohol drinking and obesity are related to decreased semen quality (Magnusdottir *et al.*, 2005; Marinelli *et al.*, 2004; Pasquali, 2006; Ramlau-Hansen *et al.*, 2007; Vine *et al.*, 1994), but in which extent those factors influence semen quality and on which underlying mechanism it is based remains unclear. Some postulate that cigarette smoking causes disturbance of the hypothalamo-pituitary-gonadal system

(Vermeulen, 1993) or mild hypoxia caused by disruption of the testicular microcirculation (Collin *et al.*, 1995), but a direct toxic effect of chemical components of cigarette smoking on spermatozoa is a more likely explanation (Zenzes *et al.*, 1999). Little is known about obesity and male subfertility, but some studies have shown lower plasma levels of sex-hormone binding globulin, total testosterone, free testosterone and FSH in obese men compared to non-obese men (Branigan *et al.*, 1999; Haffner *et al.*, 1993; Strain *et al.*, 1982). Whether weight loss or withdrawal of cigarette smoking is proven to be effective in terms of improved semen parameters remains unclear, because very scarce data are available.

Ovulation

Prior to IUI it is mandatory to confirm the presence of ovulation especially in patients who are going to be treated by IUI without stimulation. This starts by the medical history. Normal regularly menstruating women are almost always ovulatory, less than 5 % is anovulatory. Indirect confirmatory evidence of ovulation can be obtained by use of basal body temperature charts (BBT). This is a preliminary indicator of ovulation of which a mid cyclic temperature shift proves ovulation. This phenomenon is a direct effect of progestrone degeneration products on the hypothalamic temperature regulation centre. However, the interpretation of a BBT chart may sometimes be difficult and subjective (Lenton *et al.*, 1977), but it is commonly used because it is an inexpensive and non-invasive test. Other tests are described for ovulation detection, such as midluteal progesterone measurements, urinary LH test, endometrial biopsy and daily ultrasound. A study of Guermandi *et al.* (2002) compared the reliability of the BBT, a urinary stick system for LH surge and serum progesterone measurement in the midluteal phase for prediction or confirming ovulation in 101 regularly cycling infertile women(Guermandi *et al.*, 2001). In this study transvaginal ultrasound monitoring was the gold standard for ovulation detection. Although urinary LH and serum progesterone showed higher sensitivity (res. 1.0 and 0.80), specificity (res. 0.25 and 0.71) and overall accuracy (res. 0.97 and 0.79) to detect ovulation, the authors concluded that the biphasic BBT (sensitivity 0.77, specificity 0.33 and accuracy 0.74) is still a desirable method for the confirmation of ovulation because it is a simple, cheap, self-administered test for at-home use by patients.

Functional tubes

Tubal pathology is present in 15-20% of the subfertile couples (Hull 1985). In patients who are going to be treated with intrauterine insemination (IUI), patency of at least one tube should be proven before progressing to IUI. This is based on the fact that bilateral occlusion detected at laparoscopy impairs fecundity almost to zero whereas unilateral occlusion does not significantly lower natural pregnancy rates as well IUI outcome (Mol *et al.*, 1999; Steures *et al.*, 2004). Although the pregnancy outcome of IUI in patients with bilateral occlusion at laparoscopy is never described in a prospective study, it seems intuitively logical that in these cases in vitro fertilization (IVF) should be the preferred treatment option.

It is generally accepted that diagnostic laparoscopy is the gold standard in diagnosing tubal pathology and other intra abdominal causes of subfertility prior to IUI. Diagnostic laparoscopy, therefore, is frequently a standard procedure performed as final test in the fertility work up in many clinics before progressing to fertility treatment. This diagnostic scenario concerns couples eligible for IUI, as diagnostic laparoscopy is usually not performed in patients who are already planned for IVF or ICSI, because assessment of the fallopian tubes and other intra abdominal pathology is of less concern except for the presence of hydrosalpinges that can be diagnosed by ultrasonography (Strandell *et al.*, 1999).

Several studies describe riskfactors for tubal pathology and endometriosis, such as previous abdominal surgery and previous pelvic inflammatory disease (PID). However, patients without any of these risk factors can still have abnormalities as shown by laparoscopy up to 68% (Corson *et al.*, 2000; Donnez *et al.*, 1982; Musich and Behrman, 1982).

The accuracy of Chlamydia antibody titer (CAT) and hysterosalpingography (HSG) with diagnostic laparoscopy as gold standard are studied in several papers. A meta-analysis of studies, comparing CAT and laparoscopy for tubal patency and peritubal adhesions, has shown that the discriminative capacity of CAT 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 fertility treatment. Furthermore, it also can not detect tubal pathology due to other causes nor endometriosis. In some clinics in The Netherlands CAT is used in a screening strategy for the analysis of tubal function, though there is no consensus whether the CAT or the HSG, or a combination should be performed in the subfertility work-up. For example, in case of a positive test result, the laparoscopy is performed subsequently. In case of a negative test result, a HSG is performed and when normal, laparoscopy is performed when no natural pregnancy occurred in six months, or in case of an abnormal result, the laparoscopy is performed subsequently (Lardenoije and Land, 2007).

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. Its high specificity however makes it a useful test for ruling in tubal obstruction. For the evaluation of tubal patency and peritubal adhesions, but also endometriosis, HSG is not reliable and requires laparoscopy (Swart *et al.*, 1995).

Depending on the severity of the laparoscopic findings, the initial treatment decision (IUI) can be replaced by direct laparoscopic correction of the abnormality, fertility improving surgery by laparotomy, or referral to IVF. This implies that laparoscopy is not only clinically important as diagnostic test perse, but also plays an important role in making final decisions with regard to treatment. Until now, such added value of laparoscopy has not been evaluated in terms of the probability of finding abnormalities in patients willing to undergo IUI that lead to changes of treatment.

Fertilization

Assessing the ability of fertilization of the oocyte and spermatozoa is not a standard diagnostic procedure prior to IUI. Most couples who are going to be treated with IUI suffer from idiopathic subfertility. Especially in those couples it might be intuitively likely that a disorder of fertilization could be a factor influencing their fertility. The prevalence of fertilization failure or diminished fertilization among subfertile couples is unknown. This is due to the fact that fertilization can only be assessed by means of an IVF procedure to assess sperm-oocyte interaction.

There is some evidence that diminished fertilization might play a role in idiopathic subfertility. It is described that the fertilization rate in idiopathic subfertility is lower compared to tubal factor subfertility (Audibert *et al.*, 1989; Hull *et al.*, 1998; Mackenna *et al.*, 1992; Navot *et al.*, 1988). Furthermore Gurgan et al (1995) showed in a retrospective case control study that the prevalence of total fertilization failure (TFF) in couples with idiopathic subfertility who failed to conceive after IUI was more frequent compared with couples with tubal factor subfertility(Gurgan *et al.*, 1995). This appears to confirm the hypothesis that a fertilization factor might be an underlying cause of idiopathic subfertility.

If it is proven that fertilization failure is an undiscovered cause of unsuccessful IUI treatment and/or unsuccessful IVF, it could be useful to detect this factor in order to prevent unnecessary and costly treatment with IUI and/or IVF. Unfortunately, there are no studies evaluating the effectiveness of a diagnostic IVF procedure in couples with idiopathic subfertility prior to IUI treatment.

Aim of the thesis

The aim of this thesis is to asses which work-up strategies are necessary prior to IUI in relation to functional tubes, fertilization and semen quality.

Outline

Pending issues addressed in this thesis are the following:

1) What is the role of the diagnostic laparoscopy in patients willing to undergo IUI? This is the topic of chapter 2-4. Chapter 2 evaluates the accuracy of the diagnostic laparoscopy after normal HSG and before IUI. Chapter 3 questions if a laparoscopy after a normal HSG should be performed before starting IUI, and whether a postponed procedure after 6 unsuccessful cycles of IUI yields a higher number of abnormal findings. Chapter 4 investigates the additional value of laparoscopy with respect to diagnosis and further treatment decisions after an abnormal HSG.

2) Is a diagnostic IVF procedure before IUI in case of idiopathic subfertility of potential value? This is the topic of chapter 5. Here we analyse the possible role of total fertilization failure in patients with idiopathic subfertility and unsuccessful IUI, in order to assess whether there is a place for a diagnostic IVF procedure before progressing to IUI.

3) Can varicocele treatment lead to less invasive modes of assisted reproductive techniques? This is the topic of chapter 6. In this chapter we investigate whether embolization of a varicocele improves semen quality and enables use of less-invasive modes of assisted reproductive technology in subfertile men with impaired semen parameters.

Chapter 7 discusses the results and conclusions of the studies and provides recommendations for future research.

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2

Accuracy of diagnostic laparoscopy in the infertility work-up before intrauterine insemination

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Abstract

Objective: We evaluated the accuracy of diagnostic laparoscopy after normal hysterosalpingography (HSG) and before intrauterine insemination (IUI) with respect to laparoscopic findings leading to a change of treatment decisions in couples with male subfertility, cervical hostility or idiopathic infertility.

Methods: We retrospectively reviewed the surgery reports of 495 couples with medical grounds for IUI treatment, who underwent diagnostic laparoscopy as part of the infertility work up in the period 1995 until 1999 and calculated the prevalence of laparoscopic findings leading to change in treatment decision.

Results: Of 495 patients, 21 (4%) had severe abnormalities that resulted in a change of treatment to in vitro fertilization or open surgery. In 103 patients (21%), abnormalities, endometriosis (stage I- I) and adhesions, were directly treated by laparoscopic intervention, followed by IUI treatment. If surgery to remove early stage endometriosis does not improve pregnancy rates, then the laparoscopic yield would be 40 out of 495 (8.1%).

Conclusions: Diagnostic laparoscopy altered treatment decisions in an unexpectedly high number of patients before IUI. This suggests that laparoscopy may be of considerable value, provided the change in treatment is effective. Further prospective studies are required to assess whether the diagnostic use of laparoscopy is cost effective and whether interventions as result of laparoscopic findings are effective in improving pregnancy rates.

Introduction

Diagnostic laparoscopy is generally accepted as the most accurate procedure in evaluating tubal pathology and other occult intra-abdominal causes of infertility. Because treatment with intrauterine insemination (IUI) requires an optimal condition of the ovum pick up and its transport mechanism, diagnostic laparoscopy may be of value in the infertility work up program before progressing to IUI treatment. Although less invasive diagnostic tests, such as hysterosalpingography (HSG) and chlamydia antibody testing, are available, it is still a matter of debate as to how the value of these tests compares to laparoscopy in the infertility work up (Adelusi *et al*., 1995; Henig *et al*., 1991; Mol *et al*., 1997).

Because the success rates of assisted reproductive technique (ART) are improving, there is a growing tendency to start ART without previous evaluation of tubal pathologic features. When in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is the first choice of treatment (for example because of severe male factor infertility), the presence of intra-abdominal pathology would not change the final treatment decision, because the technique of IVF bypasses physiological ovum pick up and transfer to the uterus. Moreover, the probability of finding abnormalities using laparoscopy is lower in couples with severe male infertility than in couples with normal semen parameters (Aytoz *et al*., 1998).

A number of reports suggest that laparoscopy may be of added value, because it indicates intra-abdominal pathologic abnormalities in 36 to 68% of cases, even after normal HSG (al Badawi *et al*., 1999; Cundiff *et al*., 1995; Henig *et al*., 1991; Opsahl *et al*., 1993; Wood, 1983). Depending on the severity of the laparoscopic findings, the initial treatment decision (IUI) can be replaced by direct laparoscopic correction of the abnormality, fertility improving surgery by laparotomy, or referral to IVF. This implies that laparoscopy is not only a clinically important diagnostic tool, but may also be important in making treatment decisions. Until now, the added value of laparoscopy has not been evaluated in terms of the probability of finding abnormalities in patients who are willing to undergo IUI that can lead to changes in the treatment decision.

It should be recognised that diagnostic laparoscopy is an invasive and costly procedure, and is not without complications (Jansen *et al*., 1997). Because it is unclear whether laparoscopy is sufficiently effective to justify its routine performance, its contribution to diagnosis and in particular to treatment decisions should be evaluated more extensively. Where the decision to treat with IUI is based on the presence of a mild male factor or cervical hostility, it is reasonable to assume that intra abdominal pathology resulting in change of treatment might be less frequent. The aim of this retrospective study is to evaluate the accuracy of diagnostic laparoscopy before IUI with respect to laparoscopic findings leading to a change of treatment decisions in a cohort for which IUI was initially indicated.

Materials and Methods

A retrospective chart review was performed in the Department of Reproductive Medicine of the 'Vrije Universiteit' Medical Centre. All medical records of patients who had undergone a diagnostic laparoscopy between January 1995 and December 1999 were reviewed after approval of the institute's review board. Patients were included for analysis if an indication for treatment with IUI was present before the infertility investigation was finalized by laparoscopy. In our hospital, all patients undergo a diagnostic laparoscopy before IUI treatment. Clinical indications for IUI treatment included idiopathic infertility, male subfertility and cervical hostility (table 1).

Table 1. Inclusion criteria

1 Normal pelvic examination:	Absence of any palpable anomaly
2 Normal HSG:	Bilateral tubal spill of contrast medium Absence of suspicion of loculation, phimosis, salpingitis isthmica nodosa or hydrosalpinx.
3 Indication for IUI treatment:	
Male subfertility:	<20 million spermatozoa / ml < 40 % progressively motile spermatozoa or > 10 % of spermatozoa carrying antibodies after immunobead testing and >1 million progressively motile spermatozoa after processing by Percoll
Cervical hostility:	good timed postcoital test showing absent or non progressively motile spermatozoa in optimal cervical mucus in combination with normal semen samples, or when the postcoitum test was repeatedly negative regardless of the condition of the cervical mucus
Idiopathic infertility:	normal infertility investigation, i.e.ovulatory cycles as indicated by basal body temperature charts and endometrial biopsy

All diagnostic laparoscopies were performed at the end of the infertility investigation which included patient history, physical examination, a basal body temperature chart, selected endocrine laboratory tests where indicated, a postcoital test, a late luteal endometrial biopsy, at least two semen samples and a serial HSG. Serial HSG was timed in the preovulatory phase of the menstrual cycle as an outpatient procedure. A water soluble contrast medium was used, and this was injected through a cervical cannula using a autosyringe pump. During and after the injection, an x-ray examination was performed. The serial HSG frames were evaluated by a team of gynaecologists of the Department of Reproductive Medicine.

Diagnostic laparoscopy was performed as an outpatient procedure under standard conditions, namely general anaesthesia, double puncture technique and tubal patency testing with methylene dye. The laparoscopic findings were reported using the standard method in the operation reports. For this study the operation reports were reviewed and scored on the presence of frozen pelvis (dense adhesions totally enclosing the ovaries and tubes), periadnexal adhesions, proximal tubal occlusion, distal tubal occlusion such as phimosis and hydrosalpinx, and endometriosis according to the revised American Fertility Society criteria (Revised American Fertility Society, 1985).

The endpoint of this study is the number of diagnostic laparoscopies leading to a change in treatment decision where IUI is initially indicated. The results of the laparoscopies were classified as 'not altering treatment decision' and 'altering treatment decision'. The first group included patients for whom the final treatment decision was IUI. The second group included patients for whom subsequent treatment was necessary: 1) directly laparoscopic treatment of intra abdominal abnormalities (such as ablation of endometriotic implants or adhesiolysis) followed by IUI treatment, 2) fertility increasing surgery by laparotomy, and 3) IVF treatment.

The final treatment decisions were correlated with symptoms (including chronic pelvic pain, dysmenorrhea, deep vaginal dyspareunia and chronic pelvic pain) and historical risk factors such as pelvic inflammatory disease (PID), abdominal surgery, sexually transmitted diseases (STD), previous intrauterine device (IUD) use and type of infertility (primary or secondary). The symptoms and historical risk factors were collected from the medical files.

Statistical Analysis

The prognostic variables were entered into a stepwise logistic regression model, with dependent variable 'change in treatment decision'. $P \leq 0.05$ was considered statistically significant.

Results

In the study period, 773 patients underwent a diagnostic laparoscopy as part of the infertility investigation. Of those patients, 495 had normal preliminary HSG findings and were eligible for inclusion in the analysis. All 495 patients underwent a full infertility investigation. The mean age of the patient at the time of laparoscopy was 33.1 years (SD 3.9) and mean infertility duration was 3.5 years (SD 2.1). Of the 495 laparoscopies performed 323 (65%) were normal and 172 (35%) revealed pathologic abnormalities (figure 1).

However, not all abnormal findings led to changes in patient care. Laparoscopy did not change the initial treatment decision in 371 (75%) patients, but did in 124 (25%) patients. The latter treatment decisions included direct laparoscopic surgery of the abnormal findings in 103 (20.8%) cases, fertility increasing operation by laparotomy in 13 (2.6%) cases and treatment with in vitro fertilization (IVF) in 8 (1.6%) cases.

Table 2 lists the specific abnormalities as found by diagnostic laparoscopy and their subsequent treatment decisions. Generally, endometriosis of several stages was the most frequent abnormality (111 from 172, 65%) discovered at laparoscopy. Laparoscopically corrected abnormalities were mainly minimal or mild endometriosis and periadnexal adhesions. Subsequently, the abnormalities were considered sufficiently corrected to allow IUI treatment following the laparoscopy.

In eight cases, IVF was considered on finding bilateral tubal abnormalities, such as peritubal adhesions and tubal occlusion. Surprisingly, six of these patients had neither symptoms nor risk factors that could explain the pathologic conditions found by laparoscopy. In the remaining two patients, one patient had a history of previous abdominal surgery and the other had a history of previous pelvic inflammatory disease.

Not all abnormal findings were treated. Fourteen cases of minimal endometriosis and 10 cases of one-sided periadnexal adhesions were not corrected during laparoscopy before proceeding to IUI treatment, because the surgeon judged the extent of the lesions to be too small to be of significance. More exactly, the severity of untreated minimal endometriosis was limited to less

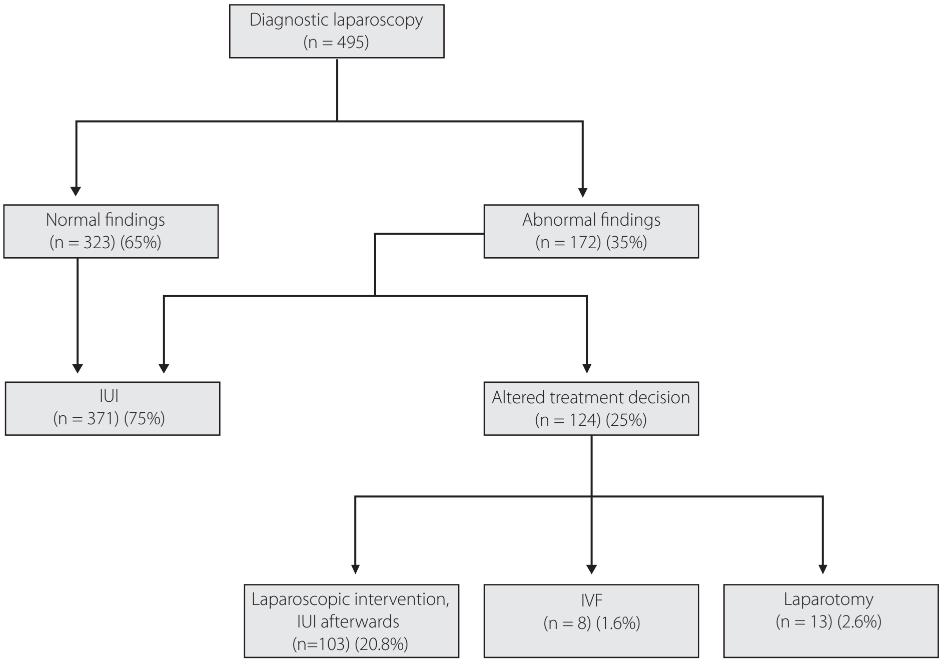

Figure 1. Findings and treatment decisions at laparoscopy

than four superficial spots and the severity of the untreated adhesions were one sided, filmy and enclosed less than one third of the adnex.

Moderate endometriosis was surgically corrected during diagnostic laparoscopy by bipolar coagulation or laser evaporation (five cases), while in two cases, moderate endometriosis was corrected during laparotomy because of the complex position of the lesions which were not

Table 2. Specific laparoscopic findings and subsequent treatment decisions

Laparoscopic findings	Treatment decision			
	IUI	Altered treatment decision		
		Direct laparoscopic intervention	Intervention by laparotomy	IVF
Normal findings	323	-	-	-
Peri-adnexal adhesions				
1-sided	10	7*	-	-
2-sided	-	7†	4||	3
Endometriosis				
Minimal	14	61‡	-	-
Mild	1	23§	-	-
Moderate	-	5	3	-
Severe	-	-	4	-
Frozen pelvis	-	-	1	2
Proximal tubal occlusion				
1-sided	12	-	-	-
Distal tubal occlusion				
Hydrosalpinx 1-sided	-	-	-	2¶
Phimosis 1-sided	1	-	-	1††
Phimosis 2-sided	-	-	1¶	-
Failure of hydrotubation**	10	-	-	-

* = including one case of 1-sided peritubal adhesions combined with 1-sided phimosis
† = including two cases of 2-sided peritubal adhesions combined with 1-sided phimosis
‡ = including six cases of endometriosis stage I combined with 1-sided occlusion
§ = including one case of endometriosis stage II combined with 1-sided tubal occlusion
|| = including one case of 2-sided adhesions combined with 1-sided phimosis
¶ = combined with 2-sided peritubal adhesions
†† = combined with contralateral periadnexal adhesions and contralateral proximal tubal occlusion
** = due to technical problems

Table 3. Symptoms and risk factors grouped by treatment decisions

Symptoms and risk factors	Treatment decision	
	IUI (n=371)	Altered treatment decision (n=124)
Chronic pelvic pain	2 / 367 (0.5%)	3 / 122 (2.5%)
Duration of infertility (years)	3.5 (±2.1)	3.5 (±1.9)
Dysmenorrhea	48 / 371 (12.9%)	14 / 124 (11.3%)
Dyspareunia	2 / 367 (0.5%)	3 / 119 (2.5%)
Infertility factor:		
Idiopathic infertility	215 (58%)	82 (66%)
Male subfertility	135 (36%)	40 (32%)
Cervical hostility	22 (6%)	2 (2%)
Previous abdominal surgery	53 / 369 (14.4%)	37 / 123 (30.1%) †
Previous IUD	43 / 371 (11.6%)	9 / 124 (7.3%)
Previous PID	10 / 369 (2.7%)	4 / 122 (3.3%)
Previous pregnancy	102 / 371 (27.5%)	39 / 124 (31.5%)
STD	11 / 371 (3.0%)	2 / 124 (1.6%)

IUD = intrauterine device; PID = pelvic inflammatory disease; STD = sexually transmitted disease
†= significant variable using stepwise regression analysis (P = 0.0005, OR = 2.41 [95% CI: 1.47 - 3.95])

approachable during laparoscopic surgery. In 27 (5.4%) cases HSG and diagnostic laparoscopy showed contrasting results. Although the HSG was judged as normal in these cases, laparoscopy revealed one-sided tubal occlusion in 20 cases, one-sided hydrosalpinx in 2 cases and phimosis in 5 cases.

The frequencies of symptoms and risk factors for pelvic disease are shown in table 3, grouped by final treatment decision. Stepwise regression analysis was performed to determine prognostic factors for altered treatment decisions. Variables included were symptoms (including chronic pelvic pain, dysmenorrhea, deep vaginal dyspareunia and chronic pelvic pain), historical risk factors (including pelvic inflammatory disease, abdominal surgery, sexually transmitted diseases, previous intrauterine device use and type of infertility [primary or secondary]) and infertility factor diagnosed before laparoscopy (idiopathic infertility, male subfertility or cervical hostility).

This analysis revealed only one significant variable, namely previous abdominal surgery (P = 0.0005, OR = 2.41 [95% CI: 1.47 - 3.95]). In the subgroup of patients with previous abdominal surgery, those with altered treatment decisions were more likely to have periadnexal adhesions (15 cases) including one frozen pelvis, minimal and mild endometriosis (19 cases) and moderate and severe endometriosis (3 cases) than those patients whose treatment had not changed. If these patients were excluded from analysis, laparoscopy still revealed abnormalities which lead to altering treatment decisions in 21% (86 of 402) of cases.

Overall, there were four (0.8%) severe perioperative complications which included a perforation of the colon that was discovered two days after laparoscopy and resulted in operative intervention by laparotomy and additional treatment with antibiotics. In two cases, the laparoscopy was complicated by an arterial bleeding after insertion of the first trocart, and, in one of these cases, a laparotomy had to be performed to stop the bleeding. Postoperative infection of the wound was seen in one patient, resulting in admission to hospital for i.v. treatment with antibiotics. In all cases the complications were resolved after treatment without permanent physical damage. Minor complications were seen in two cases, namely an uncomplicated perforation of the uterus and a rash due to an allergic reaction to the anaesthetics.

Discussion

This study shows that diagnostic laparoscopy alters treatment decisions in 25% of patients who would have been treated with IUI if this test had not been performed. These retrospective data suggest that the diagnostic laparoscopy may be of considerable value even after a normal HSG, provided the change of treatment is effective. However, some comments should be given on the specific laparoscopic findings and subsequent change of treatment decisions.

Abnormal findings were directly treated by laparoscopic intervention in 21% of patients. These interventions were mainly surgical treatment of minimal and mild endometriosis or periadnexal adhesions. Subsequently, additional treatment with IUI was recommended. In these cases, it is questionable whether the diagnostic laparoscopy should be considered as effective, because it is still a matter of debate whether such lesions affect fertility and whether treatment of these lesions results in higher pregnancy rates for IUI.

The reported prevalence of endometriosis found at laparoscopy in infertile women is 25 to 35%, where as the prevalence in the general population is 3 to 10% (Gruppo Italiano per lo Studio dell'Endometriosi, 1994; Guzick *et al*., 1994; Olive and Schwartz, 1993; Strathy *et al*., 1982). This high prevalence of endometriosis in infertile women has led to the assumption that there might be a causal relationship between infertility and the presence of endometriosis. The negative influence on fertility of moderate and severe endometriosis is plausible because of impaired tubal motility and ovum-pickup function, but the pathophysiological mechanisms of minimal and mild endometriosis have not yet been clarified.

Whatever the cause, there is evidence that surgical treatment of minimal and mild endometriosis increases fecundity in infertile patients. In a large randomized trial of laparoscopic ablation of minimal and mild endometriosis versus no treatment in infertile women, Marcoux *et al* concluded that fecundity doubled in the treatment group (Marcoux *et al*., 1997).

The outcome of this study is supported by other non-randomized cohort studies (Chong *et al*., 1990; Fayez *et al*., 1988; Hughes *et al*., 1993; Seiler *et al*., 1986) and a prospective study comparing laparoscopic laser vaporization, laparoscopic electrocoagulation, medical treatment and no treatment (Chang *et al*., 1997). They concluded that surgery was more effective than either no treatment or medical treatment. In contrast, a recent Italian study using the same design as Marcoux *et al*. found no difference in fecundity rates after surgical treatment (Parazzini, 1999). However, the Italian study used a smaller sample size and has lesser power.

The prevalence of peritubal adhesions in infertile patients ranges from 10 - 23% (al Badawi *et al*., 1999; Cundiff *et al*., 1995; Henig *et al*., 1991; Opsahl *et al*., 1993; Wood, 1983). It is well recognized that adhesions can cause infertility by impairing tubal ovum pick-up; therefore, adhesiolysis seems to be the most logical choice of treatment. It has been shown that the mean pregnancy rate after laparoscopic adhesiolysis is 42% (Saravelos *et al*., 1995). However, this is based on the findings of non-controlled studies. There is only one non-randomized controlled study showing a significant higher cumulative pregnancy rate in the treated group (32 and 45% at 12 and 24 months of follow up) compared to the control group (11 and 16%; *p* ª 0.000) (Tulandi *et al*., 1990). Unfortunately, these data have never been confirmed in a prospective randomized study.

In contrast to our expectations, patients with unexplained infertility are not at higher risk of having pathology leading to a change in treatment decision compared to patients with a known infertility factor (male subfertility or cervical hostility). This is in agreement with the conclusions of Aytoz *et al*., which indicated no statistical difference between the number of laparoscopic abnormalities in the mild male group versus the normal male group (Aytoz *et al*., 1998). However, there was statistical difference between the severe male factor group and the normal male group suggesting the better the male, the worse the female as is described by the authors.

In our study population, a history of previous abdominal surgery increases the risk of abnormal findings that led to changing a treatment decision. Some authors believe that in patients with normal HSG and without any risk factor, the laparoscopy should be delayed until non surgical treatment appeared to be unsuccessful (Cundiff *et al*., 1995; Opsahl *et al*., 1993), because this is based on the fact that besides pelvic surgery (Bahamondes *et al*., 1994; Forman *et al*., 1993), other historical factors or symptoms such as PID, pelvic pain, previous IUD use, age, severe dysmenorrhea and dyspareunia are predictive of pelvic disease (al Badawi *et al*., 1999; Forman *et al*., 1993). Delaying laparoscopy after a certain number of unsuccessful IUI cycles could lead to a decrease of the total number of laparoscopies performed. In theory, the probability of finding clinically relevant abnormalities by laparoscopy could be higher, because patients without intra abdominal pathology would already become pregnant before laparoscopy. On the other hand, delaying laparoscopy might probably also lead to inappropriate treatment of IUI, which is also expensive and stressful to patients.

Others argue that laparoscopy should be omitted from the basic infertility work up before IUI after normal HSG. If we assume that the change of treatment resulting from laparoscopic findings is effective to the outcome of IUI treatment, then 25% of patients would have been incorrectly treated with IUI. Omitting laparoscopy would probably lead to lower pregnancy rates, longer times to achieve pregnancy and more patients receiving IVF treatment. This could be more cost effective. However, the success rate of IUI in patients with abnormalities that normally should be treated otherwise than IUI has never been investigated prospectively.

If diagnostic laparoscopy is performed routinely it should be realised that this is an invasive procedure and its routine performance would lead to a considerable increase in costs. Furthermore, if surgery to remove minimal and mild endometriosis does not improve pregnancy rates, then the laparoscopic yield would be 40 out of 495 (8.1%). Under these circumstances, the additional value of diagnostic laparoscopy after a normal HSG is very low.

Although this study reflects common clinical practice, the data, particularly pregnancy rates, are incomplete due to the retrospective design of the study. Because of the retrospective nature of this study, other sources of bias, such as interobserver variability of the assessment of laparoscopic abnormalities and the subsequent treatment decision, also may be present again a result of the retrospective nature of the study. To gain more insight in the correlation of pregnancy rates with laparoscopic findings and treatment decisions, further investigation is required.

In conclusion, diagnostic laparoscopy has altered treatment decisions in an unexpectedly high number of patients in case of male subfertility, cervical hostility and idiopathic infertility. This suggests that diagnostic laparoscopy may be of considerable value, provided the change of treatment decision is effective. These findings justify further prospective studies to ascertain the role (if any) and timing of laparoscopy and whether laparoscopic interventions of intra abdominal abnormalities are effective in increasing pregnancy rates after treatment with IUI.

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3

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

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Abstract

Objective: We questioned whether a laparoscopy should be performed after a normal hysterosalpingography and before starting intrauterine inseminations (IUI) in order to detect further pelvic pathology, and whether a postponed procedure after 6 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 endpoint 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 for the IUI first (IUIF) group. The laparoscopy was performed on 64 patients in the DLSF group, 10 patients withdrew their consent from participation and 3 patients (3%) became pregnant prior to laparoscopy. In the IUIF group 23 patients remained for laparoscopy because pregnancy did not occur after 6 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 in 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.

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.*, 2003a). Several studies describe risk factors for tubal pathology, such as previous abdominal surgery and previous pelvic inflammatory disease (PID). However, up to 68% patients without any of these risk factors can still possess abnormalities as shown by laparoscopy (Corson *et al.*, 2000; Donnez *et al.*, 1982; Musich and Behrman, 1982).

Several studies describe the accuracy of CAT and HSG with diagnostic laparoscopy (DLS) as gold standard. A meta-analysis of studies comparing Chlamydia antibody titers and laparoscopy for tubal patency and peritubal adhesions has shown that the discriminative capacity of Chlamydia antibody titers in the diagnosis of any tubal pathology is comparable to that of hysterosalpingography (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 can not 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 to 68% of cases, even after normal HSG (al Badawi *et al.*, 1999; Belisle *et al.*, 1996; Corson *et al.*, 2000; Cundiff *et al.*, 1995; Henig *et al.*, 1991; Opsahl *et al.*, 1993; Wood, 1983).

According to the World Health Organization (WHO) guidelines DLS is still recommended as minimal requirement in the investigation of infertility in the female (Rowe *et al.*, 1993). However, it remains a question whether DLS in general provides more information to further diagnosis and treatment decisions. There is a growing tendency to bypass DLS 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.*, 2003b). 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 in vitro fertilization (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 also 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 second 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 (Marcoux *et al.*, 1997). To demonstrate such a difference a large study sample of at least 1000 patients would have been necessary.

We decided first to asses whether the laparoscopy as diagnostic rather than a therapeutic tool yields more abnormal findings when performed after 6 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 6 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 of 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 $x10^6$ spermatozoa per milliliter, or less than 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 age < 39 years

Exclusion criteria were a history of pelvic operations 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 $x10^6$ 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, administered by numbered masked and sealed envelopes. Patients and gynecologists 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 (DLSF group). The other group started with IUI directly (IUIF group). In this group DLS 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 ongoing pregnancy or when six cycles of IUI were finalized by a DLS. 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, surgical treatment was performed, i.e. adhesiolysis or evaporation of endometriosis. In this latter group the patient was treated with a maximum of six cycles of IUI after the operative 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-thirds 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-thirds 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 luteinising 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 3 cycles of IUI in the natural cycle, then the patient could choose between continuation of 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 hyperstimulation 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 did not start on the 15th day after insemination, a pregnancy test was carried out.

Statistical analysis

The primary endpoint 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 alpha of 0.05 and power of 80%. Taking in 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 analyze continuous data, and the chi square 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 chi square test.

Results

Patients

Between March 2001 until 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%) vs. 43 (56%)] male subfertility [23 (30%) vs. 23 (30%)] and cervical hostility [10 (13%) vs. 11 (14%), p = 0.97], primary infertility [59 (77%) vs. 58 (75%), p = 0.85], age of the female [32.3 years (95% CI 31.4-33.1) vs. 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) vs. 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 (figure 1). The analysis was carried out according to the principle of intention-to-treat.

The group characteristics in patients who underwent laparoscopy were also 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 1).

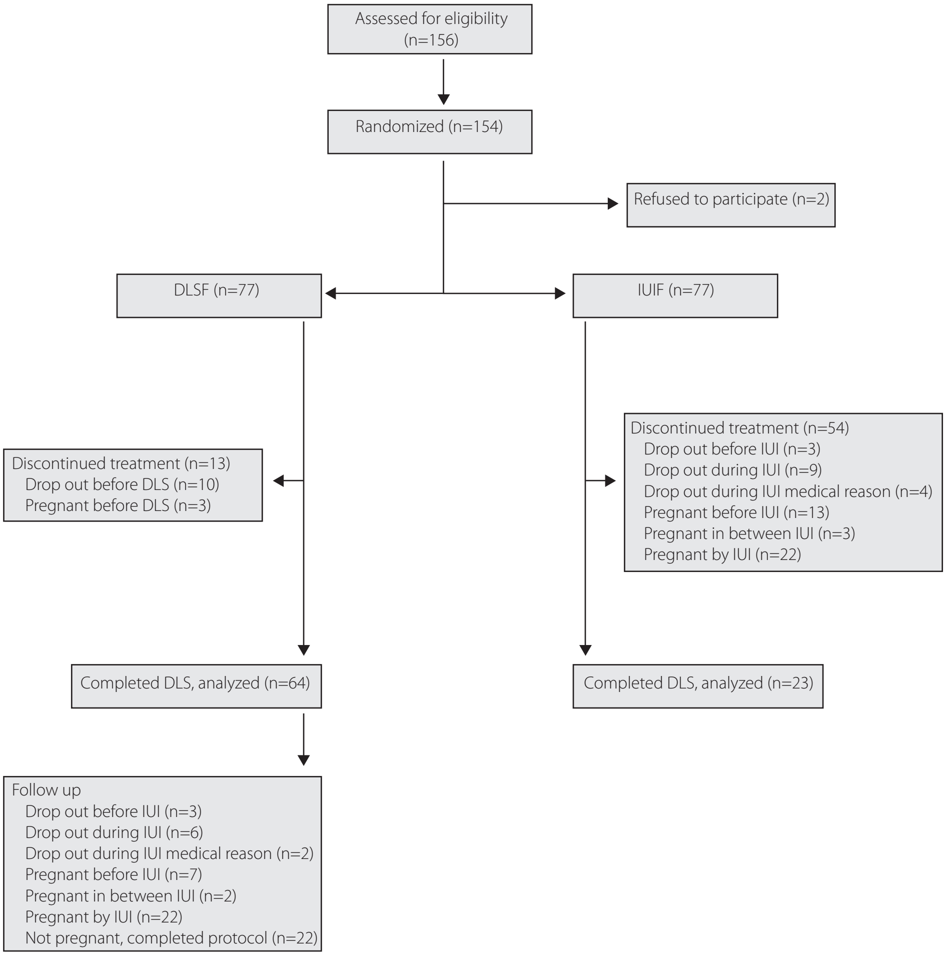

Figure 1. Trial profile

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 of these cases the abnormalities were evaporated or coagulated (table 2).

Table 1. Group characteristics

	DLSF (n=64)	IUIF (n=23)	P-value
Infertility factor			0.81
Idiopathic subfertility	37 (58%)	14 (61%)	
Male subfertility	18 (28%)	6 (26%)	
Cervical hostility	9 (14%)	3 (13%)	
Primary subfertility	51 (80%)	20 (87%)	0.54
Secondary subfertility	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 subfertility in years (95% CI)	2.9 (2.6-3.2)	2.9 (2.7-3.4)	0.93

Table 2. Findings and interventions by laparoscopy

	DLSF (n=64)	IUIF (n=23)	P- value	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%)****		

* = 2 unilateral adhesions, 1 bilateral adhesions
** = 22 stage I, 3 stage II, 2 stage III, 1 stage IV
*** = 11 stage I, 1 stage III,
**** = 1 bilateral hydrosalpinx and adhesions

Table 3. Pregnancy rate

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

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 2). 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).

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 2 natural pregnancies in between IUI treatment cycles. In the DLSF group, 22 patients became pregnant due to IUI treatment (table 3).

Of the 43 patients without an ongoing pregnancy rate in the DLSF group, 10 patients withdrew from participation prior to laparoscopy, three patients underwent laparoscopy but did not start IUI treatment at all and 6 patients stopped before finalizing 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 hyperstimulation 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 hyperstimulation 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 6 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, it would be necessary to take in account an alpha 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 on 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 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 (Chaffkin *et al.*, 1991; Crosignani and Walters, 1994; Dickey *et al.*, 1992; Dodson *et al.*, 1987; 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 extend.

Follow up of our study ended after six cycles of IUI. The subsequent obvious question concerns what 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 for 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.*, 2003b). Most likely, this 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 observation bias yielded higher number abnormalities because the surgeons were aware that the patients participated in a study. The clinical protocol for systematic classification of laparoscopic findings in our clinic is part of the routine procedure for many years, and it was the same during the retrospective study and the current study. Therefore, we consider the latter type of bias not likely.

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 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 (resp.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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4

Diagnostic laparoscopy is needed after abnormal hysterosalpingography to prevent overtreatment with IVF

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Abstract

Objective: We investigated the additional value of laparoscopy with respect to diagnosis and further treatment decisions after an abnormal hysterosalpingogram (HSG) and prior to intrauterine insemination (IUI).

Methods: In a retrospective chart review we evaluated the number of patients with an abnormal HSG who finally need IVF treatment based on the laparoscopic findings.

Results: Independent of whether the HSG showed unilateral or bilateral tubal pathology, IVF was the final treatment decision in only 74 (29%) cases because laparoscopy showed bilateral abnormalities. IUI treatment was advised in 121 (48%) patients with laparoscopically normal findings or unilateral abnormalities. Fifty-seven (23%) patients were treated by IUI after receiving laparoscopic surgery of unilateral adhesions or endometriosis stage 1-2 or after ablation of moderate-severe endometriosis in a second operation. In case of bilateral tubal abnormalities on the HSG, bilateral pathology was confirmed by laparoscopy in at least 58 (46%) patients and they were advised to be treated by IVF after laparoscopy.

Conclusions: The agreement between an abnormal HSG and abnormalities found by laparoscopy requiring IVF treatment was poor even when the HSG showed bilateral pathology. Based on these findings we conclude that laparoscopy is mandatory after an abnormal HSG in the work up prior to IUI to prevent overtreatment with IVF.

Introduction

The value of a hysterosalpingography (HSG) and diagnostic laparoscopy to evaluate mechanical factors of subfertility has been extensively studied. For this evaluation laparoscopy remains the gold standard. In the era where cost effectiveness becomes more important, it is debatable whether the laparoscopy should always be a mandatory step in the infertility work up after HSG. In recent publications the role of laparoscopy in the treatment of infertility is debated once again, particularly in the treatment of endometriosis related infertility (Hershlag and Markovitz, 2005; Littman *et al.*, 2005; Penzias, 2005).

In patients who are going to be treated with intrauterine insemination (IUI), patency of at least one tube should be proven before progressing to IUI. This is based on the fact that bilateral occlusion detected at laparoscopy impairs fecundity almost to zero whereas unilateral occlusion does not significantly lower natural pregnancy rates (Mol *et al.*, 1999). Although the pregnancy outcome of IUI in patients with bilateral occlusion at laparoscopy has never been described in a prospective study, it seems intuitively logical that in these cases IVF should be the preferred treatment option.

The accuracy of the HSG depends on its specific findings as described by a meta-analysis assessing the diagnostic value of the HSG compared to laparoscopy as gold standard (Swart *et al.*, 1995). Due to its low sensitivity of 0.65 the HSG is of limited use for detecting tubal patency and hardly reliable in the assessment of adhesions or endometriosis (Swart *et al.*, 1995). On the other hand HSG is a useful test for tubal obstruction and the authors concluded that confirmation of laparoscopy is not necessary if the HSG shows tubal obstruction (Swart *et al.*, 1995). In the case of a normal HSG, the additional value of laparoscopy is very limited in the detection of those patients who should be treated with IVF instead of IUI, because the probability of revealing tubal pathology requiring IVF is approximately 2% (Tanahatoe *et al.*, 2003).

In patients who are going to be treated with IUI, laparoscopy is still a standard procedure in our clinic after a HSG with abnormal results before progressing to IUI. In the IVF era, it seems cost effective to omit the laparoscopy especially in the case of bilateral abnormal findings at HSG such as bilateral obstruction as stated by Swart et al (Swart et al 1995). In contrast, recent studies showed that the predictive value of HSG for predicting tubal pathology and occurrence of pregnancy is poor and that the routine use of HSG in the fertility work up should be reconsidered (Perquin *et al.*, 2006; Perquin *et al.*, 2007).Therefore the aim of this study was to gain more insight into the additional value of laparoscopy with respect to diagnosis, further treatment decisions after abnormal HSG and prior to IUI and additional costs.

Methods

We retrospectively reviewed the medical records of all patients who had a diagnostic laparoscopy after an abnormal HSG as part of the infertility work up and a clinical indication for IUI in the VU University Medical Centre in Amsterdam, during the period January 1995 to December 1999 because computerized records were available of this period. Before the start of this study approval of the institute's review board was provided. Clinical indications for IUI treatment included idiopathic infertility, male subfertility and cervical hostility. Male subfertility was diagnosed when at least 3 out of 5 semen samples showed a total sperm concentration less than 20 $x10^6$/ml, or less than 40% progressively motile spermatozoa and a history of infertility of at least 1 year. Cervical hostility was defined as a negative postcoital test, performed in good cervical mucus with intercourse between 6 and 18 h prior to the test in combination with normal semen samples and a history of infertility of at least 1 year. Idiopathic subfertility included all patients with normal findings at basal infertility work up regardless of the HSG and a history of infertility of at least 3 years.

The infertility work up, including the HSG and diagnostic laparoscopy, is described elsewhere (Tanahatoe *et al.*, 2003). Abnormal HSG was defined as unilateral or bilateral abnormalities of the tubes, such as obstruction of the tubes, hydrosalpinx, phimosis, suspicion of periadnexal adhesions or combinations of these abnormalities. Obstruction was defined as absence of spill of contrast medium and hydrosalpinx as distal obstruction of the tube with enlargement of it's width. Phimosis is defined as distal constriction of the tube with spill of contrast medium. Pocketing of contrast medium on the HSG is defined as periadnexal adhesions.

The laparoscopic findings were reported using a standard method in the surgery reports. For this study the surgery reports were reviewed and scored on the presence of periadnexal adhesions, tubal obstruction, hydrosalpinx, and endometriosis according to the revised American Fertility Society (AFS) criteria (Revised American Fertility Society, 1985).

Treatment decisions after laparoscopy depended on the findings during surgery according to a standard protocol. This included that in case of no abnormalities, unilateral obstruction or unilateral hydrosalpinx patients were treated by 6 cycles of IUI and subsequently 3 cycles of IVF. In cases of one sided periadnexal adhesions or endometriosis AFS stage 1-2 the treatment consisted of direct laparoscopic intervention or a second surgery in cases of endometriosis AFS stage 3-4, such as evaporation of deep infiltrating endometriosis by laparotomy. Six cycles of IUI were then followed by 3 cycles of IVF. If bilateral pathology was seen during laparoscopy such as bilateral obstruction of the tubes, bilateral hydrosalpinx, bilateral adhesions or a combination of these abnormalities, then the treatment advice after laparoscopy was IVF.

The main endpoint of this study was the number of patients with an abnormal HSG who were finally advised to undergo IVF treatment based on the laparoscopic findings. A logistic regression analysis was performed to identify the prognostic factors for abnormal laparoscopic findings requiring IVF treatment. The following signs and symptoms were put in the logistic regression analysis: chronic pelvic pain, dysmenorrhoea, dyspareunia, chronic pelvic pain, pelvic inflammatory disease (PID), abdominal surgery, sexually transmitted diseases (STD), previous intrauterine device (IUD) use and type of infertility (primary or secondary). A stepwise regression analysis was performed considering a P value of < 0.05 statistically significant.

To analyse the expected pregnancy rate and expected costs in various diagnostic strategies, the following 3 scenarios were analysed. In the first scenario laparoscopy is always performed after abnormal HSG. This is normal practice in our clinic. In cases of at least one patent tube present diagnosed by laparoscopy then 6 cycles of IUI and 3 cycles of IVF is given. In cases of bilateral pathology diagnosed by laparoscopy the patient is treated with 3 cycles of IVF. In the second scenario laparoscopy is only performed after a unilateral abnormal HSG. In cases of a bilateral abnormal HSG a maximum of 3 IVF cycles is performed immediately instead of the laparoscopy. In the third scenario the laparoscopy is omitted in any case of uni- and bilateral abnormal HSG and is followed by 3 cycles of IVF.

For the cost effectiveness calculation the following assumptions are made. In our clinic, a laparoscopy including hospital stay costs 728 euros and an intervention, such as adhesiolysis or evaporation of endometriosis, costs 217 euros extra. One cycle of IUI stimulated with recombinant FSH costs 648 euros and one IVF cycle costs 2333 euros (Goverde *et al.*, 2000). Pregnancy rate per cycle IUI is 9% in the case of patent tubes, 7% in the case of one tube patent and the pregnancy rate per IVF cycle is 22% not adjusted for women's age (Goverde *et al.*, 2000; Steures *et al.*, 2004).

Results

During the period 1995 – 1999 laparoscopy was performed in 252 patients after an abnormal HSG for completing the infertility work up and before starting a fertility treatment. The medical records of these patients were all reviewed. The mean age of the female was 33.4 years (SD 4.0 years). The mean infertility duration at time of laparoscopy was 3.2 years (SD 2.2 years).

The HSG showed unilateral pathology in 126 patients and bilateral pathology in the same number. Unilateral pathology found by HSG consisted of obstruction in 113 patients, hydrosalpinx in 4 patients and adhesions in 9 patients (table 1). Bilateral pathology on HSG included obstruction in 62 patients, hydrosalpinx in 8 patients, adhesions in 42 patients and a combination of bilateral abnormalities in 14 patients (table 2).

Laparoscopy showed normal findings in 88 out of 252 (35%) patients. Of these, the HSG showed unilateral pathology in 52 patients and bilateral pathology in 36 patients (table 1 and 2). Regardless of the abnormalities found by HSG, unilateral and bilateral pathology was diagnosed by laparoscopy

Table 1. Unilateral abnormalities on hysterosalpingogram (HSG) versus laparoscopic findings.

Laparoscopic findings	Unilateral abnormality on HSG			Total (%)
	Obstruction (%)	Hydrosalpinx (%)	Adhesions (%)	
Normal findings	49 (43)	0	3 (33)	52 (41)
Unilateral				
Obstruction	25 (22)	1 (25)	0	26 (21)
Hydrosalpinx	0	0	0	0
Adhesions	1 (1)	0	1 (11)	2 (2)
Bilateral				
Obstruction	3 (3)	2 (50)	0	5 (4)
Hydrosalpinx	0	0	0	0
Adhesions	5 (4)	1 (25)	2 (22)	8 (6)
Combination	3 (3)	0	0	3 (2)
Endometriosis				
stage 1-2	24 (21)	0	2 (22)	26 (21)
stage 3-4	3 (3)	0	1 (11)	4 (3)
Total	113	4	9	126

in respectively 47 (19%) and 73 (29%) patients. Endometriosis stage 1-2 was found in 35 (14%) cases and stage 3-4 in 9 (4%) cases.

Overall, HSG and laparoscopy showed similar results in 68 (27%) cases. Unilateral obstruction found by laparoscopy was seen by HSG in 25 out of 41 (61%) patients. Unilateral adhesions found by laparoscopy were seen by HSG in 1 out of 6 (17%) patients (table 1). Of all patients with bilateral obstruction found by laparoscopy, HSG showed similar results in 25 out of 33 (76%) patients, in case of bilateral hydrosalpinx 4 out of 4 (100%) patients, in case of bilateral adhesions 12 out of 29 (41%) patients and bilateral combined tubal pathology 1 out of 7 (14%) patients (table 2). In 4 cases HSG showed bilateral adhesions, which was in accordance with the findings of laparoscopy, showing adhesions as part of endometriosis stage 3-4.

Regarding the whole group, the HSG was not in accordance with the laparoscopic findings in 184 (73%) patients. False positive results of the HSG showing unilateral pathology were seen in 88 out of 113 (78%) cases of unilateral obstruction, 4 out of 4 (100%) cases of unilateral hydrosalpinx and 8 out of 9 (89%) cases of unilateral adhesions (table 1). Considering bilateral pathology shown by

Table 2. Bilateral abnormalities on hysterosalpingogram (HSG) versus laparoscopic findings.

Laparoscopic finding	Bilateral abnormality on HSG				Total (%)
	Obstruction (%)	Hydrosalpinx (%)	Adhesions (%)	Combination (%)	
Normal findings	14 (23)	1 (13)	18 (43)	3 (21)	36 (29)
Unilateral					
Obstruction	11 (18)	0	0	4 (29)	15 (12)
Hydrosalpinx	0	0	0	0	0
Adhesions	0	0	3 (7)	1 (7)	4 (3)
Bilateral					
Obstruction	25 (40)	0	2 (5)	1 (7)	28 (22)
Hydrosalpinx	0	4 (50)	0	0	4 (3)
Adhesions	4 (6)	3 (38)	12 (29)	2 (14)	21 (17)
Combination	2 (3)	0	1 (2)	1 (7)	4 (3)
Endometriosis					
stage 1-2	6 (10)	0	2 (5)	1 (7)	9 (7)
stage 3-4	0	0	4 (10)	1 (7)	5 (4)
Total	62	8	42	14	126

the HSG, the HSG showed false positive results in 37 out of 62 (60%) cases of obstruction, 4 out of 8 (50%) cases of hydrosalpinx, 30 out of 42 (71%) cases of adhesions and 13 out of 14 (93%) cases of combined tubal pathology (table 2).

Of all patients 504 tubes were evaluated. Of these tubes 257 showed obstruction at the HSG. Proximal tubal obstruction at HSG was seen in 87 cases. Proximal tubal obstruction at HSG was confirmed by laparoscopy in 33 of the 87 (38%) tubes versus 59 of the 170 (35%) tubes showing distal obstruction including hydrosalpinx at HSG confirmed by laparoscopy (odds ratio = 1.1; 95% CI=0.7-2.0). As no significant difference was found in the accuracy of HSG for the diagnosis of proximal and distal tubal occlusion patients were not separated according to these abnormalities in the analyses.

Of all patients in which the HSG showed unilateral abnormalities, laparoscopy showed no abnormalities in 52 (41%) cases, unilateral pathology in 28 (22%) cases and bilateral pathology in 16 (13%) cases. The latter group with bilateral pathology ended up receiving IVF treatment (table 3). In cases of bilateral abnormalities on the HSG, bilateral pathology was confirmed by laparoscopy

Table 3. Hysterosalpingogram (HSG) results versus laparoscopic findings and treatment.

HSG results	Laparoscopic findings and treatment (%)			
	No abnormality IUI	Unilateral abnormality IUI	Intervention-IUI	IVF
Unilateral pathology	52 (41)	20 (16)	38 (30)	16 (13)
Bilateral pathology	36 (29)	13 (10)	19 (15)	58 (46)
Total	88 (35)	33 (13)	57 (23)	74 (29)

in 57 (45%) cases. At least 58 (46%) patients were advised to be treated by IVF after laparoscopy including 1 case of frozen pelvis due to endometriosis stage 4 (table 3).

Considering all patients with an abnormal HSG, IVF was the final treatment decision in 74 (29%) cases because of bilateral abnormalities (table 3). IUI treatment was advised in 121 (48%) patients with laparoscopic normal findings or unilateral abnormalities. Fifty-seven (23%) patients were treated by IUI after laparoscopic surgery of unilateral adhesions (10 cases) or endometriosis stage 1-2 (38 cases) or after ablation of moderate-severe endometriosis (9 cases) in a second operation (table 3).

The frequencies of symptoms and risk factors for pelvic disease are shown in table 4, grouped by final treatment decision. Stepwise logistic regression analysis revealed 3 prognostic factors for laparoscopic abnormalities resulting in IVF treatment. These included idiopathic subfertility, bilateral pathology on HSG and previous STD.

In the first strategy where the laparoscopy would be performed after any case of abnormal HSG the expected pregnancy rate would be 67%, in the second scenario 60% and in the third scenario 53%. Subsequently, the costs per pregnancy are respectively 9555 euros, 9978 euros and 10,513 euros. This includes all treatment cycles.

Discussion

Our data show that laparoscopy after an abnormal HSG reveals in only 29% of the patients severe abnormalities requiring IVF. Regarding particularly those cases in which the HSG shows bilateral pathology, laparoscopy detects severe abnormalities requiring IVF up to 46%. Especially in cases of bilateral obstruction and bilateral hydrosalpinx on the HSG, laparoscopy confirmed these findings in 50-60% of the cases. These findings imply that after an abnormal HSG, even in cases of bilateral pathology such as obstruction, it is still worthwhile to perform laparoscopy, since in a considerable number of patients the severity of the laparoscopic findings is limited in such a way that IUI treatment remains an option.

Although it is likely that based on our data the laparoscopy cannot be omitted, it nevertheless might be more cost effective to leave out the laparoscopy after an abnormal HSG. Intuitively such a strategy could probably lead to lower costs per pregnancy. However surprisingly, our calculated expected costs per pregnancy were higher when the laparoscopy was completely left out of the diagnostic strategy. Furthermore, the pregnancy rate was also lower compared to the scenario in which laparoscopy was performed in any case. Although these are rough estimates based on retrospective analysis, it seems that leaving out laparoscopy does not necessarily lead to lower costs and it may have an adverse effect on the pregnancy rate. Obviously, to gain more insight into the costs and pregnancy rates further prospective studies are necessary.

Is there still a place for the HSG when the laparoscopy is always performed after a HSG in the work up for IUI? In our opinion the HSG is of considerable value, since laparoscopy reveals only 2% abnormalities requiring IVF after a normal HSG (Tanahatoe *et al.*, 2003). Also in cases of unilateral pathology on the HSG, only in 13% IVF was indicated after laparoscopy. In this group 57% had normal findings or at least one patent tube and 30% had minimal abnormalities such as endometriosis stage 1-2 and unilateral adhesions. In these particular situations it can be argued whether the laparoscopy should be omitted prior to IUI. It could be more useful to postpone the laparoscopy after a few cycles of IUI because the number of patients with IVF indication is small but not negligible. Furthermore, in a considerable number of patients minimal to mild endometriosis is found and immediately treated surgically during laparoscopy. This is in accordance with the recent European Society for Human Reproduction and Embryology (ESHRE) guideline (Kennedy *et al.*, 2005) since surgical treatment of minimal and mild endometriosis increases the natural pregnancy rate (Jacobson *et al.*, 2002). Whether such surgical treatment will also improve the success rate of IUI is still a question. Moreover, there is evidence suggesting that minimal and mild endometriosis treated surgically before starting IUI may increase the cycle pregnancy rate and reduce the time to pregnancy as published by Werbrouck et al. (Werbrouck *et al.*, 2006). Some even postulate that even after previous repetitive IVF failure, laparoscopic treatment of endometriosis might be useful in terms of pregnancy rate in women with endometriosis (Littman *et al.*, 2005). In our view, the HSG has still a place in the fertility work up since it is of practical value in the allocation of the laparoscopy within treatment strategies in case of a normal HSG but probably also in case of unilateral pathology on the HSG.

Besides bilateral pathology at HSG, idiopathic subfertility and a history of previous STD were significant risk factors for pelvic disease requiring IVF treatment and are in accordance with the findings of other publications (Grodstein *et al.*, 1993; Lalos, 1988). In a meta-analysis assessing the accuracy of HSG in the diagnosis of tubal patency comparing HSG and laparoscopy results per fallopian tube, a sensitivity of 65% and a specificity of 83% were calculated (Swart *et al.*, 1995). The authors concluded that the HSG is a useful test for ruling in tubal obstruction based on its higher specificity. They recommended that tubal obstruction should not be confirmed by laparoscopy implying that in cases of bilateral tubal obstruction or bilateral hydrosalpinx immediate IVF treatment is recommended. In our study, bilateral obstruction or hydrosalpinx found by laparoscopy were seen on the HSG in 78% of cases. However, of all bilateral obstructions and hydrosalpinx found by HSG 41% was confirmed by laparoscopy and were scheduled for IVF. If in these cases laparoscopy was omitted, then about 60% were incorrectly treated with IVF. A possible explanation for this discrepancy is that tubal spasm could play a role in some of these cases. Furthermore, especially in cases of bilateral hydrosalpinx diagnosed by laparoscopy bilateral salpingectomy prior to IVF is indicated in order to optimize IVF outcome (Johnson *et al.*, 2004; Ozmen *et al.*, 2007).

Of all tubes suspicious for hydrosalpinx at HSG 8 out of 20 (40%) were confirmed by laparoscopy. In 3 cases laparoscopy showed distal tubal obstruction, in 7 cases periadnexal adhesions and in 2 cases normal tubes were found. Misdiagnosis is probably made due to too high pressure or phimosis. There were no false negative results. Our findings, however, are not in accordance to those of Mol et al. (Mol *et al.*, 1996). They showed positive and negative likelihood rates of the HSG for hydrosalpinx of 5.8 and 0.64, meaning that the HSG is a good test for detecting, but not useful for ruling out, hydrosalpinx. They also postulated that this is probably due to technical artefacts such as insufficient pressure or differences in muscle tonus.

In conclusion, laparoscopy after an abnormal HSG reveals in a considerable number of patients normal findings and abnormalities not requiring IVF treatment even when the HSG is suspected for bilateral pathology. These findings suggest that an abnormal HSG in the work up prior to IUI should not immediately lead to IVF. Whether the laparoscopy in cases of unilateral obstruction should always be performed prior to IUI, or whether it should be delayed after a few cycles of IUI is still questionable. Further studies should be performed to gain more insight into the role of laparoscopy after an abnormal HSG in the work up prior to IUI in terms of pregnancy rates and additional costs.

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5

Total fertilization failure and idiopathic subfertility

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Submitted

Abstract

Background: To gain more insight in whether failure of intrauterine insemination (IUI) treatment in patients with idiopathic subfertility could be related to diminished fertilization, the aim of this study is to compare the fertilization of an initial IVF procedure after six cycles of IUI and the fertilization of an initial IVF procedure without preceding IUI cycles in couples with idiopathic subfertility.

Methods: We performed a complimentary analysis of a randomized controlled trial, in which the number of total fertilization failure (TFF) in the first IVF procedure after unsuccessful IUI was compared to those of IVF without preceding IUI in patients with idiopathic subfertility. These patients participated in a previous study that assessed the cost effectiveness of IUI versus IVF in idiopathic subfertility and were randomized to either IUI or IVF treatment.

Results: 45 patients underwent IVF after 6 cycles of unsuccessful IUI and 58 patients underwent IVF immediately without preceding IUI. In 7 patients the IVF treatment was cancelled before ovum pick. In the IVF after unsuccessful IUI group TFF was seen in 2 of the 39 patients (5%) versus 7 of the 56 patients (13%) in the immediate IVF group. After correction for confounding factors the TFF rate was not significantly different between the two groups (p=0.08, OR 7.4; 95% CI: 0.5-14.9).

Conclusion: Our data showed that TFF in the first IVF treatment was not significantly different between couples with idiopathic subfertility undergoing IVF after failure of IUI versus those couples undergoing IVF immediately without prior IUI treatment. Apparently, impaired fertilization does not play a significant role in the success rate of IUI in patients with idiopathic subfertility.

Introduction

It is generally accepted that patients with long term idiopathic subfertility should be treated with intrauterine insemination (IUI), because it is shown to be the most cost effective treatment (Goverde *et al.*, 2000). However, a considerable number of patients have not conceived after 6 cycles of IUI. The question remains why these couples do not conceive with IUI treatment. IUI is thought to increase pregnancy chances by enhancing the exposure of one or more female gametes to a large number of male gametes. However, it is possible that factors exist that impair fertilization, implantation and placentation that cannot be identified by extensive subfertility investigation.

It is hypothesized that impaired fertilization could be a result of oocyte or sperm dysfunction (Audibert *et al.*, 1989; Hull *et al.*, 1998; Wolf *et al.*, 1996). If impaired fertilization is one of the causes of subfertility, it could play a role in failure of IUI treatment and could result in fertilization failure of an IVF procedure in these patients. From this point of view, fertilization in vitro could be the ultimate test of sperm and/or oocyte function.

Gurgan et al showed in a retrospective case control study that patients with idiopathic subfertility undergoing IVF-ET after 4-6 unsuccessful IUI cycles showed significantly more total fertilization failure (TFF) events compared to patients undergoing IVF-ET because of tubal factor subfertility (Gurgan *et al.*, 1995). The incidence of TFF was 20.4% and 7.6% in the idiopathic and tubal factor group respectively ($P < 0.005$). Moreover, TFF tended to be repetitive in couples with idiopathic subfertility. This higher incidence of TFF events in couples with idiopathic subfertility may be attributed to elimination of couples with more fertilizable gametes in previous IUI cycles.

It has been shown that fertilization rates are lower in idiopathic subfertility compared to tubal factor subfertility (Audibert *et al.*, 1989; Mackenna *et al.*, 1992; Navot *et al.*, 1988). This appears to confirm the hypothesis that a fertilization factor could be an underlying cause of idiopathic subfertility. On the other hand, in couples with idiopathic subfertility directly undergoing IVF instead of IUI treatment, TFF does not necessarily persist during subsequent IVF cycles (Lipitz *et al.*, 1993). Whether fertilization failure in idiopathic subfertility plays a role in unsuccessful IUI, is unknown.

If it is proven that TFF is an undiscovered cause of unsuccessful IUI treatment and/or unsuccessful IVF in case of idiopathic subfertility, it could be useful to detect this factor in order to prevent unnecessary and costly treatment with IUI and/or IVF. Theoretically, aside from being a therapeutic procedure an IVF attempt could be a diagnostic test in vitro for fertilization, provided that the fertilization process in vitro reflects the same situation in vivo. If fertilization is present a couple can start IUI treatment. In case of TFF it could be more cost effective to change treatment into ICSI after an IVF attempt has resulted in total fertilization failure.

To gain more insight in whether failure of IUI treatment in patients with idiopathic subfertility could be related to fertilization failure, the aim of this study is to compare the number of TFF of an initial IVF procedure after six cycles of IUI with an initial IVF procedure without preceding IUI cycles in couples with idiopathic subfertility.

Materials and methods

Patients

We performed a complimentary analysis of a randomized controlled trial in which the occurrence of TFF in the first IVF procedure after unsuccessful IUI was compared to that of IVF without preceding IUI in patients with idiopathic subfertility. Patients with idiopathic subfertility who underwent IVF after 6 unsuccessful IUI cycles were compared to patients with idiopathic subfertility who underwent IVF immediately without preceding IUI treatment. These patients participated in a previous study that assessed the cost effectiveness of IUI versus (Goverde *et al.*, 2000) IVF in idiopathic and male subfertility . In that study, patients were randomized to either IUI or IVF treatment after they had given their informed consent. Those patients who underwent 6 cycles of IUI without a positive pregnancy test in the trial were offered IVF as standard patient care after they had left the trial.

For this study approval from the institute's review board was acquired. Couples affected by male subfertility were excluded to avoid bias of impaired semen quality on fertilization rate and TFF. Male subfertility was diagnosed if at least three out of five semen analyses showed a total motile sperm count of fewer than 20 million progressively motile spermatozoa in the ejaculate, and if the remainder of the subfertility investigation showed no additional abnormalities. Couples had been diagnosed as having idiopathic subfertility if no abnormality is found after full subfertility investigation and duration of subfertility of at least 3 years. Subfertility investigation consisted of a basal body temperature chart, a post coital test, a late luteal phase endometrial biopsy, a hysterosalpingography, a diagnostic laparoscopy and at least two semen samples.

IVF Procedure

The IVF procedure in all patients was carried out as described by Goverde et al (Goverde *et al.*, 2000). Women aged 38 years or younger underwent controlled ovarian hyperstimulation with a "long" protocol with gonadotropin-releasing-hormone agonist (Decapeptyl, Ferring, Copenhagen, Denmark). Gonadotropins were given in a daily dose of two to three ampoules (150–225 IU) of human menopausal gonadotropin (Pergonal, Ares Serono) or follicle-stimulating hormone, depending on the patient's age or previous response to gonadotropins. In women older than 38 years, a "short" stimulation protocol was applied. In both protocols, gonadotropin-releasing-hormone agonists and gonadotropins were discontinued if transvaginal ultrasonography showed the presence of at least one follicle with a diameter of at least 18 mm, and a minimum of three follicles of at least 16 mm in diameter. 36 h before follicle aspiration, 10 000 IU human chorionic gonadotropin was given unless the serum oestradiol concentration exceeded 20 000 nmol/L. Follicular aspiration guided by transvaginal ultrasonography was done under systemic analgesia (7·5 mg diazepam orally and 50 mg pethidine hydrochloride intramuscularly), and all follicles present were aspirated. The retrieved oocytes were cultured in Earls'+ medium (Sigma, St Louis, MO, USA), and inseminated with Percoll-processed spermatozoa 42 h after the human chorionic gonadotropin injection. We transferred a maximum of two pre-embryos in woman 35 years of age or younger, and of three pre-embryos in women older than 35 years, 48–72 h after oocyte retrieval.

The luteal phase was supported by three doses of progesterone (200 mg; Progestan, Nourypharma, Oss, Netherlands) intravaginally daily from the day of oocyte retrieval, or, in the case of breakthrough bleeding before the 13th day of the luteal phase under progesterone treatment, by 1500 IU human chorionic gonadotropin (Pregnyl, Organon, Oss, Netherlands) intramuscularly every 48 h, starting from the second day after oocyte retrieval until a pregnancy test was done at the 15th day after oocyte retrieval.

To prepare semen, fresh and liquefied ejaculates were processed over a Percoll gradient (40/90 gradient) by centrifugation at 750 g for 15 min. The pellet was resuspended in 2 mL Earls'+ medium. The isolated spermatozoa were spun down at 300 g for 7 min, and this pellet was resuspended in 2 mL of culture medium and stored in 5% carbon dioxide in air at room temperature. Just before insemination, the spermatozoa were spun down at 200 g for 7 min.

Insemination took place between 38 and 42 hours after hCG. Eighteen hours after the moment of insemination, the fertilization of the oocytes were estimated in terms of the number of pronuclei; oocytes with two or more pronuclei were included as fertilized.

Directly before the transfer procedure, the embryo development and morphology score were determined and the best embryos were selected. Each embryo was scored 1 to 4 according to its symmetry and the extend of fragmentation. Embryo transfer was generally executed on day 3 after oocyte retrieval. If only two or fewer embryos were available the transfer was performed on day 2 after oocyte retrieval.

Statistical analysis

The primary endpoint of the study was the incidence of TFF and secondary the mean fertilization rate of the first IVF procedure in both patient groups. TFF is defined as absence of fertilization of all inseminated oocytes. Fertilization rate was calculated as the number of embryos divided by the number of inseminated oocytes. To assess whether the groups were comparable, baseline characteristics were listed, such as age, primary or secondary subfertility, duration of subfertility and TPMC after processing.

Comparison of TFF and fertilization rate were calculated after correction of factors that could influence fertilization, such as age and total progressively motile sperm count (TPMC) after processing and differences in stimulation if any. For univariate analysis the student's *t* test was used to analyze continuous data and the χ^2 test for discrete data. For multivariate analysis logistic or linear regression analysis were used.

Results

Patients

In the initial study by Goverde et al. a total of 181 couples with idiopathic subfertility were randomized to either IUI or IVF (Goverde *et al.*, 2000). Of these, 120 patients were assigned to IUI and 61 to IVF. Of the patients who underwent IUI treatment first, 45 couples continued with IVF after unsuccessful IUI treatment, 36 patients became pregnant due to IUI, 39 patients stopped treatment before, during or after IUI treatment. Of the 61 patients assigned to IVF 58 actually obtained treatment and 3 patients withdrew their informed consent. As shown in table 1 baseline characteristics were comparable in both groups regarding age, duration of subfertility and primary subfertility (table 1).

During the stimulation phase 8 patients dropped out (table 2). These included 6 patients in the IVF after unsuccessful IUI group, five because of stimulation failure and one because of hyperstimulation. In this patient oocyte retrieval and in vitro fertilization was performed but embryo transfer did not take place. Two patients in the IVF immediately group dropped out because of stimulation failure so follicle aspiration was cancelled in these patients. One patient in the IVF after unsuccessful IUI group did not have any oocytes retrieved at follicle aspiration.

Table 1. Baseline characteristics

	IVF after unsuccessful IUI (n=45)	IVF immediately (n=58)	p-value
Female age in years (SD)	33.3 (3.9)	32.6 (3.7)	0.32
Duration of subfertility in years (SD)	5.2 (2.0)	4.7 (2.0)	0.22
Primary subfertility (%) Secondary subfertility (%)	33 (73%) 12 (27%)	45 (78%) 13 (22%)	0.62

Values are mean ± standard deviation unless indicated otherwise

Treatment outcome

Oocytes were retrieved and fertilized in 39 patients in the IVF after unsuccessful IUI group versus 56 in the group starting IVF immediately. The mean number of follicles, oocytes retrieved, embryos obtained and good quality embryos were not significantly different between groups (table 2). Surprisingly, total fertilization failure showed no difference between the groups, 2 out of 39 (5%) patients in the IVF after unsuccessful IUI group versus 7 out of 56 (13%) patients in the group starting IVF immediately (p=0.23, OR 0.38; 95% confidence interval (CI): 0.07-1.92). Even after adjustment for age and TPMC after processing TFF showed no difference between groups (p=0.08, OR 7.4, 95% CI 0.5-14.9). The mean fertilization rate too was not significantly different between groups, 67.8% in the IVF after unsuccessful IUI group versus 63% in the group starting IVF immediately (p=0.48). Also after adjustment for age and TPMC after processing the fertilization rate between both groups was not different with a p-value of 0.38.

A positive pregnancy test was seen in 11 (25%) and in 12 (21%) patients in respectively the IVF after unsuccessful IUI group and the group starting IVF immediately (p=0.64, OR 0.80; 95% CI: 0.31-2.03). There was no difference in clinical pregnancy rate or in ongoing pregnancy rate (table 2). In the IVF after unsuccessful IUI group 6 (13%) ongoing pregnancies were seen versus 9 (16%) in the other group (p=0.76, OR 0.84; 95% CI: 0.27-2.55).

Table 2. Treatment characteristics

	IVF after unsuccessful IUI (n=45)	IVF immediately (n=58)	p-value
Number of canceled cycles	6 (13%)[a]	2 (3%)[b]	0.15
Total number of follicles[c]	11.1 (7.6)	11.7 (6.0)	0.67
Total number of oocytes retrieved	9.2 (6.3)	9.7 (5.9)	0.66
Total motile sperm count ($x10^6$)[d]	21.3 (21.7)	26.3 (22.8)	0.28
Total number of embryos	6.4 (4.6)	5.5 (3.9)	0.35
Fertilization rate	68 (27.7)	63 (34.7)	0.48
Number of TFF	2/39 (5%)	7/56 (13%)	0.23
Positive pregnancy test (hCG>5IU/l)	11 (25%)	12 (21%)	0.64
Clinical pregnancy rate	8 (18%)	11 (19%)	0.88
Ongoing pregnancy rate	6 (13%)	9 (16%)	0.76

Values are mean ± standard deviation unless indicated otherwise

[a] 5 patients canceled due to abcence of ovarian response. 1 patient canceled due to hyperstimulation

[b] both canceled due to abcence of ovarian response

[c] follicles > 10 mm on day of hCG administration

[d] after preparation of semen samples used for insemination

Discussion

The nature of this study was to asses whether failure of IUI treatment in patients with idiopathic subfertility could be related to fertilization failure. Our data, however, showed that the incidence of TFF and the mean fertilization rate in the first IVF treatment were not significantly different between couples with idiopathic subfertility undergoing IVF after failure of IUI versus those couples undergoing IVF immediately without prior IUI treatment.

Although several studies showed lower fertilization rates and more often TFF in idiopathic subfertility compared to tubal subfertility (Audibert *et al.*, 1989; Gurgan *et al.*, 1995; Mackenna *et al.*, 1992; Navot *et al.*, 1988), our data suggest that the contribution of impaired fertilization to negative IUI outcome seems to be limited. On the contrary, the number of TFF was surprisingly high in those patients receiving IVF immediately compared to those receiving IVF after unsuccessful IUI treatment (13% respectively 5%), but not significantly different.

Whether TFF in the first IVF cycle actually reflects a fertilization disorder in vivo is a matter of debate. TFF is observed in 5-20% in couples with normal sperm count undergoing IVF, with a substantial recurrence rate of 30-67% (Barlow *et al.*, 1990; Molloy *et al.*, 1991; Roest *et al.*, 1998; Van der Westelaken *et al.*, 2005). In a prospective study comparing the efficacy of IVF and ICSI after TFF in a previous IVF attempt, the fertilization rate in a second cycle was significantly higher after ICSI than after IVF (48% respectively 11%, $P<0.001$). The TFF recurrence rate in this study was 67% in the second cycle of IVF (Westerlaken *et al.*, 2005). This high recurrence rate of TFF implies that TFF in the first cycle could reflect a fertilization disorder.

Whether such a fertilization disorder also leads to unsuccessful IUI outcome is still a question. Because TFF tends to be repetitive in a high number of patients and that TFF is more common in patients with idiopathic subfertility after 4-6 unsuccessful IUI cycles(Gurgan *et al.*, 1995), it is possible that unsuccessful IUI in idiopathic subfertility is associated with a fertilization disorder. Therefore, we hypothesized that the incidence of TFF would be higher in patients with idiopathic subfertility, who failed to become pregnant after IUI compared with those who underwent IVF immediately. If this would be the case in a substantial number of patients, it could be clinically relevant to find out if a diagnostic IVF procedure would prevent unnecessary treatment with IUI. In the contrary, we could not find a difference in the incidence of TFF between the groups. Apparently, if there is a fertilization factor, it does not play a significant role in the success rate of IUI in patients with idiopathic subfertility. Further prospective studies should be performed to investigate the role of fertilization failure and unsuccessful IUI in idiopathic subfertility.

In conclusion, our data showed that there is no evident relation between failure of IUI treatment and fertilization failure in the first IVF cycle. Therefore, performing a so called diagnostic IVF procedure to assess a possible fertilization factor would not contribute to a better and /or more cost-effective treatment strategy for couples with idiopathic subfertility and IUI remains the first treatment of choice.

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Influence of varicocele embolization on the choice of infertility treatment

6

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Abstract

Objective: We investigated whether embolization of a varicocele improves semen quality and enables less invasive modes of assisted reproductive technology (ART) in infertile men with a physically palpable varicocele confirmed by phlebography.

Methods: In a retrospective chart review, we compared fifty patients with varicoceles that were treated with embolization with 11 patients with untreated varicoceles (control group). In both groups the clinical varicoceles had been phlebografically confirmed.
The main outcome measures were semen characteristics and mode of ART before and after treatment.

Results: Median improvements of semen parameters, such as concentration and motility after processing, were significantly greater in the embolization group than in the untreated group. In the embolization group, semen samples improved to levels requiring less invasive modes of ART in significantly more patients than in the untreated group. Deterioration of semen samples, requiring more invasive techniques, was significantly more frequent in the untreated group than in the embolization group.

Conclusions: Embolization of a varicocele in infertile men significantly improved semen, such that much more often a less invasive form of ART than was planned before treatment became feasible. Embolization of a varicocele might even prevent further deterioration of semen samples to levels requiring more invasive ART.

Introduction

Whether varicocele repair still has a significant place in the treatment of male infertility is an extensively discussed issue. It is apparent that varicocele repair results in significant improvement in semen parameters (Schlesinger *et al.*, 1994) but its potential to improve the ability to conceive spontaneously remains controversial. There are only a few randomized controlled trials studying the effect of varicocele repair on spontaneous pregnancy rates, however, the results are conflicting probably owing to clinical and statistical heterogeneity and lack of methodological quality (Breznik *et al.*, 1993; Madgar *et al.*, 1995; Nieschlag *et al.*, 1998; Nilsson *et al.*, 1979; Yamamoto *et al.*, 1996).
In the era of improving success rates of advanced forms of assisted reproductive techniques (ART), the question whether varicocele repair affects the ability to conceive spontaneously is of less importance. More interesting is whether varicocele repair results in improvement of semen parameters such that a less invasive mode of ART can be applied. The choice of ART in male infertility depends on the extent of semen defects: increased severity of the defect warrants a more expensive, and more importantly, a technically and physically more invasive mode of ART, such as in vitro fertilization (IVF) or intra cytoplasmatic sperm injection (ICSI). From this point of view, the necessity of diagnosis and treatment of any possible cause of male infertility is still warranted before progressing to assisted reproduction, to minimize the use of these invasive and costly techniques. Treatment of varicocele by varicocelectomy or embolization significantly improves semen parameters (Nieschlag *et al.*, 1998). Observational, uncontrolled studies have shown that surgical treatment by varicocelectomy also results in such improvement of semen quality, such that 40-66% of the couples altered candidacy for another mode of ART (Cayan *et al.*, 2002; Matkov *et al.*, 2001). Whether the same effect might be seen after embolization, a less invasive technique than varicocelectomy, has not yet been reported. In our hospital, the male partner in infertile couples, who presents with impaired semen samples and a varicocele at physical examination, is offered phlebography for confirmation of the varicocele as the current standard of care. If the diagnosis is confirmed, then embolization will be performed in the same session.
To assess whether varicocele repair by embolization affects semen quality in terms of altered mode of ART in infertile men with impaired semen parameters, we identified patients who underwent embolization after phlebographic confirmation of the varicocele and compared changes in semen parameters and mode of ART with those of a control group of untreated infertile men with phlebografically confirmed varicoceles.

Materials and methods

We performed a retrospective data review of men who presented for infertility investigation at the Department of Reproductive Medicine of the 'Vrije Universiteit' Medical Centre (Amsterdam, The Netherlands) between January 1990 and December 2000, and who subsequently underwent phlebography as diagnostic test of their clinical varicoceles. Institutional Review Board Approval was obtained for the study.

A total of sixty-one patients were identified with complete pre- and postwash semen samples available for the period before and after phlebography and could be included for analysis. This includes 50 patients with varicoceles treated with embolization and 11 patients with untreated varicoceles who were used as control group. In both groups the clinical varicoceles had been phlebografically confirmed. Reasons for no treatment in the control group included the following: the catheter could not be positioned at the level of the insufficient vein (5 patients), inaccessibility of the anatomical position of the insufficient vein (4 patients), the procedure was complicated by luxation of the coil that could be pulled out after manipulation (1 patient), and in embolization was not performed due to extravasation of the spermatic vein (1 patient).

All patients were referred to our clinic for infertility investigation. The male infertility work up included physical examination, hormonal screening and semen analyses. Female infertility work up included patient's history, physical examination, a basal body temperature chart, selected endocrine laboratory tests when indicated, a postcoital test, a late luteal endometrial biopsy and a serial hysterosalpingogram. Male factor infertility was diagnosed if at least three out of five semen analyses showed a total sperm concentration of $< 20 \times 10^6$ spermatozoa per millilitre and/or a percentage of progressive motility of < 40%. Physical evaluation of the varicocele was performed in accordance with the World Health Organisation (WHO) criteria: grade I, only palpable during Valsalva manoeuvre; grade II, palpable in upright position at room temperature; grade III visible in upright position at room temperature.

Only patients diagnosed with male infertility and a clinical varicocele were offered phlebography as gold standard for the evaluation of the varicocele. The technique of phlebography involved selective catheterization of the internal spermatic vein via the right femoral route under local x-ray examination. After confirmation of the varicocele, embolisation of the spermatic vein was performed in the same setting using occluding platinum spring coils.

All patients had at least one semen sample with prewash and postwash semen analysis before and after phlebography. To be consistent we used the semen sample performed 1 to 3 months before embolization and the semen sample done 6-8 months after embolization for data analysis of this study. To prepare semen for post wash analysis, fresh and liquefied semen were processed by Percoll 40/80 gradient centrifugation.

The patients were stratified into four groups based on the postwash total progressively motile sperm count (postwash TPMC) of the semen sample before embolization. These groups were determined by their modes of ART that would have been performed instead of varicocele repair. Assisted reproductive technique includes any infertility treatment for male subfertility such as IUI, IVF and ICSI. IUI treatment is defined as a postwash TPMC of $> 1 \times 10^6$, IVF when the postwash TPMC is 0.6 to 1×10^6, ICSI when the postwash TPMC is 0.1 to 0.6×10^6 and patients are not eligible for any form of ART in cases of a postwash TPMC is $< 0.1 \times 10^6$. On the basis of postwash TPMC of semen samples after embolization, the patients were restratified into the same modes of ART and into an 'expectant management' mode defined as prewash normal semen parameters (total sperm concentration of $> 20 \times 10^6$ spermatozoa per millilitre and progressive motility of > 40%) and postwash TPMC of > 1 million.

Statistical analysis

Chi square analysis was used to compare changes in mode of ART after treatment in the group of patients who underwent embolization to the group of untreated infertile men with phlebografically confirmed varicoceles. Differences in change of semen characteristics before and after embolisation between the two groups were tested by the nonparametric Mann-Whitney U tests for continuous data with $p<0.05$ considered significant.

Results

Between the embolization and the phlebography-only group there were no significant differences in age (median [interquartile range]: 32.8 [30.1-37.2] years versus 34.3 [32.0-36.7] years), duration of infertility (3.2 [1.7-4.5] years versus 2.3 [1.8-4.6] years) and number of primary infertility (43[86%] versus 8{73%]). In the embolization group, unilateral varicocele was seen in 39 cases (grade I, II and III in 11, 20 and 8 patients) and the remaining 11 patients had bilateral disease (1 patient maximally grade I, 3 patients maximally grade II and 7 patients maximally grade III). In the phlebography only group, unilateral varicocele was seen in 9 patients (grade I, II and III in 4, 3 and 2 patients respectively) and bilateral disease was seen in 2 patients of maximally grade II. The distribution of the grades of the varicoceles in the embolization group was not significantly different compared to the phlebography only group ($p = 0.773$).

In the embolization group, the prewash total sperm concentration significantly increased from 4.6 (interquartile range 1.1 - 9.9) $\times 10^6$/mL to 5.3 (interquartile range 2.1 - 20.1) $\times 10^6$/mL after embolization ($p=0.015$). In the phlebography only group the median prewash total sperm concentration decreased from 5.5 (interquartile range 2.5 - 20.0) million per millilitre to 4.7 (interquartile range

Table 1. Median differences in semen parameters

Semen characteristic	Embolization	Phlebography only	p-value
Total sperm concentration (10^6/ml)	1.0 (-1.3 to 12.1)	-1.8 (-16.0 to 0.02)	0.009
Progressively motile spermatozoa (%)	14 (-2 to 32)	18 (2 to 33)	0.4
Postwash TPMC (10^6)	0.5 (0.03 to -3.9)	-0.3 (-1.2 to -0.1)	0.0005

Note: numbers are differences between semen parameter before minus after embolization, therefore the numbers can be negative in some cases. Values are medians (interquartile range).

Table 2. Number of patients assigned to the various modes of ART before and after treatment

Patient group	ART before	ART after				
		Exp. manag.	IUI	IVF	ICSI	Not eligible
Embolization						
IUI	9	2	5	1	1	0
IVF	3	1	1	1	0	0
ICSI	27	4	10	3	8	2
Not eligible	11	0	3	0	3	5
Phlebography only						
IUI	6	0	3	1	2	0
IVF	0	-	-	-	-	-
ICSI	3	0	0	0	2	1
Not eligible	2	0	0	1	0	1

Table 3. Number of patients assigned to another mode of ART after treatment

ART change	Embolization	Phlebography only	p-value
Upgraded	27 / 50 (54%)	1 / 11 (9%)	0.008
Degraded	4 / 39 (10%)	4 / 9 (44%)	0.031

1.7 - 10.6) million per millilitre (p=0.091). Differences in total sperm concentration before and after treatment were significantly greater in the embolization group than in the phlebography only group: 1.0 (interquartile range –1.3 - 12.1) x 10^6/mL and –1.8 (interquartile range –16.0 - 0.02) x 10^6/mL (p=0.009), see table 1.

The prewash percentage progressive motility increased from 23% (9-34%) to 37% (20-58%) in the embolization group and from 27.0% (7-33%) to 45.0% (33-57%) in the phlebography only group. The difference in percentage progressive motilility before and after embolization or phlebography alone was not statistically different between the groups, resp. 14% (–2 - 32%) and 18 % (2 - 33%)

(p=0.4.) However, the postwash TPMC increased from 0.2 (0.1 – 0.5) x 10^6 to 1.1 (0.2 – 4.6) x 10^6 after embolization with a median increase of 0.5 (0.03 – 3.9) x 10^6, which was significantly higher than in the phlebography only group in which a decrease in postwash TPMC was seen from 1.0 (0.2 - 2.4) x 10^6 to 0.4 (0.1 – 1.1) x 10^6 with median difference of –0.3 (–1.2 to -0.1) x 10^6 (p<0.0005), see table 1.

On the basis of the postwash TPMC of semen samples before embolization, 9 patients were assigned to IUI, 3 to IVF, 27 to ICSI and 11 were not eligible for any ART treatment in the embolization group. After embolization, improvement to another mode of ART in the treatment group was seen in 27 (54%) cases (table III). This included 2 patients primarily assigned to IUI who improved to expectant management, 2 patients primarily assigned to IVF improved to IUI and to expectant management, 17 patients assigned to ICSI who improved to expectant management (4 patients), to IUI (10 patients) and to IVF (3 patients), and 6 patients who were not eligible for ART improved to ICSI (3 patients) and to IUI (3 patients).

In the phlebography only group, 6 patients were assigned to IUI, 3 patients to ICSI and 2 patients were not eligible for any ART treatment before phlebography (table 2).

Improvement of semen parameters to another mode of ART after phlebography alone was seen in 1 (9%) patient who improved from being ineligible for any ART to IVF treatment. The number of patients improving to another mode of ART was significantly higher in the embolization group than in the phlebography only group, 56% versus 9% (p=0.008), see table 3.

In the embolization group, deterioration to another mode of ART was seen in 4 (10%) of 39 patients. Two patients assigned to IUI degraded after embolization, (1 to IVF and 1 to ICSI), and 2 ICSI patients degraded to being ineligible for any ART treatment. Deterioration to another mode of ART was seen in 4 of 9 patients (44%) in the phlebography only group, which was statistically greater than in the embolization group (p=0.031). This included 3 cases assigned to IUI of whom 2 degraded to IVF and 1 to ICSI, and 1 assigned to ICSI degraded to being ineligible for any ART treatment (table 2). For clarity, in the analysis of deterioration to another mode of ART we excluded patients who were not eligible for any ART treatment before phlebography owing to very severe semen defects, because in these cases further deterioration to another mode of ART was not possible. Overall, there were 13 patients who were not eligible for any ART treatment, (11 and 2 patients respectively in the embolization and phlebography only group).

Discussion

This controlled study shows that compared with no treatment embolization, of a physically palpable varicocele confirmed by phlebography in infertile men with impaired semen samples resulted in significant improvement of semen quality, thus making patientseligible for less invasive modes of ART. Besides this improvement in treatment modality, the embolization also resulted in higher levels of total sperm concentration and postwash TPMC. These findings support the hypothesis that varicocele repair might be useful before starting ART to allow less invasive ART treatment approaches.

Furthermore, improved sperm parameters per se lead to higher pregnancy rates of ART (Berg *et al.*, 1997; Donnelly *et al.*, 1998). Optimizing sperm quality is of great importance when it can make technically more complicated modes of ART, such as IVF and ICSI, unnecessary. Both those reproductive techniques require ovarian stimulation and ovarian puncture, which are a burden to patients and require extensive laboratory effort. In addition, taking in account the probability that ICSI might have adverse effects on the off-spring (Johnson, 1998), upgrading sperm quality such that the patient is eligible for IVF, IUI (or even has a normal sperm count) might be of benefit. Although we did not perform a cost benefit analysis, it is not unlikely that varicocele repair results in a reduction of costs, given that less invasive modes of ART are also less expensive. Others have shown that increased sperm parameters are associated with lower costs per delivery (Van Voorhis *et al.*, 1998).

In the present study, decreases in semen quality necessitating more difficult forms of ART were significantly greater in the phlebography-only group. This implies that embolization of a varicocele might also prevent further deterioration of semen quality to levels requiring more invasive forms of ART. This could mean that a varicocele is a progressively deleterious effect for sperm quality (Chehval and Purcell, 1992; Cozzolino and Lipshultz, 2001; Gorelick and Goldstein, 1993; Witt and Lipshultz, 1993). One follow up study of infertile male with a varicocele described a significant deterioration in sperm density and motility which suggests progressive testicular deterioration in these patients (Chehval and Purcell, 1992).

There are some limitations to our study. Owing to the retrospective design, pregnancy rates were not included because the long term follow-up after embolization or phlebography only was not always complete. For this reason we could not perform a reliable analysis with regard to costs per pregnancy. Another point of limitation is the small number of patients studied. Nevertheless, in spite the small group sizes, especially of the phlebography-only group, we actually found significant improving effects for embolization.

The phlebography only group may not be completely comparable to the embolization group. However, it was in our view the only control group that could be used in this retrospective data analysis. To the best of our knoledge, this is the first reported study on this subject that included a control group of patients undergoing no treatment; this provides further, though limited, insight in the effect of varicocele treatment in an ART setting.

Finally, it could be argued that selection bias might have occurred owing to the anatomical differences between varicoceles that allow embolization and those that do not, with implications for spermatogenesis (Jarow *et al.*, 1996). We cannot rule out this possibility; however, in this study the distribution of grades of varicoceles found by physical examination between groups was not different which implies that the observed deterioration of semen in the control group is not likely due to differences in varicocele size.

Ideally, further studies should be performed to gain more insight in to the effectiveness of embolization of varicoceles. To assess whether embolization of varicoceles improves semen such that a less invasive form of ART becomes feasible, a prospective trial should be performed randomizing patients to embolization before treatment with ART or direct treatment with ART without varicocele repair. The final endpoint should be costs per delivery. For the time being, because ICSI and IVF (especially ICSI) are invasive procedures that might have long-term adverse effects on offspring(11), embolization should be recommended to infertile patients with seminal defects and a phlebographically confirmed varicocele before progressing to further ART treatment.

In conclusion, this retrospective analysis shows that embolization of a varicocele in infertile men significantly improved semen such that (much more often than untreated patients) a less-invasive form of ART became feasible. Embolization of a varicocele might even prevent further deterioration of semen samples to levels requiring more invasive ART. These findings justify further prospective studies to gain more insight in to the effectiveness of varicocele treatment to seminal improvement and the additional costs. For the time being embolisation should have a place in ART.

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7

General Discussion

Parts of this chapter are based on the publication:

Investigation of the infertile couple: should diagnostic laparoscopy be performed in the infertility work up program in patients undergoing intrauterine insemination?

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This thesis aimed to gain more insight in which work-up strategies are necessary to perform IUI. To perform IUI, conditions such as an adequate quantity and quality of progressively motile spermatozoa, the presence of ovulation, functional fallopian tubes, the capability of fertilization of the gametes and implantation of the embryo are required. To evaluate which work-up strategies are useful to analyze these conditions and/or how to optimize them prior to IUI, we studied the accuracy and timing of diagnostic laparoscopy after HSG to analyze tubal function, the role of fertilization failure in idiopathic subfertility in order to asses whether the ability to fertilize should be tested prior to IUI and the role of embolization of a varicocele in order to optimize semen quality.

Tubal function

The role of the diagnostic laparoscopy prior to IUI was evaluated in several ways. We studied the value of the diagnostic laparoscopy 1) after normal HSG, 2) after abnormal HSG in terms of laparoscopic findings leading to a change of treatment modality and 3) whether a postponed procedure after 6 unsuccessful cycles of IUI yields a higher number of abnormal findings after normal HSG.

The value of diagnostic laparoscopy after a normal HSG

First, we studied the accuracy of diagnostic laparoscopy after normal HSG and prior to IUI with respect to laparoscopic findings leading to a change of treatment decisions. This retrospective analysis showed that diagnostic laparoscopy altered treatment decisions in an unexpectedly high number of patients after a normal HSG and before IUI. This suggests that laparoscopy may be of considerable value, provided the change in treatment is effective.

In our study, most laparoscopic findings concerned tubal adhesions and minimal or mild endometriosis. In these cases, laparoscopy was not only diagnostic but also therapeutic, because of laparoscopic removal of tubal adhesions and coagulation or laser evaporation of endometriosis. Therefore, the use of "diagnostic" laparoscopy in infertility work up is in addition potentially of clinical value for improving pregnancy rate through interventions.

In case of adhesions, there are no studies comparing fecundity rate after laparoscopic adhesiolysis to no treatment. Only one non-randomized study compared open adhesiolysis versus no treatment and found significantly more pregnancies in the treatment group compared to the control group (Tulandi *et al.*, 1990).

Concerning treatment of endometriosis, there are two randomized controlled trials comparing laparoscopic ablation of minimal and mild endometriosis with no treatment (Marcoux *et al.*, 1997; Parazzini, 1999). The largest study of Marcoux et al. showed an increased effect, but on the contrary, the smaller study of Parazzini et al. could not show a difference. A systematic review combining the results of these two trials showed that surgical treatment is favourable instead of expectant management (OR for pregnancy 1.6; 95% CI: 1.1-2.6) (Jacobson *et al.*, 2002). However, the authors stated that the relevant trials have some methodological problems. Therefore, the outcome of this review should be interpreted carefully until further research in this area is performed.

The reported prevalence of endometriosis found at laparoscopy in subfertile women is 25-35%, where as the prevalence in the general population is probably 3-10% (Candiani *et al.*, 1991; Gruppo Italiano per lo Studio dell'Endometriosi, 1994; Guzick *et al.*, 1994; Olive and Schwartz, 1993; Strathy *et al.*, 1982). This high prevalence of endometriosis in infertile women has led to the assumption that there might be a causal relationship between subfertility and the presence of endometriosis.

In severe stages of endometriosis, the negative influence on fertility can be understood by the impaired tubal motility and ovum pick up function, but in less severe stages the pathofysiology can not fully be explained by this mechanism and some hypothesize that immunological factors may play a role in endometriosis-associated infertility (Harada *et al.*, 2001). Although the mechanism of subfertility associated with minimal and mild endometriosis remains unclear, treatment with controlled ovarian hyperstimulation and IUI enhances monthly pregnancy rates compared to that of expectant management in subfertile patients with minimal to mild endometriosis (Deaton *et al.*, 1990; Tummon *et al.*, 1997; Werbrouck *et al.*, 2006). There is also evidence that medical treatment by gonadotrophin-releasing hormone agonist of minimal and mild endometriosis prior to IUI enhances the pregnancy rate of IUI (Kim *et al.*, 1996). Future studies should determine if prior surgical treatment in these cases will increase pregnancy rates after IUI or whether directly proceeding to IUI would be equally or more beneficial. However, it is not unlikely that the laparoscopic surgical treatment will significantly enhance pregnancy rates of IUI, since surgical treatment increases spontaneous pregnancy rates.

So, there is some evidence that laparoscopic surgery of the most frequently found abnormalities leads to higher fecundity rates. It seems therefore quite logical that the same effect counts for pregnancy rates after IUI. So far, this has not yet been demonstrated. In theory, assuming that the change of treatment resulting from laparoscopic findings is effective to the outcome of IUI treatment, then 25% of the patients would have been incorrectly treated with IUI, if diagnostic laparoscopy had not been performed as is shown in chapter 2. This means that not performing the laparoscopy may lead to lower pregnancy rates or to longer time to achieve pregnancy. Furthermore, if direct treatment with IVF after unsuccessful IUI is applied, then this strategy could also lead to more patients ending up in IVF treatment.

However, the success rate of IUI in patients with abnormalities that normally should be treated otherwise than with IUI has never been investigated prospectively or when to time diagnostic laparoscopy in patients who normally are scheduled for IUI. Further studies should assess whether diagnostic laparoscopy is effective prior to IUI in terms of pregnancy rates and in terms of number of abnormal findings with clinical consequences. Additionally, it should be studied if delayed performance of diagnostic laparoscopy after a few unsuccessful cycles of IUI instead of prior to IUI is more effective in terms of pregnancy rates and number of abnormal findings. Furthermore, the effect of laparoscopic interventions of intra abdominal abnormalities should be assessed in terms of pregnancy rates of IUI treatment.

The value of a postponed diagnostic laparoscopy

Given the invasive and costly nature of the laparoscopy, we investigated the timing of the laparoscopy and questioned if the laparoscopy should always be performed before starting IUI or if it should be postponed after a few unsuccessful cycles of IUI. Theoretically, along the way of 6 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 performed to a higher yield of abnormal findings with clinical implications.

Therefore we performed a randomized controlled trial comparing the accuracy of a standard laparoscopy prior to IUI to a laparoscopy performed after 6 unsuccessful cycles of IUI. This trial showed that laparoscopy performed after 6 cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences in comparison to those performed prior to IUI treatment.

This is in contrast to our initial hypothesis. We expected a concentration of patients with laparoscopic abnormalities among those who did not become pregnant, but our results showed no difference. We speculate that this concentration did not substantially occur, because there is probably no profound change in pregnancy rate upon the laparoscopic intervention that was done prior to the IUI procedure. A possible absence of a substantial effect on pregnancy rate of the laparoscopic intervention could be explained on two ways. In the first place it is possible that most of the observed and treated abnormities, including minimal and mild endometriosis and adhesions, play a minor or no role in subfertility, and secondary it could be that the applied intervention is ineffective. This however seems to be contrasting to existing data. As already mentioned in the former section, 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 to the outcome of expectant management (Jacobson *et al.*, 2002). 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 (Chaffkin *et al.*, 1991; Crosignani and Walters, 1994; Dickey *et al.*, 1992; Dodson *et al.*, 1987; 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 compared with the prevalence after 6 cycles of IUI. Apparently such minimal and mild endometriosis and adhesions probably impair the IUI outcome to a very limited extend.

In summary, these findings suggest that the impact of the detection and the laparoscopic treatment of observed pelvic pathology prior to IUI seem negligible in terms of IUI outcome. Based on this outcome we question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. For future research prospective randomized studies should be performed to determine the effect of laparoscopic interventions, such as evaporation or coagulation of minimal and mild endometriosis and adhesiolysis, on the success rate of IUI in terms of pregnancy rate.

The value of the diagnostic laparoscopy after an abnormal HSG

Furthermore we investigated the additional value of laparoscopy with respect to diagnosis and further treatment decisions after an abnormal HSG and prior to IUI. Our data showed that laparoscopy after an abnormal HSG reveals in only 29% of the patients severe abnormalities requiring IVF. Regarding particularly those cases in which the HSG shows bilateral pathology, laparoscopy detects severe abnormalities requiring IVF up to 46%. Especially in case of bilateral obstruction and bilateral hydrosalpinx on the HSG, laparoscopy confirmed these findings in 50-60% of the cases. These findings imply that after an abnormal HSG, even in case of bilateral pathology such as obstruction, laparoscopy is still worthwhile to perform, since in a considerable number of patients the severity of the laparoscopic findings is limited in such a way that IUI treatment remains an option.

Based on these findings we conclude that laparoscopy is still mandatory after an abnormal HSG in the work up prior to IUI to prevent overtreatment with IVF. Whether the laparoscopy in case of unilateral obstruction should always be performed prior to IUI, or whether it should be delayed after a few cycles of IUI, is still questionable.

Is there still a place for the HSG when the laparoscopy is always performed after a HSG in the work up for IUI? Regarding its test characteristics, a sensitivity of 0.65 and a specificity of 0.83 for tubal patency, the clinical significance of HSG is limited (Swart *et al.*, 1995). However, we strongly suggest not abandoning the HSG from the work up prior to IUI. As shown in chapter 2 laparoscopy reveals only in 2% abnormalities requiring IVF in patients with a normal HSG (Tanahatoe *et al.*, 2003).

In our opinion, HSG should be used in the strategy for the decision whether the laparoscopy should be performed prior to IUI or not, because the prevalence of tubal pathology at laparoscopy after normal HSG is very low. In case of a normal HSG the laparoscopy should be omitted prior to IUI and in case of abnormal HSG results a diagnostic laparoscopy should be performed prior to further treatment. In such a strategy, the HSG can prevent unnecessary laparoscopies in a considerable amount of patients. Such a strategy does not compromise the pregnancy rate as described by Perquin et al. (Perquin *et al.,* 2006). They showed in a randomized trial that the cumulative pregnancy rate was similar in a strategy where the fertility work up included a HSG prior to diagnostic laparoscopy compared with a strategy without HSG. However, the authors concluded that the HSG instead of the laparoscopy is the unnecessary test and that the HSG should be omitted. Further prospective studies should be performed to analyze which diagnostic strategy is most cost-effective.

Chlamydia antibody testing is a non-invasive method in the diagnosis of tubal pathology. The accuracy of Chlamydia antibody titers in the diagnosis of any tubal pathology is comparable to that of hysterosalpingography (HSG) in the diagnosis of tubal occlusion (Mol *et al.*, 1997). If the definition of any tubal pathology is changed into extensive adhesions and/or bilateral distal tubal occlusion, the positive and negative likelyhood ratio (LR) are improved (Land *et al.*, 1998). In the selection which patients are likely to benefit from laparoscopy prior to IUI, the role of the CAT is debatable. Can the CAT replace the HSG and if so, does it influence the pregnancy rate of IUI in a strategy where a normal CAT is followed by IUI treatment instead of further tubal patency testing? Patients with relatively poor prognostic fertility prospects benefit from a strategy starting with HSG with regard to cost-effectiveness and in case of relatively good fertility prognosis the strategy should start with CAT (Mol *et al.*, 2001). In patients who already have an indication to be treated with IUI because of impaired semen samples or long-term subfertility, a strategy starting with HSG instead of CAT is probably more cost-effective because this population has a relatively poor prognostic fertility prospect. However, a recent study showed that a combination of medical history taking and CAT testing improves the selection of patients for laparoscopy instead of either medical history taking alone or CAT testing alone (Coppus *et al.*, 2007). Further studies should be performed whether CAT and medical history taking is of value compared to the HSG in the selection for laparoscopy prior to IUI.

For future research we suggest to perform a randomized controlled trial comparing several strategies where the laparoscopy is in- or excluded depending on the findings of the HSG and the CAT in patients undergoing IUI. The main outcome should be pregnancy rate, time to pregnancy and costs. For the time being, we suggest a laparoscopy after abnormal HSG results.

Fertilization

We analysed the possible role of impaired fertilization in patients with idiopathic subfertility and unsuccessful IUI in order to assess whether there is a place for a diagnostic IVF procedure to evaluate fertilization before progressing to IUI. In a complimentary analysis of a previous randomized controlled trial (Goverde *et al.*, 2000) we compared the number of total fertilization failure of an initial IVF procedure after six cycles of IUI with the number of total fertilization failure of an initial IVF procedure without preceding IUI cycles in couples with idiopathic subfertility. In contrast to our hypothesis, the analysis did not show more cases of total fertilization failure in patients undergoing IVF after unsuccessful IUI.

Although several studies showed lower fertilization rates and more often TFF in idiopathic subfertility compared to tubal subfertility (Audibert *et al.*, 1989; Mackenna *et al.*, 1992; Navot *et al.*, 1988), our findings imply that there is no evident relation between failure of IUI treatment and total fertilization failure in the first IVF cycle. Performing a so called diagnostic IVF procedure to assess a possible fertilization factor would not contribute to a better and /or more cost-effective treatment strategy for couples with idiopathic subfertility and IUI remains the first treatment of choice.

Sperm quality and the role of varicocele embolization

One of the aims of this thesis was to study the role of embolization of a varicocele in the subfertile male in order to optimize semen quality providing a less invasive mode of ART. Our data showed that embolization of a varicocele in subfertile males significantly improved semen, such that much more often a less invasive form of ART became feasible than was planned before treatment. Additionally, embolization of a varicocele may even prevent further deterioration of semen samples to levels requiring more invasive ART.

In male subfertility associated with a varicocele, the effectiveness of its treatment in relation to natural pregnancy is debated. A systematic review evaluating the effect of varicocele treatment on pregnancy rate in subfertile couples, showed no beneficial effect of varicocele treatment over expectant management in subfertility couples in whom varicocele in the man is the only abnormal finding (Evers *et al.*, 2001). However, in the era of ART it is of interest whether varicocele repair results in any improvement of semen parameters allowing application of less invasive mode of ART. Furthermore, improvement of sperm parameters per se lead to higher pregnancy rates of ART (Agarwal *et al.*, 2007; Berg *et al.*, 1997; Donnelly *et al.*, 1998). Our findings and the results of other studies evaluating the surgical effect of varicocelectomy support the hypothesis that varicocele repair might be useful before starting ART in allowing less invasive ART treatment approaches (Cayan *et al.*, 2002; Matkov *et al.*, 2001; Tanahatoe *et al.*, 2004). Considering the fact that these studies are uncontrolled, we recommend to perform further prospective randomized studies assessing the effect of varicocele embolization in view of improvement of semen parameters, improvement of ART modality and, most important, improvement of ART outcome in terms of pregnancy and live birth

Epilogue and recommendations for future research

In this thesis, we studied the accuracy and timing of diagnostic laparoscopy after HSG to analyze tubal function, whether the ability to fertilize should be tested prior to IUI and the role of embolization of a varicocele in order to optimize semen quality.

Tubal function

We showed that diagnostic laparoscopy altered treatment decisions in an unexpectedly high number of patients after a normal HSG and before IUI. This suggests that laparoscopy may be of considerable value, provided the change in treatment is effective. Additionally, we showed that laparoscopy performed after 6 cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences in comparison to those performed prior to IUI treatment. These findings suggest that the impact of the detection and the laparoscopic treatment of observed pelvic pathology prior to IUI seem negligible in terms of IUI outcome. As a consequence, we question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. For future research prospective randomized studies should be performed to determine the effect of laparoscopic interventions, such as evaporation or coagulation of minimal and mild endometriosis and adhesiolysis, on the success rate of IUI in terms of pregnancy rate.

In case of an abnormal HSG we conclude that laparoscopy is still mandatory in the work up prior to IUI to prevent overtreatment with IVF. For future research it might be useful to perform a prospective randomized trial comparing several strategies where the laparoscopy is in- or excluded depending on the findings of the HSG. The main outcome should be pregnancy rate, time to pregnancy and cost effectiveness.

In summary, there are no convincing data to perform the diagnostic laparoscopy routinely after a normal HSG and prior to IUI, or to postpone the laparoscopy after six unsuccessful IUI cycles. In case of an abnormal HSG, we recommend to perform a diagnostic laparoscopy routinely prior to further treatment even when the HSG shows bilateral obstruction.

Fertilization

Our data showed that TFF and the fertilization rate in the first IVF treatment were not significantly different between couples with idiopathic subfertility undergoing IVF after failure of IUI versus those couples undergoing IVF immediately without prior IUI treatment. Apparently, impaired fertilization does not seem to play a major role in the success rate of IUI in patients with idiopathic subfertility. Therefore, we do not recommend a diagnostic IVF procedure prior to IUI in couples with couples with idiopathic subfertility.

Sperm quality and the role of varicocele embolization

We concluded that embolization of a varicocele in subfertile men significantly improved semen in such a way that much more often a less invasive form of ART became feasible as was planned before treatment. Furthermore, we found that embolization of a varicocele might even prevent further deterioration of semen samples to levels requiring more invasive ART. Therefore, in our opinion, there is still a place for treatment of a varicocele in order to improve semen prior to fertility treatment. However, we recommend performing a randomized controlled trial to study the effectiveness of the embolization of a varicocele versus no treatment in order to find out whether there is an increasing effect on sperm parameters, improvement of ART modality and most importantly improvement in ART outcome in terms of pregnancy and live birth.

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Summary

To perform IUI some conditions are required. This includes 1) a certain amount of progressively motile spermatozoa, 2) the presence of ovulation, 3) the presence of functional fallopian tubes, 4) the capability of fertilization of the gametes and 5) the ability of implantation of the embryo. The aim of this thesis is to asses which work-up strategies are necessary to perform IUI in relation to functional tubes, fertilization and semen quality.

Chapter 1

Chapter 1 gives an overview which diagnostic tests are available to analyze the above mentioned conditions required to perform IUI and how to optimize these factors prior to IUI. Furthermore, the aim and outline of the thesis is described in this chapter.

Chapter 2

This chapter evaluates the accuracy of diagnostic laparoscopy after normal hysterosalpingography (HSG) and prior to intrauterine insemination (IUI) with respect to laparoscopic findings leading to a change of treatment decisions in couples with male subfertility, cervical hostility or idiopathic subfertility. This cohort study evaluates the prevalence of laparoscopic findings leading to change in treatment decision in subfertile patients who had undergone diagnostic laparoscopy after a normal HSG and before IUI in a period of 5 years. Of 495 patients, 4% had severe abnormalities which resulted in a change of treatment to in vitro fertilization (IVF) or open surgery. In 21% abnormalities such as endometriosis (stage I-II) and adhesions, were directly treated by laparoscopic intervention, followed by IUI treatment. Based on these findings we conclude that diagnostic laparoscopy altered treatment decisions in an unexpectedly high number of patients before IUI. This suggests that laparoscopy may be of considerable value, provided the change in treatment is effective. Further prospective studies are required to assess whether the diagnostic use of laparoscopy is cost effective and whether interventions as result of laparoscopic findings are effective in improving pregnancy rates.

Chapter 3

In this chapter we question if a laparoscopy after a HSG should be performed before starting IUI in order to detect further pelvic pathology, and whether a postponed procedure after 6 unsuccessful cycles of IUI yields a higher number of abnormal findings. In a randomized controlled trial the accuracy of a standard laparoscopy prior to IUI is compared to a laparoscopy performed after 6 unsuccessful cycles of IUI. The major endpoint was the number of diagnostic laparoscopies

revealing pelvic pathology with consequence for further treatment, such as laparoscopic surgical intervention, IVF or secondary surgery.
We found that laparoscopy performed after 6 cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences in comparison to 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 seem negligible in terms of IUI outcome. Based on our findings, we question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. However, before bypassing diagnostic laparoscopy after a normal HSG and prior to IUI, further prospective studies of sufficient power should be performed to determine the effect of laparoscopic interventions on the success rate of IUI treatment in order to completely rule out the laparoscopy from the diagnostic route prior to IUI.

Chapter 4

This chapter investigated the additional value of laparoscopy with respect to diagnosis and further treatment decisions after an abnormal HSG and prior to IUI. Independent whether the HSG showed unilateral or bilateral tubal pathology, IVF was the final treatment decision in only 29% because laparoscopy showed bilateral abnormalities. IUI treatment was advised in 48% because the laparoscopy showed normal findings or unilateral abnormalities. 23% were treated by IUI after receiving laparoscopic surgery of unilateral adhesions or endometriosis stage 1-2 or after ablation of moderate-severe endometriosis in a second operation. In case of bilateral tubal abnormalities on the HSG, bilateral pathology was confirmed by laparoscopy in at least 46% of the patients and they were advised to be treated by IVF after laparoscopy. Regarding these findings the correlation between an abnormal HSG and abnormalities found by laparoscopy requiring IVF treatment is poor even when the HSG shows bilateral pathology. Based on these findings we conclude that laparoscopy is mandatory after an abnormal HSG in the work up prior to IUI to prevent overtreatment with IVF.

Chapter 5

To gain more insight in whether failure of IUI treatment in patients with idiopathic subfertility could be related to diminished fertilization, the aim of this study is to compare the number of total fertilization failure of an initial IVF procedure after six cycles of IUI with the number of toltal fertilization failure of an initial IVF procedure without preceding IUI cycles in couples with idiopathic subfertility. Therefore we performed a complimentary analysis of a randomized controlled trial in which the number of total fertilization rate (TFF) in the first IVF procedure after unsuccessful IUI was compared to those of IVF without preceding IUI in patients with idiopathic subfertility. These patients participated in a study that assessed the cost effectiveness of IUI versus IVF in idiopathic subfertility and were randomized to either IUI or IVF treatment. In this study, we found that the TFF rate was not significantly different between groups. Impaired fertilization apparently does not seem to play a role in the success rate of IUI in patients with idiopathic subfertility. Therefore, a diagnostic IVF procedure is probably not effective to prevent unsuccessful IUI.

Chapter 6

This chapter studies the role of embolization of a varicocele in subfertile men with impaired semen parameters in order to optimize semen quality and to enable use of less invasive modes of ART.

By means of a retrospective chart review 50 patients with varicoceles who were treated with embolization and 11 patients with untreated varicoceles were compared. In both groups the clinical varicoceles had been phlebografically confirmed. The main outcome measures included semen characteristics and mode of ART before and after embolization. Median improvements of semen parameters such as concentration and motility after processing were significantly higher in the embolization group than in the untreated group. In the embolization group, semen samples improved to levels requiring less invasive modes of ART in significantly more cases than in the untreated group. Deterioration of semen samples requiring more invasive techniques, was significantly more frequent in the untreated group than in the embolization group. We concluded that embolization of a varicocele in subfertile men significantly improved semen, such that much more often a less invasive form of ART than was planned before treatment became feasible. Embolization of a varicocele might even prevent further deterioration of semen samples to levels requiring more invasive ART. These findings justify further prospective studies to gain more insight in the effectiveness of varicocele treatment on sperm parameters, improvement of ART modality and improvement in ART outcome in terms of pregnancy rate.

Chapter 7

The findings of the studies described in this thesis are summarized and discussed in this chapter. In the evaluation of the fallopian tubes we concluded that laparoscopy may be of considerable value after a normal HSG and prior to IUI, provided the change in treatment is effective.

We showed that laparoscopy performed after 6 cycles of unsuccessful IUI did not detect more abnormalities with clinical consequences in comparison to those performed prior to IUI treatment. Based on our findings, we question the value of routinely performing a diagnostic and/or therapeutic laparoscopy prior to IUI treatment. However, before bypassing diagnostic laparoscopy after a normal HSG and prior to IUI, further prospective studies of sufficient power should be performed to determine the effect of laparoscopic interventions on the success rate of IUI treatment in order to completely rule out the laparoscopy from the diagnostic route prior to IUI.

We concluded that laparoscopy is still mandatory after an abnormal HSG in the work up prior to IUI to prevent overtreatment with IVF, because a diagnostic laparoscopy after an abnormal HSG reveals in a small number of patients severe abnormalities requiring IVF and in a considerable number of patients the severity of the laparoscopic findings is limited that IUI treatment remains an option.

Evaluation of fertilization prior to IUI is not recommended, because we found no evident relation between failure of IUI treatment and diminished fertilization in the first IVF cycle.

In case of semen quality we found that embolization of a varicocele in subfertile males significantly improved semen that a less invasive form of ART became feasible as was planned before treatment. Furthermore, embolization of a varicocele may even prevent further deterioration of semen samples to levels requiring more invasive ART. Therefore we think that embolisation should have a place in assisted reproductive technology. Furthermore, we recommend a randomized controlled trial to gain more insight in the effectiveness of varicocele embolization to seminal improvement, improvement of ART modality and improvement in ART outcome in terms of pregnancy rate.

Nederlandse samenvatting

Om de behandeling met intrauteriene inseminaties (IUI) zo optimaal mogelijlk te laten verlopen zijn een aantal factoren noodzakelijk. Deze factoren betreffen 1) voldoende progressief motiele spermatozoa, 2) het optreden van een ovulatie, 3) doorgankelijke tuba fallopii, 4) het optreden van de bevruchting en 5) het optreden van implantatie. In dit proefschrift wordt onderzocht welke onderzoeksstrategieen nodig zijn voorafgaand aan IUI ter analyse en het optimaliseren van doorgankelijkheid van de tubae, bevruchting en semen kwaliteit.

Hoofdstuk 1

Dit hoofdstuk geeft een overzicht van welke diagnostische testen beschikbaar zijn voor de analyse van de bovengenoemde factoren, die nodig zijn om IUI te kunnen verrichten. Tevens worden de mogelijkheden om de genoemde factoren te optimaliseren besproken. Aansluitend wordt het doel en de opzet van dit proefschrift uiteengezet.

Hoofdstuk 2

In dit hoofdstuk wordt de accuraatheid van de diagnostische laparoscopie na een normaal hysterosalpingogram (HSG) en voorafgaand aan intrauteriene inseminatie (IUI) bestudeerd. Om te onderzoeken hoe vaak de bevindingen bij laparoscopie tot een beleidswijziging hebben geleid, werd een cohortonderzoek verricht. Dit cohort betrof alle subfertiele patiënten die in een periode van 5 jaar een laparoscopie hebben ondergaan in het kader van het orienterend fertiliteitsonderzoek. Alleen patienten met een IUI-indicatie en een normaal HSG werden geanalyseerd. Van de 495 patienten werden bij 172 patienten (35%) intra-abdominale afwijkingen geconstateerd. Bij tenminste 124 van de 495 patienten (25%) werden afwijkingen gezien die ook daadwerkelijk therapeutische consequenties hebben gehad.

Deze therapeutische consequenties betrof directe laparoscopische coagulatie of laserevaporisatie van minimale en milde endometriose (AFS graad I-II) en milde peritubaire adhaesies bij 103 patienten (21 %). Bij 13 patienten (2.6%) werd besloten tot fertiliteitsbevorderende chirurgie middels laparotomie vanwege ernstige peritubaire adhaesies, matige tot ernstige endometriose (AFS graad III-IV) en bilaterale distale tubaobstructie. Tenslotte werd bij 8 patienten (1.6%) tot IVF besloten vanwege zeer uitgebreide peritubaire adhaesies, hydrosalpinx en bilaterale tubaobstructie

Samengevat wordt bij 1 op de 4 patienten met een IUI-indicatie bij laparoscopie afwijkingen gevonden die leiden tot een andere behandeling dan IUI. Dit suggereert dat de diagnostische laparoscopie mogelijk van aanzienlijke toegevoegde waarde is zelfs na een normaal HSG onder de aanname dat de veranderde behandeling ook leidt tot betere zwangerschapskansen. Nader prospectief onderzoek zou moeten uitwijzen of de diagnostische laparoscopie na een normaal

HSG en voorafgaand aan IUI voldoende effectief is en of laparoscopische interventie van de gevonden afwijkingen daadwerkelijk leidt tot betere zwangerschaps kansen.

Hoofdstuk 3

In een gerandomiseerde studie wordt de effectiviteit van de timing van de laparoscopie geevalueerd bij patienten die IUI ondergaan en een normaal HSG hebben. Hierbij wordt het aantal afwijkingen met consequentie voor verdere behandeling vastgesteld middels de laparoscopie, welke verricht is voorafgaand aan IUI-behandeling, vergeleken met de laparoscopie verricht na 6 onsuccesvolle cycli IUI. In de groep waarbij de laparoscopie na 6 onsuccesvolle IUI behandelingen werd verricht, werden niet meer afwijkingen gevonden ten opzichte van de laparoscopie verricht voorafgaand aan de IUI-behandeling. Op basis van deze gegevens kan geconcludeerd worden dat het afwezig zijn van een significante toename in afwijkende bevindingen na 6 onsuccessvolle IUI behandelingen doet vermoeden dat de bijdrage van de laparoscopie op de uitkomst van IUI beperkt zou kunnen zijn. Als gevolg hiervan twijfelen wij aan de waarde van het routinematig uitvoeren van de diagnostische en/of aansluitend therapeutische laparoscopie voorafgaand aan de IUI-behandeling. Nader prospectief onderzoek van voldoende power zou verricht moeten worden om meer inzicht te krijgen in het effect van laparoscopische interventies op de uitkomst van IUI.

Hoofdstuk 4

In dit hoofdstuk wordt de toegevoegde waarde van de laparoscopie ten aanzien van de diagnose en verdere behandeling na een afwijkend HSG onderzocht bij patienten met een IUI-indicatie. Na een afwijkend HSG, ongeacht of er sprake was van een- of tweezijdige afwijkingen, werd middels de laparoscopie in slechts 29% van de gevallen tweezijdige afwijkingen geconstateerd waarna besloten werd tot IVF. Behandeling middels IUI werd geadviseerd in 48% gezien de laparoscopie geen of eenzijdige afwijkingen toonde. Drieentwintig procent onderging IUI-behandeling na laparoscopische behandeling van unilaterale adhesies, endometriose AFS graad 1-2 of na ablatie van endometriose AFS graad 3-4 tijdens een tweede operatie. In de groep met tweezijdige tuba afwijkingen op het HSG bleek 46% ook tweezijdige tubaafwijkingen te hebben bij de laparoscopie en werd er besloten tot IVF-behandeling. Op basis van deze bevindingen wordt geconcludeerd dat de correlatie tussen een afwijkend HSG en de afwijkingen vastsgesteld middels laparoscopie met IVF-behandeling als gevolg zeer matig is, ook als het HSG tweezijdige afwijkingen vertoond. Als gevolg hiervan concluderen wij dat het verrichten van de laparoscopie na een afwijkend HSG bij patienten met een IUI-indicatie noodzakelijk is ter preventie van overbehandeling met IVF.

Hoofdstuk 5

Om meer inzicht te krijgen of onsuccesvolle IUI-behandeling gerelateerd is aan verstoorde fertilisatie bij idiopathische subfertiliteit, wordt in dit onderzoek de fertilisatie van een eerste IVF procedure na 6 onsuccesvolle IUI cycli vergeleken met die van een eerste IVF procedure zonder voorafgaande IUI-behandeling bij patienten met idiopathische subfertiliteit. Hiervoor werd een aanvullende analyse verricht van een prospectief gerandomiseerde studie. Het aantal totale fertilisatiefalen (TFF) in de groep die IVF onderging na 6 onsuccesvolle IUI-cycli werd vergeleken met het aantal TFF in de groep die direct IVF onderging zonder voorafgaand IUI. De onderzochte patienten participeerden in een studie die de kosten-effectectiviteit van IUI versus IVF evalueerde en werden in die studie gerandomiseerd voor 6 cycli IUI danwel IVF. Na correctie voor confounders zoals leeftijd en totaal aantal progressief motiele spermatozoa, was het percentage TFF niet significant verschillend tussen de groepen. Waarschijnlijk speelt verstoorde fertilisatie geen rol in het al dan niet slagen van de IUI-behandeling bij patienten met idiopathische subfertiliteit. In dit kader is het verrichten van een diagnostische IVF-procedure niet zinvol.

Hoofdstuk 6

Dit hoofdstuk bestudeert de plaats van het emboliseren van een varicocele bij subfertiele mannen. Het doel van de embolisatie is het optimaliseren van de semenkwaliteit met als gevolg dat een minder invasieve voortplantingsbehandeling mogelijk wordt.

Door middel van een retrospectief onderzoek worden 50 patienten met een varicocele die een embolisatie hebben ondergaan vergeleken met 11 patienten met een varicocele die geen behandeling hebben gekregen. In beide groepen werden de palpabele varicoceles bevestigd middels phlebografie. De primaire uitkomstmaten betroffen semenkarakteristieken en de voortplantingsbehandeling voor en na de embolisatie. De spermaconcentratie en motiliteit na bewerking bleek in de embolisatie groep significant hoger dan in de onbehandelde groep. Tevens verbeterde de semenkwaliteit in die mate dat in significant meer patienten een minder invasieve vorm van voortplantingsbehandeling toegepast kon worden ten opzichte van de onbehandelde groep. Bovendien werd frequenter een verslechtering van semenkwaliteit waargenomen in de onbehandelde groep, waardoor juist een meer invasieve manier van voortplantingsbehandeling toegepast zou moeten worden.

Op basis van bovenstaande gegevens kunnen we concluderen dat embolisatie van een varicocele bij subfertiele mannen semenkwaliteit in die mate kan verbeteren dat een minder invasieve manier van voortplantingsbehandeling toegepast kan worden. Embolisatie van een varicocele bij subfertiele mannen lijkt ook verslechtering van de semenkwaliteit te voorkomen. Op basis van deze bevindingen zou nader prospectief onderzoek gerechtvaardigd zijn om meer inzicht te krijgen in de effectiviteit van de behandeling van de varicocele middels een embolisatie.

Hoofdstuk 7

De bevindingen van de studies die beschreven zijn in dit proefschrift worden in dit hoofdstuk samengevat en bediscussieerd.

Ten aanzien van de evaluatie van de doorgankelijkheid van de tubae kan geconcludeerd worden dat de laparoscopie verricht na een normaal HSG en voorafgaand aan IUI van aanzienlijk waarde zou kunnen zijn op voorwaarde dat de beleidswijziging ook effectief is. Vervolgens werd een prospectief gerandomiseerd onderzoek verricht naar de timing van de laparoscopie na een normaal HSG. Dit onderzoek wees uit dat in de groep waarbij de laparoscopie verricht werd na 6 onsuccesvolle IUI cycli niet meer afwijkingen werd gevonden ten opzichte van de groep die de laparoscopie voorafgaand aan IUI onderging. Dit doet vermoeden dat de bijdrage van de laparoscopie op de uitkomst van IUI beperkt zou kunnen zijn. Daarom twijfelen wij aan de waarde van het routinematig uitvoeren van de diagnostische en/of aansluitend therapeutische laparoscopie voorafgaand aan de IUI-behandeling. Ten aanzien van de rol van de laparoscopie na een afwijkend HSG en voorafgaand aan behandeling met IUI, concluderen wij dat de laparoscopie noodzakelijk is om overbehandeling met IVF te voorkomen gezien bij een aanzienlijk aantal de afwijkingen gering zijn en IUI vooralsnog een optie blijft.

Evaluatie van de fertilisatie voorafgaand aan IUI wordt niet geadviseerd gezien wij geen evidente relatie konden aantonen tussen het falen van de IUI-behandeling en verminderde fertilisatie.

Wat betreft semenkwaliteit wijst ons onderzoek uit dat embolisatie van een varicocele bij subfertiele mannen de kwaliteit van het semen in die mate verbetert dat een minder invasieve manier van voortplantingstechniek mogelijk wordt ten opzichte van voor de behandeling. Bovendien lijkt embolisatie van een varicocele verslechtering van de semenkwaliteit naar niveau's waarvoor meer invasieve voortplantingstechnieken geindiceerd zijn te voorkomen. Op basis van deze gegevens zijn wij van mening dat embolisatie vooralsnog een plaats heeft voorafgaand aan voortplantingstechnieken. Gezien dit onderzoek een retrospectief onderzoek betreft, adviseren wij om nader onderzoek te verrichten in de vorm van een gerandomiseerde studie om op een prospectieve manier meer inzicht te krijgen in het effect van de embolisatie van de varicocele op semenkwaliteit en uiteindelijk zwangerschap.

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Curriculum Vitae

Sandra Joan Tanahatoe werd op 28 december 1971 geboren te Ede, dochter van Ferdinand Willem Tanahatoe en Irene Hyronima Tanahatoe-Dumanauw. In 1990 behaalde zij haar voorbereidend wetenschappelijk onderwijs diploma aan het Christelijk Streeklyceum te Ede. Zij studeerde geneeskunde aan de Rijks Universiteit te Leiden en behaalde het artsexamen in 1998.

Na een jaar werkzaam te zijn geweest als AGNIO Verloskunde en Gynaecologie aan het Academisch Medisch Centrum te Amsterdam, werd zij vanaf februari 2000 adjunct-onderzoeker aan de afdeling Voortplantingsgeneeskunde van het Vrije Universiteit medisch centrum. Aldaar starte zij met het wetenschappelijk onderzoek dat geleid heeft tot dit proefschrift (promotor Prof. Dr. R. Homburg, co-promotor Dr. C.B. Lambalk en Dr. P.G.A. Hompes). Tevens volgde zij de Masteropleiding Epidemiologie aan het EMGO instituut, Vrije Universiteit te Amsterdam en ontving het diploma Master of Epidemiology in mei 2006.

In oktober 2002 begon zij de opleiding tot gynaecoloog in het Onze Lieve Vrouw Gasthuis in Amsterdam (opleiders Dr. M.F. Schutte en Prof. Dr. J.M.M. van Lith) en in het Vrije Universiteit medisch centrum (opleiders Prof. Dr. H.P. van Geijn en Prof. Dr. H.A.M Brölmann). Momenteel is zij werkzaam als Chef de Clinique in het Onze Lieve Vrouwe Gasthuis te Amsterdam.

Zij woont samen met Jorn Fokkens en samen hebben zij een zoon Indiana (geboren 20 oktober 2006).

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