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## Clinical work-up strategies before IUI

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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 assess 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 total 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 phlebographically 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.