Chapter 1

General introduction
Intrauterine insemination (IUI) is the most widely used fertility enhancing treatment in the world. In many guidelines it is the first step in the treatment cascade in couples with unexplained subfertility and male subfertility.\textsuperscript{1-3} In an IUI cycle, the partner’s semen is processed and inseminated directly in the uterine cavity at the time of ovulation. The rationale for performing IUI is that motile spermatozoa are concentrated in a small volume and inseminated directly into the uterine cavity near to the released oocyte, thus bypassing the cervix.\textsuperscript{4,5}

There is a wide variation in practice in how to perform IUI. This variation is due to the complexity of IUI. An IUI cycle is a cascade of several interventions in each of which modifications can be made, such as the use of controlled ovarian stimulation to achieve growth of more than one follicle. This multfollicular growth can be performed with various drugs and stimulation regimens.\textsuperscript{6,7} At the same time monitoring of follicular growth must be performed to optimize timing and induction of ovulation.\textsuperscript{8} These interventions in the follicular phase are then followed by techniques in the second phase of the IUI treatment cycle, i.e. preparation of semen samples, optimal timing of insemination (which can be performed once or twice) and (im-) mobilisation immediately after the insemination.\textsuperscript{9-11} All these interventions may vary considerably from centre to centre.

This variation in daily practice and the ensuing need for uniformity in treatment has lead to a growing number of randomized controlled trials and meta-analyses.

In the past decades several variations of conventional IUI were developed to optimize pregnancy rates. To solve the possible problem of progressive decline of the number of spermatozoa along the length of the genital tract- just a minor amount of spermatozoa are found in the Pouch of Douglas after conventional IUI- fallopian tube sperm perfusion (FSP) was introduced in 1992.\textsuperscript{12} With this method some millilitres of processed sperm are flushed into the fallopian tubes under pressure with the hypothetical effect of enhancing pregnancy chances. A meta-analysis of RCT's with 595 couples showed however that there is no evidence that this technique generates higher pregnancy rates than normal IUI.\textsuperscript{13}

Intra uterine insemination as a treatment for unexplained en mild male subfertility is usually combined with mild ovarian hyperstimulation (MOH). Since ovarian stimulation is associated with an increased risk of multiple pregnancies and therefore increased maternal/perinatal morbidity and perinatal mortality, stimulation regimens have been developed with the ultimate goal of enhancing live-birth rates and keeping multiple pregnancies to a minimum.\textsuperscript{14,15} In comparing several treatment regimens for MOH in IUI it was found that gonadotropins seem the most effective drugs. Anti-oestrogens appear cost-effective, but seem some-what less effective compared to gonadotropins. When gonadotropins are used, a daily low-dosage protocol is advised.\textsuperscript{16}

Some of the problems arising from mild ovarian stimulation are premature luteinization and asynchronous ovarian follicular development. Several RCT’s have addressed this issue by adding GnRH-agonists or GnRH-antagonists. GnRH-agonists were found to increase the
number of multiple pregnancies and the risk for ovarian hyperstimulation but could not increase pregnancy rates. In adding GnRH-antagonists to the ovarian stimulation regime, it was found that premature LH-surges were significantly reduced but live birth rates remained unaffected. Therefore GnRH-agonists and antagonists are not recommended for use in IUI treatment protocols.17

When the actual insemination is to be performed, adequate timing is of great importance. It was suggested that differences in treatment outcome were partially related to the timing of insemination.8 Therefore several study groups investigated the effect of double insemination versus one single insemination. The Cochrane meta-analysis updated in 2007 found, based on five small trials en one larger trial, a beneficial effect in favour of double insemination especially in couples with mild male subfertility.10 However, several trials not included in the review published thereafter could not reproduce these findings and found no difference in live birth rate.18,19

Apart from optimizing treatment success through optimizing various aspects of the treatment, the prognosis of a couple on natural conception has recently been identified as an important issue and is nowadays part of clinical decision making; The quintessence of prognosis is that IUI is only offered to a couple if the probability of a treatment independent pregnancy is very low and the success rate after IUI clearly exceeds this probability. To be able to make adequate and reliable predictions in clinical practice, formal prediction models, in which the contribution of each fertility-determining factor is quantified, have been developed in the recent past. One model on natural conception has been validated in an external population and predicts accurately the chances of a treatment independent pregnancy among subfertile ovulatory couples.20

In 2004 an IUI prediction model was developed.21 By calculating the chances of an ongoing pregnancy after IUI, benefit from IUI in comparison to expectant management can be determined. Before the model is available for clinical use external validation is yet to be performed.

By using these models and comparing the prognoses generated by the models for the couple, they can be counselled on an individual basis. Such an approach can prevent overtreatment, decrease the misuse of facilities and other resources and minimise the risk of multiple pregnancy generated by premature treatment.

In couples with unexplained subfertility or mild male subfertility and a treatment independent prognosis on pregnancy over 40% expectant management is generally advised. A prognosis below 30% should be an incentive to start treatment. In patients with an intermediate prognosis (30-40%) the threshold of treatment or expectant management was previously assessed. it was found that in these couples expectant management was just as effective as immediate start of treatment with IUI within the first six months after diagnosis.22
BACKGROUND

When we started the project described in this thesis, it was recognized that the need for an IUI prediction model for clinical use was urgent, because there were none available but one. Because newly developed prediction models tend to generate chances which are better than realized in clinical practice, we decided to perform an external validation of this model.

When homologous intrauterine insemination is commenced, information on the optimum number of cycles to perform is essential. Exact data on the optimum number of cycles, as a possible limit to which insemination is effective, was lacking, and advice on the optimum number of cycles to perform varied between three to 12 cycle in literature. We therefore aimed to perform a large cohort study to understand the effectiveness after six cycles.

When the actual insemination is performed, it seems important to consider the position of the woman right after the insemination. In most clinics it is common practice to immediately mobilize women after insemination in lithotomy position. The thought is that by inseminating spermatozoa in the uterus, the chance of conception is no longer influenced by the female position because of the rapid sperm transport inside the uterus and fallopian tubes. However, one small randomized trial found contradictory results: significantly higher pregnancy rates were found in couples in which the women were immobilized for a short period of time directly after the insemination. Because the trial was quite small and the difference between the study groups was remarkably large we decided a larger trial was needed.

As previously discussed, patients with unexplained and mild male subfertility and an intermediate prognosis, are advised to wait for another six months before to start with IUI-MOH. If the advice not to start treatment in the first six months is valid, the issue of long-term effectiveness and cumulative costs becomes important to address. To answer this question, a long term follow up of this trial was needed.

When the decision to start IUI has been taken, the majority of couples with male and unexplained subfertility will be advised to start IUI with mild ovarian stimulation. Since this is associated with a high number of multiple pregnancies it has been suggested that alternative treatments such as IVF with elective single embryo transfer (IVF-eSET) might reduce multiple pregnancies, while maintaining acceptable pregnancy rates. However no randomized trials comparing IUI-MOH with IVF-eSET in treatment naïve patients had been performed yet and the feasibility of such a trial was unknown. We decided to perform a pilot trial to explore this problem.

Finally we decided to address the problem of patient dropout. Drop out from fertility treatment is a well known phenomenon, even in reimbursed fertility programmes. To understand the reasons for couples to stop IUI treatment and to understand the possible effect on pregnancy rates due to selective dropout, a large cohort study was needed.
OUTLINE OF THE THESIS

Chapter 2 Reports on the results of an external validation of a prediction model that predicts the outcome of intrauterine insemination. The study was a descriptive prospective validation study testing the accuracy and performance of the model by calibration and discriminative capacity.

Chapter 3 Reports on a multicentre retrospective cohort study analysing 3714 couples who underwent 15, 303 cycles of IUI. Ongoing pregnancy rates were calculated up to the ninth cycle. The aim of this study was to analyse if pregnancy rates after the sixth cycle are acceptable, justifying continuation of treatment up to nine cycles.

Chapter 4 Reports on the results of a randomised controlled trial evaluating the effect of 15 minutes of immobilisation versus immediate mobilisation after IUI. Main outcome measure was ongoing pregnancy rate per couple.

Chapter 5 Describes the long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. The aim of this study was to evaluate if expectant management for six months in terms of long-term effectiveness is comparable to that of immediate treatment with IUI, while the cumulative long-term costs of expectant management remain lower.

Chapter 6 Is a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation in couples with unexplained subfertility and unfavorable prognosis. Main outcome was ongoing pregnancy rate per couple.

Chapter 7 Evaluates couples undergoing intrauterine insemination who continue treatment until six cycles or ongoing pregnancy versus couples that drop out from treatment. Prognostic profile and reasons for dropping out are reported.

Chapter 8 Presents the summary of this thesis and provides suggestions for future research.
REFERENCES


