

Chapter 11

Summary, conclusions and implications

Summary

Subfertility affects 10 to 15% of the couples with a desire to conceive. In current practise, intrauterine insemination (IUI) is the treatment of first choice if subfertility is due to a cervical factor, male factor or if subfertility is unexplained. The downside of IUI is that it is associated with high financial costs, and that the addition of controlled ovarian hyperstimulation increases the risk of multiple pregnancy. For these reasons, IUI should only be performed in couples in whom there is an appropriate trade off between proven effectiveness, safety and costs.

Before the writing of this thesis, many studies had addressed the effectiveness of IUI for various indications and for different IUI protocols. Still, some important gaps in our knowledge remained. For instance, in The Netherlands, no data were available on the number of IUI cycles performed, the efficacy of the IUI programs and the multiple pregnancy rates after IUI. Data on the effectiveness of IUI compared with expectant management were scarce, and there was no knowledge about the preferences of the couples in deciding for IUI or not.

Although prognostic models which allow the selection of couples who will benefit from treatment have been introduced in the last decade, there were no studies available which took the prognosis into account to select their study population for IUI.

The aim of this thesis was to fill the gaps in our knowledge. We assessed the results of IUI in The Netherlands and compared them with data reported in the international literature. Moreover, we performed randomised clinical trials that examined the effectiveness of IUI (with or without controlled ovarian hyperstimulation) in unexplained subfertility and cervical factor subfertility. We also developed and validated a prediction model for the probability of pregnancy after IUI. Finally, we performed a meta-analysis to evaluate today's knowledge of the effectiveness of IUI in unexplained subfertility, cervical factor subfertility and male subfertility.

Chapter 1 gives an outline of this thesis.

Intrauterine insemination in The Netherlands

Chapter 2 addresses the effectiveness of IUI in The Netherlands in comparison to the effectiveness of IUI reported in international literature.

In a retrospective study we assessed the results of IUI in The Netherlands and compared them with data reported in the international literature. We used data from 2003 taken from annual reports and reports from individual gynaecologists. By extrapolation, the total number of IUI cycles performed that year nationwide, and the related outcomes, was estimated. IUI was performed in 91 of the 101 hospitals. Of these hospitals 58 (64%) registered their IUI results and performed 19,846 IUI cycles. The mean pregnancy rate per cycle was 9.0% and the

mean ongoing pregnancy rate per cycle was 7.3%. Multiple pregnancies occurred in 9.5% of the ongoing pregnancies. Extrapolation of the data suggested that in The Netherlands yearly, approximately 28,500 IUI cycles are performed, of which approximately 2,000 result in an ongoing pregnancy. The number of multiple pregnancies following IUI is estimated to be 180 (9.0% per ongoing pregnancy).

According to the national IVF registry, 9761 IVF cycles were started in 2003, resulting in 2,028 ongoing pregnancies (20.8% per cycle) and 439 twin pregnancies (21.6% per ongoing pregnancy).

In conclusion, the pregnancy rate per IUI cycle in The Netherlands (9.0%) is comparable to that reported in the international literature (8.7%). The contribution made by IUI to the number of multiple pregnancies in The Netherlands is much smaller than the contribution made by IVF.

Intrauterine insemination in unexplained subfertility

In Chapter 3 we present the comparison of the effectiveness of IUI with controlled ovarian hyperstimulation to expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous pregnancy in the next 12 months.

In 20 to 30% of couples visiting their gynaecologist for subfertility no reason is found for their subfertility during basic fertility work-up. IUI with COH is commonly used as first-line treatment in these couples. Since such treatment has drawbacks, especially the increased risk of multiple pregnancy, a couple's chance of achieving a spontaneous ongoing pregnancy should be considered first to identify those couples most likely to benefit from treatment. We aimed to assess the effectiveness of IUI with COH compared with expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy. An intermediate prognosis was defined as a probability of a spontaneous ongoing pregnancy between 30% and 40% within 12 months. We randomly assigned 253 couples to either IUI with COH for 6 months or expectant management for 6 months. The primary endpoint was ongoing pregnancy within 6 months. Analysis was by intention to treat.

Of the 253 couples enrolled, 127 were assigned to IUI with COH and 126 to expectant management. In the intervention group, 42 women (33%) conceived and 29 pregnancies were ongoing (23%). In the expectant management group, 40 women (32%) conceived and 34 pregnancies were ongoing (27%) (relative risk 0.85, 95% CI 0.63 to 1.1). There was one twin in each group, and one woman in the intervention group conceived triplets.

In conclusion, we can exclude a large beneficial effect of IUI with COH in couples with unexplained subfertility and an intermediate prognosis. Expectant management for 6 months is therefore justified in these couples.

Intrauterine insemination in cervical factor subfertility

In Chapter 4 we describe a randomised clinical trial which addresses the effectiveness of IUI compared to expectant management in couples with an isolated cervical factor.

In 5% of the subfertile couples a cervical factor is found during the basic fertility work-up. Data on the effectiveness of IUI for cervical factor subfertility are scarce and conflicting.

Four randomised studies have reported on the effectiveness of IUI compared to timed intercourse in couples with cervical factor subfertility. Two studies clearly indicated a beneficial effect of IUI, whereas two others did not report such an effect. The discrepancies might be explained by their small sample size. Pooling of the data of these trials could provide a better estimate, but this is not possible due to the quality of the trials and heterogeneity in the participant characteristics and interventions.

In view of these issues, we assessed the effectiveness of IUI compared to expectant management in couples with isolated cervical factor subfertility. Subfertile couples with an isolated cervical factor, diagnosed by a well-timed, non-progressive post-coital test (PCT) with normal semen parameters and no additional factors that reduce fertility, were randomly assigned to IUI for six months or expectant management for six months.

In the first three cycles, IUI was performed without controlled ovarian hyperstimulation (COH). If these attempts failed, subsequent IUI cycles were performed with COH. The primary endpoint was ongoing pregnancy within 6 months. Analysis was by intention to treat. Of the 101 couples enrolled, 52 couples were allocated to IUI and 49 couples were allocated to expectant management. In both groups, one couple did not meet the inclusion criteria and therefore these couples were excluded from the analyses.

In the IUI group, 26 women (51%) conceived, of which 22 pregnancies were ongoing (43%). In the expectant management group, 16 women (33%) conceived, of which 13 pregnancies were ongoing (27%). (relative risk 1.6 (95% CI 0.91 to 2.8)). There was one multiple pregnancy in the group allocated to IUI. This trial suggests a beneficial effect of IUI in couples with an isolated cervical factor.

Chapter 5 *deals with the results of a historical cohort study that focuses on the additional benefit of controlled ovarian hyperstimulation in IUI in couples with cervical factor subfertility.*

Intrauterine insemination can be performed with or without controlled ovarian hyperstimulation (COH). Studies, randomised or non-randomised, in which the additional benefit of COH on IUI for cervical factor subfertility was assessed, were lacking.

The aim of the study described in chapter 5 was therefore to assess whether controlled ovarian hyperstimulation in IUI is of additional benefit in cervical factor subfertility.

We performed a historical cohort study among couples with cervical factor subfertility, treated with IUI. A cervical factor was diagnosed by a well-timed non-progressive postcoital test with normal semen parameters. We compared ongoing pregnancy rate per cycle in groups treated with IUI with or without COH. We tabulated ongoing pregnancy rates per cycle number and compared the effectiveness of COH by stratified univariable analysis.

We included 181 couples who underwent 330 cycles without COH and 417 cycles with COH. Ongoing pregnancy rates in IUI cycles without and with COH were 9.7% and 12.7%, respectively (OR 1.4, 95% CI 0.85 to 2.2). The pregnancy rates in IUI without COH in cycles 1, 2, 3 and 4 were 14%, 11%, 6% and 15%, respectively. For IUI with COH, these rates were 17%, 15%, 14% and 16%.

Although the data indicate that COH improves the pregnancy rate over IUI without COH, IUI without COH generates acceptable pregnancy rates in couples with cervical factor subfertility.

We therefore conclude that IUI without COH should be seriously considered in couples with cervical factor subfertility since it bears no increased risk for multiple pregnancy.

Chapter 6 gives the results of a randomised clinical trial on the additional benefit of controlled ovarian hyperstimulation in IUI in couples with an abnormal post coital test.

Intrauterine insemination can be performed with or without COH. Controlled ovarian hyperstimulation carries the risk of multiple pregnancies. It poses a burden to the couple and is costly due to the use of gonadotropins and the need for monitoring follicular development and growth. These drawbacks are only warranted if addition of COH to IUI results in a substantial gain in ongoing pregnancy rate.

Before this thesis, there were no randomised clinical trials on the incremental value of COH in IUI in cervical factor subfertility and male subfertility in couples with a poor prognosis. A poor prognosis was defined as a probability of a spontaneous ongoing pregnancy lower than 30% within 12 months.

Therefore, we aimed to assess whether controlled ovarian hyperstimulation in IUI is of additional value in couples with an abnormal PCT, due to a cervical factor or a male factor and a poor prognosis of an ongoing spontaneous pregnancy because of additional factors that reduce fertility. Subfertile couples with a well-timed non-progressive post-coital test (PCT) and additional factors that reduce fertility, were randomly assigned to three cycles of IUI with COH or three cycles of IUI without COH. The primary endpoint was ongoing pregnancy within three IUI cycles. Analysis was by intention to treat. We randomly allocated 132 couples to IUI with COH and 133 to IUI without COH. We observed 33 pregnancies (25%) in the couples allocated to IUI with COH, of which 28 were ongoing (21%), versus 28 pregnancies (21%) in the couples allocated to IUI without COH, of which 23 were ongoing (17%) (relative risk 1.2 (95% CI 0.75 to 2.0)). Two multiple pregnancies occurred in the IUI with COH group and one in the IUI without COH group.

From these data we conclude that, IUI with COH leads to comparable pregnancy rates as IUI without COH in couples with an abnormal PCT and a poor prognosis. We therefore advise to perform IUI without COH in couples with an abnormal PCT.

Prognosis after intrauterine insemination

Chapter 7 presents a prognostic model for the prediction of an ongoing pregnancy after intrauterine insemination.

Although IUI is a commonly used treatment, a reliable prediction of an ongoing pregnancy could not be given for an individual couple. Several studies have demonstrated in univariable analyses that the outcome of IUI is dependent on various variables.

Only a few studies have assessed the prognostic value of these variables in a multivariable approach and used these variables in a model. Some variables, i.e. the number of pre-ovulatory follicles as well as semen concentration at time of the insemination, are not of help in deciding which couples to offer IUI, as data on these items are not known before start of treatment. In addition, all models were based on a small number of patients and suffered therefore from a lack of statistical power.

The aim of the study presented in chapter 7 was therefore to develop a model to predict the ongoing pregnancy rate after IUI in various cycle numbers.

In a retrospective cohort study data from four fertility centers in The Netherlands were used. Couples of whom the female partner had a regular cycle and who had been treated with IUI were selected and IUI cycles with or without COH were analyzed for ongoing pregnancies. Overall, 3,371 couples were included who underwent 14,968 cycles. There were 1,229 (8.2%) pregnancies, of which 1,000 (6.7%) pregnancies were ongoing. Logistic regression analysis demonstrated that increasing maternal age, longer duration of subfertility, presence of male factor subfertility, one-sided tubal pathology, endometriosis, uterine anomalies, and increasing number of cycles were unfavorable predictors for an ongoing pregnancy. Cervical factor and use of ovarian hyperstimulation were favorable predictors. The area under the receiver-operating characteristic curve was 0.59. When couples were divided in four categories based on prognosis, the difference between the predicted and observed chance, i.e. calibration, was less than 0.5% in each of the four groups.

Although the model had a relatively poor discriminative capacity, data on calibration showed that the selected prognostic factors allow distinction between couples with a poor prognosis and couples with a good prognosis. After external validation, this model could be of use in patient counseling and clinical decision-making.

In Chapter 8 the prognostic model for the prediction of an ongoing pregnancy after intrauterine insemination developed in chapter 7 is validated in an external population.

Since a prediction model tends to perform better in the population in which it was constructed, external validation is a crucial step before the model can be used in daily practice.

The aim of the study presented in chapter 8 was therefore to validate the IUI prediction model developed in chapter 7, in prospectively collected data from an external population. Data were collected from seven fertility centres in The Netherlands. Couples of whom the female partner had a regular cycle and who had been treated with IUI were selected and IUI cycles with or without COH were analyzed for ongoing pregnancies. Performance of the prediction model was assessed by calibration and discriminative capacity. Calibration was assessed by comparing the predicted ongoing pregnancy rate to the observed ongoing pregnancy rate. Discriminative capacity was assessed with receiver operating characteristic (ROC) analysis. For daily practice, a score chart of the validated model was developed to estimate the chance of an ongoing pregnancy after IUI per treatment cycle. We included 1,079 subfertile couples who underwent 4,244 cycles of IUI. There were 278 ongoing pregnancies, i.e. an ongoing pregnancy rate of 6.6% per cycle. External validation of the model showed good calibration. The predicted probability was always within 1.5% of the mean observed probability. The area under the ROC-curve was 0.56 (95% CI 0.53 to 0.59). We conclude that the prediction model was able to make a good distinction between couples with good pregnancy chances and poor pregnancy chances after IUI. After this external validation we feel that this model can be used in clinical practice.

Patients' preferences in intrauterine insemination

Chapter 9 focuses on the patient's preferences in deciding between intrauterine insemination and expectant management.

It is generally acknowledged that patients' preferences should be incorporated into medical decision making. Several studies have shown that patients' perspectives on the burden and benefits of therapy can differ from those of health professionals. Physicians should therefore explicitly and actively seek for patients' preferences. The aim of this study was to document patients' preferences for IUI versus expectant management, and their valuation of the risks of IUI.

Forty subfertile couples were offered scenarios in which the treatment-independent pregnancy chance was varied against a fixed pregnancy chance after IUI without or with controlled ovarian hyperstimulation (COH) of 8% and 12% per cycle, respectively. The treatment-independent pregnancy chance within 12 months was initially set at 100%, and subsequently reduced until couples switched preferences. We also investigated the impact of the risks on ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy on their preference. When pregnancy was guaranteed within a year, all couples would opt for expectant management. Most couples switched to IUI without COH at a 60% chance of a treatment-independent pregnancy and to IUI with COH between a 40%-60% chance. In case the risk of OHSS was set at 10%, a large majority of the couples preferred expectant management to IUI. At a risk of a multiple pregnancy of 100%, 77% of the couples would still prefer IUI.

In conclusion, the majority of couples prefer IUI with or without COH when the treatment-independent pregnancy chance in the next 12 months is under 40% and 50%, respectively. The risk of a multiple pregnancy does not affect their preference for IUI, whereas IUI is rejected when the risk of OHSS exceeds 10%.

State of the art in intrauterine insemination

Chapter 10 *presents a systematic review and a comprehensive series of meta-analyses on the effectiveness of IUI in couples with unexplained subfertility, cervical factor subfertility and male subfertility.*

Intrauterine insemination (IUI) is the first line treatment in couples with unexplained subfertility, cervical factor subfertility and male subfertility.

To appraise the effectiveness of IUI for these three indications, we performed a systematic review and a comprehensive series of meta-analyses. We included Cochrane reviews and searched the literature for additional studies. Outcomes were live birth, ongoing pregnancy, clinical pregnancy and multiple pregnancy.

We were able to include 14 studies reporting on IUI for unexplained subfertility, two studies reporting on IUI for cervical factor subfertility and nine studies reporting on IUI in male subfertility. In couples with unexplained subfertility, IUI without controlled ovarian hyperstimulation (COH) was associated with higher ongoing pregnancy rates than expectant management (relative risk (RR) 1.3, (95% CI 0.84 to 1.9)), whereas IUI with COH was more effective than IUI without COH (RR 1.8, (95% CI 1.2 to 2.7)). However, in couples with relatively good prospects for spontaneous pregnancy, there was no benefit from IUI with COH over expectant management. In couples with a cervical factor, IUI without COH was associated with higher pregnancy rates compared to expectant management (RR 1.6, (95% CI 0.87 to 3.1)), but addition of COH did not further improve the pregnancy rates (RR 1.0, (95% CI 0.59 to 1.8)). In couples with male subfertility, IUI was more effective than expectant management, although the limited power of the included studies hampers strong conclusions. In these couples, addition of COH also had no extra benefit (RR 0.92, (95% CI 0.46 to 1.8)). Studies comparing IUI and IVF were rare, limiting assessment of the strategy of IVF as first line treatment.

Despite the fact that IUI is one of the most frequently used treatments in reproductive medicine, our review shows that the number of studies assessing its effectiveness is limited and that most of these studies had small sample sizes. This results in imprecise effect estimates, as demonstrated by the non significant effects and large confidence intervals. Also, many studies did not adhere to present quality standards for design, conduct and report of clinical trials. Therefore, there is an urgent need for more RCTs in which IUI is compared to expectant management or IVF.

Clinical implications

This thesis shows that in subfertile couples in whom the woman has a regular cycle, a basic fertility work-up should end with the calculation of the probability of a spontaneous ongoing pregnancy.

In couples with an unexplained subfertility and a good prognosis, i.e. 30 to 40% chance of a spontaneous ongoing pregnancy in the next 12 months, expectant management should be advised. In case of a poor prognosis (spontaneous pregnancy chance < 30%), treatment could be offered. At present, it is unknown whether IUI with COH should be treatment of first choice, or that couples should be advised to proceed with another modality of assisted reproductive treatment.

The PCT deserves in our opinion a place in the fertility work-up to identify couples with an isolated cervical factor. These couples can be offered IUI without COH because this will increase their pregnancy chance compared to expectant management. In these couples the addition of controlled ovarian hyperstimulation to IUI would not result in a substantial gain in ongoing pregnancy rate, but does increase the risk of multiple pregnancies. Therefore IUI should be given without the addition of COH, especially in the first three cycles.

During this study a prognostic approach has already been introduced into the renewed Dutch guideline on the fertility work-up (Guideline 1, 2004). To facilitate the implementation of prediction models, we developed a registration program with algorithms for the prediction of pregnancy chances. This registration program (OFO-base) is now being used in 25 fertility centers in The Netherlands.

Future research implications

Randomised clinical trials are needed on the effectiveness of IUI in couples with unexplained subfertility and a poor prognosis. Randomised clinical trials comparing IUI with and without COH versus expectant management could bring this information. However, it could be more effective to start in these couples directly with mild modalities of IVF, i.e. IVF with single embryo transfer or IVF in the manipulated natural cycle. These issues are now being studied in the SETI study and in the INES study.

In couples with a cervical factor and a poor prognosis a trial which compares IUI with and without COH to expectant management and to IVF could be very informative. For male subfertility there is no valid evidence at all on how to treat these couples and consequently this field lies wide open for further study

