Intrauterine insemination: Fine-tuning a treatment
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Chapter 8

General discussion and summary
GENERAL DISCUSSION

Intrauterine insemination has been a treatment of all times. The first scientifically described homologous insemination was performed in London by the Scottish physiologist and surgeon John Hunter in 1790. He advised a man with severe hypospadia to collect his semen directly after coitus in a syringe and introduce it into the vagina of his wife. The woman conceived after this procedure. Initially, the techniques of insemination were rather curious and the success rates were amazingly high; homologous insemination was practiced in France by Girault as early as 1838 and appeared to be successful in 8 out of ten cases. Numerous scientific reports appeared between the mid eighteen hundreds and the beginning of 1900 in which it appeared that homologous insemination was successfully practiced by medical experts in France, England, Germany and the United States. Between 1900 and World War II the number of reports on homologous insemination declined since there was a growing interest in artificial insemination with donor semen. Methods for freezing and thawing of semen were developed which led to the possibility of insemination without the necessity of freshly produced semen by husbands or donors. A new indication for insemination arose from this newly developed technique, called the “distance indication”: wives of soldiers sent to war could be inseminated with their husband frozen and thawed semen.

It took until 1984 before the first randomised clinical trial was published in The Lancet. This trial investigated the effectiveness of intra uterine insemination in 35 couples with men with poor semen quality. The paper described a cross-over-trial design in which the couples were initially randomised into three groups: 14 couples started with a single act of natural intercourse based on the basal body temperature, 7 couples started with a single act of natural intercourse the day after the LH-surge and 14 couples started with a single IUI of washed sperm on the day after the LH-surge. After completing four cycles of each procedure patients switched to one of the other two alternatives. They registered 8 pregnancies out of 39 IUI cycles versus one pregnancy after 34 cycles of BBT-timed intercourse and no pregnancies after 38 cycles of LH-timed intercourse. Since the trial was small the effectiveness of IUI could not be proven. Soon more and more randomised and non randomised studies were published and the effectiveness was no longer doubted. Studies on IUI now focussed on spreading the number of indications and fine-tuning the treatment in terms of sperm washing procedures and use of superovulating medication.

Intrauterine insemination for unexplained and male subfertility

During the writing of this manuscript, a critical re-appraisal of the literature and updating of Cochrane reports resulted in questioning the actual contribution of intrauterine insemination for unexplained or male subfertility. In unexplained subfertility there is evidence that IUI with ovarian stimulation increases the live birth rate compared to IUI alone. The likelihood of pregnancy was also increased for treatment with IUI compared to...
timed intercourse in stimulated cycles. One adequately powered multicentre trial showed no evidence of effect of IUI in natural cycles compared with expectant management.\textsuperscript{17} When we decided to perform a long-term follow up of the randomized trial of Steures \textit{et al.}, (IUI-MOH versus expectant management in unexplained subfertility), our initial hypothesis was that after the first six months with more or less equal numbers of live births between the two groups, the non-treated group would take a leap in time-to-pregnancy when they would start IUI-MOH. However, in three years time in which couples underwent IUI-MOH, IVF/ICSI or refrained from further treatment we found no difference in time to ongoing pregnancy between the immediate treatment group and expectant management group. However, the expectant management group underwent significantly less IUI and IVF treatment cycles compared to the group that received immediate treatment with IUI-MOH.\textsuperscript{18} Overlooking these results the effect of IUI alone is questionable; the major effect- if any- is possibly due to aggressive ovarian stimulation, which in turn increases the risk of multiple pregnancies.

As advised in the Cochrane analyses couples should be informed on the risk of IUI-MOH and the possibility of alternative options.\textsuperscript{15}

**Risk of multiple pregnancies, search for alternatives**

IVF with elective single embryo-transfer is considered as a possible effective tool in preventing multiple pregnancies in an IVF population. Reports of multiple rates between 0-5\% have been reported in trials.\textsuperscript{19-20} Continuing on these data, our hypothesis was that IVF-eSET might also be an effective tool to prevent multiple pregnancies in a treatment-na\-\textsuperscript{ive} IUI population. In our pilot study, to our surprise, we found a rather high multiple pregnancy rate (14\% per ongoing pregnancy) caused by a considerable rate of double embryo transfers (25\%). Moreover, in the limited time-horizon of four months, we found equal numbers of ongoing pregnancies and live-births, suggesting that IVF-eSET does not seem a superior treatment in these couples in prevention of multiple pregnancies and achieving an ongoing pregnancy. One possible explanation might be the difficulty of selecting the embryo with the highest implantation potential for transfer.\textsuperscript{21-24} These preliminary results emphasize the need for large definitive trials with a longer treatment time and longer follow-up period to determine more precisely the pregnancy rates and multiple pregnancy rates of both treatments IVF-eSET and IUI-MOH.

From the recently published Cochrane review on IVF for unexplained subfertility, also no definitive conclusions could be drawn to choose for IVF as a superior treatment since adverse effects and costs are unsufficiently clarified.\textsuperscript{25} If the decision has been made to start IUI, usually with MOH, pregnancy rates up to 40\% are achievable after nine cycles. Since the quintessence in fertility treatment is repeating treatment cycles, couples should not be motivated to skip or discontinue IUI prematurely and to switch to more aggressive treatments such as IVF/ICS before superiority has been proven.
In modern society this is a moot point. A shift to premature and more aggressive treatment with IVF-ICSI is visible and this is worrisome. Current society is shifting towards a situation in which couples should obtain a family in the shortest period possible and the possibility of expectant management is increasingly difficult for a couple. Besides this, family planning is increasingly becoming merchandise in which desperate couples are willing to pay large amounts of money. Moreover, there is emerging evidence to indicate that IVF may predispose individuals to increased incidence of obesity, elevated blood pressure, fasting glucose and triglycerides and subclinical hypothyroidism.

Implications for future research
In The Netherlands IUI with or without MOH is performed in 90% of the hospitals with over 28 000 cycles each year. About 10% of all ongoing pregnancies resulted in a multiple pregnancy. In a relatively young population with unexplained or mild male subfertility, in which only gonadotropins are used, multiple rates are sometimes higher. For some the use of gonadotroping has become a “20th century relic” and the use of alternative medications mostly Clomiphene citrate is advocated as a more cost-effective alternative. Available studies on the subject are relatively small and larger trials are needed.

In prevention of multiple pregnancies, the search for alternative treatment strategies is an ongoing quest. Hopefully the INeS-study which compares IUI-MOH, IVF with single embryo transfer and Modified Natural cycle IVF will bring light to this question. Although more and more difficult nowadays, also larger trials evaluating expectant management versus IUI-MOH and IVF are needed to identify the actual contribution of these treatments in patients with unexplained subfertility.
REFERENCES


SUMMARY

This thesis reports on various aspects that determine optimal treatment of subfertile couples with intrauterine insemination (IUI). It describes the first step in clinical decision making that is deciding whether IUI is a suitable option for the subfertile couple. The first developed multivariate model, predicting an ongoing pregnancy after IUI, was externally validated and found to be suitable for daily clinical use. The number of IUI treatment cycles to perform is discussed as well as the effect of a short period of bedrest after intrauterine insemination. We performed a long-term follow up of couples with unexplained subfertility who were initially randomized for expected management or immediate treatment with IUI and mild ovarian hyperstimulation (IUI-MOH). In search of an alternative treatment-option to prevent multiple pregnancies after IUI-MOH, but to maintain acceptable pregnancy rates we performed a pilot trial evaluating the effect of IVF with elective single embryo-transfer (IVF-eSET) versus IUI-MOH in treatment-naïve subfertile couples. Finally, we evaluated the effect of drop-out of subfertile couples from an IUI programme on cumulative pregnancy rates after IUI.

In chapter 1 we describe that IUI is still one of the most frequently applied treatments for male and unexplained subfertility. There is a wide variation in practice in how to perform IUI due to the complexity of the treatment: such as type and use of ovarian stimulation, follicular monitoring and timing of ovulation, and the number of inseminations to perform. This variation in daily practice and the ensuing need for best practice has lead to a growing number of randomized controlled trials en meta-analyses. A number of the most relevant Cochrane reviews, RCT's and cohort-studies are summarized in short.

In Chapter 2 the performance of a prediction model for an ongoing pregnancy after intra-uterine insemination is assessed in a general subfertile population by means of accuracy (calibration) and discriminative capacity. The prediction model has been evaluated among 1079 couples whom underwent 4244 IUI cycles in seven fertility clinics. There were 278 ongoing pregnancies that is an ongoing pregnancy rate of 6.6% per cycle. External validation of the model shows good calibration. The predicted probability never differed by more than 1.5% of the mean observed probability. The discriminative capacity is comparable to the one of the development model (c-statistic 0.56).

Chapter 3 reports on the number of IUI treatment cycles that should be performed in terms of cumulative pregnancy rates. In total 3714 couples who underwent 15303 cycles of IUI were included. In 70% of cycles, mild ovarian hyperstimulation was used. Mean ongoing pregnancy rate was 5.6% per cycle. Ongoing pregnancy rates in the seventh, eighth and ninth cycle were 5.1%, 6.7% and 4.6%, respectively. The calculated cumulative ongoing pregnancy rate was 18% after the third cycle, 30% after the seventh cycle and 41% after the ninth cycle. We conclude that conducting IUI up to nine cycles instead of six is a valid option for subfertile couples.

In chapter 4 we describe a randomized clinical trial which addresses the effectiveness of 15 minutes of immobilization in supine position subsequent to intrauterine insemination.
versus immediate mobilization. In total 391 couples were randomised; 199 couples were allocated to 15 minutes of immobilisation after intrauterine insemination, and 192 couples were allocated to immediate mobilisation (control group). The ongoing pregnancy rate per couple was significantly higher in the immobilisation group than in the control group: 27% versus 18%; RR 1.5 (CI 1.1-2.2). Live birth rates were 27% in the immobilisation group and 17% in the control group: RR 1.6 (1.1-2.4). In the immobilisation group, the ongoing pregnancy rates in the first, second, and third treatment cycles were 10%, 10%, and 7%. The corresponding rates in the mobilisation group were 7%, 5%, and 5%. We conclude that in treatment with intrauterine insemination, 15 minutes’ immobilisation after insemination is an effective modification and should be offered to all women treated with intrauterine insemination.

Chapter 5 reports on the long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. The original randomized trial had found that treatment with intrauterine insemination and controlled ovarian stimulation (IUI-COS) did not increase ongoing pregnancy rates compared with expectant management (EM) in couples with unexplained subfertility in the first six months after diagnosis. The long-term cost-effectiveness of a policy of initial expectant management was unknown. After the first six months couples (n=253, at 26 public clinics, the Netherlands) were treated according to local protocol, usually IUI-COS followed by IVF. We followed couples until 3 years after randomization and registered pregnancies and resources used. We found that time to ongoing pregnancy did not differ between groups (log-rank test P=0.98). Cumulative ongoing pregnancy rates were 72-73% for EM and IUI-COS groups, respectively, RR 0.99 (CI 0.85-1.1). Estimated mean costs per couple were € 3424 (CI € 880-€ 5968) in the EM group and € 6040 (CI € 4055-€ 8125) in the IUI-COS group resulting in an estimated saving of € 2616 per couple (CI € 385-€ 4847) in favour of EM. We conclude that initial EM for 6 months results in a considerable cost-saving with no delay in achieving pregnancy or jeopardizing the chance of pregnancy.

Chapter 6 describes a randomized controlled pilot trial in couples with unexplained subfertility and unfavorable prognosis for a spontaneous pregnancy, comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. We randomly allocated 116 women to IVF-eSET (n = 58) or IUI-COH (n = 58). There were 14 ongoing pregnancies (24%) in the IVF-eSET group and 12 pregnancies (21%) in the IUI-COS group (RR 1.17; CI 0.60-2.30). There were two twin pregnancies in the IVF-eSET group (14%) and two twin pregnancies and one triplet pregnancy in the IUI-COH group (25%). The conclusion was that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment. However, elective single embryo transfer does not seem an effective strategy in preventing multiple pregnancies in this particular population. This trial provides evidence for the feasibility and highlights the importance of a large definitive trial to determine the effectiveness and side effects of both strategies.
Chapter 7 evaluates whether baseline characteristics and prognostic profiles differ between couples who drop-out from IUI and couples that continue IUI, and the reasons for couples dropping-out from IUI programs. A retrospective observational cohort study was performed in three fertility centres in the Netherlands. We studied 803 couples who underwent 3,579 IUI cycles. 221 Couples dropped-out (28%) which meant they had not reached an ongoing pregnancy or completed six cycles. Couples dropping-out completed 2.8 (SD±1.4) cycles per couple compared to 4.5 (SD±2.3) cycles per couple for those continuing treatment. Couples dropping-out had a higher female age, longer duration of subfertility and higher basal FSH. Mean prognosis to achieve an ongoing pregnancy after IUI at start of treatment was significantly lower (7.9%; SD±2.4) per cycle for couples who dropped-out compared to couples continuing treatment (8.5%; SD±2.5). Of the dropouts, 100 couples (45%) were actively censored from the IUI-programme. The other 121 couples (55%) who dropped-out did so due to personal reasons. 54 couples (24%) were lost to follow-up.

We found significant differences in prognostic profile between couples continuing treatment and couples dropping-out, although these differences seem limited from a clinical perspective. We conclude that overestimation of ongoing pregnancy rates after IUI due to couples dropping-out is limited.