Unexplained subfertility
Tjon-Kon-Fat, R.I.

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Chapter 10

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SUMMARY

This thesis illuminates the path of couples with unexplained subfertility from diagnosis to treatment. When guiding these couples through their journey, crucial questions are if, when and how to treat. Any decision to start treatment should depend on the trade-off between the four treatment dimensions i.e. burden, effectiveness, safety and costs in relation to treatment (Dancet et al., 2014).

Common first-line treatments for couples with unexplained subfertility are intrauterine insemination (IUI) and in vitro fertilisation (IVF) (Dutch Society of Obstetrics and Gynaecology (NVOG), 2010; National Institute for Health and Care Excellence, 2013). Advancements in IVF have resulted in a considerable increase in pregnancy rates. Milder stimulation regimens have been introduced and better laboratory procedures have been put in place, all leading to elective single embryo transfer substantially reducing the number of multiple pregnancies (Pandian et al., 2013). This has led to IVF being put forward as a potentially more cost-effective and safer option compared to IUI. Yet IUI has also advanced in recent years, less aggressive ovarian stimulation protocols result in less multiple pregnancies without decreasing ongoing pregnancy rates (van Rumste et al., 2008). In view of these –recent– developments, it is unclear what the best first-line treatment is for couples with unexplained subfertility is.

In chapter 1 we provide a general introduction and the aims of this thesis. In chapter 2 we critically assess the effectiveness and safety of IUI and IVF as first-line treatment for couples with unexplained subfertility. We present the evidence on the effectiveness and safety of IUI and IVF based on Cochrane reviews, which suggest that there is insufficient evidence to conclude that IUI or IVF are effective compared to no treatment in couples with unexplained subfertility. We therefore stated that it is high time to provide proper scientific evidence for the effectiveness of IUI or lack thereof, and we invited the medical community to start RCTs comparing IUI to no treatment.

In chapter 3 we describe the results of a randomised controlled non-inferiority trial in which we compared the effectiveness of three cycles of in vitro fertilisation (IVF) with single embryo transfer (SET) plus frozen embryo cycles and six cycles of IVF in a modified natural cycle (MNC) to six cycles intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) within 12 months after randomisation. Couples with unexplained or
mild male subfertility, a female partner aged 18 to 38 years and an unfavourable prognosis for natural conception, i.e. a predicted chance of less than 30% in the upcoming twelve months, were eligible to participate. The primary outcome was the birth of a healthy child resulting from a singleton pregnancy conceived within 12 months after randomisation. 602 couples were randomly assigned to IVF-SET (N=201), IVF-MNC (N=194) or IUI-COH (N=207). 104 (52%) couples delivered a healthy child in the IVF-SET group, 83 (43%) in the IVF-MNC group and 97 (47%) in the IUI-COH group. The relative risk of IVF-SET compared to IUI was 1.10 (95%CI: 0.91 to 1.34) and for IVF-MNC compared to IUI was 0.91 (95%CI: 0.73-1.14). Multiple pregnancy rates were 6% after IVF-SET, 5% after IVF-MNC and 7% after IUI-COH. This led us to conclude that IVF-SET and IVF-MNC were non-inferior to IUI-COH with regards to the birth of a healthy child. Our recommendation was that IUI-COH should remain first-line treatment for these couples.

In chapter 4 we describe a cost-effectiveness analysis alongside the trial described in chapter 3. We collected data on resource use related to treatment, medication and pregnancy from the case report forms. We calculated unit costs from various sources. For each of the three strategies, we calculated the mean costs and effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated for IVF-SET compared to IUI-COH and for IVF-MNC compared to IUI-COH. The mean costs per couple were €7187 for IVF-SET, €8206 for IVF-MNC and €5070 for IUI-COH. Compared with IUI-COH, the costs for IVF-SET and IVF-MNC were significantly higher (mean differences €2117; 95%CI: €1544 - €2657 and €3136, 95%CI: €2519 - €3754, respectively). The ICER for IVF-SET compared with IUI-COH was €43,375 for the birth of an additional healthy child. In the comparison of IVF-MNC to IUI-COH, the latter was the dominant strategy, i.e. more effective at lower costs. These data reinforce our recommendation of chapter 3 that IUI-COH should remain first-line treatment for these couples.

In Chapter 5 we aimed to identify couples that could benefit from immediate IVF over IUI-COH. We assessed whether female age, duration of subfertility or prewash total motile count (TMC) can help to identify couples that would benefit from IVF over IUI-COH. We performed a secondary data-analysis of a multicenter open-label randomized controlled trial, in which 116 couples with unexplained or mild male subfertility were randomly allocated to one cycle of IVF with elective single embryo transfer with subsequent frozen-thawed embryo transfers or 3 cycles of IUI-COH. The primary outcome was an ongoing pregnancy within 4 months after randomization. For each prognostic factor we developed a logistic
regression model to predict ongoing pregnancy with that prognostic factor, treatment and a factor-by-treatment interaction term. Female age and duration of subfertility were not associated with better ongoing pregnancy chances after IVF compared to IUI-COH ($p$-value for interaction=0.65 and 0.26, respectively). Only when TMC was lower than 110 ($\times 10^6$ spermatozoa/mL), the probability of ongoing pregnancy was higher in women allocated to IVF ($p$-value for interaction=0.06). In couples with unexplained or mild male subfertility, a low TMC might lead to higher pregnancy rates after IVF than after IUI-COH. This finding needs to be validated in larger trials before a TMC-based treatment selection strategy can be applied in clinical practice.

In Chapter 6 we report on a study evaluating treatment selection markers in couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception. We used data from the INeS trial, in which couples were randomly allocated to IVF-SET, IVF in a modified natural cycle or IUI-COH. In view of the aim of this study, we only used data of the comparison between IVF-SET (201 couples) and IUI-COH (207 couples). We pre-defined the following baseline characteristics as potential treatment selection markers: female age, ethnicity, smoking status, type of subfertility (primary/secondary), duration of subfertility, body mass index, pre-wash total motile count (TMC) and Hunault prediction score. For each potential treatment selection marker, we explored the association with the chances of a healthy child after IVF-SET and IUI-COH and tested if there was an interaction with treatment. Given the exploratory nature of our analysis, we used a $p$-value of 0.1. None of the markers was associated with higher chances of a healthy child from IVF-SET compared to IUI-COH ($p$-value for interaction >0.10), leading us to conclude that we could not identify couples with unexplained or mild male subfertility who would have had higher chances of a healthy child from immediate IVF-SET than from IUI-COH.

In Chapter 7 we evaluate natural conception rates in couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception after the completion of the fertility work-up. We performed a secondary analysis of a randomised controlled trial including couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception. The detailed data collection in this trial allowed us to study the exact periods that couples were not receiving treatment. Couples were allocated to either three cycles IVF with single embryo transfer (SET, n=201), six cycles of IVF in a modified natural cycle (MNC, n=194) or six cycles of IUI (n=207) with controlled ovarian hyperstimulation (COH). We split the dataset into periods during which couples were treated (IVF-SET, IVF-MNC or
IUI-COH) and periods during which they were not treated. Couples were at risk for natural conception in the periods before, in between and after treatment. The primary outcome for this analysis was ongoing pregnancy resulting from natural conception. We performed a Cox proportional hazards analysis with a time-varying covariate with four categories: IVF-SET, IVF-MNC, IUI-COH and no treatment. We estimated the expected 12-month ongoing pregnancy rate for couples had they not received treatment. In the 602 included couples, the mean age of the female partner was 33.6 years and the mean duration of subfertility was 3.6 years. There were 342 ongoing pregnancies, of which 77 (23%) resulted from natural conception. The average observed fractions of ongoing pregnancies after natural conception were 4.1% per month in the first trimester of the year, 1.2% in the second, 1.7% in the third, and 1.2% in the fourth trimester of the year. The estimated cumulative natural conception rate after 12 months was 24.5% (95%CI: 19.4% to 29.2%). We conclude that couples with unexplained subfertility with a low calculated probability to conceive naturally still have about a one in four chance of a pregnancy without treatment within 12 months. We trust that this finding will add to building an evidence-informed, shared decision-process in couples who are about to start fertility treatment.

In chapter 8 we evaluate if there are differences between clinics in couples’ natural conception chances. We performed a secondary data-analysis of a prospective cohort study among 2916 subfertile couples recruited in 21 clinics. We excluded couples who had a fertility disorder i.e. one or two-sided tubal pathology, ovulation disorder, total motile sperm count <3 x 10^6. After completion of the fertility work-up, included couples were counseled for expectant management for at least six months or followed until the first day of treatment. We estimated Kaplan Meier survival curves and a logrank statistic. We determined crude and adjusted hazard ratios, adjusted for patient characteristics and the type of clinic and we also ascertained hazard ratios with Empirical Bayes estimates. We performed validation of the prediction model per clinic through calibration. We found significant differences between clinics in the chances of ongoing pregnancy (P<0.001); even after adjustment for female age, duration of subfertility, percentage of progressive motile sperm, primary/secondary subfertility and post-coital test (p<0.001). Adjusted hazard ratios and Empirical Bayes estimates ranged from 0.50 and 2.21, and 0.58 to 1.53, respectively. In the multivariable analysis, the type of clinic was not significant (P = 0.11). Calibration gave an average intercept of -0.25 (95% range: -1.04-0.53) and average slope of 0.81 (95% range: 0.03–1.60). Our findings suggest that the synthesis model to predict natural conception is useful overall in clinical practice, but in a minority of clinics the model is not
well calibrated. Updating the synthesis model to include a center-specific baseline chance on natural conception might improve the synthesis model for certain clinics.

In chapter 9 we describe a protocol for a systematic review and network meta-analysis on treatment strategies for couples with unexplained subfertility. Existing systematic reviews can only evaluate comparisons of two head to head interventions. Yet, as there is a wide range of available treatments, these reviews cannot summarize all the available data. Network meta-analysis provides a way of assessing the most effective and safe intervention by not only using head to head direct comparisons, but also by indirectly comparing interventions that have not been directly assessed in randomised controlled trials. These results will help guide clinicians in offering the best first-line treatment for couples with unexplained subfertility.

**IMPLICATIONS FOR PRACTICE**

Based upon the results of this thesis we have the following recommendations for clinical practice. First, we recommend that couples be counselled on their chances of pregnancy without treatment. To calculate the chance of natural conception for the following year, the Hunault model gives the most reliable estimate (van der Steeg *et al.*, 2006). These couples can then make an informed decision to start or delay treatment based on the best available evidence.

Second, until future data show otherwise, we recommend maintaining IUI as first line treatment for couples with unexplained subfertility and low probability of natural conception. We have demonstrated that in terms of effectiveness, safety and costs, there is no evidence to support replacing IUI as first line treatment by IVF. Although IUI has been implemented into clinical practice without proven evidence of its effectiveness, it currently is still an appropriate first-line treatment, until new data shows otherwise.
IMPLICATIONS FOR FUTURE RESEARCH

Based upon the results of this thesis we have the following recommendations for future research. First, we need prediction models that will not only calculate the chances of pregnancy for each intervention and the chances without treatment separately, but one that can predict all these chances in one model. This would allow for more individualized decision-making. To date such a model does not exist. Currently, in the Netherlands, nationwide electronic medical record system has been implemented which contains all information on the fertility work-up and the phases of treatment. These prospective cohorts could be useful for calculating the chances of pregnancy for each treatment as well as unassisted reproduction after the completion of the fertility work-up. A potential limitation to the use of these cohorts is the risk of selection bias, as the start of treatment may be dependent on the current national and local guidelines, the perceived chances of pregnancy with or without treatment by the physician and ultimately the choice of each individual couple. Also these cohorts might reflect the treatment strategies of local or national guidelines, and might not be generalizable to other populations. Yet, this seems the only way forward, until large randomised trials have been completed that compare the various first-line treatments to unassisted reproduction in the same or a similar population of couples.

Second, we feel that it is high time to provide scientific evidence for the effectiveness of IUI and IVF as first-line treatment for couples with unexplained subfertility. Although these interventions have been used in clinical practice for decades, there are still only few RCTs evaluating IUI or IVF compared with no treatment. There will be resistance from those that unequivocally believe in the effectiveness of these treatments, arguing that couples are being deprived of interventions that could shorten their time to pregnancy. Yet, to state the obvious, innate beliefs in the effects of these interventions cannot outweigh scientific evidence. It might not be an easy path to take, but we cannot continue exposing couples to possibly ineffective interventions, which carry risks and cost money. We have reached the stage at which the only way forward is to perform the urgently needed RCTs to finally provide evidence of the effectiveness and safety of these first-line treatments.

Third, network meta-analyses can be implemented more in reproductive medicine. Standard systematic reviews and meta-analysis ultimately only evaluate head to head comparisons, and do not, for instance, answer the question which one of the many interventions for couples with unexplained subfertility, is the most effective and safest. Network meta-analysis is a way to answer these type of questions by not only incorporating
head to head direct comparisons, but also by using indirect comparison techniques for treatments that have not been directly assessed in randomised controlled trials. Network meta-analyses can also be used to identify gaps in research. Such knowledge is helpful in designing future trials.
REFERENCES


