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SUMMARY

Tailored expectant management in reproductive medicine

Subfertility is defined as a failure to conceive after at least one year of regular unprotected intercourse. It affects approximately 10% of couples in their reproductive lives (Boivin et al. 2007; Gnoth et al. 2003). The incidence of subfertility is increasing in the developed world mainly due to postponement of maternity. After a basic fertility work up about 25% of all subfertile couples is diagnosed with unexplained subfertility, 30% with a mild male factor, 5% with a severe male factor, 20% with an ovulation disorder and in 20% of the couples other diagnoses are made.

In couples with unexplained or mild male subfertility, i.e. >50% of all subfertile couples, fertility treatments as intra uterine insemination (IUI) with or without ovarian stimulation (OS) and in vitro fertilisation (IVF) are not always leading to higher pregnancy rates than expectant management. To select couples for expectant management prognostic models that predict the chance of natural conception have been developed. One large randomised controlled trial showed that if chances of natural conception are intermediate or good, an expectant management for 6-12 months is as effective as IUI with OS. We call this strategy, i.e. expectant management in couples with good prospects of natural conception, tailored expectant management (TEM). TEM is not always practiced, leading to overtreatment, unnecessary complications and costs. A common complication of fertility treatment is a multiple pregnancy, which is associated with a higher morbidity and mortality in both mothers and neonates.

It is unclear how TEM is implemented in the Netherlands, but two large prospective cohort studies suggest a poor implementation. This thesis aimed to contribute to the implementation of TEM. To improve the implementation of TEM a systematic approach is needed including: acquiring data of current practice; identification of potential determinants; analysis of barriers and facilitators for the implementation, development of an implementation strategy and finally an evaluation of the implementation strategy. In this thesis this systematic approach was used to gain insight in the options to improve the implementation of TEM.

In addition to the implementation study we aimed in the second part of this thesis to evaluate the applicability of prognosis of natural conception. This evaluation was twofold. Firstly, we compared two selection methods for fertility treatment: a funding based selection strategy used in New Zealand and a selection strategy based on the validated prognostic model of Hunault. In New Zealand public funding for fertility treatment is restricted to subfertile women who are unlikely to conceive naturally, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). In the Netherlands couples are selected for treatment based on their prognosis of natural conception. The performance of both selection methods were compared in a New Zealand cohort of 663 couples.

Secondly, we aimed to explore the selective capacities of the prognostic model predicting the chance of natural conception in more detail. At the moment it is unclear if prognosis can help the physician to choose the proper - i.e. most (cost-) effective- treatment for subfertile couples with unexplained or mild male subfertility. In this last part of the thesis we will evaluate if prognosis can select couples for a specific treatment. We addressed this issue by analysing individual patient data (IPD) of published randomised controlled trials. Authors of published randomised trials comparing expectant management (EM), intracervical insemination (ICI), IUI, all three with or without OS and IVF, in couples with unexplained or male subfertility were contacted and invited to share their original data. In all datasets, we calculated the chances of natural conception for each couple with the validated prognostic model. We then constructed prognosis-by-treatment curves and tested whether prognosis can help to choose the most effective treatment strategy for the individual couple.

Chapter 1 gives an outline and describes the objectives of this thesis.

Chapter 2 reports the results of a cohort study in which we assessed risk factors for non-adherence to tailored expectant management (TEM). Couples with mild male, unexplained and cervical subfertility were included in this multicentre prospective cohort study. If the probability of natural conception according to the prognostic model of Hunault within 12 months was $\geq 40\%$, the study protocol advised an expectant management for 6–12 months. Multivariable logistic regression was used to identify patient and clinical characteristics associated with non-adherence to TEM. In total 3021 couples were included in this cohort of whom 1130 (38%) had a $\geq 40\%$ probability of natural conception. Follow-up was available for 1020 (90%) couples of whom 214 (21%) had started treatment between 6 and 12 months and 153 (15%) within 6 months.

A higher female age and a longer duration of subfertility were associated with treatment within 6 months (OR: 1.06, 95% CI: 1.01–1.1; OR: 1.4; 95% CI: 1.1–1.8). A fertility doctor in a clinical team reduced the risk of treatment within 6 months (OR: 0.62; 95% CI: 0.39–0.99). We concluded that in couples with a favorable prognosis of natural conception, there is considerable overtreatment, especially if the woman is older and duration of the subfertility is longer. The presence of a fertility doctor in a clinic may prevent early treatment.

In **chapter 3** we aimed to identify any barriers or facilitators for tailored expectant management among professionals and subfertile couples. A qualitative study was performed with semi structured in-depth interviews among 21 subfertile patients who were counselled for TEM. In addition, three focus-group interviews were held with 21 professionals within the field of reproductive medicine. Two theoretical models were used to guide the interviews and the analyses. The primary outcome was the set of identified barriers and facilitators which influence implementation of TEM.

Among the subfertile couples, main barriers were a lack of confidence in natural conception, a perception that expectant management is a waste of time, inappropriate expectations prior to the first consultation, misunderstanding the reason for expectant management and overestimation of the success rates of treatment. Both couples and professionals saw the lack of patient information materials as a barrier. Among the professionals, limited knowledge about prognostic models leading to a decision in favour of treatment was recognized as a main barrier. A main facilitator mentioned by the professionals was better management of patients' expectations.

Chapter 4 describes a nationwide survey to assess the prevalence of the barriers and facilitators identified in chapter 3 and to evaluate which factors predict patients' appreciation of TEM and professionals' adherence to TEM. Two questionnaires were developed based on the identified barriers and facilitators and sent to 195 couples and 167 professionals. Multivariate analysis was performed to evaluate which factors predicted patients' appreciation of TEM and professional adherence to TEM.

In total, 118 (61%) couples and 117 (70%) professionals responded and 96 couples and 117 professionals were included in the analysis. Patients' mean appreciation of TEM was 5.7, on a 10-point Likert scale. Patients with a lower appreciation of TEM had a higher need for patient information ($p = 0.047$). The professionals reported a mean adherence to TEM of 63%. Adherence to TEM was higher when professionals were fertility doctors ($p = 0.041$). Facilitators in the clinical domain were associated with a higher adherence to TEM ($p = 0.091$). Barriers in the professional domain had a negative impact on adherence to TEM ($p = 0.008$).

Chapter 5 describes the study protocol of an ongoing cluster randomized trial that tests a multifaceted implementation strategy to improve the implementation of tailored expectant management (TEM). Current implementation of TEM is not optimal (chapter 2). Based on the barriers and facilitators of TEM that were identified among professionals and subfertile couples in chapter 3 and 4, we developed a multifaceted implementation strategy. This implementation strategy focuses on infertile couples and their care providers i.e. general practitioners (GPs), fertility doctors and gynecologists. The implementation strategy addresses three levels: (1) Patient level: education materials in the form of a patient information leaflet and a website; (2) Professional level: audit and feedback, educational outreach visit, communication training and access to a digital version of the prognostic model of Hunault on a website; (3) Organizational level: providing a protocol based on the guideline. In a cluster randomized trial, 25 clinics and their allied practitioners units are randomized between the multifaceted implementation strategy and care as usual. The effect of the implementation strategy, i.e. the percentage guideline adherence on TEM, will be evaluated by pre- and post-randomization data collection. Furthermore there will be a process and cost evaluation of the strategy.

Chapter 6 describes a study on the performance and measure of agreement of two fertility treatment selection methods: the CPAC score and the prognostic model of Hunault. In New Zealand public funding for fertility treatment is restricted to subfertile women who are unlikely to conceive naturally, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). In this study this CPAC score was compared with the prognostic model developed in the Netherlands (the Hunault model).

For this comparison a New Zealand (NZ) cohort of 663 couples with unexplained subfertility was used. Of the 663 couples referred, 249 (38%) couples had unexplained subfertility. Of 246 women with follow-up data, there were 143 (58%) who had a live birth or ongoing pregnancy during the follow up period of 4-5 years, 65 (26%) after fertility treatment and 78 (32%) after natural conception.

There were 100 couples (41%) who had a Hunault prediction score of $< 30\%$, which is the treatment threshold according the Dutch National Fertility guidelines and 36 (15%) couples who had a CPAC score of >65 , which is the New Zealand threshold for publically funded treatment. There were 69 couples (28%) who met the threshold for treatment in the Netherlands, but did not meet the New Zealand threshold for public funding. The kappa coefficient as a measure of agreement of the two scores and their treatment thresholds was 0.30 suggesting a fair agreement. The discriminative capacity was comparable between the two selection methods (AUC: 0.63), but the Hunault model performed better in calibration.

In **chapter 7** the study protocol of an individual patient data (IPD) analysis of the relation between the prognostic profile of subfertile couples and treatment outcome after EM, IUI and IVF is described. Most studies that evaluated the effectiveness of these treatment options have not taken the couples' prognosis into account, which may or may not influence the effect of treatment. Individual patient data analyses allow us to take these prognostic factors into account, and to evaluate their effect on treatment outcome. This study aimed to use anonymised data from relevant published trials to perform an individual patient data meta-analysis, evaluating the effect of couples' prognosis on the effectiveness of EM, IUI, with or without COS, and IVF. Based on earlier systematic reviews and an updated search, randomised controlled trials were considered for inclusion. Authors of the included studies were invited to share their original anonymised data. The data were assessed on validity, quality and completeness. The prognosis of the individual couple was calculated and its' effect on treatment outcome analysed.

Chapter 8 reports the results of the study protocol described in chapter 7. We acquired data from 8 RCTs, including 2,550 couples. In three studies the more invasive treatment strategies appeared less effective in couples with a high chance of natural conception, but this difference did not reach statistical significance (p-value for interaction 0.71, 0.31 and 0.19). In one study the strategies with OS (IUI and ICI) led to higher pregnancy rates than unstimulated strategies, regardless of prognosis, but at the expense of a high twin rate. In two studies, the more invasive treatments strategies appeared more effective in couples

with a good prognosis, but this difference did not reach statistical significance (p-value for interaction 0.38 and 0.68 respectively). In one study, prognosis was already incorporated in the inclusion criteria and its' differential effect on treatment effect was limited. The only study that compared EM with IVF included 38 couples, and was too small for a precise estimate. Our analyses exclude large differential effects of prognosis on effectiveness of fertility treatment.