Reproductive choices in women with poor ovarian reserve and recurrent miscarriages
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Summary
Worldwide, more and more women are having their first child later in life. This delayed child bearing has major repercussions, because as women get older reproductive problems such as age-related subfertility and miscarriages lay on the lure. As older women have lower natural conception rates, more women turn to assisted reproductive technology for conception, but are then faced with the fact that also in IVF female age is the most important predictive factor for chances of success. One of the consequences of advanced female age in IVF is a poor response to ovarian hyperstimulation which reflects a physiologic decline in ovarian reserve of primordial follicles (ie poor ovarian reserve). Also in young women a poor response to ovarian hyperstimulation may occur, which then reflects a pathologic decline in number and quality of primordial follicles. There is evidence that the addition of rLH to recombinant follicle stimulating hormone (rFSH) during controlled ovarian hyperstimulation (COS) increases ongoing pregnancy rates in women with poor ovarian reserve. When women finally conceive, either through IVF or through natural conception, the next obstacle is the risk of a miscarriage and 3% of all women will experience 2 or more miscarriages before 20 weeks pregnancy. Recurrent miscarriage (RM) is a distressing condition for the affected couple and a frustrating problem for the clinician, because in most cases there is no effective therapy. Pre-implantation genetic screening (PGS) and pre-implantation genetic diagnosis (PGD) are interventions that have been proposed to increase pregnancy rates and also to lower miscarriage rates in women with RM. Apart from these medical-technical options, supportive care for women with RM is recommended by guidelines, but what these women actually perceive and prefer as supportive care has never been investigated.

In this thesis we hypothesized that the higher ongoing pregnancy rates described in women with poor ovarian reserve after COS with the addition of rLH to rFSH compared to COS with rFSH alone is due to an increase in quality embryos. We investigated the effect of rLH-addition for COS on the quality of embryos in women with a poor ovarian reserve defined as women aged 35 to 41 years old and women younger than 35 years old with a FSH level >12 IU/ml and an AFC ≤ 5. As the addition of rLH requires an extra subcutaneous injection and costs we asked women’s perspectives on an additional injection of rLH with respect to live birth rates and ‘out of pocket’ costs. Since PGS and PGD are invasive and require IVF, the claim that PGS and PGD increases live birth rates in women with RM should be substantiated and therefore we systematically collected the evidence as published in the literature. Finally, we investigated what women with RM perceive and prefer as supportive care.

Chapter 1 gives an outline and describes the objectives of this thesis.
Chapter 2 gives the results of a randomized controlled trial that investigates the effect of rLH-addition to rFSH for COS on the quality of embryos in women with poor ovarian reserve. There was evidence of a beneficial effect of the addition of rLH to ovarian hyperstimulation with FSH in COS on ongoing pregnancy rates in women with poor ovarian reserve. Given the role of rLH in the maturation of the oocyte and effect on embryo quality, the benefit of rLH on pregnancy rates in these women may be mediated through an increase in embryo quality. At the time we started research, there were no randomised controlled trials of the effect of rLH on embryo quality in women with poor ovarian reserve. Two-hundred-forty-four women with poor ovarian reserve, defined as all women aged 35 to 41 years old and women younger than 35 years old with a FSH level >12 IU/ml and an antral follicle count ≤ 5, awaiting their first IVF were randomly allocated to rFSH and rLH (2:1 ratio) or rFSH alone (control group); 116 women were allocated to the rLH group and 128 women were allocated the control group. The primary outcome was proportion of top-quality embryos per woman i.e. three days after oocyte retrieval. Analysis was by intention to treat. Proportion of top-quality embryos per woman was 17% in the rLH group and 11% in the control group (Mean difference 0.06; 95%CI -0.01 to 0.14). From these data we conclude that there was a non-significant increase in the proportion of top-quality embryos per woman when rLH was added to rFSH during COS in women with poor ovarian reserve.

Chapter 3 investigates women’s perspectives on an additional injection of rLH with respect to live birth rates and ‘out of pocket’ costs in a discrete choice experiment. Next to this possible beneficial effect of adding rLH to COS there are two potential drawbacks of adding rLH to COS; women have to administer extra subcutaneous injections and daily rLH injections generate additional costs. Two-hundred-thirty-four women eligible for IVF were asked to choose between IVF treatments that differed in live birth rate after one IVF cycle, the amount of self administered subcutaneous injections and ‘out of pocket’ costs or reimbursement. In total 206 questionnaires were analysed. An increase of one daily subcutaneous injection did not alter women’s preference. Live birth rate and costs did have a statistical significant (p<0.001) impact on women’s choice for an IVF treatment. Patient characteristics such as age, parity, duration of subfertility and income significantly influenced the effect of costs on women’s preferences. Depending on these characteristics, women were willing to pay a thousand euros of out of pocket costs if it is compensated with at least a live birth rate ranging from 5% to 14%. These results show that an extra daily injection will not cause a woman to refrain from a certain IVF treatment, but to compensate for the out of pocket costs of this extra daily injection the expected live birth rate should at least be 6%.
Chapter 4 presents a systematic review that assesses live birth rates and miscarriage rates after PGS or natural conception for couples with unexplained RM. MEDLINE, EMBASE and the Cochrane database were searched until December 2009. Randomized trials and cohort studies describing reproductive outcome in couples with unexplained RM after PGS and/or after natural conception were included. Primary outcome measure was live birth rate per couple. Secondary outcome measure was miscarriage rate per couple. No randomized controlled trials or comparative studies comparing PGS with natural conception in couples with unexplained RM were found. Four observational studies reporting on the reproductive outcome of 181 couples after PGS conception and 7 studies reporting on the reproductive outcome of 261 couples after natural conception were found. Live birth rate per couple after PGS varied between 19% and 46% (mean 35%; median 40%), and miscarriage rate ranged from 0% to 10% (mean 9%; median 9%). Live birth rate per couple after natural conception varied between 11% and 61% (mean 41%; median 36%), and miscarriage rate ranged from 14% to 52% (mean 28%; median 25%). Until data from randomized controlled trials become available, this review summarizes the best available evidence of the efficacy of PGS versus natural conception. At present, there is insufficient evidence to recommend PGS as a method to increase live birth rates in couples with unexplained RM.

Chapter 5 reviews the reproductive outcome after PGD in couples with RM carrying a structural chromosome abnormality, as well as the reproductive outcome of these couples after natural conception. MEDLINE, EMBASE and the Cochrane database were searched until April 2009. Trials, patient series and case reports describing reproductive outcome in couples with RM carrying a structural chromosome abnormality after natural conception and/or after PGD were included. Primary outcome measure was live birth rate per couple. Secondary outcome measure was miscarriage rate per couple. No randomized controlled trials or cohort studies comparing natural conception with PGD in couples with RM carrying a structural chromosome abnormality were found. Four observational studies reporting on the reproductive outcome of 469 couples after natural conception and 21 studies reporting on the reproductive outcome of 126 couples after PGD were found. Live birth rate per couple after natural conception varied between 33% and 60% (median 55.5%) and miscarriage rate ranged from 21% to 40% (median 34%). Live birth rate per couple after PGD varied between 0% and 100% (median 31%), and miscarriage rate ranged from 0% to 50% (median 0%). Currently, there is insufficient evidence to recommend PGD as a method to increase live birth rates in couples with RM carrying a structural chromosome abnormality.

Chapter 6 presents an exploratory investigation of what women with unexplained RM prefer as supportive care during their next pregnancy. What these women themselves
prefer as supportive care in their next pregnancy has never been substantiated. We performed explorative, semi-structured, in-depth interviews among 15 women with unexplained RM who were actively seeking conception. The topic list and the open questions in the interviews were based on information acquired at expert panel meetings and supplemented with the sparse literature on this topic. Women identified 20 different supportive care options; 16 of these options were preferred for their next pregnancy. Examples of the preferred supportive care were early and frequently repeated ultrasounds, \( \beta \text{HCG} \) monitoring, practical advice concerning lifestyle and diet, emotional support in the form of counselling, a clear policy for the upcoming 12 weeks and medication. The four supportive care options that were not preferred by the women were admittance to a hospital ward on the same gestational age as previous miscarriages, Complementary Alternative Medicine, ultrasound every other day and receiving supportive care from their general practitioner. Our study identified several relevant preferences for supportive care in women with unexplained RM. Many of these can be offered by the gynaecologist and will help in guaranteeing high quality patient-centred care.

Chapter 7 investigates which supportive care options are most frequently preferred by women with RM in their next pregnancy and which patient characteristics predict the need for supportive care. A questionnaire study was conducted in 266 women with RM ( \( \geq 2 \) miscarriages) in three hospitals in the Netherlands. Two-hundred-sixty-six women diagnosed with RM were sent a questionnaire. The questionnaire assessed characteristics of the women, quantified supportive care options identified by the qualitative study presented in Chapter 6 and analysed women’s characteristics (age, ethnicity, education level, parity, pregnancy during questionnaire and time passed since last miscarriage) to elucidate the preferences of the different groups. In total 171 questionnaires were analysed. Women with RM preferred the following supportive care options for their next pregnancy; a plan for the first trimester (80%) and care by one doctor (70%) preferably a gynaecologist or doctor specialized in RM that shows understanding (88%), takes them seriously (87%), has knowledge of their obstetric history (86%), listens to them (86%) gives information about RM (84%), shows empathy (76%), informs on progress (74%) and enquires about emotional needs (60%). Access to ultrasound examination during symptoms (88%), directly after a positive pregnancy test (67%) and every two weeks a repeat ultrasound (66%) were preferred by the majority of women with RM. Finally, 61% of women would prefer to talk to a medical or psychological professional after their next miscarriage. The majority of women did not prefer admittance to a hospital ward at the same gestational age as previous miscarriages (65%) nor bereavement therapy (66%).
The mean preference on a scale from 1-10 for supportive care was 8.0 for women with RM. Ethnicity, education level, parity, pregnancy at the time of the survey and time passed since the last miscarriage proved to be predictors in the preference of different supportive care options, female age did not. These results show that women with RM preferred several types of medical supportive care from a gynaecologist or doctor specialized in RM who takes them seriously. Women from ethnic minorities and women who were not pregnant during the questionnaire were the two patient groups that preferred the highest number of supportive care options. These data allow for tailor made supportive care in women with RM.

In Chapter 8 the findings of this thesis are discussed, clinical implications are given and future research recommendations are made.