Reproductive choices in women with poor ovarian reserve and recurrent miscarriages
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Introduction
Worldwide, more and more women are having their first child later in life (Mathews and Hamilton, 2009). This delayed child bearing has major repercussions, because - as women get older - reproductive problems such as subfertility and miscarriages lay on the lure (Wood, 1989, Brigham et al., 1999).

In the Netherlands, delayed childbearing is evident, as the mean age of women who become mothers for the first time has increased over the last 17 years from 24.8 to 29.4 years. This makes Dutch women among the oldest mothers in the world (Mathews and Hamilton, 2009). As older women have lower natural conception rates (te Velde and Pearson, 2002), more women turn to assisted reproductive technology for conception. As a consequence, the mean age of women undergoing IVF is increasing year after year (de Mouzon et al., 2010).

IVF is not a guarantee for success in older women, considering that female age is the most important predictive factor for chances of pregnancy after IVF (Hughes et al., 1989; Lintsen et al. 2007; van Loendersloot et al., 2010; Broer et al., 2011). 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 (i.e. poor ovarian reserve) (Pellicer et al., 1994; Beckers et al., 2002; de Boer et al., 2002; Lawson et al., 2003). 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 (Jacobs et al., 1990; El-Toukhy et al., 2002).

The term poor response was introduced in 1983, as it became evident that ovarian response after ovarian hyperstimulation in IVF differed between women (Garcia et al., 1983). Poor response was defined as a peak estradiol level <300 pg/mL (1100pmol/L). Since then poor ovarian response has become a collective term that is defined in numerous ways based on different diagnostic tests or patient characteristics; i.e. ovarian response to an IVF treatment cycle, female age, peak estradiol level, basal follicle stimulating hormone (FSH) level, anti-müllerian hormone (AMH) level, basal antral follicle count (AFC), number of mature follicles, number of oocytes at follicle aspiration, dose of gonadotrophins used and/or embryo quality (Klinkert, thesis 2005). This definition is probably so broad because the term poor response was coined before the introduction of ovarian function tests such as AFC, FSH and AMH. Poor response actually describes the clinical manifestation of a poor ovarian reserve. This is supported by the fact that ovarian function tests are good predictors for ovarian response after IVF (van Rooij et al., 2002; Broekmans et al., 2006; Kwee et al., 2007, Broer et al., 2009).

Poor ovarian reserve is a common clinical problem, with 26% of IVF cycles resulting in poor response (Pellicer et al., 1987; Keay et al., 1997). Women with poor ovarian reserve that do proceed to follicle aspiration produce low numbers of oocytes and embryos and have low pregnancy rates and high miscarriage rates (Jenkins et al., 1991;
Ulug et al., 2003; Haadsma et al., 2010). As this is an increasing problem, it is evident that more research should be conducted on this subject.

When women finally conceive, either through IVF or through natural conception, the next obstacle is the risk of a miscarriage. Miscarriages are a frequent complication of pregnancy with one out of every nine pregnancies ending in a spontaneous first trimester miscarriage (Nybo Andersen et al., 2000). Three percent of all women will experience 2 or more miscarriages before 20 weeks pregnancy (Regan and Rai, 2000). Current diagnostic procedures for recurrent miscarriage (RM) identify aetiological factors as structural chromosome abnormalities, antiphospholipid syndrome, endocrine disorders and uterine abnormalities in approximately 50% of these couples (Christiansen et al., 2005, Jauniaux et al., 2006). The other 50% are diagnosed as couples with unexplained RM (Rai and Regan, 2006). Even though a cause for RM can be found in 50% of the women, only women with RM resulting from antiphospholipid syndrome have a potentially effective treatment namely the use of anti-coagulants (Rai et al., 1997; Empson et al., 2011).

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. Even so, clinicians often propose non-evidence based diagnosis and treatment and find it difficult to adhere to the guidelines that state that treatment for these couples should not be commenced upon (Franssen et al., 2007). One of the most frequently mentioned barriers for good adherence to the Dutch guideline on RM was that doctors find it difficult to refuse demands of insistent patients (van den Boogaard et al., 2011). Thus, women with unexplained RM are eager and willing to try any form of treatment and clinicians are challenged to withhold from non evidence based treatment.

Supportive care is frequently offered to women with unexplained RM, reporting live birth rates up to 85% (Javert, 1954; Stray-Pedersen and Stray-Pedersen, 1984; Liddell et al., 1991; Clifford et al., 1997, Brigham et al., 1999). Current guidelines from the European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommend supportive care during the next pregnancy for women with unexplained RM (RCOG, 2003; Jauniaux et al., 2006), suggesting it has a beneficial effect.

Nevertheless, there are several issues with implementing this recommendation. First, supportive care for women with unexplained RM is an ill-defined concept (van den Boogaard et al., 2011). Second, no uniform treatment protocol can be distilled from studies on supportive care, because the care offered in these studies varied widely from early ultra sound investigation during the next pregnancy, to relaxation tapes and admittance to the hospital ward on the same gestational age as previous miscarriages. Third, what the women themselves prefer as supportive care in their next pregnancy has never been investigated.
Background of the research described in this thesis

In 2007, when we started the studies that led to this thesis, the addition of recombinant luteinizing hormone (rLH) to ovarian stimulation protocols in IVF was becoming more and more a topic of research in women with poor ovarian reserve. There was evidence that the addition of an injection rLH to recombinant follicle stimulating hormone (rFSH) increased ongoing pregnancy rates in women with poor ovarian reserve. Studies indicated that the addition of rLH resulted in higher implantation rates in women aged 35 years or older (Marrs et al., 2004; Humaidan et al., 2004). A meta-analysis of randomized clinical trials comparing the addition of rLH to rFSH with rFSH alone had just been completed and confirmed the beneficial effect on pregnancy rates in these women. The pooled estimate of ongoing pregnancy per woman was a significant 10% higher in women co-treated with rLH compared to the women treated with rFSH alone (OR 1.85, 95% CI 1.10-3.11) (Mochtart et al., 2007). However, the exact mechanism through which rLH increases ongoing pregnancy rates in this population remained unclear.

We set out to explore the possible beneficial effect of rLH on embryo quality in women with a 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 AFC ≤ 5.

What women prefer when it comes to injections during IVF had not been investigated at that time and the addition of rLH means an extra daily subcutaneous injection in an already invasive and burdensome treatment (Eugster and Vingerhoets, 1999). There is data that suggests that women prefer an IVF treatment with less injections rather than more, but the studies generating this data, were designed to investigate the reasons why women drop out of treatment and not how women receiving IVF perceive treatment aspects (Fauser et al., 1999; Olivius et al., 2004; Heijnen et al., 2007; Verberg et al., 2008; Verberg et al., 2009; Domar et al., 2010). To elucidate how women precieve injections, we investigated patients’ perspectives on an extra daily injection during an IVF treatment.

An intervention approaching the issue of low pregnancy rates in women of increased age from a completely different angle is pre-implantation genetic screening (PGS). In PGS embryos are selected for transfer based on the ploidy status of a single blastomere biopsied from that embryo (Gianaroli et al., 1997; Munné et al., 1999). However, in 2007, a trial revealed that in women of advanced maternal age PGS in fact decreased pregnancy rates (Mastenbroek et al., 2007). The results showed an ongoing pregnancy rate of 25% in the PGS group compared to 37% in the control group (rate ratio: 0.69: 95% CI: 0.51-0.93).
Besides women of advanced age, couples with unexplained RM have also been suggested as candidates for PGS. The rationale behind the use of PGS in case of unexplained RM was that aneuploidy of the embryo may be the cause of the RM (Gianaroli et al., 2002; Werlin et al., 2003; Rubio et al., 2005; Munné et al., 2005; Mantzouratou et al., 2007). Similarly, Pre-implantation Genetic Diagnosis (PGD) was proposed to improve live birth rates and decrease miscarriage rates in couples with RM who carry a structural chromosome abnormality (Munné et al., 2000; Otani et al., 2006). The rationale behind the use of PGD for this purpose was that relatively more live births are achieved and that the number of miscarriages can be reduced by eliminating the transfer of unbalanced embryos. Since PGS and PGD are invasive and require IVF, the claim that PGS and PGD increases live birth rates should be substantiated beyond any reasonable doubt before this technique is introduced into daily clinical practice.

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 (RCOG, 2003; Jauniaux et al., 2006). Therefore an important goal of our research was to qualify and quantify supportive care options for women with RM.
Outline of the thesis

Chapter 2 evaluates the effect of adding rLH to rFSH for controlled ovarian hyperstimulation in IVF on embryo quality in women with poor ovarian reserve defined as women aged 35 to 41 years and women younger than 35 years with a FSH level \( >12 \text{ IU/ml} \) and an AFC \( \leq 5 \). By means of a randomized controlled trial we included 224 women awaiting their first IVF/ICSI cycle between August 2008 and April 2010. The primary outcome was the rate of top-quality embryos, defined as the percentage of embryos per woman that develop into a top-quality embryo on the day of transfer, i.e. three days after follicle aspiration. Secondary outcomes were the number of stimulation days until hCG administration, the number of follicles \( \geq 17 \text{ mm} \) on the day of hCG administration, the number of oocytes, the fertilization rate, the number of embryos, the number of women with \( \geq 1 \) top-quality embryo, the biochemical, clinical and ongoing pregnancy rate and the miscarriage rate.

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. Two-hundred-twenty-three of 234 women eligible for IVF returned the questionnaire (response rate 95%) and finally 206 questionnaires were analysed. Women 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. A model was developed to estimate the relative weights that women place on these attributes and to distinguish which patient characteristics (age, parity, duration of subfertility, income, previous treatment with subcutaneous injections and diagnosis of the subfertility) influence decision making.

Chapter 4 reviews systematically the literature on the effect of PGS on the live birth rate and miscarriage rate in couples with unexplained RM. Results of four studies reporting on the reproductive outcome of couples with unexplained RM receiving PGS and four studies reporting on the reproductive outcome of these couples after natural conception are presented.

Chapter 5 reviews systematically the literature on the effect of PGD on the live birth rate and miscarriage rate in couples with RM carrying a structural chromosome abnormality. Results of 21 studies reporting on reproductive outcomes of carrier couples with RM receiving PGD and four studies reporting on the reproductive outcomes of couples after natural conception are presented.
Chapter 6 provides qualitative data on what women with unexplained RM prefer as supportive care during their next pregnancy. Fifteen explorative, semi-structured, in-depth interviews were performed among women with unexplained RM.

Chapter 7 identifies the main preferred and non-preferred supportive care options for women with recurrent miscarriages in their next pregnancy. By means of a questionnaire returned by 174 of 266 women (response rate 65%) preferences were elucidated and a multivariable model was estimated including patient characteristics (ethnicity, education level, parity, pregnancy during questionnaire and timeline of previous miscarriage) to further quantify the preferred and non-preferred supportive care options.

Chapter 8 provides a general discussion of the results presented in this thesis and outlines their clinical implications. Finally suggestions for future research for women with poor ovarian reserve and in couples with unexplained RM are given.

Chapter 9 summarizes the data presented in this thesis.
References


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