Reproductive choices in women with poor ovarian reserve and recurrent miscarriages
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General Discussion
Solving reproductive problems such as age-related subfertility and miscarriages seems simple enough: women should not postpone childbearing. Yet women continue to do just this (Mathews and Hamilton, 2009). The reason women postpone childbearing has its roots in a continuously changing society (CBS, 2009; SCP, 2011).

Postponing child bearing in the Netherlands
Until the late nineteen-sixties conception of children was a self-evident part of life. Most people decided to get married after a period of engagement and the desire to have children was rarely discussed; the birth of children followed naturally (Beets, 2008). After the introduction of birth control in the form of “the pill” in 1963, fertility patterns changed dramatically. Oral contraception paved the way for the postponement or annulment of having children (de Graaf, 1998).

In the Netherlands shortly after the Second World War in 1946, a record number of 284,000 babies were born. In the nineteen-sixties, this number was around 240,000 babies per year and in the nineteen-seventies, the number fell to about 175,000 babies a year. This decrease in the nineteen-seventies was caused by social factors such as secularization, emancipation, individualization and by the availability of contraception (van Nimwegen and Beets, 1994).

At that time, a growing number of young couples found social welfare and a career equally important or more important than a family life with children. A feeling of impending overpopulation prevailed among many Dutch, considering that the prediction in 1965 for the Dutch population was 21 million before the end of the twentieth century (Beets and de Graaf, 1980). The introduction and acceptance of
reliable contraception provided a reliable and safe method to postpone pregnancy for the first time.

Starting from the beginning of the nineteen-nineties a slow increase of the number of babies born per year was seen up to 185,000 babies per year in 2009. The reason for this annual increase was the favourable economic climate (CBS, 2008; van Duin, 2009). It is expected that in the coming years there will –again- be a declining number of babies born, due to the declining number of women that are in their reproductive life span, an obvious consequence of the reproductive behaviour in the previous decades.

In addition to this decline in number of women of reproductive age, structural and cultural factors play a role in the declining number of babies born: parenthood is postponed. This delay of parenthood is closely related to educational level (Beets, 2007). Due to educational expansion far more women can and do seek higher education before they enter the workforce. By the time women have a diploma, find a good job and are well incorporated in the labour market, they are generally no longer so young (Kravdal and Rindfuss 2008, Mills et al., 2011). Also, having children is not perceived as a duty anymore (SCP, 2011). Values such as self-development and autonomy are in addition to parenting considered important (van de Kaa, 2001).

A survey study performed in 2008 among 3997 Dutch women reported that the two main reasons women postpone motherhood are because they want to enjoy their freedom (20%) and they do not have a partner (18%). Ten percent of the respondents postponed children because of their career. Other reasons women postponed motherhood had to do with their current partner; 10% mentioned that their relationship was not stable enough and in 4% of the women their partner was not ready for children. Finally, 9% of the women had doubts about ever wanting a child (CBS, 2009). The remaining 29% of the women had various reasons such as finishing their degree (4%), health reasons (3%), financial problems (3%), problems conceiving (2%), unsuitable living situation (1%), and other non-defined reasons (16%).

In the late nineteen-seventies, about 70% of women in the Netherlands had a child when they were younger than 30 years. At this moment only one third of women younger than 30 years do. The average age of women at the birth of their first child is currently 29.4 years. Women with a higher education are on average 34 years at the birth of their first child (SCP, 2009). The proportion of mothers aged 40 years or older has quadrupled from 1% in 1980 to over 4% in 2009 and over one fourth of these women are a first-time mother at age 40 or above. This development has to do with postponement of children and with “repartnering” (Wobma and de Graaf, 2009).

We too experience the effect of postponement of childbearing in our Centre for Reproductive Medicine as the average age of the women visiting our centre for the first time was 35 in 2009.
Women with poor ovarian reserve

Many women who have postponed child bearing will experience subfertility and will ultimately turn to in vitro fertilization (IVF), but IVF is no panacea for age related subfertility. One of the major problems of IVF in older women is poor response to controlled ovarian hyperstimulation (COS) 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). Women of advanced female age, but also younger women with high FSH levels and a low antral follicle count (AFC), have low pregnancy rates after IVF or intracytoplasmic sperm injection (ICSI) (Jenkins et al., 1991; Ulug et al., 2003).

The addition of recombinant luteinizing hormone (rLH) to COS showed a beneficial effect on pregnancy rates in these women (Mochtar et al., 2007). This led us to hypothesize that rLH increases embryo quality thereby leading to higher pregnancy rates. Although we indeed found an increase in the rate of top-quality embryos per woman and more women had at least one top-quality embryo in the rLH group, the difference was not statistically significant (Chapter 2).

This may be because there is no difference in embryo quality or because the power needed to demonstrate a difference was not achieved; we included 244 women in our trial and in total 893 embryos were found instead of the anticipated 1040 embryos. This was due to cycle cancellations, lack of oocytes after follicle aspiration and total fertilisation failure in both study groups (in total 18% in the rLH group and in total 23% in the control group). This indicates that the women in this study had an even poorer ovarian function than expected and really represent women with an extremely poor prognosis. Because power was not reached, it still remains undecided if the biological explanation for the higher ongoing pregnancy rate with the addition of rLH can be attributed to an increase of top quality embryos. More studies are needed to investigate this. Adding the pregnancy results of our trial and the results of a recently published large prospective randomized study (Bosch et al., 2010) to the available data in the Cochrane review, the significant beneficial effect of rLH addition on ongoing pregnancy rates in women with poor ovarian reserve holds (OR 1.39 95% CI: 1.01-1.92).

Even though there is a positive effect of rLH on ongoing pregnancy rates there are also two potential drawbacks of adding rLH to COS; women have to administer extra daily subcutaneous injections and the rLH injections generate additional costs.

Patient preference studies in reproductive medicine have clearly demonstrated that live birth rates are the pivotal factors for women in their decision making (Nieuwkerk et al., 1998; Steures et al., 2005; Bayram et al., 2005; Twisk et al., 2006; van Mello et al., 2010). On the other hand, monetary resources in society are not unlimited and health care workers are to provide the most cost effective treatment. Public financing of ART ranges from virtually no subsidization in the USA, to funding of a limited...
number of cycles in most European countries and to unrestricted reimbursement with co-payments in Australia (Hughes and Giacomini 2001, Nachtigall 2006; Chambers et al., 2009, Connolly et al., 2010). In the Netherlands, where state funding is currently available for up to three attempts, the costs of an additional rLH injection are as of yet not reimbursed. A recent study demonstrated that a price increase in ART treatment, associated with the introduction of co-payment for ART, reduced utilization for IVF (Connolly et al., 2009). This suggests that when treatment access is dependent on user fees, costs are preventative for many patients (Connolly et al., 2010).

Next to the costs of an extra injection, what women prefer when it comes to injections during IVF has not been studied. We do know that IVF is perceived as an invasive and burdensome treatment (Kopitzke et al., 1991; Edelmann et al., 1994; Eugster and Vingerhoets 1999). This burden and distress even causes women to drop out of treatment for the following reasons; psychological burden, poor prognosis, relationship problems and physical burden (Olivius et al., 2004; Verberg et al., 2008; Domar et al., 2010). The physical burden encompasses infection, ovarian hyperstimulation syndrome and administration of subcutaneous injections (Olivius et al., 2004; Verberg et al., 2008; Domar et al., 2010). These data suggests that women prefer an IVF treatment with less injections rather than more, but the studies generating these data, were designed to investigate the reasons why women drop out of treatment and not how women receiving IVF perceive treatment aspects like for instance injections.

We therefore started a patient preference study in the form of a discrete choice experiment (DCE) to investigate women’s perspectives on an additional injection of rLH with respect to live birth rates and ‘out of pocket’ costs. We found 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 3).

The fact that women did not find an extra injection a reason to refrain from IVF and costs only started to matter when live birth rates were under 6%, suggest that IVF treatments with the least injections are not per se considered the most “patient friendly” by patients themselves.

In summary, the addition of rLH to COS gives a higher ongoing pregnancy rate than COS with rFSH alone, potentially by increasing embryo quality, and women do not find an extra injection a reason to refrain from IVF, but before we recommend the addition of rLH to all IVF treatments in women with poor ovarian reserve we should put our findings into the context of other gondotrophins with an intrinsic LH activity, such as highly purified hMG (hp hMG) which has been demonstrated to result in a higher live birth rate compared to rFSH alone (OR 1.19 95% CI: 1.01-1.93) (Coomarasamy et al., 2008; van Wely et al., 2011).
From a cost-effective point of view hp hMG is favourable compared to rFSH (Connolly et al., 2008; Melo et al., 2010; Wex-Wechowski et al., 2010). Hp hMG is relatively cheap, and is well available. There are major considerations to recommending COS with hp HMG for women with poor ovarian reserve. First, the trials included in the meta-analysis that compare hp hMG with rFSH were all performed in a standard IVF population, and no subgroup analysis could be done on women with poor ovarian reserve. Only one study, not included in the meta-analysis, compared rFSH (150 IU) and hpHMG (150 IU) to rFSH (375 IU) stimulation in women non responsive to 300 IU rFSH and reported significantly higher number of oocytes retrieved in the rFSH/hpHMG group and (not-significant) more pregnancies (De Placido et al., 2001). Second, hMG is a urinary product that next to FSH and LH can contain unwanted proteins such as prions. Although menopausal urine donors are screened for symptomatic neurological disease, incubation of Creutzfeldt-Jakob disease (CJD) is impossible to exclude by non-invasive testing. Also, the purification processes for different urine-derived preparations are unable to remove prion proteins from the source material (Van Dorsselae et al., 2011). Third, even though hp hMG is cheaper than rLH, Chapter 3 of this thesis shows that women are willing to pay out of pocket costs for a live birth rate above 6%. Fourth, there are no sufficiently powered randomized controlled trials that have investigated ongoing pregnancy rates in women receiving IVF with HMG compared to rLH/rFSH stimulation, let alone in women with poor ovarian reserve.

In view of this, as of yet there is no evidence to recommend COS with hp HMG for women with poor ovarian reserve. COS with the addition of rLH to rFSH can be recommended for these women, but it is important to note that before considering the addition of rLH as standard treatment in women with poor ovarian reserve, its costs should be balanced against its potential benefits with proper cost effectiveness studies.

Further research should focus on the effect of hp hMG on women with poor ovarian reserve. An Individual Patient Data meta-analysis could be used to uncover data on these women from the studies already preformed comparing hp hMG with rFSH. If hp hMG is proven superior in this group, the next step is to investigate effect of hp hMG compared to rLH and rFSH in women with poor ovarian reserve. This can be investigated with randomized controlled trials or an Individual Patient Data meta-analysis.

Women with recurrent miscarriage: the role of invasive techniques

Next to tailoring ovarian hyperstimulation regimens to enhance IVF success rates, investigating embryos for aneuploidies by means of pre-implantation genetic screening (PGS) is another intervention that has been proposed to increase pregnancy rates and also to lower miscarriage rates.
The rationale behind the use of PGS was that aneuploidy of the embryo leads to embryonic death, implantation failure and/or miscarriages and that testing embryos for aneuploidies helps to choose the “right” embryo for transfer thereby lowering miscarriage rates and improving ongoing pregnancy rates in women with advanced maternal age (Gianaroli et al., 1997; Munne et al., 1999). The use of PGS rapidly expanded to other indications like unexplained recurrent miscarriage (RM). The rationale 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; Munne et al., 2005; Mantzouratou et al., 2007). Similarly, pre-implantation genetic diagnosis (PGD) was proposed to improve live birth rates, decrease miscarriage rates and decrease the chance of unbalanced offspring in couples with RM who carry a structural chromosome abnormality (Munne et al., 2000; Otani et al., 2006). The idea behind the use of PGD for this purpose was that an unbalanced embryo causes the miscarriage and that embryo selection eliminates the chance of an unbalanced offspring.

Both women with unexplained RM and couples with RM who carry a structural chromosome abnormality have a good prognosis for natural conception and live birth (Brigham et al., 1999; Franssen et al., 2006). By reviewing the literature on PGS in women with unexplained RM and the literature on PGD in carrier couples with RM, we found that there is insufficient data indicating that PGS or PGD improves live birth rates in women with unexplained RM or couples with RM who carry a structural chromosome abnormality compared to natural conception. Furthermore, couples with RM who carry a structural chromosome abnormality have a low risk of viable offspring (~0.8%) with unbalanced chromosomal abnormalities and no studies reported that viable unbalanced offspring occurred after PGD (Chapter 4; Chapter 5).

It is our opinion that, currently, there are insufficient arguments to introduce PGS and/or PGD, with its high costs and potential complications related to the IVF procedure, into the daily clinical practice for couples with unexplained RM and couples carrying a structural chromosome abnormality. The need for comparative studies of high quality is urgent.

Women with recurrent miscarriage: supportive care
Next to these invasive techniques, other interventions to increase live birth rates have been studied in women with RM. A Cochrane review reported the effects of various forms of immunotherapy, such as paternal cell immunization and immunoglobulin infusions, and found no significant beneficial effect on live birth rate of any of these techniques (Porter et al., 2006).

During the time span of this thesis a large trial showed that neither aspirin combined with low-molecular-weight heparin nor aspirin alone improved the live-birth rate, as compared with placebo, among women with unexplained RM (Kaandorp et al., 2010).
So only for women with RM resulting from antiphospholipid syndrome a potentially effective treatment namely the use of anti-coagulants is available (Rai et al., 1997, Empson et al., 2011). This leaves the vast majority of women with recurrent miscarriages without a treatment, which is one of the reasons why RM is a distressing condition for the affected couple and a frustrating problem for the clinician.

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 E et al., 2006), suggesting it has a beneficial effect. Supportive care is regularly offered to these women 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) but what these women themselves perceive and prefer as supportive care has never been investigated until this thesis. The results of our qualitative and quantitative studies indicate that women with RM are in need of supportive care during their next pregnancy. In the qualitative study women identified, 20 different supportive care options, of which 16 were preferred during their next pregnancy (Chapter 6). The women sought these supportive care options in their next pregnancy for reassurance, comfort, certainty, trust, and to feel understood and supported. From these 20 different options identified in the qualitative study we developed a survey study that investigated which supportive care options women with RM find most important (Chapter 7). Women with RM preferred different types of medical supportive care from a gynaecologist or doctor specialized in RM who takes them seriously. We also identified characteristics that predict the need for supportive care and found that especially 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.

The results of this study can help lessen frustration for both women with RM and doctors, because we now know which supportive care options women with RM find most important. This will bring clinicians a step closer to effectively helping and understanding women with RM. Also, considering the differences in preferences of the subgroups of women, tailor-made supportive care can now be offered to women with RM.

However, although we now know what women with RM want when it comes to supportive care, the kinds of supportive care that women want are not always feasible in our current health care system, for example ethnic minorities prefer admittance to a hospital ward at the same gestational age of a previous miscarriage. To put our findings into context the next step should be to investigate doctors’ views, on supportive care for women with RM to ensure practicability and enhance shared decision making.
The results of the focus group interviews and questionnaires presented in this thesis can be incorporated in the guidelines for the management of couples with recurrent miscarriages.

There are many more issues to be addressed in future studies for women with recurrent miscarriages. First of all, we should investigate all potential aetiological factors for the strength of association with recurrent miscarriages. Then examine if the current diagnostic tests and treatments are adequate. Finally, update guidelines and make sure they are implemented and adhered to (van den Boogaard et al., 2011a).

Just recently, results of studies on couples with RM who carry a structural chromosome abnormalities indicate that these couples should be counselled for their good prognosis of a successful conception and low chances of a child with an unbalanced structural chromosome abnormality (Thesis Franssen 2010). Also more and more evidence is accumulating on the association between thyroid autoimmunity and RM (van den Boogaard et al., 2011b; Thangaratinam et al., 2011).

In light of our current knowledge, future topics for research should include treatment with thyroxin in a randomised setting in this subgroup of women, treatment with low-molecular-weight heparin in women with RM and trombophilia, metroplasty in women with RM and a septate uterus (TRUST trial number: NTR1676), supplementation of progesterone in women with unexplained RM (PROMISE trial number: ISRCTN92644181).

Although these trials should be done, it is important to realize that the current paradigm of RM and its management are firmly anchored in the conjecture that pre-existent disease, often much more relevant to subfertility, also underpins RM. Yet, two studies that analyze time to pregnancy in 811 recurrent miscarriage patients revealed that 35-40% could be considered as ‘superfertile’, here defined as a mean time to pregnancy of 3 months or less (Salker et al., 2010, thesis Kaandorp 2011). An explanation of this superfertility may be that there is a failure in decidualizing endometrial stromal cells that serve as biosensors of embryo quality, which enables maternal recognition and elimination of compromised pregnancies (Teklenburg et al., 2010a). In other words due to a disfunctioning endometrium abnormal embryos implant and finally result in a clinical miscarriage (Teklenburg et al., 2010b). If these findings are true, than there is no treatment for this condition considering that a miscarriage is a delayed “clean-up” mechanism for an abnormal embryo.

Nevertheless, currently, supportive care, pre-conceptional lifestyle counselling and making women aware of their childbearing postponement attitudes can be given to all women with RM independent of aetiological factors and a disfunctioning endometrium.
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