Summary

Chapter 1

Over the past 20 years, attention has been mainly focussed on how to improve pregnancy rates in IVF while the appropriate balance between success, risks and costs has been inadequately addressed. The most important complication of IVF is multiple pregnancy. Preterm delivery and low birth weight is the major cause of mortality and morbidity in multiple pregnancy. Another serious complication in IVF is the ovarian hyperstimulation syndrome. The incidence of multiple pregnancies can be decreased by the transfer of one embryo in women younger than 38 and two embryos in women of 38 years and older and by identifying those treatment cycles at particular risk of leading to multiple pregnancy. The ovarian hyperstimulation syndrome and other complications of IVF can be prevented by applying milder stimulation protocols. To compare different treatment strategies (stimulation protocol and embryo transfer policy) it is important to use a simple and clear consistent definition of success in IVF.

Chapter 2

Changing the way in which successful in vitro fertilisation (IVF) treatment is defined offers a tool to improve efficacy while reducing costs and complications of treatment. Crucial to this paradigm shift is the move away from considering outcomes in terms of the single IVF cycle, and towards the started IVF treatment as a whole. We propose the most informative endpoint of success in IVF to be the term singleton birth rate per started IVF treatment (or per given time period) in the overall context of patient discomfort, complications and costs. These endpoints are not only important for patients but also for clinicians, health economists and policy makers. Such an approach would encourage the development of patient friendly and cheaper stimulation protocols with less stress, discomfort and side effects. The combination of mild ovarian stimulation with single embryo transfer may provide the same overall pregnancy rate per total IVF treatment, achieved in the same amount of time for similar direct costs, but with reduced patient stress and discomfort, and the near complete elimination of multiple pregnancies. This would offer major health and indirect cost benefits. If IVF success rates were to be expressed in terms of delivery of a term single baby per IVF treatment (or in a given treatment period), the introduction of single embryo transfer on a large scale would be facilitated.

Chapter 3

The meta-analysis described in this section was conducted to compare outcomes of standard in vitro fertilization (IVF) in women presenting with polycystic ovary syndrome (PCOS) and non-PCOS patients. Studies in which PCOS patients undergoing IVF were compared with a matched –no male factor- control group were considered for this review. A definition consistent with the Rotterdam consensus criteria of PCOS was required and all patients within a given study had to be treated with the same ovarian stimulation protocol. Information regarding patient characteristics and pregnancy outcome was also required. Nine out of a total of 290 identified studies reporting data on 458 PCOS patients (793 cycles) and 694 matched controls (1116 cycles) fulfilled these inclusion criteria. PCOS patients demonstrated a significantly reduced chance of oocyte retrieval per started cycle, (odds ratio (OR) 0.5 (95% CI 0.2;1.0)). However, no difference was observed in chance of embryo transfer per oocyte retrieval between the groups (OR 0.7 (95% CI 0.4;1.3)). Significantly more oocytes per retrieval were obtained in PCOS patients compared with controls (random effects estimate 3.4 (95% CI 1.7;5.1). The number of oocytes fertilized did not differ significantly between PCOS patients and controls, weighted mean difference (WMD) 0.1 oocytes (95% CI -1.4;1.6). No significant difference was observed in the clinical pregnancy rates per started cycle, OR 1.0 (95% CI 0.8;1.3). The incidence of ovarian hyperstimulation syndrome (OHSS) after oocyte retrieval was rarely reported. This meta-analysis demonstrates an increased cancellation rate, but more oocytes retrieved per retrieval and a lower fertilization rate in PCOS undergoing IVF. Overall PCOS and control patients achieved similar pregnancy and live birth rates per cycle.

Chapter 4

The aim of this chapter is to answer the question whether dual instead of triple embryo transfer in subsequent cycles in patients over 38 years will substantially reduce the number of multiple pregnancies while the chance of a term live birth remains at an acceptable level. A randomised controlled two-centre trial was performed. 45 patients, 38 years or older were randomised. Dual embryo transfer over a maximum of 4 cycles (DET-group) or triple embryo transfer over a maximum of 3 cycles (TET-group) was performed. The cumulative term live birth rate was 47.3% after 4 cycles in the DET-group and 40.5% after 3 cycles in the TET-group. The difference between the DET and the TET-group is 6.8% in favour of the DET-group (95% CI -25;38) (p=0.7). The multiple pregnancy rates in the DET and TET-group were 0% (95% CI 0;24) and 30% (95% CI 7;65), respectively (p=0.05). In the DET patients the mean number of treatment cycles was 2.9 compared to 2.1 in the TET-group (p=0.01). In women of 38 years and older a dual embryo transfer strategy after

IVF may result in similar cumulative term live birth rates compared with a triple embryo transfer strategy provided that a higher number of treatment cycles is accepted.

Chapter 5

This chapter discusses the design of a clinical study to evaluate the effectiveness, health economics and patient discomfort of two treatment algorithms in in-vitro fertilisation (IVF), involving differences in both ovarian hyperstimulation and embryo transfer policies. A randomised controlled clinical trial was performed in two large centres. The tested treatment strategies are: A) mild ovarian hyperstimulation (including GnRH antagonist co-treatment) together with the transfer of a single embryo, versus a standard hyperstimulation regimen (with GnRH agonist long protocol co-treatment), and the transfer of two embryos. The primary study endpoints were; (1) pregnancy within one year after randomisation leading to term live birth; (2) total costs per couple and child up to 6 weeks after expected delivery, and (3) overall patient discomfort within one year of randomisation. Power considerations for this study were an overall cumulative pregnancy rate of 45% with the standard treatment strategy and non-inferiority of the new treatment strategy was defined as a no more than 12.5% lower live birth rate compared to the standard treatment strategy. For a power of 80% and alpha = 0.05, a total number of 400 subjects was required. Analysis will be performed according to the intention-to-treat principle. The trial is an ongoing two-centre trial in The Netherlands. As anticipated, from February 2002 until March 2004, 410 patients have been enrolled in the study. Further follow-up (12 months for treatment, and 9 months for pregnancy) is required for live birth as endpoint. Inclusion of study participants has been very good and is completed. Final data analysis can be performed at the end of 2005.

Chapter 6

The aim of this chapter was to establish whether a mild in-vitro fertilization treatment strategy can achieve the same term live birth rate within 1 year compared to standard treatment, while reducing patient discomfort, multiple pregnancies and cost. A randomised controlled two-arm, two-centre effectiveness trial was performed. Four hundred and four patients were assigned to undergo either a mild stimulation/gonadotropin releasing hormone (GnRH) antagonist co-treatment protocol combined with single embryo transfer or a standard stimulation/GnRH agonist long-protocol in combination with the transfer of two embryos. The primary study endpoints were; (1) pregnancy within one year after randomisation leading to term live birth; (2) total costs per couple and child

up to 6 weeks after expected delivery, and (3) overall patient discomfort within one year of randomisation. The cumulative pregnancy rate resulting in term live birth after 1 year was 43.4% in the mild treatment group and 44.7% in the standard treatment group. The respective multiple pregnancy rate per couple was 0.5% versus 13.1% (P<0.001) and total costs were €8,333 versus €10,745 (P=0.006). The areas under the cumulative score curves for anxiety, depression, physical discomfort and sleep quality within one year were equal between the two treatment groups. Mild ovarian stimulation together with single embryo transfer in IVF can result in similar cumulative term live birth rates and patient discomfort over 1 year of treatment compared to standard stimulation with two embryo transfer, while significantly reducing multiple pregnancy rates, and overall costs.

Chapter 7

This chapter compared the economic costs of a mild treatment strategy and single embryo transfer to the standard treatment strategy with dual embryo transfer. 404 patients were randomly assigned to; (I) mild ovarian stimulation/gonadotropin-releasing hormone (GnRH) antagonist co-treatment and single embryo transfer, or (II) standard ovarian stimulation/GnRH agonist co-treatment and dual embryo transfer. The primary outcome parameter was total costs of IVF treatment within 12 months after randomisation including costs of resulting pregnancy and postnatal costs of the mother and the infant(s) up to six weeks after term. The mild strategy was associated with lower hospital costs per IVF cycle (€1,569 versus €1,987; p=0.001) and, despite a significantly increased number of IVF cycles (1.7 versus 2.3; p<0.001), in lower average total costs during the first year (€8,333 versus €10,745; p=0.006). This was mainly due to higher costs of the obstetric and postnatal period for the standard strategy. The higher delivery costs and longer hospital admission of mother and child were mainly caused by multiple pregnancies. The cost per ongoing pregnancy leading to term live birth was €19,156 in the mild strategy and €24,038 in the standard strategy. Despite an increased mean number of IVF cycles within one year, from an economical perspective, the mild treatment strategy is more advantageous, assuming equal effectiveness. This advantage will further increase in the long-term, due to health economic benefits arising from physical and mental handicaps later in life.

Chapter 8

This chapter discusses the conclusions which could be drawn from the work presented in the current thesis. The proposed optimal outcome parameter in this thesis is the cumulative term live birth rate per time period or per treatment period. This should be

weighed against the associated discomfort, complications and costs. The first randomised controlled trial in this thesis showed that in women of 38 years and older the transfer of 2 embryos after IVF may result in similar cumulative term live births compared with transfer of 3 embryos provided that a higher number of treatment cycles is accepted. The principle finding of this thesis is that the application of a mild strategy in women under 38 years do not reduce the chance of achieving the goal of a pregnancy leading to a term live birth within 1 year. The way to define success in IVF proposed in this thesis and the described study can contribute to the introduction of single embryo transfer on a large scale.