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Introduction
On 25 July 1978 at 11.47 PM Louise Brown was born as the first IVF baby ever. Since then, the number of in vitro fertilization cycles has increased rapidly: in the United Kingdom 6,650 cycles were performed in 1991 and 61,726 cycles in 2011 (1;2). In the Netherlands, 11,154 cycles were performed in 1996 and 16,668 cycles in 2011 (3). Since its introduction more than 5 million babies have been born worldwide using IVF (4). IVF is currently one of the most widely used interventions for infertility.

The increase in the number of IVF cycles is not caused by a sudden epidemic of infertility, but mainly by increased access to IVF and by expansion of the indications for IVF. At first, IVF was initiated in couples with bilateral tubal occlusion (5). In 1992 intracytoplasmic sperm injection (ICSI) was initiated in couples with severe male subfertility. Later on IVF was also applied in couples with unexplained subfertility, cervical hostility, failed ovulation induction, endometriosis, or unilateral tubal pathology (6-8). The major difference between the original indication and the indications for which IVF is conducted nowadays, is that the couples with bilateral tubal pathology or azoopermia have zero chance of natural conception and completely depend on IVF/ICSI for getting pregnant, whilst couples with other indications are subfertile, and do have chances of natural conception, which may or may not be better than with IVF. For them, these chances have to be balanced against those with IVF.

In contrast to patients’ perception, IVF does not guarantee success; almost 50% of couples that start with IVF will not achieve a pregnancy through IVF even if they undergo multiple cycles (9). Given this limited success, it seems logical to offer IVF only to couples with reasonable chances of success and to discontinue treatment when chances are low and do not outweigh the burden and costs associated with treatment. Unfortunately, evidence from randomised trials confirming the effectiveness of IVF over natural conception in couples without bilateral tubal pathology or severe male factor is scarce. In fact only one single, small trial of only 51 couples has compared in couples with unexplained subfertility one cycle of IVF to three months of natural conception (10). The live birth rate was significantly higher with a single cycle of IVF (RR 12.4, 95% CI 1.72-89) (11). Due to paucity of data from randomised trials the effectiveness of IVF relative to natural conception remains unproven. So, until larger randomized trials with a prolonged duration of follow-up (more than one cycle), and with sufficient power are performed, the only way to prevent overtreatment and to counsel couples properly is selection based on the couple’s prognosis.

Unfortunately, gynecologists are not able to estimate the probability of achieving a pregnancy with IVF accurately (12). To support counseling, patient selection and clinical decision making in IVF, a number of prediction models have been developed in the past (7;13). Several models are of limited use since they were developed before current clinical and laboratory protocols were established (14-24). Most models do not include the transfer of frozen–thawed embryos, an essential component of modern day IVF.
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A number of models calculate pregnancy chances only for the first IVF cycle, whilst other models calculate pregnancy chances only after one or more failed IVF cycle.

The decisions to start or continue IVF are now largely guided by expert opinion. This approach ignores predictive factors other than female age and is not refined enough for clinical practice. It may lead to futile treatment or to wrongfully refraining from treatment.

The second major concern in current IVF practice is the high multiple pregnancy rate. In reproductive medicine the goal of every fertility treatment is live birth. Until a decade ago, one of the most common approaches to increase the likelihood of pregnancy in IVF was to transfer multiple embryos into the uterine cavity. This approach indeed resulted in high pregnancy rates but also increased the risk of multiple pregnancies. Initially, a multiple pregnancy was felt to be justified in what was largely an experimental treatment with poor pregnancy and live birth rates. In the last two decades pregnancy rates have increased substantially but multiple pregnancy rates remained high. The high multiple pregnancy rates caused concern, since multiple pregnancies are associated with an increase in maternal and perinatal morbidity and mortality as well as costs.

To curtail the multiple pregnancy rates, several treatment strategies have been evaluated over the years. The first strategy was to reduce triple embryo transfers and to increase double embryo transfers. This indeed prevented most triplets, but did not diminish the rate of twin pregnancies. As a result, single embryo transfer was introduced. The first randomized trial to compare elective single embryo transfer (eSET) with double embryo transfer (DET) was performed in 1999 in Belgium in women under 34 undergoing their first IVF/ICSI cycle. Since then, two systematic reviews and meta-analyses of randomized trials have been performed, based on synthesized aggregated data and individual patient data on eSET versus double embryo transfer (DET) in women with a good prognosis, i.e. women younger than 36 years and with at least two good quality embryos. These meta-analyses showed that, although eSET minimized the odds of multiple pregnancies, it also halved the odds of a live birth per fresh cycle. Subsequent transfer of a single frozen thawed embryo resulted in comparable cumulative live birth rates to those after DET. Although eSET is now an accepted policy for women with a good prognosis, the majority of women currently undergoing IVF have an intermediate or poor prognosis, such as women over 35 with several failed IVF cycles. For these women it is less clear how many embryos have to be transferred to obtain high pregnancy rates at low multiple pregnancy rates.
BACKGROUND OF THE RESEARCH OF THIS THESIS

At the start of the studies described in this thesis, there was only one IVF prediction model with good predictive performance that could be used in clinical practice (24). Yet, an IVF prediction model that predicts pregnancy chances during the complete IVF procedure, after failed cycles, and after fresh and frozen-thawed embryo transfer, did not exist. Also, if one uses a model and embarks on IVF, the ultimate goal is a singleton, since multiple pregnancies are associated with higher maternal and neonatal morbidity and mortality. At the start of the work reported in this thesis multiple pregnancy rates associated with IVF were still too high, and it was not clear how many embryos should be transferred in the general IVF population to obtain high pregnancy rates at low multiple pregnancy rates. Optimization of embryo transfer strategies was thus necessary.

We first externally validated the Templeton prediction model developed in 1996 in a more recent dataset, as IVF has progressed substantially during the last two decades we thought it was questionable whether the model was still valid in current clinical practice.

We then performed a systematic review and meta-analysis of the literature to identify candidate predictive factors and developed, based upon the identified factors, an IVF prediction model that could calculate pregnancy chances prior to the start of the first IVF cycle as well as after one or more failed cycles, and one that would take into account pregnancy chances after both fresh- and frozen-thawed embryo transfers.

We also compared different strategies to optimize embryo transfer and to reduce the multiple pregnancy rates whilst maintaining optimal pregnancy rates. In a prospective cohort we evaluated the results of a differentiated embryo transfer policy based on the prognostic profile of a woman, i.e. female age, cycle number and embryo quality.

We then developed an individualized embryo transfer strategy by building an embryo implantation model that ranks embryos based on their implantation potential and extended this model to an embryo transfer model that is not only able to calculate pregnancy chances after IVF, but also the chances of a single- or multiple pregnancy after single-, double, or triple embryo transfer.

OUTLINE OF THIS THESIS

Part one: Prognosis with in vitro fertilization
Chapter 2 presents an external validation of the IVF model developed by Templeton et al. in 1996. The performance of the prediction model was assessed in terms of discrimination, i.e. the area under the receiver operation characteristic (ROC) curve (AUC), and calibration. We evaluated likely causes for miscalibration by refitting the Templeton model to our data.
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Chapter 3 provides a systematic review and meta-analysis of published literature on nine predictive factors for success in IVF: age, type of infertility, indication, duration of infertility, basal FSH, number of oocytes, fertilization method, number of embryos transferred and embryo quality. Fourteen studies were identified. For five factors a summary odds ratio is presented.

Chapter 4 reports on the development of a new IVF prediction model that is able to calculate pregnancy chances prior to the start of the first IVF cycle as well as after one or more failed cycles. We collected data on couples who had been treated with IVF or ICSI between January 2001 and July 2009 at the Center for Reproductive Medicine at the Academic Medical Center, University of Amsterdam. A model was developed using multivariable logistic regression and a blockwise model building strategy to calculate the probability of a pregnancy with IVF, including fresh and frozen-thawed embryo transfers from the same cycle. The model was validated in additional data from couples treated between August 2009 and April 2011 at the same center.

Chapter 5 provides an overview on predictive factors in IVF, the available prediction models in IVF and provides key principles that can be used to critically appraise the literature on prediction models in IVF.

Part two: Optimizing embryo transfer strategies

In the prospective cohort study reported in Chapter 6 we evaluated in a tailored embryo transfer policy based on the prognostic profile of the couple. Between August 2006 and April 2011 we adhered to the following embryo transfer protocol at the Center for Reproductive Medicine at the Academic Medical Center, University of Amsterdam: single embryo transfer (SET) was performed followed by double embryo transfer (DET) in frozen embryo transfer cycles in women with a good prognosis (aged <35 years, first cycle, ≥1 top quality embryo). DET was performed in both fresh and frozen cycles in women with an intermediate prognosis (<35 years, first cycle and no top quality embryo available, or aged <35 years and ≥1 failed cycles, or aged 35-38 years). Triple embryo transfer (TET) in both fresh and frozen cycles was performed in women with a poor prognosis (aged ≥ 39 years).

Chapter 7 reports on the development of a prediction model to rank embryos within a single IVF/ICSI cycle according to their ongoing implantation potential. We prospectively studied embryo transfers on day 3 between January 2004 and July 2009 at the Center for Reproductive Medicine at the Academic Medical Center, University of Amsterdam. We evaluated pronuclear score, early cleavage, number of blastomeres on day 2 and day 3, morphological score on day 2 and day 3 as potential predictors for implantation. A model was developed using multivariable logistic regression. The prediction model was externally, temporally validated on embryo transfer data between August 2009 and September 2011 from the same center.
Chapter 1

Chapter 8 reports on the development of an embryo transfer model that is able to calculate the probability of an ongoing pregnancy as well as the probability of multiple pregnancy after single-, double embryo or triple embryo transfer. We collected data on couples who had been treated with IVF or ICSI between January 2004 and April 2011 at the Center for Reproductive Medicine at the Academic Medical Center, University of Amsterdam. The embryo transfer model consists of two components: variables specific to the transferred embryo(s), such as the number of blastomeres and variables specific to the couple, including maternal and treatment factors that affect all embryos equally. The model was based on the two previously developed models described in chapters 4 and 7. The performance of the prediction model was assessed in terms of discrimination, i.e. the area under the receiver operation characteristic curve (AUC) and calibration.

Chapter 9 summarizes the data presented in this thesis with implications for further research.
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REFERENCES


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