Predicting IVF outcome
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Summary and implications for further research
At 11.47 PM on 25 July 1978, the world’s first IVF baby, Louise Joy Brown, was born at Oldham and District Hospital in Greater Manchester. Since the birth of Louise Brown, the number of in vitro fertilization cycles has increased rapidly and it is estimated that today over 5 million IVF babies were born worldwide. IVF is currently one of the most widely used intervention for infertility and the number of cycles is increasing each year even further.

The increase in the number of IVF cycles has not been caused by a sudden epidemic of infertility, but mainly by increased access to IVF and by expansion of the indications for IVF, such as severe male subfertility, unexplained subfertility, cervical hostility, failed ovulation induction, endometriosis, or unilateral tubal pathology. The major difference between the original indication and the ‘newer’ IVF indications is that the couples with bilateral tubal pathology have zero chances of natural conception and completely depend on IVF 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 those with IVF. Due to paucity of data from randomized trials proving the effectiveness of IVF for unexplained infertility, relative to natural conception, the only way to prevent overtreatment at this moment is selection based on the couple’s prognosis. Unfortunately, gynecologists are not able to estimate the probability of achieving a pregnancy with IVF very accurately. Prediction models can help to improve counseling, patient selection and clinical decision making in IVF. Until now, a prediction model that predicts pregnancy chances during the complete IVF procedure, also after failed cycles, and after fresh and frozen-thawed embryo transfer, did not exist.

Soon after the introduction of IVF, pregnancy chances increased but also multiple pregnancy rates. This was caused by the transfer of multiple embryos into the uterine cavity, to increase the likelihood of pregnancy with IVF. 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. A logical solution to this recent epidemic of twins would be to transfer only one embryo. Although single embryo transfer (SET) 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 optimal pregnancy rates and low multiple pregnancy rates.

Chapter 1 gives an outline and describes the objectives of this thesis.
PART ONE: PROGNOSIS WITH IN VITRO FERTILIZATION

In 2009 a systematic review on prediction models in reproductive medicine was published, suggesting that the prediction model developed Templeton et al. in 1996 was the only IVF prediction model with a good predictive performance that could be used for predicting pregnancy chances with IVF. Since the development of this prediction model, IVF has progressed substantially; we thought it questionable whether the model was still valid in current clinical practice.

Chapter 2 describes the external validation of the Templeton prediction model. The performance of the prediction model was assessed in terms of discrimination, i.e. the area under the receiver operation characteristic (ROC) curve, and calibration. The area under the ROC curve for the Templeton model was 0.61. Calibration showed a significant and systematic underestimation of success in IVF. Although the Templeton model can distinguish somewhat between women with a high and a low success rate in IVF, it systematically underestimates pregnancy chances and has therefore limited value for current IVF practice.

To develop an improved IVF prediction model the first step we took was the identification of candidate predictors. Chapter 3 systematically reviews nine predictive factors for success in IVF. MEDLINE and EMBASE were systematically searched up to August 2009. Studies were included if they reported an unconditional odds ratio or whenever one could be calculated for one or more of the following factors: age, type of infertility, indication for IVF, duration of infertility, basal FSH, number of oocytes, fertilization method, number of embryos transferred and embryo quality. Fourteen studies were identified. We found negative associations between pregnancy and female age (OR: 0.95, 95% CI: 0.94 to 0.96), duration of subfertility (OR: 0.99, 95% CI: 0.98 to 1.00) and basal FSH (OR: 0.94, 95% CI: 0.88 to 1.00), and a positive association with number of oocytes (OR 1.04, 95% CI: 1.02 to 1.07). No significant association was found for type of infertility and fertilization method. In all studies better embryo quality was associated with higher chances of pregnancy but, as these studies used different factors or combinations of embryo factors to report embryo quality, it was not possible to pool the data and calculate a summary odds ratio. A summary odds ratio could also not be calculated for IVF indication and number of embryos transferred, because studies reporting on these factors used different reference categories. Female age, duration of subfertility, bFSH and number of oocytes, all reflecting ovarian function, are predictors of pregnancy after IVF.

Chapter 4 describes the development of our improved IVF prediction model, which calculates pregnancy chances prior to the start of the first IVF cycle as well as after one or more failed cycles, and takes pregnancy chances after fresh- and frozen-thawed embryo transfer from the same cycle into account. The model was developed on data of 2,621 cycles in 1,326 couples, using multivariable logistic regression and a blockwise
model building strategy. The model was validated in additional data from 440 couples treated between August 2009 and April 2011 at the same center. Thirteen variables were included in the final prediction model: female age, duration of subfertility, previous ongoing pregnancy, male subfertility, diminished ovarian reserve, endometriosis, basal FSH, number of failed IVF cycles, fertilization, number of embryos, mean morphological score per day 3 embryo, presence of eight-cell embryos on day 3, and presence of morulae on day 3. In validation the model had moderate discriminative capacity (c-statistic 0.68, 95% confidence interval: 0.63 to 0.73) but calibrated well, with a range from 0.01 to 0.56 in calculated probabilities. Our prediction model enables the accurate individualized calculation of the probability of an ongoing pregnancy with IVF. This IVF model presented here is able to calculate the chances of an ongoing pregnancy with IVF, both for the first cycle and after any number of failed cycles. Incorporating the model in counselling couples considering IVF may strengthen evidence-based, individualized decision-making and a rational use of scarce resources.

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. Over 21 papers have reported on the development and/or validation of prediction models in IVF. Of these 21 papers, only two models had a good performance after external validation. Impact analyses have not yet been performed for any of these models. Future research should focus more on updating existing prediction models and adjust or recalibrate them to the local circumstances or setting rather than developing new prediction models.

PART TWO: OPTIMIZING EMBRYO TRANSFER STRATEGIES

In any IVF cycle the question arises which embryo should be transferred, and how many embryos, to obtain optimal pregnancy rates with low multiple pregnancy rates. Chapter 6 presents the results of 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). The cumulative ongoing pregnancy rate in women with a good prognosis was 43%, with a multiple pregnancy rate of 2%. In women with an intermediate prognosis this was 27% and 23%, respectively. Corresponding rates were 18% and 13% in women with a poor prognosis. The data in this study can
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be used to guide current practice, by performing SET in women with a good prognosis and TET in women with a poor prognosis. The embryo transfer strategy in women with an intermediate prognosis requires further improvement possibly by refining the transfer strategy according to the ovarian response after ovarian stimulation.

Our final aim was to develop an individualized embryo transfer strategy that takes the complete prognostic profile of the woman into account; to achieve optimal pregnancy rates at low risk of multiple pregnancies. The first step in the development of such a model was to evaluate embryo quality more extensively. 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 validated on embryo transfer data collected between August 2009 and September 2011 in the same center. Five factors were included in the final prediction model: early cleavage, number of blastomeres on day 2, number of blastomeres on day 3, the morphological score on day 3 and presence of morulae on day 3. In the external validation the model showed moderate discriminative capacity (c-statistic 0.70) and calibrated well. The model was able to distinguish embryos with high ongoing implantation potential from embryos with moderate or low ongoing implantation potential. The model can be used by embryologists as an objective tool to rank embryos according to their implantation potential thereby aiding the selection of embryos for transfer.

Chapter 8 reports on the development of a multivariable embryo transfer model for cleavage stage embryos on day 3 to calculate the probability of a pregnancy and the chances of multiple pregnancy after single, double embryo or triple embryo transfer. The embryo transfer model consists of two components: variables specific to the transferred embryo(s), such as embryo quality and variables specific to the couple, such as a range of maternal factors, treatment and cycle data that affect all embryos equally. We combined two previously described models, one for ranking embryos and one for estimating pregnancy chances. 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.

In total, 2,201 IVF/ICSI cycles in 1297 couples could be included in our analyses. The embryo transfer model includes the following variables specific for the couple: female age, duration of subfertility, previous ongoing pregnancy, male subfertility diminished ovarian reserve, endometriosis, basal FSH and number of failed IVF cycles and in case of a failed IVF cycle: presence of absence fertilization, number of embryos, mean morphological score,
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presence of 8-cell embryos and presence of morulae on Day 3 of the previous cycle, and the following variables specific for the actual IVF cycle: early cleavage, number of blastomeres on day 2, number of blastomeres on day 3, the morphological score on day 3 and presence of morulae on day 3. The model calibrated well. The AUC for predicting pregnancy was 0.692 and multiple pregnancy was relatively high, at 0.778

Our model may aid in the decision how many embryos to transfer in any specific woman with any specific embryos to prevent a multiple pregnancy without reducing the chances of a singleton pregnancy. Wider applicability of this model requires external validation in databases from other centers.

IMPLICATIONS OF THIS THESIS

The prediction models discussed in this thesis could help to improve every day IVF practice. Before the introduction of prediction models, most clinical decisions and embryo selection procedures were based on expert opinion. With the prediction models presented in this thesis a more evidence-based treatment strategy is possible, and also a more ‘patient tailored’ treatment. Imagine a couple with an indication for IVF/ICSI because of unexplained subfertility. Their fertility specialist will calculate, with the IVF model (Chapter 4), their chances of a pregnancy with IVF/ICSI. Together with their fertility specialist, the couple can decide if their chances outweigh the burden and risk of an IVF cycle. If they decide to start with IVF, have undergone oocyte retrieval, and embryos have developed, the embryologist can rank the embryos by their implantation potential, with the embryo model (Chapter 7). Before the embryo transfer, the embryologist can calculate, with the embryo transfer model (Chapter 8), their pregnancy chances and multiple pregnancy chances, with the best embryo or with different combinations of embryos. If they fail to get pregnant, the fertility specialist will calculate again, with the IVF model (Chapter 4), their chances of a pregnancy in the subsequent cycle.

We suggest that IVF prediction models can potentially lead to more efficient practice, prevent overtreatment, improve embryo selection and lower multiple pregnancy rates. Yet, three important questions remain: how high should the probability of a pregnancy with IVF be before starting or continuing treatment, what are acceptable multiple pregnancy rates, and do these rates differ between women with different prognostic profiles?

The threshold for starting or continuing an IVF cycle is not described in any guideline and is definitely not set in stone. It is very likely that this threshold will differ between different stakeholders, between subfertile couples, fertility specialists or insurance companies. Further research is necessary to explore this threshold and factors driving the differences.
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It is also unclear what an acceptable multiple pregnancy rate is. When considering the risks and benefits associated with the number of embryos to be transferred, the number of desired children should also be taken into consideration (1). Most couples aspire to have more than one child. As fertility potential decreases with increasing female age, older women with an intermediate or poor prognosis often do not have enough time for a second child. For these women a twin pregnancy may be the only chance to conceive and deliver two children. Many studies have shown that a significant proportion of women have a clear preference for a twin pregnancy, regardless of any intervention trying to influence this preference (2-7). So, when deciding how many embryos to transfer, the focus should not be solely on associated health care costs with twin pregnancies, but should equally take into account the preference of the couples undergoing treatment.

The development of prediction models is a continuous process; as patient populations may shift during the years the group of patients used for the development and validation of prediction model may differ from the current population. Reproductive techniques may also evolve and new biomarkers with predictive value may become available. To safeguard valid predictions for future patients, regularly updating and adapting the prediction model to the new setting is necessary. The best way to achieve this is may be by developing national electronic databases to collect large numbers of IVF cycles, so that models can be updated more easily.

Until larger randomized controlled trials comparing IVF with natural conception and different embryo transfers strategies in all prognostic categories are performed, we believe that incorporating prediction models in counselling can strengthen the evidence-based, individualized decision-making and lead to a more rational use of scarce resources.
REFERENCES


