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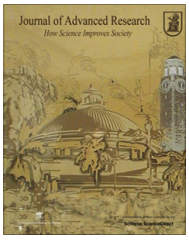

MINI REVIEW

Prediction models in *in vitro* fertilization; where are we? A mini review

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ABSTRACT

Since the introduction of *in vitro* fertilization (IVF) in 1978, over five million babies have been born worldwide using IVF. Contrary to the perception of many, IVF does not guarantee success. Almost 50% of couples that start IVF will remain childless, even if they undergo multiple IVF cycles. The decision to start or pursue with IVF is challenging due to the high cost, the burden of the treatment, and the uncertain outcome. In optimal counseling on chances of a pregnancy with IVF, prediction models may play a role, since doctors are not able to correctly predict pregnancy chances. There are three phases of prediction model development: model derivation, model validation, and impact analysis. This review 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. We will address these points by the three phases of model development.

Introduction

Since the birth of Louise Brown in 1978, over five million babies have been born worldwide using *in vitro* fertilization (IVF) [1]. The number of *in vitro* fertilization cycles has increased rapidly; in 2006, 458,759 cycles were reported in 32 European countries, 99,199 cycles in the USA and 50,275 cycles in Australia and New Zealand [2–4]. The number of cycles is increasing each year even further.

The increase in IVF cycles is not caused by a sudden epidemic of infertility, but by increased access to IVF, and by an expansion of the indications for IVF. Initially, IVF was performed in couples with bilateral tubal occlusion [5]. In 1992, intracytoplasmic sperm injection (ICSI) was first introduced and initiated in couples with severe male subfertility [6]. Later on, IVF/ICSI was also applied in couples without an absolute indication for IVF, such as unexplained subfertility, cervical hostility, failed ovulation induction, endometriosis, or unilateral tubal pathology [7,8]. The major difference between the original indication and the indications for which IVF is

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conducted nowadays is that the couples with bilateral tubal pathology or severe male subfertility have a zero chance of natural conception and completely depend on IVF/ICSI for a pregnancy, while couples with the newer indications are subfertile: they do have chances of natural conception, which may or may not be better than with IVF.

Despite the lack of evidence that IVF is effective in couples without an absolute IVF indication, IVF is often considered as a last resort for all subfertile couples regardless of the etiology of their subfertility [7–12]. Contrary to the perception of many, IVF does not guarantee success; almost 38–49% of couples that start IVF will remain childless, even if they undergo six IVF cycles [13]. Subfertile couples should therefore be well informed about the chances of success with IVF before starting their first or before continuing with a new IVF cycle. Based on a couple's specific probability, one should decide whether the chances of success with IVF justify the burden, risks, and costs of the treatment. The threshold at which probability to start or to continue treatment may differ between different stakeholders, such as insurance companies, the tax payer, and the patients.

In optimal counseling on chances of a pregnancy after IVF, pregnancy prediction models may play a role, since doctors are not able to correctly predict pregnancy chances [14,15]. Predictions made by clinicians on the basis of clinical experience or "gut-feeling" have only slight to fair reproducibility, indicating that these predictions are likely to be inaccurate [15].

The efforts to develop prediction models for IVF reflect the need for such models in clinical practice. This need can be explained by the inability of diagnostic tests to detect factors that indicate subfertility with near 100% certainty in patients. Accurate diagnostic tests would allow treatment to focus on specific factors [16]. As IVF is currently used as an empirical treatment and not as a causal intervention for a specific disorder, there is a strong need to distinguish between couples with a good and a poor prognosis [16]. In the absence of randomized clinical trials, evaluating the effectiveness of IVF prediction models can be used to counsel couples.

The development of a prediction model can be divided into three phases: model derivation, model validation, and impact analysis [16,17] (Fig. 1). In the model derivation phase, predictors are identified, based on prior knowledge, and the weight of each predictor (regression coefficient) is calculated. In the model validation phase, the performance of the model, i.e. model's ability to predict outcome is evaluated, and also the "generalizability" or "transportability" of the model is evaluated. The third and final phase consists of impact analysis. The impact analysis establishes whether the prediction model improves doctors' decisions by evaluating the effect on patient outcome [16,17].

This review 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. We will address these points by the three phases of model development: model derivation, model validation, and impact analysis.

Phase 1: model derivation

Identification of predictors

Candidate predictors are variables that are chosen to be studied for their predictive performance. These can include subject demographics, clinical history, physical examination, disease characteristics, test results, and previous treatments [18]. The identification of candidate predictors is preferably based on subject knowledge, on pathophysiological mechanisms, or the results of previous studies. Studied predictors should be clearly defined, standardized, and reproducible to enhance generalizability and application of study results to practice [18]. Researchers frequently measure more predictors than can reasonably be analyzed. When the number of predictors is much larger than the number of outcome events, there is a risk of overestimating the predictive performance of the model. To reduce the risk of false positive findings (predictors), at least 10 individuals having (developed) the event of interest are needed per candidate variable/predictor to allow for reliable prediction modeling [19].

A recent systematic review and meta-analysis on predictive factors in IVF evaluated nine predictive factors: female age, duration of subfertility, type of subfertility, indication for IVF, basal follicle stimulating hormone (bFSH), fertilization method, number of oocytes, number of embryos transferred, and embryo quality [20].

Female age is one of the most important prediction factors for success with IVF. Increasing female age was associated with lower pregnancy chances in IVF (OR 0.95, 95% CI: 0.94–0.96) [20]. The decrease in fertility sets in after the age of 30 years, with a marked decline after 35 years for both spontaneous as IVF-induced pregnancies [20–23]. The biological explanation for the declining chances to conceive with increasing female age most likely lies in the diminished ovarian reserve: the decrease in both quantity and quality of oocytes [24]. Diminished ovarian reserve generally leads to a poor

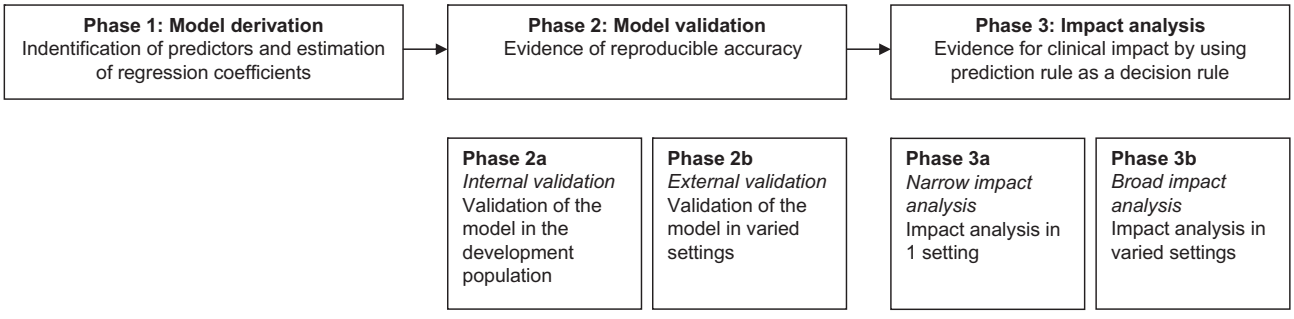

Fig. 1 Three phases of model development.