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Predicting live birth for poor ovarian responders: the PROsPeR concept

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KEY MESSAGE
PROsPeR is a simple and accurate live-birth estimate designed specifically for poor ovarian responders and is suitable for routine practice. PROsPeR produces a score (0, 1 or 2), with the predicted live-birth rate reduced by a factor of three with each additional predictor present.

A B S T R A C T

Research Question: A number of live-birth predictive models are available, and despite clinical interest these are rarely used owing to poor performance. In addition, no predictive models specifically for poor ovarian responders (POR) are available. The aim of the current project was to develop a clinically applicable tool for predicting live birth for PORs receiving recombinant human FSH [r-hFSH].

Design: A model was developed to predict live birth in PORs receiving r-hFSH, using data from the ESPART trial. Initially, two models were developed separately: one for patients with data from a previous assisted reproductive technology (ART) cycle and one for ART treatment-naïve patients. Subsequently, the simplified Poor Responder Outcome Prediction (PROsPeR) concept was derived.

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Results: PROsPeR considers three predictors and categorizes PORs into three scores, with predicted the live-birth rate divided by three with each worsening category. When adequately calibrated, a discrimination score up to area under the receiver operating characteristic (AUC_{ROC}) (95% CI) of 0.84 (0.79 to 0.88) was observed, which is superior to previously published models. Lower discriminations were observed when the PROsPeR model was used to evaluate the patients who received both r-hFSH and recombinant human LH in the ESPART study (AUC_{ROC} [95% CI] 0.66 [0.61 to 0.71]) and when all the patients included in the ESPART study were evaluated (AUC_{ROC} [95% CI] 0.68 [0.61 to 0.72]).

Conclusions: This model, specific to PORs receiving r-hFSH, constitutes the best compromise between precision and simplicity, and is suitable for routine practice.

Introduction

Assisted reproductive technology (ART) treatment can have a significant emotional effect on patients, making appropriate counselling of patients an essential aspect of infertility care (Verhaak et al., 2010; American Society for Reproductive Medicine, 2016; Eijkemans et al., 2017). This includes the management of expectations before treatment is initiated, in particular ensuring that patients are aware of their chances of success. Furthermore, to ensure patients have the greatest chance of a live birth, it is important that treatment is individualized, including selection of the most appropriate treatment and dosing for ovarian stimulation (La Marca and Sunkara, 2014a, 2014b; Teixeira and Martins, 2014). A number of models have been developed with the aim of predicting outcomes for the infertile patient. These might also be used to individualize treatment and may be relevant when developing clinical trials (McLernon et al., 2016; Nelson and Lawlor, 2011; Porcu et al., 2013; Templeton et al., 1996).

The best known of these, the Templeton, Nelson and McLernon models, were developed using data from the UK Human Fertilisation and Embryology Authority. The Templeton model, which was created using data from 39,961 cycles carried out between 1991 and 1994, is generally considered the best despite poor discrimination, which is the extent to which the prediction is exact (Templeton et al., 1996). Furthermore, it is the only model to have been externally validated using non-UK data (Leushuis et al., 2009). The Nelson model was developed more recently using data from 144,018 cycles carried out between 2003 and 2007 (Nelson and Lawlor, 2011), and has been externally validated using UK data, demonstrating comparable performance to the Templeton model (Smith et al., 2015). More recently, McLernon et al. (2016) developed two complementary models using data from 184,269 fresh and frozen–thawed embryo transfer cycles carried out between 1999 and 2008, one based on predictors available before treatment is initiated and the other including predictors available once treatment has been commenced (McLernon et al., 2016). The latter two models still require external validation. These models involve similar, well-established predictors, including, but not limited to, female age, duration of infertility, number of previous successful or unsuccessful IVF cycles (an IVF cycle is considered successful if it results in a live birth), pregnancy history and whether infertility was caused by tubal pathology.

Despite interest in predicting outcomes, these models are rarely used in clinical practice, as their discrimination and calibration remain unconvincing (Arvis et al., 2012; Leushuis et al., 2009; van Loendersloot et al., 2011). This lack of precision has several potential explanations: (A) a model aiming to predict outcomes for all patients may be too ambitious, as predictors may affect outcomes differently depending on the cause and severity of infertility or on the particular subgroup (La Marca and Sunkara, 2014a); (B) within these patient subgroups, important effects of the type and dose of medication selected for ovarian stimulation were found (Lehert et al., 2014; Mochtar et al., 2017; Santi et al., 2017). Furthermore, models not accounting for a given medication fail to provide comparisons between alternative treatments, which probably constitutes the most important use of these models in actual clinical practice; (C) the centre has a major effect on live-birth prediction, and the wholesale application of a predictive model whose development was based on data from one or several centres to another centre is known to provide biased predictions (Arvis et al., 2012); (D) the models are not easy to use, requiring a computer to conduct the calculations.

Despite knowledge of these issues, to date, no practical solution has been proposed for easily adapting a simple predictive model that accounts for a specific treatment, subpopulations and centres.

For the model described herein, a pragmatic decision was made about the choice of patient subgroup, based on the availability of data, and considerations about which subgroup would benefit most from a predictive model. Poor ovarian response (POR), which affects between 5.6% and 35.1% of the infertile population (Oudendijk et al., 2012), is associated with the poorest reproductive outcomes (La Marca et al., 2015; Yang et al., 2016). Counselling and appropriate treatment selection are, therefore, of particular importance for these patients. To date, models have been developed using data from the overall population of infertile patients, and their applicability for patients with POR remains unproven. Therefore, the development of such a tool is not only justified, but can be considered to be a priority.

Owing to the fairly recent release of the European Society of Human Reproduction and Embryology Bologna Criteria (EBC) in 2011 (Ferraretti et al., 2011), no specific large datasets are available to build predictive models for patients with POR and, because of the likelihood of missing data, a retrospective database analysis would likely provide lower quality data with which to develop such a model. The ESPART (Efficacy and Safety of Pergoveris® in Assisted Reproductive Technology) study, the largest randomized controlled trial in patients with POR to date, investigated the effect of recombinant human LH (r-hLH) supplementation to recombinant human FSH (r-hFSH) for ovarian stimulation in patients with POR using criteria based on, but stricter than, the EBC (Humaidan et al., 2017a). These stricter criteria, including exclusion of women aged 41 years or over, were used to remove diagnostic subjectivity, reduce patient heterogeneity and exclude patients with the worst reproductive prognosis (Humaidan et al., 2017a). Moreover, an extensive list of baseline variables was recorded during the ESPART study that could be used as outcome

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