The use of big data to inform individualized ovarian stimulation for infertility care is still in its infancy

Souter et al. (1) are to be congratulated for their attempt to use large data sets, involving 2 previous multicenter infertility trials and a total of 1,650 women, aiming to identify predictors allowing for more patient-tailored ovarian stimulation for infertility. Indeed, individualized rather than group medicine is rapidly gaining ground in medicine, especially in areas such as oncology and hematology. Next to the well-known gold standard of randomized controlled trials (RCTs), novel research methodologies such as multivariate prediction analyses assessing possible associations between individual patient characteristics and subsequent treatment outcomes have been developed. The validity of prediction analyses next to RCTs is being increasingly recognized. Unfortunately, the development of individualized approaches in infertility care has received insufficient attention so far, and for that reason, all new initiatives should be welcomed with great enthusiasm.

Previous attempts to personalize approaches in infertility care predominantly focused on pregnancy chances in unexplained infertility without medical intervention, assessing chances for tubal disease on the basis of chlamydia antibody blood levels, pregnancy chances (and even pregnancy complications) after ovulation induction in women with polycystic ovary syndrome (PCOS), and ovarian response to standard stimulation for in vitro fertilization (2, 3).

However, after examining the details of the study at hand, I remain unconvinced that the data provided are robust enough to justify promoting the use of the designed e-health tool in the clinical care of individualized ovarian stimulation. The observed receiver operating characteristic curves of the developed tests to predict a clinical pregnancy should be characterized as "fair" at best. Considering the distinct heterogeneity of all data analyzed, this can hardly come as a surprise.

First of all, it should be acknowledged that the current study represents a post hoc analysis of previously undertaken RCTs. The observed overall pregnancy rates reported in both studies were low (27.7%) and comparable for both patient categories involved. The most significant predictors of the probability of pregnancy involve patient's and partner's age, body mass index, type of treatment, and maximum medication dose. The 2 previous trials included in the current analysis were designed to test different hypotheses, and consequently, a clear and focused research question underlying the current analysis is lacking. Moreover, several potential shortcomings of the current association analysis should be considered: different patient categories (involving 2 notoriously heterogeneous but very different conditions: PCOS and unexplained infertility) are grouped together; different interventions (ovarian stimulation for the treatment of anovulatory infertility [i.e., ovulation induction] and/or ovarian stimulation for the induction of multiple follicle development in ovulatory women diagnosed with unexplained infertility) are combined; and even study endpoints are mixed (i.e., ongoing pregnancy and multiple pregnancy per stimulation cycle and cumulative for multiple cycles). Combining both apples and oranges may not allow for solid and robust conclusions and recommendations, although the big number of women involved in the current analysis may to some extent compensate for these potential shortcomings.

A combined analysis of all parameters mentioned earlier can only be performed under the assumption that a possible association between initial patient characteristics and the primary outcome of the intervention is independent from patient diagnosis, the intervention chosen, and the primary outcome defined. I remain unconvinced that this is indeed the case, and I would, therefore, prefer the analysis of both patient groups and different interventions separately. In addition, I would propose cumulative ongoing singleton pregnancy (live birth would be even better) rates and, if possible, "time to pregnancy" as the most impactful and clinically relevant study endpoints.

Allow me to focus on 2 examples to illustrate my point of view. Although largely ignored in the current study by Souter et al. (1), predictors of ovulation induction outcome in women with PCOS have been studied quite extensively before. Patient characteristics such as female age, body mass index, free androgen index, the extent of cycle abnormality, and the duration of infertility have all been identified as useful predictors (4, 5). It should also be emphasized that predictors for achieving ovulation in anovulatory women after ovulation induction treatments have shown to be different from predictors of pregnancy in women who do ovulate. A 1-step approach as applied in the current study may obscure relevant findings. In contrast, patients with unexplained infertility are ovulatory by definition, and consequently, combining the analysis of both patient categories may induce bias. Second, using antimüllerian hormone (AMH) as a marker of ovarian reserve may be completely different for women with PCOS (exhibiting markedly elevated AMH levels, with ongoing uncertainty concerning its use as marker for ovarian reserve in this particular patient category because of the lack of normative data) compared with unexplained infertility where ovarian function is normal by definition. Hence, using AMH as an ovarian reserve marker possibly predicting infertility treatment outcome combining both patient categories is problematic.

It should also be noted that no less than 16 variables (patient characteristics) have been studied by Souter et al. (1) as potential predictors of treatment outcome, which relates to the power to detect any associations at all, especially in subgroups. Finally, one of the key recommendations in multivariate prediction sciences is that any initial finding should be studied prospectively in another independent patient population to validate the developed prediction model. As far as I can see, this has not yet been performed, and therefore, promoting its clinical use seems premature.

In summary, a paradigm shift is currently ongoing in advancing healthcare, moving away from mass medicine (the "one-size-fits all" approach) toward more patient-

tailored individualized care. Infertility care is slowly catching up in developing such novel strategies. Doctors should focus on counseling infertile patients (or couples) regarding what is and what is not medically feasible under different circumstances. Subsequently, the optimal treatment strategy for any given patient should jointly (also referred to as "shared decision-making") be identified also taking personal circumstances, preferences, and patient characteristics into consideration.

In conclusion, next to well-designed, prospective, cohort follow-up studies in carefully phenotyped patient groups, the use of existing large data sets may also aid in developing more patient-tailored approaches in infertility care. Standardized phenotyping (possible also using contemporary biomarkers and genetic markers) of patients, defining primary study endpoints most relevant to patients, along with the external validation of findings, seems crucial in advancing the field of individualized infertility care.

Bartholomeus C.J. M. Fauser, M.D., Ph.D.
University Medical Center and University of Utrecht, Utrecht, the Netherlands

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