Which factors are most predictive for live birth after in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) treatments? Analysis of 100 prospectively recorded variables in 8,400 IVF/ICSI single-embryo transfers

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Objective: To construct a prediction model for live birth after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment and single-embryo transfer (SET) after 2 days of embryo culture.
Design: Prospective observational cohort study.
Setting: University-affiliated private infertility center.
Patient(s): SET in 8,451 IVF/ICSI treatments in 5,699 unselected consecutive couples during 1999–2014.
Intervention(s): A total of 100 basal patient characteristics and treatment data were analyzed for associations with live birth after IVF/ICSI (adjusted for repeated treatments) and subsequently combined for prediction model construction.
Main Outcome Measure(s): Live birth rate (LBR) and performance of live birth prediction model.
Result(s): Embryo score, treatment history, ovarian sensitivity index (OSI; number of oocytes/total dose of FSH administered), female age, infertility cause, endometrial thickness, and female height were all independent predictors of live birth. A prediction model (training data set; n = 5,722) based on these variables showed moderate discrimination, but predicted LBR with high accuracy in subgroups of patients, with LBR estimates ranging from <10% to >40%. Outcomes were similar in an internal validation data set (n = 2,460).
Conclusion(s): Based on 100 variables prospectively recorded during a 15-year period, a model for live birth prediction after strict SET was constructed and showed excellent calibration in internal validation. For the first time, female height qualified as a predictor of live birth after IVF/ICSI. (Fertil Steril® 2017;107:641–8. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF, prediction model, live birth rate, multiple pregnancy, single-embryo transfer

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In vitro fertilization (IVF) has become a standard method for most types of fertility problems. The high twin pregnancy rate arising from IVF has been recognized as a significant public health issue, leading to policies encouraging or mandating increased use of single-embryo transfer (SET) in many countries (1). Prediction models have been developed to improve counseling of the couples, to help tailor treatment protocols, and to provide guidance in the choice between transferring one (SET) or two (double-embryo transfer; DET) or more (2–6) embryos.

Such a model, predicting clinical pregnancy, was developed in our center in 2003, based on 2,266 IVF treatments and DET (7, 8). The model has been shown to be effective in reducing twin rates at a preserved high pregnancy rate (1, 8) and is currently in use at several clinics. SET is the standard procedure in Sweden following national legislation in 2003, with DET being performed in the minority of the treatments with a predicted low twin risk. This change in strategy has resulted in a dramatic decrease in multiple pregnancies and a concomitant improvement in perinatal morbidity and mortality (1, 9–11). Increased knowledge about the factors that determine the chance of success in assisted reproductive techniques (ART) would have an impact on the guidance for using SET or DET in individual cases.

Our aim with the present study was to construct a new model from SETs and with the use of live birth as end point, as opposed to the previous model which was derived from primarily DETs and used clinical pregnancy as end point. The strategy of evaluating only SET permits individual traceability from scoring to implantation for every embryo transferred, and because a large number of variables were scored prospectively in a very large group of patients, the results could be used as general information about what factors ultimately determine success in ART.

MATERIALS AND METHODS

Patients undergoing IVF and intracytoplasmic sperm injection (ICSI) treatment at the Carl von Linné Clinic (Uppsala, Sweden) from January 1999 to December 2014 were enrolled. All fresh IVF/ICSI treatments leading to SET on day 2 after oocyte retrieval were included, representing 46% of all treatments during the period. The criteria leading to SET were >15% duplex risk according to the existing prediction model, earlier obstetrical or perinatal complications, and/or intercurrent disease. A total of 8,451 treatments from 5,699 couples were included (a couple could contribute with several treatments). Women's ages were 19–43 years with both median and mean of 34 years. Indications for IVF were anovulation (8.2%), male factor (25.9%), tubal factor (10.3%), endometriosis (4.8%), unexplained (44.7%), and other (6.1%). The Regional Ethics Committee at the University of Uppsala approved the study and waived the need for written informed consents (EPN Dnr 2012/036; 2012-07-05).

All data were prospectively collected before and during IVF/ICSI treatment. Obstetrical and treatment history were self-reported (and in most cases supported by medical charts), as well as smoking habits and the woman's height and weight. Weight was also measured on the day of oocyte retrieval, and basal and actual body mass index (BMI) were calculated from these data. Data from the infertility work-up, such as duration and type of subfertility and sperm analyses, were collected. Patients underwent ovarian stimulation as previously described (12, 13) with the use of a long GnRH agonist in 88% of treatments and a GnRH antagonist in 12%, with recombinant FSH in 74% of treatments and hMG in 26%. In most cases, the down-regulation period was 2–3 weeks, and the GnRH-agonist dose was halved or abolished during the ovarian stimulation phase, also in patients with a diagnosis of endometriosis. During treatment, variables of the treatment and the resulting effects were recorded. All 100 variables that were collected are presented in Supplemental Table 1 (available online at www.fertstert.org).

The relationships between the explanatory variables and live birth rate (LBR) were explored by means of generalized estimating equations (GEE), because this method accounts for dependencies within subjects (several treatments for the same couple) (14, 15). First, univariate GEE regression models were estimated with the use of LBR as the dependent variable for all putative explanatory variables. Variables with P values $<.1$ were selected for further analysis. If the correlation between some variables chosen in the previous step was ≥ 0.8, these variables were tested in a bivariate GEE regression model and the covariate with the higher P value was excluded from further analysis. Thereafter, to prevent overfitting of the model, the data was randomly divided into two parts: 70% of all observations were used for the primary analyses (training set; n = 5,722) and 30% of observations were used for internal model validation (validation set; n = 2,460). The model was developed with the use of GEE multivariate regression by means of a forward selection method. For the final model, all pair-wise correlations as well as multicollinearity among all the predictors were examined. The model is presented with the odds ratio (OR), 95% confidence interval (CI), and P value for each predictor.

The performance of the model was evaluated by means of c-statistics and calibration. The c-statistic, equivalent to the area under the receiver operating characteristic curve, assesses the model's discriminative capacity. Calibration refers to the level of agreement between the estimated and the observed probabilities of a given event. Calibration was assessed by means of Hosmer-Lemeshow test. All analyses were performed with the use of the statistical software SAS (v. 9.4; SAS Institut). The standard $P<.05$ was considered to be statistically significant in all tests.

RESULTS

Among the 100 variables collected before and during treatment, 36 variables qualified for model derivation (Supplemental Table 2, available online at www.fertstert.org). The best prediction model contained seven predictors, as presented in Table 1. Two hundred sixty-nine cycles (3%) did not have complete data for all seven of these predictors and could therefore not be part of the final analysis. Eligible for the analysis were 8,182 treatment cycles in 5,699 couples. Seventy percent, i.e., 5,722 treatments from 4,434 couples, were

TABLE 1

The final prediction model: predictors for live birth after IVF/ICSI treatment(s) (trt) and single-embryo transfer, with their categories, odds ratios (ORs) with confidence intervals (CIs), and *P* values.

Parameter	Value	OR (95% CI)	*P* value
IMC score	<1.5	1.00	
	1.5–2	2.81 (1.79–4.42)	<.0001
	2–2.5	3.64 (2.46–5.37)	<.0001
	>2.5	4.68 (3.22–6.81)	<.0001
Treatment history	0 trt, 0 child; 1–6 trt, ≥1 child	1.00	
	1–6 trt, 0 child; ≥7 trt, ≥1 child	0.76 (0.67–0.86)	<.0001
	≥7 trt, 0 child	0.23 (0.08–0.62)	.0040
OSI	<0.87	1.00	
	0.87–1.85	1.41 (1.17–1.70)	.0002
	>1.85	1.56 (1.29–1.88)	<.0001
Female age	≤28 y	1.00	
	29–35 y	0.85 (0.70–1.03)	.0945
	36 y	0.70 (0.54–0.91)	.0076
	37–38 y	0.46 (0.36–0.58)	<.0001
	39–40 y	0.37 (0.28–0.49)	<.0001
	41 y	0.22 (0.13–0.37)	<.0001
	42–43 y	0.14 (0.06–0.30)	<.0001
Endometrial thickness	>10 mm	1.00	
	7–10 mm	0.86 (0.76–0.99)	.0211
	<7 mm	0.49 (0.26–0.92)	.0281
Infertility cause	Tubal factor	1.00	
	Anovulation	1.71 (1.28–2.27)	.0002
	Endometriosis	1.65 (1.18–2.31)	.0035
	Male	1.52 (1.20–1.92)	.0004
	Unexplained	1.47 (1.18–1.83)	.0007
	Other	1.68 (1.22–2.33)	.0018
Female height (cm)		1.011 (1.002–1.021)	.0227

Note: IMC score = integrated morphology-cleavage embryo score; OSI = ovarian sensitivity index.

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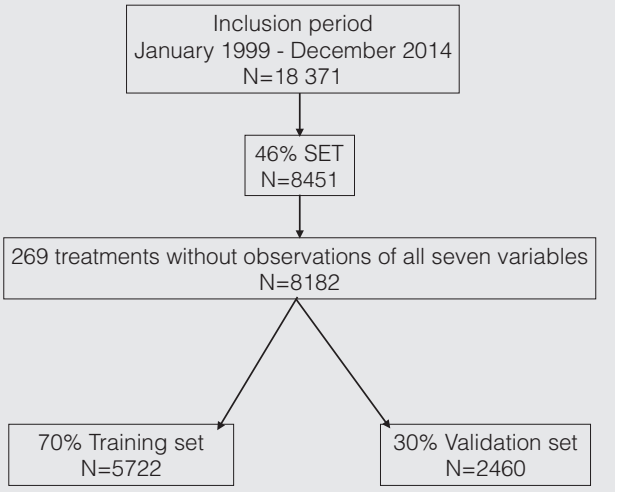
FIGURE 1



Treatments included in the development and validation of the prediction model. SET = single-embryo transfer.

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used for the training set, and 2,460 treatments from 2,217 couples were used for the validation set (Fig. 1).

The overall LBR was 28.2%: 28.6% in the training set and 27.3% in the validation set. LBR increased during the study period, from 25.2% 1999–2004 to 29.5% 2010–2014. Adjusting the model with a time factor did not, however, change the ORs for the other variables in the model (data not presented). The results from the final model (training set), i.e., the predictive factors for LBR after IVF/ICSI, with their ORs, CIs, and *P* values, are presented in Table 1. The univariate effects of the seven predictive factors on LBR are illustrated in Figure 2. There was no significant multicollinearity among the predictors (data not shown). Some of the predictors were derived from two or more variables in the data.

Embryo score, the integrated morphology-cleavage (IMC) score (7), is an algorithm that incorporates three variables that rank the likelihood of embryo implantation (number of blastomeres, evenness of blastomere size, and the proportion of mononucleated blastomeres). The score was converted to a categorical variable with four groups to identify poor-, moderate-, good-, and top-quality embryos. The odds of success with IVF treatment for couples with top-quality embryos was 4.7 times higher than for couples with poor-quality embryos (OR 4.68, 95% CI 3.22–6.81 [Table 1]; LBR 6.9%–31.9% [Fig. 2]).

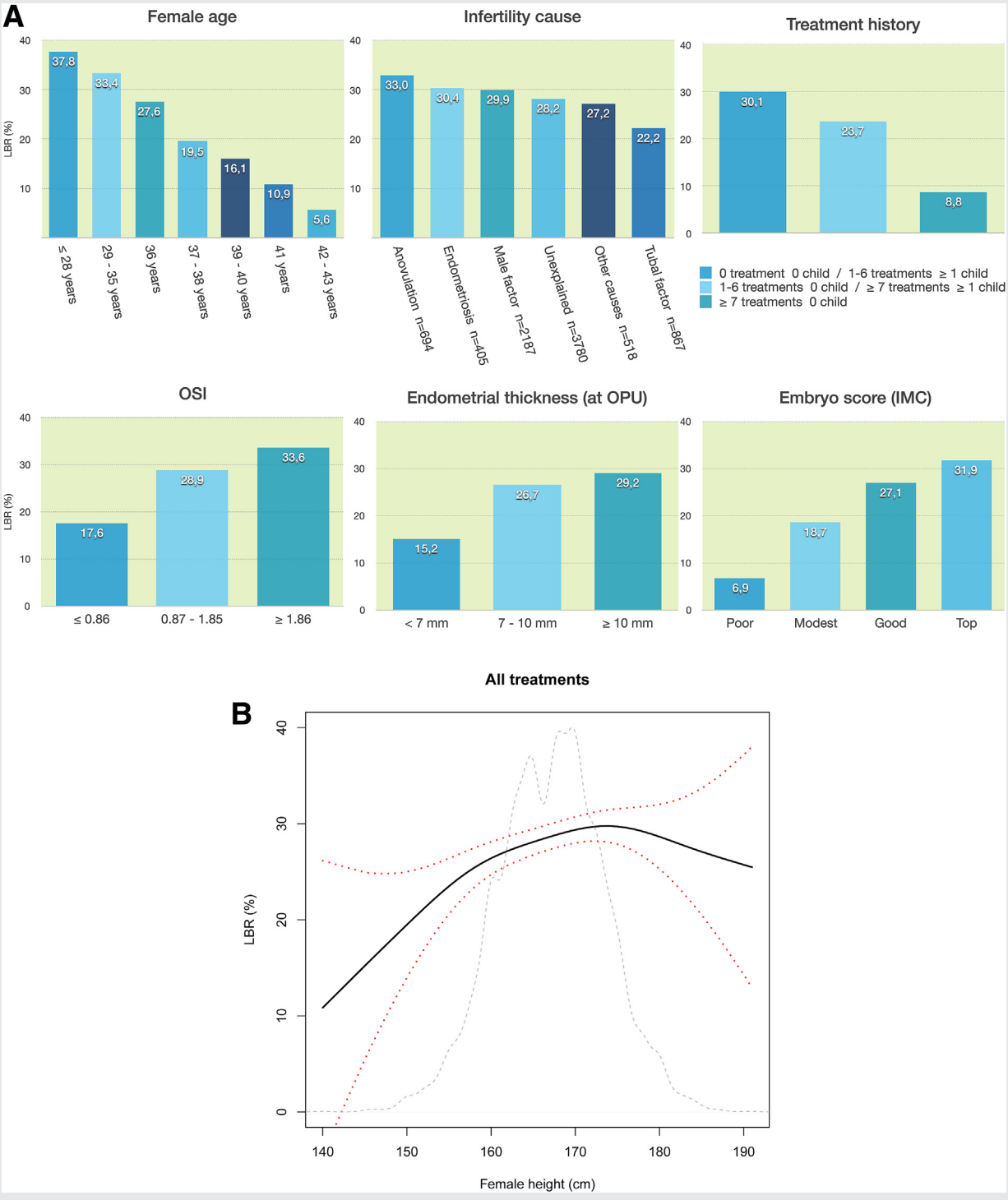
Treatment history is a variable describing the success rate in previous fresh and frozen-thawed treatment cycles. Three groups were defined. The poorest prognosis was found for couples that had undergone more than six previous treatments without any live birth (LBR 8.8%), whereas the best prognosis was found for couples who either underwent their first treatment or had at least one child after a maximum of six embryo transfers (LBR 30.1% [Fig. 2]; OR 0.23–1 [Table 1]).

Ovarian sensitivity index (OSI) is a composite variable to measure ovarian response. It is derived with the use of the formula: OSI = log(number of eggs recovered × 1,000/total dose of FSH) (16). Three groups were formed to identify low, medium, and high response. The odds of a live birth with IVF treatment in the high-response group was 1.6 times higher than the odds in the low-response group (OR 1.56, 95% CI 1.29–1.88 [Table 1]; LBR 17.6%–33.6% [Fig. 2]).

Regarding female age, a two-way frequency table was obtained with a decrease in live birth rates after 28 years of age, and another after 35 years of age. LBRs were almost equal for patients 37 and 38 years of age and subsequently decreased. Based on these thresholds, age was grouped into seven groups, as shown in Figure 2 (LBR 5.6%–37.8%, OR 0.14–1; Table 1).

Endometrial thickness measured on the day of oocyte retrieval showed a nonlinear relationship with both pregnancy and live birth. It was found that women with an endometrium thinner than 7 mm were less likely to have a successful treatment. LBR with an endometrium <7 mm was 15.2% compared with 29.2% with an endometrium >10 mm (Fig. 2, OR 0.49–1; Table 1).

FIGURE 2



(**A**) Independent predictors included in the model and their respective univariate association with live birth rate (LBR). OSI = ovarian sensitivity index; IMC embryo score = integrated morphology-cleavage embryo score; OPU = ovum pick-up. (**B**) Female height in cm and its univariate association with LBR. The *solid black curve* is linear between 157 and 175 cm, where 85% of the observations are located (*dashed gray curve*). In the extremes the observations are too few and confidence intervals too broad (*dotted red curve*) to draw conclusions.

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Infertility cause is a categorical variable with six categories. The number of observations in each category and respective LBRs are presented in Figure 2 (LBR 22.2%–33.0%, OR 1–1.71; Table 1). Tubal factor was associated with the lowest LBRs, whereas anovulation was associated with the best outcome.

Female height is a continuous variable measured in centimeters. Female height was positively correlated with live birth. For a 1-unit increase in female height (1 cm) the odds increased by 1.1% (OR 1.011, 95% CI 1.002–1.021; Table 1).

The c-statistic, i.e., the integrated measurement of sensitivity and specificity, for the model in the training set was 0.67. The calibration, i.e., the association between predicted and observed mean live birth rates in subgroups of couples with live birth probabilities from <10% to >50%, as assessed by the Hosmer-Lemeshow test, showed a *P* value of 0.90. Figure 3 indicates very good model calibration.

The ORs in the validation set were similar to the corresponding ORs in the training set. The c-statistic also was similar (0.68). Again, the model calibrated well (*P*=.88; Hosmer-Lemeshow test; Fig. 3).

DISCUSSION

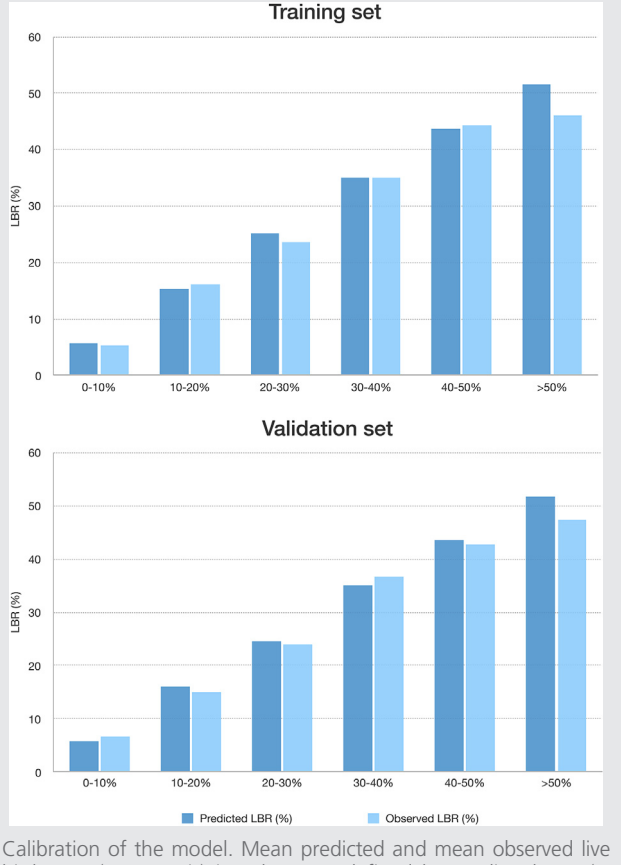
This prospective cohort study of 8,451 IVF/ICSI treatments is, to our knowledge, the largest study reporting on treatments performed with the use of SETs only, leading to the development of a prediction model to calculate the chances of live birth after IVF/ICSI. The model has modest discriminating power but excellent calibration. We used data that were prospectively collected in consecutive IVF patients during a period of 15 years for the development of the model. The model was internally validated in a data set that had not been used for the model construction. Out of 100 collected variables, the best model contains seven independently significant predictors: embryo score, treatment history, ovarian response measured as OSI, female age, infertility cause, endometrial thickness, and female height. Among these variables, all have been previously shown to be associated with IVF/ICSI outcome except female height, which was a novel and unexpected finding.

An important strength of this study is that, because the data were derived from SETs only, it allows the tracing of each individual transferred embryo. Most studies on factors influencing implantation potential are based on treatments with transfers of multiple embryos, precluding traceability of the individual embryo in other than treatments leading to either no implantation or implantation of the same number of embryos as transferred (4, 8, 17–20). The IMC embryo score was earlier developed at the clinic (7, 21). From five easily scored variables, three variables were incorporated into this embryo score. It is included in the prediction model of clinical pregnancy after DET. Prospective application of that model to select for SET or DET proved that the model was highly effective as a means to reduce twin implantation rates (from 28% to 2%) at preserved pregnancy rates (1, 7, 8). Most previous studies dichotomize embryo quality into top quality and non-top quality, whereas the present study thus used an evidence-based graded scoring. The IMC score turned out to be one of the most powerful predictors of live birth.

Treatment history, i.e., the number of previous successful/failed IVF treatments (including thaw cycles) demonstrated a strong predictive value for live birth after IVF/ICSI in this study, as in several previous studies (3, 4, 19, 22). Our data analysis resulted in three levels for this composite variable, confirming previous findings for a positive effect of a previous successful treatment as well as a relatively small reduction in expected LBR per failed treatment. Of note, previous pregnancy (without treatment) and duration of infertility did not qualify for the final model, which is at variance with other reports (3, 4, 17, 22).

Ovarian response is often measured as the total number of oocytes retrieved (23–27) or as the total number of embryos derived (4, 17) in models that predict pregnancy or live birth. However, results from mild stimulation protocols have shown that women with expected high response, stimulated with a very low dose of FSH resulting in a low oocyte yield, still have high live birth rates (28). Conversely, women with reduced response to controlled ovarian hyperstimulation, who after prolonged stimulation and/or increased doses of FSH, finally have a normal number of oocytes retrieved, still exhibit reduced chances (29–31). Also, the total amount of gonadotropins used per se is highly correlated with pregnancy chance (32). Thus, measures of the resulting variable (total number of oocytes or embryos) may be too crude to fully reflect the ovarian

FIGURE 3



Calibration of the model. Mean predicted and mean observed live birth rate (LBR; *y*-axis) in subgroups defined by predicted LBR (*x*-axis) in training and validation sets. Test for calibration, Hosmer-Lemeshow: *P*=.90 and *P*=.88, respectively.

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response. Instead, we used the OSI, which takes into account both the power of stimulus—the total dose of FSH—and the resulting effect—the number of oocytes retrieved (16). We previously showed that this ratio was log-normally distributed in a large IVF population and that it was more closely associated with LBR than oocyte yield only (16). It is well established that ovarian response is tightly associated with markers of ovarian reserve. We deliberately did not include basal markers of ovarian reserve, such as basal levels of FSH and LH, antral follicle count, and antimüllerian hormone (AMH) levels, in the data analysis (12, 13, 33, 34). The reason for this was that no single reliable measurement for ovarian reserve was used during the 15 years period of data collection. Furthermore, OSI correlated closely with different ovarian reserve tests in other studies, and OSI has proved to be as least as predictive of LBR as AMH level (16, 32, 34, 35).

Not surprisingly, female age was negatively correlated with live birth after IVF/ICSI. This is the most established predictor included in every prediction model for pregnancy or live birth after IVF/ICSI or as a standard to which a model is compared (3–5, 17, 22, 25, 26, 36). In the present study, the relation between female age and LBR was nonlinear, with marked decreases in LBR after 28, 35, and 38 years.

As in earlier studies, infertility cause qualified as an independent predictor, which was mainly because of the low success rates associated with tubal subfertility. This finding corroborates most (23, 26, 37, 38), but not all (25), previous reports. Anovulation, including mainly women with polycystic ovary syndrome, proved to be the most favorable diagnosis, again in line with several previous reports (13, 31, 34). Endometriosis was not associated with a reduced prognosis, in accordance with some (17, 23, 26, 39–41), but not all (4), previous studies. It should be underscored that no prolonged down-regulation was performed in women with a diagnosis of endometriosis, including those with a visible endometrioma.

Male-related factors were nonsignificant as predictors, even in univariate analysis. This is in line with other prediction models for pregnancy or live birth after IVF/ICSI (3, 19, 42). The probable explanation for this is that ICSI provides an effective treatment of male infertility.

Women with a thin endometrium at the time of ovum pick-up, i.e., <7 mm, constituted a small subgroup of the cohort with significantly lower LBR, whereas women with an endometrium >10 mm exhibited the best outcome. A thin endometrium is known to be negatively associated with reproductive outcome, but it occurs infrequently. Endometrial thickness as a tool to decide on cycle cancellation can not be justified with the current knowledge (43, 44).

A strength of the present study is that the population is large and that the model is developed from a high number of variables recorded prospectively within a single clinic. It is interesting that with this approach, an unexpected variable stands out as a new predictor. To our knowledge, female height has not previously been proposed as a predictor for IVF/ICSI outcome. Some prediction models include BMI (5, 18, 45, 46). BMI was univariately negatively associated with LBR in the present study, but not after multivariate analysis. In our own previous prediction model (8), female height, like BMI, correlated univariately with clinical pregnancy rate after IVF/ICSI, but not after multiple regression modeling. The fact that the outcome studied in the present model was live birth may have had an influence on this. Associations have previously been described between female height and dizygotic twinning, both spontaneously and after IVF (positively), and between female height and risk of premature birth (negatively) (47–56). Human height has steadily increased over the past centuries, which has been interpreted as a consequence of improvements of health and nutrition (57). It could be speculated that growth factors involved in procreation might also be involved in body growth. This new finding of an association between female height and live birth after IVF/ICSI has to be confirmed and studied further in future studies.

The discriminative capacity of the model was modest, as is usually the case for prediction models in reproductive medicine. Previous prediction models for probability of pregnancy after IVF have presented c-statistics of 0.5–0.68 (2, 4, 5). More importantly, the test for calibration in the present study was excellent, with a high P value in the Hosmer-Lemeshow test, both in the training set and in the validation set. The interpretation of this finding is that there is a good correspondence between the predicted chance of success and the observed success rate in all subgroups of couples, covering the entire range of probabilities. The model thus has a high capacity to distinguish between couples with poor, moderate, or high chances of success. This makes it useful in the daily clinical practice, enabling more detailed and individualized counseling to the couple. The information could also be used in the development of a model to decide which patients are best served by SET and which patients need DET when aiming at low multiple birth rates with preserved pregnancy rates. Not least, the high performance of the model to predict treatment outcome in patient subgroups makes it an excellent tool for physicians to refine and tailor treatment protocols. Knowing the expected outcome, the effect of a change in treatment strategy can easily be evaluated. The same applies for different protocols for subgroups of patients or even the occurrence of an unexpected event. Data can be fed back to the model continuously, creating a data-driven refinement of treatment strategies.

Because this prediction model was developed in a single clinic, to be applicable to other IVF centers it needs to be validated externally. It is also restricted to fresh day 2 embryo transfers. With the increasing use of prolonged culture, a useful modern prediction model for LBR after IVF should include embryo scores up to the blastocyst stage. Ideally, a prediction model in ART should predict the cumulative LBR and include frozen-thawed embryo transfers. These limitations of the present study are aims of ongoing studies at our center.

In conclusion, in this large prospective study of 8,451 SETs, we constructed a prediction model for live birth, with modest discrimination but excellent calibration. The model confirms embryo score, treatment history, ovarian sensitivity, female age, endometrial thickness, and infertility cause as independent predictors. In addition, for the first time, female

height appears as an independent predictor of live birth after IVF/ICSI. It is suggested that prediction models like this are used to improve patient counseling before and during IVF, to give guidance in the choice of SET or DET, and as a tool for data-driven refinement of treatment strategies.

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SUPPLEMENTAL TABLE 1

The 100 variables prospectively recorded before and during IVF/ICSI treatment, with *P* values for their respective associations with live birth rate.

Variable name	*P* value
Infertility duration	.0043
Infertility cause	<.0001
Number of pregnancies	<.0001
Parity	.4875
Number of spontaneous abortions	.0081
Number of legal abortions	.0071
Number of ectopic pregnancies	.0019
Number of pregnancies in the couple	.0007
Number of children in the couple	.0536
Number of IUIs	.7043
Number of IUI pregnancies	.7836
Number of IUI children	.9081
Number of IVF treatments	<.0001
Number of IVF pregnancies	.5194
Number of IVF children	.0396
Number of frozen/thawed treatments	.1478
Number of frozen/thawed pregnancies	.5702
Number of frozen/thawed children	.6596
Treatment history[a]	<.0001
Female age (at OPU)	<.0001
Age group	<.0001
Female height	.0031
Female weight (at OPU)	.0851
Female BMI (at OPU)	.0018
Smoking woman (yes/no)	.0832
Smoking man (yes/no)	.0527
Dipping/chewing tobacco man (yes/no)	.6582
Stimulation type (agonist/antagonist)	.0089
Stimulation drug (FSH/hMG)	<.0001
Antagonist drug	.0140
Altered GnRH-dose at injection start	.0008
Total dose of FSH/hMG	<.0001
Days of FSH/hMG stimulation	.0220
Mean daily dose of FSH/hMG	<.0001
Maximum dose of FSH/hMG	<.0001
Days of stimulation and coasting	.0149
Total dose of antagonist drug	.6491
OPU number of order at OPU day	.3796
Number of follicles >20 mm (at OPU)	<.0001
Number of follicles 15–20 mm (at OPU)	<.0001
Number of follicles <15 mm (at OPU)	<.0001
Total number of follicles	<.0001
Size of largest follicle (at OPU)	.1011
Free fluid at OPU	.0099
Uterus anteflexion/retroflexion (at OPU)	.8993
Endometrium type at OPU (hypo/iso/hyperechogenic)	.0101
Endometrium thickness (at OPU)	.0060
Endometrial thickness group	<.0001
Total number of eggs	<.0001
Ovarian sensitivity index	<.0001
Number of eggs to IVF	.0128
Number of eggs to ICSI	.0022
Number of eggs injected (ICSI)	<.0001
Total sperm count before preparation	.1855
Total sperm count after preparation	.0909
Time from OPU to insemination	.8707
Time point of OPU	.9589
Time point of insemination	.5926
Method (IVF/ICSI/combined)	.1829
Sperm fresh/frozen	.4118
Number of embryos cleaved on day 2 after IVF	.0001
Percentage of embryos cleaved on day 2 after IVF	<.0001
Number of embryos cleaved on day 2 after ICSI	<.0001
Percentage of embryos cleaved on day 2 after ICSI	.0036
Total number of cleaved embryos on day 2	<.0001

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SUPPLEMENTAL TABLE 1

Continued.

Variable name	*P* value
Average fragmentation on day 2 after IVF	.0627
Average fragmentation on day 2 after ICSI	.8701
Average fragmentation on day 2, total	.2419
Number of embryos frozen	.0851
Number of blastomeres (embryo transferred)	<.0001
Degree of fragmentation (embryo transferred)	<.0001
Evenness of size of blastomeres (embryo transferred)	<.0001
Symmetry of cleavage (embryo transferred)	.0029
Proportion of mononucleated blastomeres (embryo transferred)	<.0001
IVF/ICSI (embryo transferred)	.4077
Doctor performing transfer	.0173
Time point of embryo transfer	.2656
Change of catheter at embryo transfer (yes/no)	.0002
Elective single-embryo transfer (yes/no)	<.0001
Time from fertilization check to day 2 embryo check	.2504
Time from fertilization check to ET	.3827
Time from day 2 embryo check to ET	.9729
Time from hCG to fertilization check	.9109
Time from hCG to day 2 embryo check	.9488
Time from hCG to ET	.7752
Time from hCG to insemination	.9450
Time from hCG to OPU	.3544
Time from hCG to sperm ejaculation	.8972
Time from insemination to fertilization check	.1943
Time from insemination to day 2 embryo check	.9051
Time from insemination to ET	.3850
Time from OPU to fertilization check	.2283
Time from OPU to day 2 embryo check	.5989
Time from OPU to ET	.2850
Time from sperm ejaculation to OPU	.7185
Time from sperm ejaculation to ET	.1680
Time from sperm ejaculation to fertilization check	.5760
Time from sperm ejaculation to day 2 embryo check	.1663
IMC embryo score 1–10 points	<.0001
IMC embryo score (poor/modest/good/top quality)	<.0001

Note: BMI = body mass index; ET = embryo transfer; IMC = integrated morphology-cleavage; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = in vitro fertilization; OPU = ovum pick-up.

[a] Treatment history: success rate in previous fresh and frozen/thawed treatments expressed as three groups: 0 treatment (trt) and 0 child, or 1–6 trt and ≥1 child; 1–6 trt and 0 child, or ≥7 trt and ≥1 child; and ≥7 trt and 0 child.

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SUPPLEMENTAL TABLE 2

The 36 variables included in multivariable regression analysis.

Infertility duration
Infertility cause
Number of pregnancies
Number of spontaneous abortions
Number of legal abortions
Number of ectopic abortions
Number of pregnancies in the couple
Number of children in the couple
Number of IVF treatments
Number of IVF children
Treatment history[a]
Female age
Age group
Female height
Female weight
Female body mass index
Smoking woman (yes/no)
Smoking man (yes/no)
Stimulation type (agonist/antagonist)
Stimulation drug (FSH/hMG)
Antagonist drug
Altered GnRH dose at injection start
Total dose of FSH/hMG
Days of FSH/hMG stimulation
Days of FSH/hMG stimulation and coasting
Total number of follicles
Free fluid at OPU
Endometrium type at OPU (hypo/iso/hyperechogenic)
Endometrium thickness (at OPU)
Endometrial thickness group
Total number of eggs
Ovarian sensitivity index[b]
Total number of embryos cleaved on day 2
Change of catheter at embryo transfer (yes/no)
Elective single-embryo transfer (yes/no)
IMC embryo score (poor/modest/good/top quality)

Note: IMC = integrated morphology-cleavage; IVF = in vitro fertilization; OPU = ovum pick-up.
[a] Treatment history: success rate in previous fresh and frozen/thawed treatments expressed as three groups: 0 treatment (trt) and 0 child, or 1–6 trt and ≥1 child; 1–6 trt and 0 child, or ≥7 trt and ≥1 child; and ≥7 trt and 0 child.
[b] OSI = log(number of retrieved oocytes × 1,000/total dose FSH).

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