Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women

David J McLernon,[1] Ewout W Steyerberg,[2] Egbert R te Velde,[2] Amanda J Lee,[1] Siladitya Bhattacharya[3]

[1]Medical Statistics Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen AB25 2ZD, UK

[2]Department of Public Health, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, Netherlands

[3]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

Correspondence to: D J McLernon d.mclernon@abdn.ac.uk

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To develop a prediction model to estimate the chances of a live birth over multiple complete cycles of in vitro fertilisation (IVF) based on a couple's specific characteristics and treatment information.

DESIGN
Population based cohort study.

SETTING
All licensed IVF clinics in the UK. National data from the Human Fertilisation and Embryology Authority register.

PARTICIPANTS
All 253 417 women who started IVF (including intracytoplasmic sperm injection) treatment in the UK from 1999 to 2008 using their own eggs and partner's sperm.

MAIN OUTCOME MEASURE
Two clinical prediction models were developed to estimate the individualised cumulative chance of a first live birth over a maximum of six complete cycles of IVF—one model using information available before starting treatment and the other based on additional information collected during the first IVF attempt. A complete cycle is defined as all fresh and frozen-thawed embryo transfers arising from one episode of ovarian stimulation.

RESULTS
After exclusions, 113 873 women with 184 269 complete cycles were included, of whom 33 154 (29.1%) had a live birth after their first complete cycle and 48 925 (43.0%) after six complete cycles. Key pretreatment predictors of live birth were the woman's age (31 *v* 37 years; adjusted odds ratio 1.66, 95% confidence interval 1.62 to 1.71) and duration of infertility (3 *v* 6 years; 1.09, 1.08 to 1.10). Post-treatment predictors included number of eggs collected (13 *v* 5 eggs; 1.29, 1.27 to 1.32), cryopreservation of embryos (1.91, 1.86 to 1.96), the woman's age (1.53, 1.49 to 1.58), and stage of embryos transferred (eg, double blastocyst *v* double cleavage; 1.79, 1.67 to 1.91). Pretreatment, a 30 year old woman with two years of unexplained primary infertility has a 46% chance of having a live birth from the first complete cycle of IVF and a 79% chance over three complete cycles. If she then has five eggs collected in her first complete cycle followed by a single cleavage stage embryo transfer (with no embryos left for freezing) her chances change to 28% and 56%, respectively.

CONCLUSIONS
This study provides an individualised estimate of a couple's cumulative chances of having a baby over a complete package of IVF both before treatment and after the first fresh embryo transfer. This novel resource may help couples plan their treatment and prepare emotionally and financially for their IVF journey.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Although the success of in vitro fertilisation (IVF) has generally been reported as the livebirth rate in a single fresh embryo transfer, the increase in embryo cryopreservation has meant that cumulative livebirth rates are more informative

Previous prediction models have either only estimated the individualised chances of a live birth after a single fresh embryo transfer or ignored the contribution of frozen embryo transfers to the cumulative chances of a live birth

Failure to take account of all embryo transfer attempts has meant that such prediction models have not proved to be useful as counselling tools as the first treatment does not always succeed

WHAT THIS STUDY ADDS

Our novel prediction models estimate the cumulative chances of a live birth over six complete cycles (including replacement of fresh and frozen embryos) of IVF before treatment and after the first fresh embryo transfer attempt

The cumulative aspect of our prediction models will aid clinicians by supporting their clinical knowledge when communicating to couples their personalised chances of a live birth over an entire package of IVF treatment.

The cumulative aspect of our prediction models will also help couples plan their time and prepare emotionally and financially for their complete IVF journey

Introduction
In the United Kingdom, one in six couples experience difficulties conceiving.[1] In vitro fertilisation (IVF) is the recommended treatment of choice for all couples with continued unresolved fertility problems.[2] By the end of 2013 over five million people were born as a result of IVF or intracytoplasmic sperm injection (ICSI).[3]

Although the success of IVF and ICSI has conventionally been reported as the livebirth rate in a single fresh cycle,[4 5] widespread use of embryo cryopreservation in the past two decades has meant that cumulative livebirth rates, which include frozen embryo replacements as well as subsequent treatment episodes, are more informative, as they empower couples and clinicians to make strategic decisions about care over a period of time.[6] However, cumulative livebirth rates are often reported either as one overall average rate or stratified by the woman's age or type of infertility at a national or IVF clinic level.[7-11] Given that many other patient and treatment characteristics can affect the success of IVF or ICSI,[12] it can be difficult for clinicians to counsel couples as to their individualised chances of success over a complete package of IVF or ICSI treatment.

A clinical prediction model that could estimate the cumulative chances of a live birth before IVF or ICSI begins and that could provide a revised estimate of the

expected outcomes after one or more treatment cycles would be critical for patient counselling and informing decision making in IVF. No such model currently exists. We therefore estimated the predicted cumulative probability of a first live birth over multiple complete cycles of IVF or ICSI at initial consultation before treatment starts (pretreatment) and after the first attempt at fresh embryo transfer, when treatment specific information is available (post-treatment).

Methods

Database

The Human Fertilisation and Embryology Authority (HFEA) has collected data on all licensed fertility treatments in the UK since 1992. An anonymised HFEA database is freely available online for research purposes.[13-16] This version only contains data at the individual (fresh or frozen) IVF treatment level, with no link between treatment and individual women—a requirement when estimating the cumulative probability of a live birth. However, a more detailed version of the HFEA database is available for research purposes under strict conditions, which links all IVF treatments to complete cycles and to individual women and allows estimation of the cumulative probability of a live birth.[15 17] Following approval by the North of Scotland research ethics committee, the Confidentiality Advisory Group, and the HFEA register research panel, anonymised data on all treatments linked to each woman undergoing IVF or ICSI were made available to the authors.

Study population

In this population based cohort study, records of all complete IVF and ICSI cycles—defined as all attempts at fresh and frozen embryo transfer resulting from one episode of ovarian stimulation—in women who started their first ovarian stimulation in the UK between January 1999 and September 2008 were extracted up until September 2009 when exposure to IVF ended. Data from October 2009 onwards were not included in the analysis because consent for patient data on IVF or ICSI to be used in research changed from "presumed" to "required" at that point. Including such years would have led to falsely higher discontinuation rates owing to women opting not to disclose their treatment information in later complete cycles. Women who had any element of treatment involving donor insemination, egg donation, and surrogacy were not included in the requested database. Supplementary figure A1 details further exclusion criteria made on receipt of the data.

Baseline characteristics

Baseline characteristics of couples included the woman's age, duration of infertility (years), type of infertility (categorised as diagnosis of tubal, endometriosis, anovulation, male factor, or unexplained), previous pregnancy status of the couple (yes versus no), treatment type (ICSI versus IVF), and year of first egg retrieval. Treatment level characteristics from the attempt at fresh embryo transfer of the first complete cycle included number of eggs collected, number of embryos transferred, stage of embryo transfer (cleavage versus blastocyst), and whether embryos were frozen (cryopreservation of embryos).

Outcome

We estimated the cumulative chances of a first live birth for a couple having up to six complete cycles of IVF. One complete cycle included all fresh and frozen embryo transfers resulting from one episode of ovarian stimulation.

Statistical analysis

We developed two clinical prediction models to use before and after treatment.

Pretreatment model—for a couple about to embark on IVF or ICSI, we estimated the cumulative probability of a live birth over a maximum of six complete cycles using the characteristics of the couple and whether they planned to undergo IVF or ICSI.

Post-treatment model—to update the cumulative probability of live birth after the first attempt at embryo transfer, we included treatment specific characteristics from the first complete cycle along with the characteristics of the couple from the pretreatment model.

Model development

We used a discrete time logistic regression model to predict the chance of a live birth after a maximum of six cumulative complete cycles of IVF or ICSI, where a complete cycle included a fresh embryo transfer and any associated frozen-thawed embryo transfers. To assess the predicted probability of a live birth in the ith complete cycle conditional on no live birth having occurred before that complete cycle, we treated the complete cycle number as a discrete time variable. From this model, we calculated the cumulative probability of a live birth over sequential complete cycles up to complete cycle 6.

Initially we fitted univariable models to assess the effect of individual predictors (adjusting for complete cycle number) on live birth. The woman's age, treatment year, and number of eggs retrieved all had nonlinear relations with the probability of a live birth so were modelled using restricted cubic splines. Effect estimates were presented for the interquartile range (25th v 75th centile values, or 75th v 25th centile values).[18]

A manual backward selection process was used to determine the final multivariable discrete time logistic regression model to predict live birth over successive complete cycles of IVF or ICSI. In this procedure, complete cycle number, the woman's age, duration of infertility, and number of eggs collected (for post-treatment model only) were always included and could not be removed because these are known predictors of pregnancy outcomes after IVF.[12] All of the other available predictors (listed as baseline characteristic) were subjected to the selection process. Women who had no eggs collected were excluded from the post-treatment model because it would not be possible to achieve a live birth in the first complete cycle. Therefore we fitted a separate model for these women. Since IVF centres have varying success rates, we also considered a random intercept for

the effect of IVF centre as recommended in recent studies.[19] [20] To quantify variation between centres, we calculated the 95% range for centre effect.

Missing data

Where data were missing for any predictor, we compared the characteristics of women with complete data with those for women with missing data. Single imputation was performed for those predictors with missing information. This procedure assumes that missingness was random, conditional on the observed predictors and outcome.

Predictive ability

To determine the explanatory value of each predictor relative to the entire set we calculated the adequacy statistic.[21] The adequacy is the proportion of the total explained variation in the outcome that is explained by the individual predictor.[22]

We used the C index to assess the ability of the multivariable models to discriminate between couples at high and low chances of a live birth.[23] Because the performance of the models with and without the random effect of centre were shown to be similar, we considered the fixed effects model to be the final model.

To assess whether the model calibration was too optimistic within the database from which the model was developed, we used bootstrapping for internal validation (see supplementary text S1).[18] By internally validating the calibration slope of the model we could determine whether the model underestimated or overestimated predictions.[18] A perfect slope should equal 1.

Treatment continuation

A further analysis was done to investigate the effect of predictors on continuing to a second complete cycle of IVF in women who did not have a live birth in complete cycle 1. The methods and results of this are reported in the appendix (see supplementary text S2). Statistical analysis was carried out using SAS (V.9.3) (SAS Institute, Cary, NC).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are plans to disseminate the results of the research to patients affected by fertility issues via national fertility charities and the Human Fertilisation and Embryology Authority.

Results

After exclusions, the dataset included 113 873 couples who underwent 184 269 complete cycles of IVF or ICSI (see supplementary figure A1). Table 1 shows the distribution of the characteristics of the couples and those of their first complete cycle (defined as all fresh and frozen embryo transfers resulting from one episode of ovarian stimulation), which resulted in a live birth in 33 154 (29%) women (fig 1). Of the remaining 80 719 couples only 45 384 (56%) went on to have a second complete cycle. Overall, 43% of couples had a live birth over the first six complete cycles of IVF or ICSI. The median time to follow-up for those not having a live birth was 1515 days (interquartile range 669-2631). Thirty per cent of all live births were multiples. Supplementary text S1 provides detailed information on missing data.

Predicting the cumulative chances of a live birth

Individually, all patient and treatment level characteristics had statistically significant univariable associations with live birth, except for unexplained infertility (see supplementary table A1). Figure 2 shows the unadjusted relation between the predicted probability of live birth in the first complete cycle and the woman's age, duration of infertility, treatment year, and number of

Table 1 | Characteristics of couples and their treatment at first complete cycle of in vitro fertilisation (IVF). Values are numbers (percentages) unless stated otherwise

Characteristics	Data
No of women	113 873
No of complete cycles	184 269
Patient characteristics	
Mean (SD) age of women	34.1 (5)
Median (interquartile range) duration of infertility (years)	4 (3-6)
Missing	18 225 (16)
No previous pregnancy in couple	75 541 (66)
Previous pregnancy in couple	28 070 (25)
Missing*	10 262 (9)
Type of infertility:	
Tubal	26 545 (23)
Anovulatory	15 942 (14)
Male factor	49 753 (44)
Unexplained	32 693 (29)
Endometriosis	7590 (7)
>1 type	13 414 (12)
Year of first egg retrieval:	
1999-2001	29 451 (26)
2002-04	34 472 (30)
2005-08	49 950 (44)
Treatment characteristics at complete cycle 1	
IVF	67 511 (59)
Intracytoplasmic sperm injection	46 362 (41)
Median No (interquartile range) of eggs collected	8 (5-13)
Median No (interquartile range) of embryos created	5 (2-8)
Median No (interquartile range) of embryos frozen	0 (0-1)
Cryopreservation of embryos	28 950 (25)
No of frozen treatments:	
0	103 726 (91)
1	8270 (7)
2	1568 (1)
3	246 (0.2)
≥4	63 (0.1)
No of embryos transferred and stage, first fresh treatment:	
No transfer	15 501 (14)
Single cleavage stage	9248 (8)
Single blastocyst stage	662 (1)
Double cleavage stage	75 701 (66)
Double blastocyst stage	2960 (3)
Triple cleavage stage	8649 (8)
Triple blastocyst stage	130 (0.1)
Missing	1022 (1)

*Missing values for previous pregnancy occurred in 2008. Since only 13% were recorded as not having a previous pregnancy in 2008 the whole year was imputed.
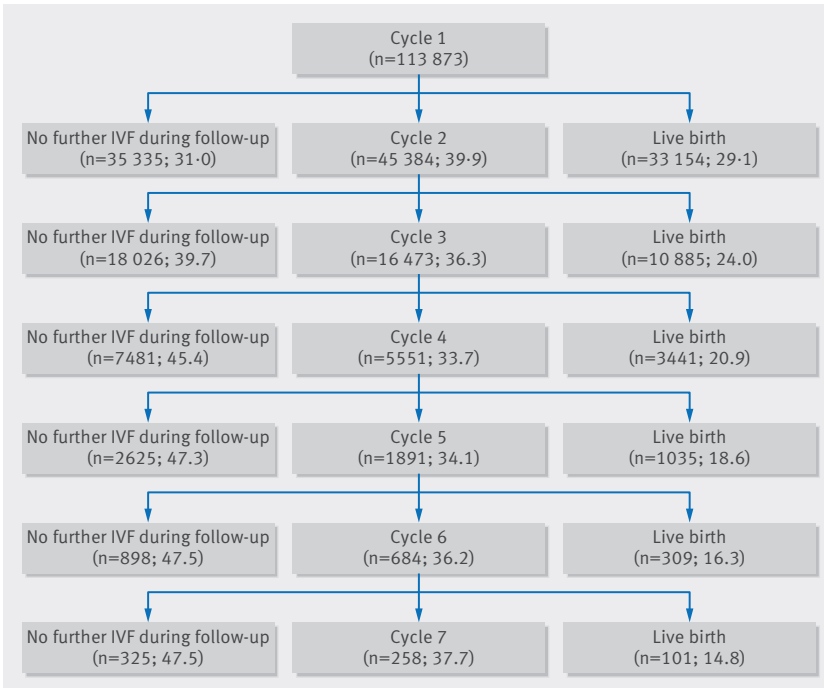
Fig 1 | Number of women having a live birth, not having a live birth but continuing in vitro fertilisation (IVF), or not having a live birth and not continuing IVF (during follow-up) over six complete cycles of IVF

eggs collected. The chances of a live birth declined after age 30 and decreased linearly with increasing duration of infertility. Increasing egg numbers improved the chance of live birth considerably until 13 eggs. Year of treatment showed a positive effect from 2006 onwards.

Pretreatment model
The factors that predicted the cumulative chances of having a live birth over a maximum of six complete cycles (in a multivariable model) were the woman's age, duration of infertility, treatment type, year, tubal infertility, male factor infertility, unexplained infertility, anovulation, and previous pregnancy, with age explaining 85% of the total variation explained by all the factors (table 2 and supplementary table A2). The odds of a live birth decreased with every increasing complete cycle—eg, the odds of a live birth after complete cycle 2 was 21% lower than the odds of a live birth after complete cycle 1, and the odds after complete cycle 6 were 56% less than after complete cycle 1. With increasing woman's age the odds of a live birth over six complete cycles decreased (31 *v* 37 years; adjusted odds ratio 1.66, 95% confidence interval 1.62 to 1.71). Increasing duration of infertility reduced the odds of a live birth (3 *v* 6 years; 1.09, 1.08 to 1.10). Couples with a diagnosis of tubal or male factor infertility had around a 10% reduced chance of a live birth, whereas couples with
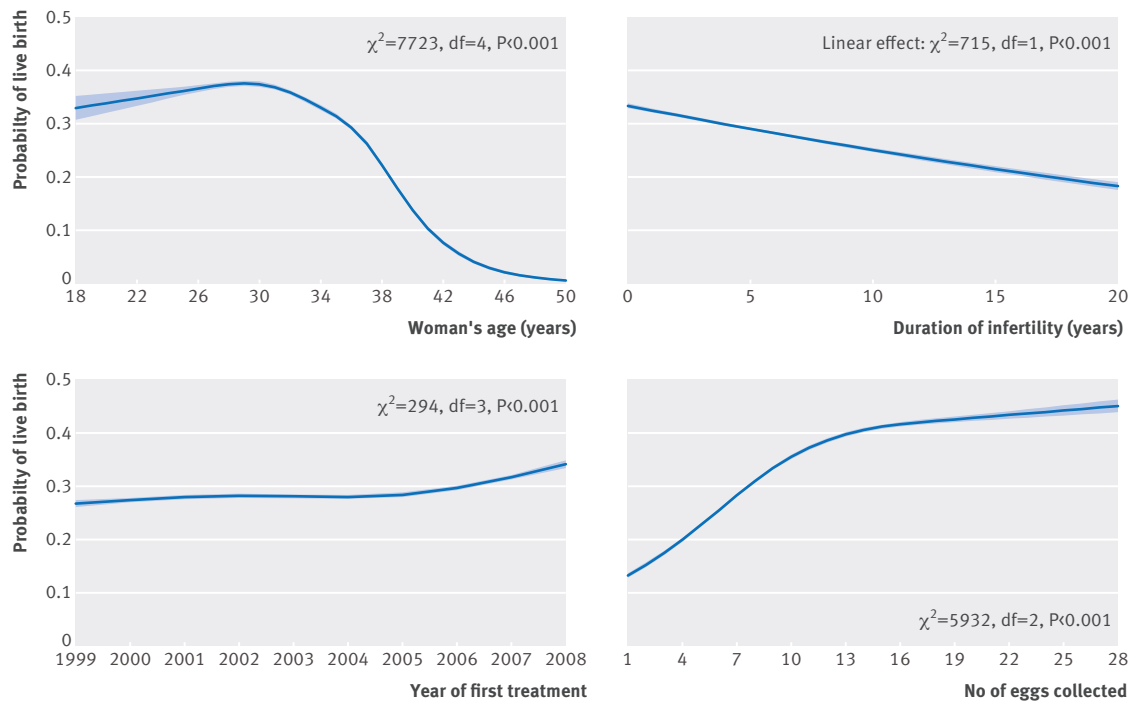

Fig 2 | Plots showing unadjusted (univariable) relations between the following continuous baseline variables and a live birth in the first complete cycle of in vitro fertilisation. (A) Woman's age (years); (B) duration of infertility (years); (C) year of first complete cycle, and (D) number of eggs retrieved in first complete cycle. Each panel depicts the probability of live birth (solid curve) with 95% confidence bands as a function of the baseline variable. The degrees of freedom (df) associated with the χ^2 statistic in each case depend on the complexity of the relation between the variable and the log odds of live birth. Where df >1, the relation was non-linear and characterised by restricted cubic spline functions. Where df=1, the relation was linear even though the plot shown here, which reflects live birth (rather than the log odds), exhibits a non-linear relation

Table 2 | Effect and importance (in decreasing order) of each predictor on live birth over multiple complete cycles of in vitro fertilisation (IVF) adjusted for patient characteristics (pretreatment model)

Predictors	Odds ratio (95% CI)	P value	Adequacy
Intercept		<0.001	
Complete cycle No:			
1 (reference)	1		
2	0.79 (0.77 to 0.81)	<0.001	
3	0.66 (0.64 to 0.69)	<0.001	
4	0.57 (0.53 to 0.61)	<0.001	
5	0.49 (0.43 to 0.55)	<0.001	
6	0.44 (0.36 to 0.55)	<0.001	
Patient characteristics:			
Woman's age, 31 v 37 years*	1.66 (1.62 to 1.71)	<0.001	0.846
Duration, 3 v 6 years	1.09 (1.08 to 1.10)	<0.001	0.078
Treatment type, ICSI v IVF	1.24 (1.21 to 1.28)	<0.001	0.047
Year first complete cycle started, 2006 v 2001*	1.20 (1.16 to 1.24)	<0.001	0.032
Tubal infertility, yes v no	0.91 (0.88 to 0.94)	<0.001	0.012
Male factor infertility, yes v no	0.90 (0.87 to 0.94)	<0.001	0.009
Unexplained infertility, yes v no	1.06 (1.03 to 1.10)	<0.001	0.001
Anovulatory infertility, yes v no	1.05 (1.01 to 1.09)	0.01	0.001
Previous pregnancy in couple, no v yes	0.93 (0.90 to 0.95)	<0.001	0.0002

ICSI=intracytoplasmic sperm injection.
*Interquartile odds ratio was calculated to aid interpretation of continuous predictors of age, duration of infertility, and year first complete cycle started. It is defined as the ratio of the odds of a live birth for the 75th centile and the odds of a live birth for the 25th centile of the predictor.
Nagelkerke's R^2 (amount of explained variation in model)=7.9%; Tjur's coefficient of discrimination=5.1%.

Table 3 | Effect and importance (in decreasing order) of each predictor on live birth over multiple complete cycles of in vitro fertilisation (IVF) adjusted for patient characteristics and treatment information at first complete cycle (post-treatment model)

Predictors	Odds ratio (95% CI)	P value	Adequacy
Intercept		<0.001	
Complete cycle No:			
1 (Reference)	1		
2	0.82 (0.80 to 0.85)	<0.001	
3	0.70 (0.67 to 0.73)	<0.001	
4	0.60 (0.56 to 0.65)	<0.001	
5	0.51 (0.44 to 0.58)	<0.001	
6	0.46 (0.37 to 0.58)	<0.001	
Patient characteristics			
Woman's age to 31 v 37 years*	1.53 (1.49 to 1.58.)	<0.001	0.435
Duration to 3 v 6 years	1.06 (1.05 to 1.08)	<0.001	0.036
Year first complete cycle started to 2006 v 2001*	1.29 (1.26 to 1.32)	<0.001	0.018
Tubal infertility to yes v no	0.80 (0.78 to 0.83)	<0.001	0.007
Previous pregnancy in couple to no v yes	0.95 (0.93 to 0.98)	<0.001	0.0001
Treatment information at first complete cycle			
Cryopreservation of embryos to yes v no	1.91 (1.86 to 1.96)	<0.001	0.387
No of eggs collected to 13 v 5*	1.29 (1.27 to 1.32)	<0.001	0.378
Stage of embryos transferred:		<0.001	0.123
Double cleavage	1		
No embryos transferred	0.34 (0.32 to 0.36)	<0.001	
Single cleavage	0.57 (0.54 to 0.60)	<0.001	
Single blastocyst	1.07 (0.93 to 1.24)	0.35	
Double blastocyst	1.79 (1.67 to 1.91)	<0.001	
Triple cleavage	1.02 (0.98 to 1.07)	0.36	
Triple blastocyst	1.58 (1.15 to 2.14)	0.004	
Treatment type to ICSI v IVF	0.91 (0.89 to 0.93)	<0.001	0.002

ICSI=intracytoplasmic sperm injection.
*Interquartile odds ratio was calculated to aid interpretation of continuous predictors of age, duration of infertility, year first complete cycle started, and eggs collected. It is defined as the ratio of the odds of a live birth for the 75th centile and the odds of a live birth for the 25 centile of the predictor.
Nagelkerke's R^2 (amount of explained variation in model)=14.7%; Tjur's coefficient of discrimination=510.3%.

unexplained infertility or anovulation had slightly increased chances of success. Couples without a previous pregnancy had slightly decreased odds of live birth (0.93, 0.90 to 0.95). Couples who underwent ICSI had a 24% increased chance of a live birth than those who underwent IVF.

Post-treatment model
After the first fresh embryo transfer, the odds of a live birth increased with egg number, doubled in cases where embryos were cryopreserved, and decreased by 9% if the treatment was ICSI (table 3). The chances of a live birth over six complete cycles were lower after transfer of a single cleavage stage fresh embryo compared with transfer of a double cleavage stage fresh embryo. The effects of the predictors which also appeared in the pretreatment model were similar, apart from ICSI compared with IVF. Woman's age, cryopreservation of embryos, and number of eggs each explained a similar high amount of the total variation explained by all the factors (see supplementary table A3). Supplementary table A4 shows the results for women who had no eggs collected.

Assessing ability to predict cumulative live birth
The C index for the pretreatment model was 0.73 (0.72 to 0.74) and for the post-treatment model was 0.72 (0.71 to 0.73). The optimism adjusted calibration slope in both models was almost one (0.996 and 0.998, respectively) suggesting no overfitting of predictor effects.

Examples of predicting cumulative live birth for specific couples
Figure 3 shows an example of pretreatment predictions in different case scenarios. Part A shows the cumulative predicted probability of live birth over six complete cycles for couples starting ICSI for male factor infertility. The figure shows the probabilities for women aged 30 and 40 with either two or five years of infertility. While duration is less influential, younger women have a much higher chance of success, with a probability of 0.47 in complete cycle 1 (with two years' duration of infertility) increasing to 0.94 over six complete cycles (0.19 to 0.57 for 40 year old women). Similar predictions were found for couples with unexplained infertility who underwent IVF treatment in their first complete cycle.

Post-treatment, the predictions for the above scenarios were updated using information from the fresh treatment of the first complete cycle. The top line from figure 4 represents a woman with an excellent prognosis—aged 30 years, non-tubal infertility, 15 eggs collected, embryos cryopreserved, and a single fresh blastocyst transfer in the first complete cycle. The probability of success in complete cycle 1 is 0.68. Cumulatively this increases to 0.89 over two complete cycles and rises to just under 1 over four complete cycles. The lower line in the chart represents a poorer prognosis—a woman aged 40 who had IVF, five eggs collected, no embryos frozen, and a single cleavage stage fresh embryo transferred in the first complete
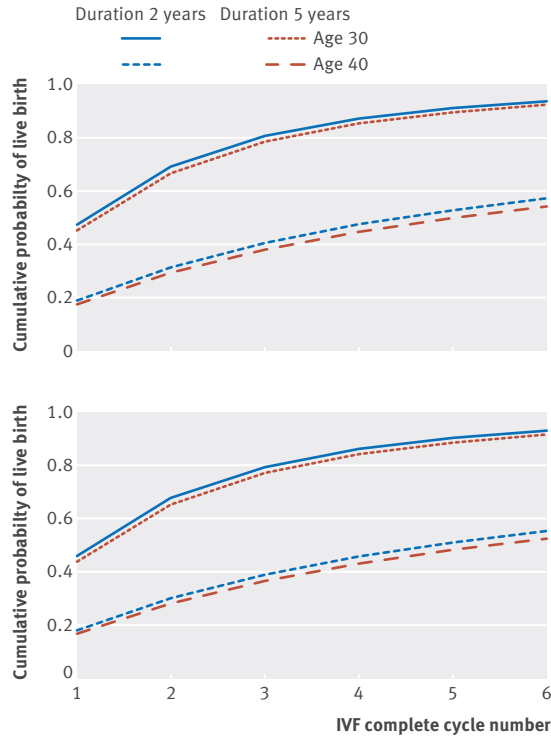
Fig 3 | Example of pretreatment model predicting cumulative probability of live birth over six complete cycles of in vitro fertilisation (IVF) for women aged 30 or 40 with two or five years of primary infertility who have: (A) male factor infertility and had treatment by intracytoplasmic sperm injection; (B) unexplained infertility and underwent IVF
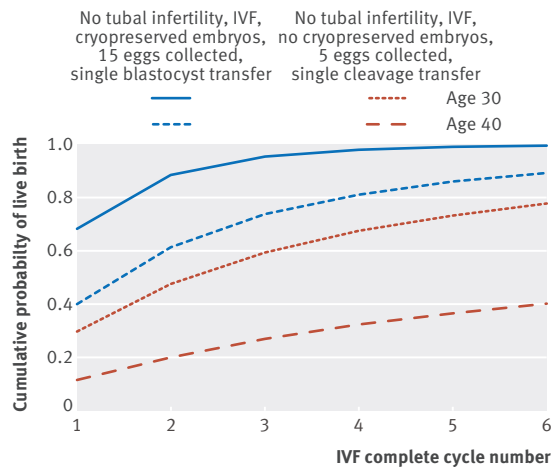

Fig 4 | Example of post-treatment model predicting cumulative probability of live birth over six complete cycles of in vitro fertilisation (IVF) for different patient and treatment characteristics (these patients have all had primary infertility for two years)

cycle. Her chance of a live birth is 0.11 in complete cycle 1 increasing to 0.20 over two complete cycles (0.41 over six). See supplementary text S3 for the formulas used to calculate the individualised cumulative predictions.

Sensitivity analyses

The effects from both models fitted using couples with complete data only were similar to those from the imputed models (see supplementary tables A5-A7).

In centres with low birth rates (2.5th centile of the random effect distribution), the odds of a live birth were 0.61 times that of the average, whereas in centres with high livebirth rates (97.5th centile) the odds of a live birth were 1.65 times the average, after adjustment for the post-treatment predictors. The predictor effects from the models with the random intercept were similar to those from the fixed effects only model (see supplementary tables A8 and A9). The C indices were similar when fixed (from fixed effects model), marginal, or conditional (from random effects model) estimates of the predicted probabilities were used. A random slope for centre had no statistically significant effect.

Discussion

We have estimated the individualised chances of having a liveborn baby over a complete package of in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment at two time points. In couples embarking on IVF or ICSI we found that increasing age of the woman (from 30 years) was far the best predictor of live birth. After transfer of a fresh embryo in the first complete cycle, aside from the woman's age, increasing number of eggs collected and the cryopreservation of embryos were the next best predictors.

Strengths and weaknesses of this study

This study successfully predicted the chances of cumulative live birth over six complete cycles of IVF or ICSI using personalised information from national data over 10 years.

Treatment year was highly associated with live birth, signifying improvements in technology over time. Since the last year in our study period was 2008, we checked for underestimation of predictions owing to improvements in assisted conception since 2008. This was done by inflating the predictions from 2008 in the model to 2013, the latest year with published national livebirth rates on the Human Fertilisation and Embryology Authority website.[24] The livebirth rate for each treatment cycle started using the woman's own fresh eggs was 25.8% in 2008, and reduced to 25.2% in 2009 before slowly rising back to 25.8% in 2012.[25] In 2013 the rate increased to 26.5%. The intercept of the model was inflated by the difference between the 2008 and 2013 rates (on the log odds scale). Such an adjustment increased the predicted probabilities by up to a maximum of 0.009 (and by a mean of 0.007). In our new online calculator (https://w3.abdn.ac.uk/clsm/opis), predictions are computed using the 2013 estimate.

Unlike previous studies, we investigated heterogeneity in IVF centre effects using random effect intercepts as we had anonymised centre identifiers. Although there was some variation in the odds of live birth across centres, the ability of the model to predict using predictions conditioned on centres from the random effects model were no better than using standard estimates

from the fixed effects model without adjustment for centre. Therefore, for reasons of generalisability, and because centre was anonymous, we advise using the fixed effects models.

Two models have been developed that may be used by clinicians at two different time points to estimate a couple's chances of having a live birth over one or more complete cycles of IVF. At these particular times points (before IVF and after first transfer of a fresh embryo) only information on the couple and treatment available at those times can be used to make predictions. Therefore at the point when the pre-IVF model will be used by clinicians to counsel couples as to their future chances of success, the woman's age, duration of infertility, type of infertility, previous pregnancy status of the couple, and treatment type are known. The post-IVF model revises these estimates using updated information from the first attempt at a fresh embryo transfer. We acknowledge that information from future complete cycles would provide more precise predictions, but our models reflect a more real life setting where such information is not available at the time of counselling. These models will provide an indication of the couple's future chances of achieving a live birth over a complete package of IVF at the beginning of treatment.

One limitation concerns the effect of calendar time on future frozen embryo transfers in the first complete cycle. For example, a woman may decide to have a frozen embryo transfer five years after the embryos were frozen. However, unless there were changes to her uterine environment, time is unlikely to decrease her chance of a live birth as the embryos were created using eggs retrieved five years earlier. Furthermore, we did not adjust for the time between complete cycles of IVF or ICSI nor for the change in predictors with each sequential complete cycle. The reason for this is because such information is not known at the time predictions are made.

We were unable to adjust for other potentially important predictors that were not available in the HFEA dataset. These include body mass index of the woman, ethnicity, smoking status, alcohol intake, and measures of ovarian reserve such as antral follicle count. A systematic review concluded that women's age, duration of infertility, number of eggs collected, and basal follicle stimulating hormone level were the most important predictors of IVF or ICSI success.[12] Of these, only the last predictor was unavailable in our analysis. Smoking and alcohol consumption in both sexes have been shown to have an association with IVF success.[26-28] Although the availability of these potential predictors would have been valuable, the quality and completeness of routinely collected data on smoking and alcohol is questionable owing to being self reported.[29 30]

One of the model assumptions was that those couples who discontinue treatment without a live birth still have the same chance of a live birth as those who continue, after correction for predictor effects. This assumption only applies to women with obvious barriers to continuing treatment, such as a lack of funds, divorce, or death. However, most discontinue because they have a lower chance of success.[31] The reason for

treatment withdrawal was unfortunately not available. Studies have tried to discount optimal estimates by the same fixed percentage across all individuals.[11 32] However, such an approach is flawed because the chances of continuing treatment are highly likely to vary widely depending on a couple's characteristics (see supplementary text S2). By using a modelling approach to predict cumulative live birth we have adjusted for treatment continuation based on the covariates (such as the woman's age) as available.

Internal validation of the models showed that the optimism in the calibration slopes was minimal (owing to the large sample size). Because our model was developed using the UK national IVF registry database with the intention of being used in the UK there is no urgent need to externally validate on data from another geographical location,[33] especially since IVF practice and policy varies across countries. Before the model is applied in other settings we recommend validation, specifically an assessment of the calibration of the model predictions. In the future, temporal validation on an up-to-date UK database is important to ensure that the model is robust to changes in UK IVF policy. Further work will involve sourcing a suitable database with which to carry out such a study.

Strengths and weaknesses in relation to previous studies

Many studies have reported the chance of a live birth after IVF or ICSI.[13 34-36] However, for different reasons they do not predict cumulative live birth over multiple complete cycles of IVF or ICSI. They either make predictions for the first transfer of a fresh embryo only,[34] make predictions for individual embryo transfer episodes but with no linkage between cycle and woman (a necessary requirement for calculating cumulative outcomes over multiple cycles),[13] or only adjust for the number of previous failed cycles.[36] One study[37] produced a similar model to ours, but this did not reflect usual practice as it only made cumulative predictions up to three fresh embryo transfer attempts and excluded any associated frozen embryo transfers. In an age where the emphasis is on reducing multiple births and increasing single embryo transfers,[2] a complete cycle definition aids interpretability of results for clinicians and couples who want to know the chances of a live birth over an entire IVF programme.[38]

For fertility models, calibration in an external cohort tends to be the more important measure of performance than discrimination owing to the homogeneity of the population being studied.[39] Discrimination assessments tend to result in C indices of around 0.65 at best. However, the C index for both models is, as far as we know, the highest found for IVF models to date. This might be due to the large sample size, carefully capturing non-linearity, the effect of complete cycle number, or a combination of the three.

Interpretation and clinical importance

These are the first models to predict individualised chances of live birth over a course of complete IVF cycles.

The results are relevant not only for individual couples and their clinicians but also for funders and policy makers in determining access to state or insurance funded IVF.[2] The models have been converted into an online calculator that can be used to estimate the probability of live birth based on the characteristics of the couple and treatment (https://w3.abdn.ac.uk/clsm/opis).

The most appropriate use of these models is to serve as a counselling tool to help shape expectations for couples who would ideally like to know their overall chance of having a baby over a complete IVF or ICSI journey. As an example, the probability of a live birth in the first complete cycle for a couple with primary unexplained infertility for two years and the woman aged 30 undergoing IVF is 0.46 (0.93 over six complete cycles). After transfer of a single cleavage embryo following the collection of five eggs and no embryos cryopreserved, the probability decreases to 0.29 (0.78 over six complete cycles). Before treatment is started, clinicians would use these predictions to support their clinical knowledge when communicating to couples their chance of successful treatment over a complete IVF programme. Following the first embryo transfer, when treatment information is available, clinicians can then use the revised predictions to offer reassurance to couples about their future chances over multiple complete cycles. Existing models that only inform the chances of a liveborn baby after the first fresh cycle are not useful because the first treatment does not always succeed. The results from our model might help couples plan their time and prepare emotionally and financially for their complete IVF journey.

Currently we do not advise that these models be used to make decisions around whether or not couples should have IVF treatment. The reason for this is because their impact on clinical pathways, health outcomes, and costs need to be investigated and shown to be beneficial before doctors and couples can be persuaded to use them for decision making.[40 41] Furthermore, for a model to be truly useful for decisions around whether or not to treat it needs to provide estimates of the change in the absolute benefit of treatment over time, which would require information on couples under expectant management—that is, do not receive treatment.[42] Unfortunately, such information is not available in the HFEA database or elsewhere at a national level.

We confirmed the reduction in the chance of live birth with increasing age, increasing duration of infertility, and previous pregnancy.[13 35 36] Before starting IVF or ICSI, unexplained infertility and anovulation were associated with an increased chance of live birth, whereas male factor and tubal infertility had a negative association. However, apart from tubal infertility these associations disappeared when predictions were updated using additional information from the first fresh embryo transfer. This suggests that treatment information overrides the effect of the different types of infertility—women with a high number of eggs who have cryopreserved embryos might reflect mild infertility encompassing most women in the unexplained, male factor, and anovulation categories.

Further research

In addition to temporal validation, external validation on national registry data from other countries might realise the potential of our models to be recalibrated (if required) and used in those populations.

Conclusions

Many couples with fertility problems embarking on IVF will undergo several complete cycles—each involving a fresh embryo transfer potentially followed by one or more frozen embryo transfers in order to achieve their first live birth. This study has developed a novel calculator that can predict the cumulative chances of a live birth for an individual couple over a package of complete IVF cycles. This tool will help to shape couples' expectations allowing them to plan their treatments more efficiently and to prepare emotionally and financially.

1   Oakley L, Doyle P, Maconochie N. Lifetime prevalence of infertility and infertility treatment in the UK: results from a population-based survey of reproduction. Hum Reprod 2008;23:447-50. doi:10.1093/humrep/dem369.

2   National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. 2013. https://www.nice.org.uk/guidance/cg156/evidence/full-guideline-188539453.

3   Adamson GD, Tabangin M, Macaluso M, de Mouzon J. The number of babies born globally after treatment with the assisted reproductive technologies (ART). *Fertil Steril* 2013;100:S42. doi:10.1016/j.fertnstert.2013.07.1807.

4   Vrtacnik U, Vrtacnik Bokal E, Devjak R. Cumulative delivery rate after providing full reimbursement in vitro fertilization programme: a 6-years survey. *Biomed Res Int* 2014;2014:850478. doi:10.1155/2014/850478.

5   Abuzeid MI, Bolonduro O, La Chance J, et al. Cumulative live birth rate and assisted reproduction: impact of female age and transfer day. *Facts Views Vis Obgyn* 2014;6:145-9.

6   Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? *Hum Reprod* 2015;30:2703-7.

7   Luke B, Brown MB, Wantman E, et al. Cumulative birth rates with linked assisted reproductive technology cycles. *N Engl J Med* 2012;366:2483-91. doi:10.1056/NEJMoa1110238.

8   Macaldowie A, Wang YA, Chambers GM, Sullivan EA. National Perinatal Epidemiology and Statistics Unit, the University of New South Wales, Sydney. Assisted reproduction technology in Australia and New Zealand 2011. 2013. https://npesu.unsw.edu.au/surveillance/assisted-reproductive-technology-australia-new-zealand-2011.

9   Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. *N Engl J Med* 2009;360:236-43. doi:10.1056/NEJMoa0803072.

10   McLernon DJ, Maheshwari A, Lee AJ, Bhattacharya S. Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women. *Hum Reprod* 2016;31:572-81. doi:10.1093/humrep/dev336.

11   Smith ADAC, Tilling K, Nelson SM, Lawlor DA. Live–birth rate associated with repeat in vitro fertilization treatment cycles. *JAMA* 2015;314:2654-62. doi:10.1001/jama.2015.17296.

12   van Loendersloot LL, van Wely M, Limpens J, Bossuyt PMM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. *Hum Reprod Update* 2010;16:577-89. doi:10.1093/humupd/dmq015.

13   Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med* 2011;8:e1000386. doi:10.1371/journal.pmed.1000386.

14   Bhattacharya S, Maheshwari A, Mollison J. Factors associated with failed treatment: an analysis of 121,744 women embarking on their first IVF cycles. *PLoS One* 2013;8:e82249. doi:10.1371/journal.pone.0082249.

15   Human Fertilisation and Embryology Authority. Access anonymised HFEA data. 2013b. http://www.hfea.gov.uk/5874.html.

16   Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Hum Reprod* 2011;26:1768-74. doi:10.1093/humrep/der106.

17   Williams CL, Bunch KJ, Stiller CA, et al. Cancer risk among children born after assisted conception. *N Engl J Med* 2013;369:1819-27. doi:10.1056/NEJMoa1301675.

18   Steyerberg EW. *Clinical prediction models: a practical approach to development, validation and updating.* Springer, 2009doi:10.1007/978-0-387-77244-8.

19   te Velde ER, Nieboer D, Lintsen AM, et al. Comparison of two models predicting IVF success; the effect of time trends on model performance. *Hum Reprod* 2014;29:57-64. doi:10.1093/humrep/det393.

20   Bouwmeester W, Twisk JWR, Kappen TH, van Klei WA, Moons KGM, Vergouwe Y. Prediction models for clustered data: comparison of a random intercept and standard regression model. *BMC Med Res Methodol* 2013;13:19. doi:10.1186/1471-2288-13-19.

21   Harrell FE. *Regression modeling strategies with applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis.* Springer, 2001.

22   Thompson D. Ranking Predictors in logistic regression, SAS Institute: Paper D10–2009. 2009. http://www.mwsug.org/proceedings/2009/stats/MWSUG-2009-D10.pdf.

23   Harrell FE Jr, , Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

24   Human Fertilisation and Embryology Authority. Fertility treatment in 2013: trends and figures. 2013a. http://www.hfea.gov.uk/docs/HFEA_Fertility_Trends_and_Figures_2013.pdf.

25   Human Fertilisation and Embryology Authority. Facts and figures for researchers and the media. 2015. http://www.hfea.gov.uk/99.html.

26   Joesbury KA, Edirisinghe WR, Phillips MR, Yovich JL. Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. *Hum Reprod* 1998;13:1506-13. doi:10.1093/humrep/13.6.1506.

27   Soares SR, Melo MA. Cigarette smoking and reproductive function. *Curr Opin Obstet Gynecol* 2008;20:281-91. doi:10.1097/GCO.0b013e3282fc9c1e

28   Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. *Obstet Gynecol* 2011;117:136-42. doi:10.1097/AOG.0b013e31820090e1.

29   Boniface S, Kneale J, Shelton N. Drinking pattern is more strongly associated with under-reporting of alcohol consumption than socio-demographic factors: evidence from a mixed-methods study. *BMC Public Health* 2014;14:1297. doi:10.1186/1471-2458-14-1297.

30   Håkonsen LB, Ernst A, Ramlau-Hansen CH. Maternal cigarette smoking during pregnancy and reproductive health in children: a review of epidemiological studies. *Asian J Androl* 2014;16:39-49. doi:10.4103/1008-682X.122351.

31   Te Velde ER, Koudstaal J, Eimers JM. Assisted conception for infertility. *BMJ* 1992;305:1097-8. doi:10.1136/bmj.305.6861.1097-d.

32   Stolwijk AM, Wetzels AMM, Braat DDM. Cumulative probability of achieving an ongoing pregnancy after in-vitro fertilization and intracytoplasmic sperm injection according to a woman's age, subfertility diagnosis and primary or secondary subfertility. *Hum Reprod* 2000;15:203-9. doi:10.1093/humrep/15.1.203.

33   Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med* 2015;13:1. doi:10.1186/s12916-014-0241-z.

34   Dhillon RK, McLernon DJ, Smith PP, et al. Predicting the chance of live birth for women undergoing IVF: a novel pretreatment counselling tool. *Hum Reprod* 2016;31:84-92. doi:10.1093/humrep/dev268.

35   Leushuis E, van der Steeg JW, Steures P, et al. Prediction models in reproductive medicine: a critical appraisal. *Hum Reprod Update* 2009;15:537-52. doi:10.1093/humupd/dmp013.

36   van Loendersloot LL, van Wely M, Repping S, Bossuyt PMM, van der Veen F. Individualized decision-making in IVF: calculating the chances of pregnancy. *Hum Reprod* 2013;28:2972-80. doi:10.1093/humrep/det315.

37   Luke B, Brown MB, Wantman E, et al. A prediction model for live birth and multiple births within the first three cycles of assisted reproductive technology. *Fertil Steril* 2014;102:744-52. doi:10.1016/j.fertnstert.2014.05.020.

38   Stern JE, Hickman TN, Kinzer D, Penzias AS, Ball GD, Gibbons WE. Can the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) be used to accurately report clinic total reproductive potential (TRP)? *Fertil Steril* 2012;97:886-9. doi:10.1016/j.fertnstert.2012.01.091.

39   Coppus SFPJ, van der Veen F, Opmeer BC, Mol BWJ, Bossuyt PMM. Evaluating prediction models in reproductive medicine. *Hum Reprod* 2009;24:1774-8. doi:10.1093/humrep/dep109.

40   Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med* 2006;144:201-9. doi:10.7326/0003-4819-144-3-200602070-00009.

41   Moons KGM, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012;98:691-8. doi:10.1136/heartjnl-2011-301247.

42   McLernon DJ, te Velde ER, Steyerberg EW, Mol BWJ, Bhattacharya S. Clinical prediction models to inform individualized decision-making in subfertile couples: a stratified medicine approach. *Hum Reprod* 2014;29:1851-8. doi:10.1093/humrep/deu173.

Supplementary information: Additional tables