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ORIGINAL ARTICLE *Infertility*

Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles

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BACKGROUND: While live birth is the principal clinical outcome following *in vitro* fertilization (IVF) treatment, the number of eggs retrieved following ovarian stimulation is often used as a surrogate outcome in clinical practice and research. The aim of this study was to explore the association between egg number and live birth following IVF treatment and identify the number of eggs that would optimize the IVF outcome.

METHODS: Anonymized data on all IVF cycles performed in the UK from April 1991 to June 2008 were obtained from the Human Fertilization and Embryology Authority (HFEA). We analysed data from 400 135 IVF cycles. A logistic model was fitted to predict live birth using fractional polynomials to handle the number of eggs as a continuous independent variable. The prediction model, which was validated on a separate HFEA data set, allowed the estimation of the probability of live birth for a given number of eggs, stratified by age group. We produced a nomogram to predict the live birth rate (LBR) following IVF based on the number of eggs and the age of the female.

RESULTS: The median number of eggs retrieved per cycle was 9 [inter-quartile range (IQR) 6–13]. The overall LBR was 21.3% per fresh IVF cycle. There was a strong association between the number of eggs and LBR; LBR rose with an increasing number of eggs up to ~15, plateaued between 15 and 20 eggs and steadily declined beyond 20 eggs. During 2006–2007, the predicted LBR for women with 15 eggs retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16%, respectively. There was a steady increase in the LBR per egg retrieved over time since 1991.

CONCLUSION: The relationship between the number of eggs and live birth, across all female age groups, suggests that the number of eggs in IVF is a robust surrogate outcome for clinical success. The results showed a non-linear relationship between the number of eggs and LBR following IVF treatment. The number of eggs to maximize the LBR is ~15.

Key words: IVF treatment / egg numbers / live birth / nomogram

Introduction

The primary aim of *in vitro* fertilization (IVF) treatment is to achieve a term live birth. However, as the number of eggs retrieved is considered to be an important prognostic variable, IVF treatment protocols aim to optimize this outcome. Studies evaluating IVF treatment regimens and ovarian reserve tests such as anti-müllerian hormone or antral follicle count often use the number of eggs as a surrogate outcome. However, this practice has been criticized (Vail and Gardener, 2003) as the relationship between the number of eggs and live birth is poorly understood.

Previous work on the relationship between the number of eggs retrieved and pregnancy rates following IVF, based on data from single centres and involving small sample sizes, has shown conflicting results (Meniru and Craft 1997; Letterie *et al.*, 2005; Kably Ambe *et al.*, 2008; Molina Hita Ma. del *et al.*, 2008; Hamoda *et al.*, 2010). None has reported live birth rates (LBRs), but instead focused on rates of clinical or ongoing pregnancy. The aim of our study was to determine the association between the number of eggs retrieved and the LBR in fresh IVF cycles, based on the analysis of a large national database involving 400 135 IVF treatment cycles.

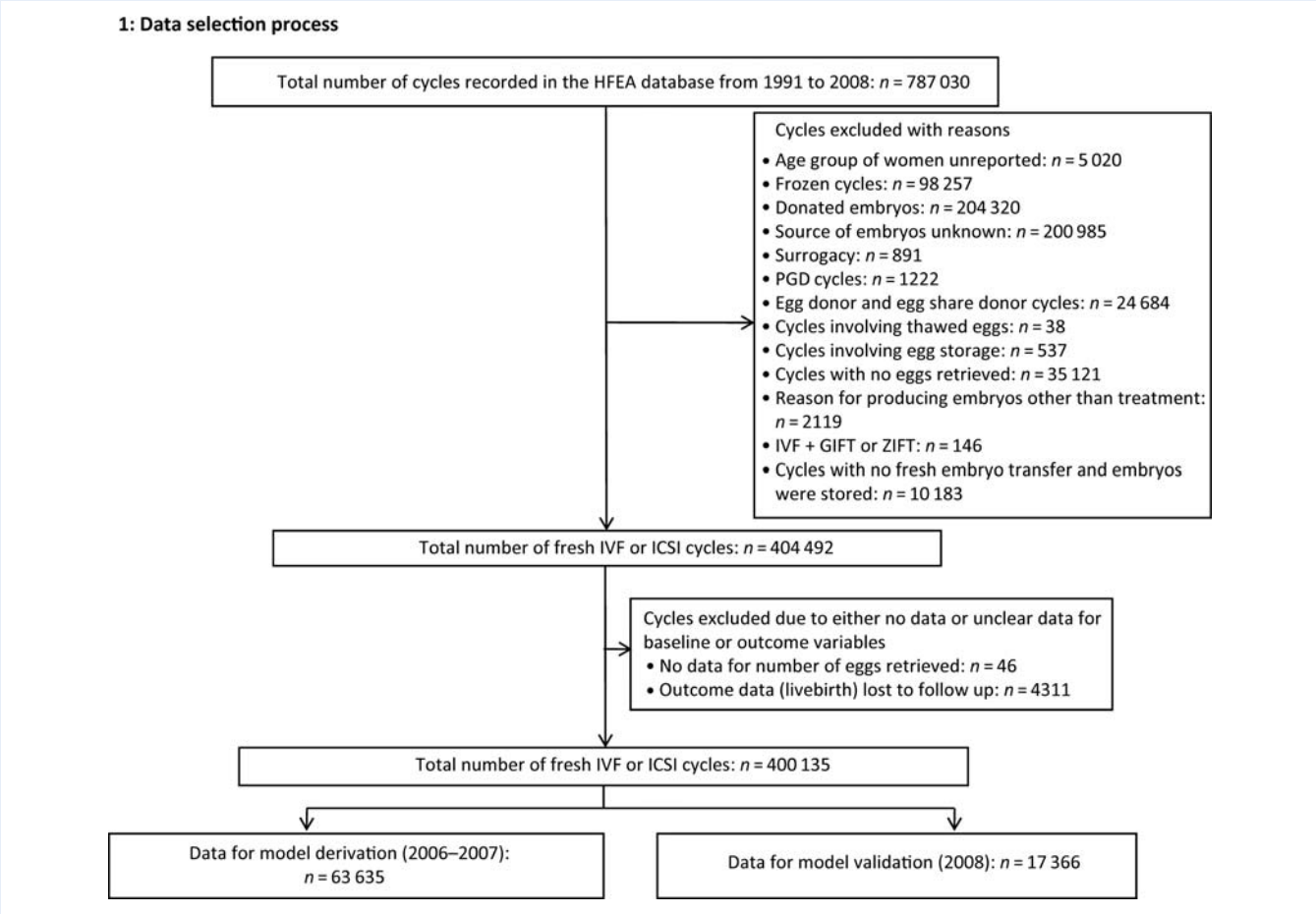

Figure 1 Data selection process.

Materials and Methods

Anonymized data were obtained from the Human Fertilization and Embryology Authority (HFEA) for all IVF cycles performed in the UK from April 1991 to June 2008 (www.hfea.gov.uk/5874.html, HFEA authority). The HFEA, which is the statutory regulator of assisted conception treatment in the UK, has collected data on all IVF treatment cycles performed in the UK since its inception in 1991. Overall, 787 030 IVF cycles were recorded in this period. For the purpose of the study, cycles involving gamete or zygote intra-fallopian transfer (GIFT, ZIFT), egg donation, egg sharing, embryo donation or where the source of embryos was not specified, preimplantation genetic diagnosis, surrogacy, oocyte cryopreservation, frozen embryo replacement, and cycles where no eggs were retrieved or all embryos were frozen were excluded from the analysis. Information was obtained on the number of eggs retrieved, age group (18–34, 35–37, 38–39, 40 years and over), treatment period (1991–2008) and live birth outcome. A live birth is defined as any birth event in which at least one baby is born alive.

Statistical analysis

We described the characteristics of the cohort using absolute and relative frequencies for categorical variables, and means and medians with measures of spread for continuous variables. We computed crude LBRs for the whole cohort, and stratified by period of treatment and age.

To explore the association between the number of eggs and live birth outcome, we fitted a maximum likelihood logistic model with live birth outcome as the dependent variable and using a fractional polynomial to handle the number of eggs as a continuous independent variable. We used the closed test procedure for function selection as described by Royston and Sauerbrei (2008). We also introduced in the model indicator variables for age and period of treatment. We computed robust standard errors to account for the non-independence of observations from multiple treatment cycles in a single participant.

The model calibration and discrimination ability was assessed by the Hosmer–Lemeshow test and the c-index statistic. The live birth outcome has substantially improved over the four time periods and thus, for the development of the prediction model, we used the data set generated after 2006. As the age of the woman has a significant impact in determining the probability of a live birth, we computed this probability stratified by age group.

To validate our model, we split the cohort into two parts according to the period of treatment. The first, comprising cycles performed between 2006 and 2007, was used to derive the model, while data generated from 2008 onwards were used to validate it. Finally, we constructed a nomogram to calculate the probability of a live birth based on the number of eggs and age.

Table I Characteristics of the cohort (n = 400 135).

Characteristic	n (%)
Age (given categories)	
18–34 years	200 982 (50.2)
35–37 years	97 345 (24.3)
38–39 years	51 385 (12.8)
40 years and over	50 423 (12.6)
Number of previous IVF cycles	
0	230 924 (58.8)
1	87 471 (22.3)
2	40 994 (10.4)
3 or more	33 157 (8.5)
Previous LB (yes)	18 633 (4.7)
Cause of infertility[a]	
Male factor	221 047 (56.3)
Tubal disease	117 722 (30.3)
Ovulatory disorder	46 071 (11.9)
Endometriosis	29 804 (7.5)
Unexplained	131 652 (33.7)
Treatment type	
IVF	247 640 (61.9)
ICSI	151 788 (37.9)
Unknown	707 (0.2)
Eggs retrieved (Fig. 2a)	
Median (IQR)	9 (6–13)
Embryos created (Fig. 2b)	
Median (IQR)	5 (3–8)
Treatment cycles in each period	
1991–1995	72 682 (18.2)
1996–2000	117 050 (29.3)
2001–2005	129 402 (32.3)
2006 onwards	81 001 (20.2)

[a]The causes of infertility are not mutually exclusive.

Results

The data selection process with the numbers of cycles excluded (with reasons for exclusion) is provided in Fig. 1. Of an initial total of 787 030 cycles, 400 135 were eligible for analysis. Characteristics of the analysis cohort are given in Table I. Half of all cycles were conducted on women between 18 and 34 years of age, while 12.6% were in women 40 years or over. The major cause of infertility was male factor (56.3%), and conventional IVF was used in the majority (61.9%) of cycles.

The median number of eggs retrieved was 9 [inter-quartile range (IQR) 6–13; Fig. 2a] and the median number of embryos created was 5 (IQR 3–8; Fig. 2b). The overall LBR in the entire cohort was 21.3% [95% confidence interval (CI): 21.2–21.4%], with a gradual rise over the four time periods in this study (14.9% in 1991–1995, 19.8% in 1996–2000, 23.2% in 2001–2005 and 25.6% in 2006–2008).

Association between the number of eggs and live birth

There was a strong association between the number of eggs and the LBR (Fig. 3a) which rose with increasing number of eggs up to ~15, plateaued between 15 and 20 eggs and steadily declined beyond 20 eggs. The same pattern was observed in all four of the time periods. For a given number of eggs, LBRs increased over time (Fig. 3b) but decreased with increasing age (Fig. 3c).

Predicting live birth

To ensure that the predicted LBR was relevant to current practice, the predictive model was derived from observations generated from data on treatments from 2006 to 2007. The data from 2008 were used for model validation. The final model, which includes non-linear terms for the number of eggs and age as an indicator variables, closely fits with observed data (Fig. 4). The functional form of the model with coefficients and their robust standard errors is provided in Appendix (Supplementary data). The model was well calibrated (Hosmer–Lemeshow $\chi^2 = 3.92$, df = 8, $P = 0.86$) and the c-index was 0.65.

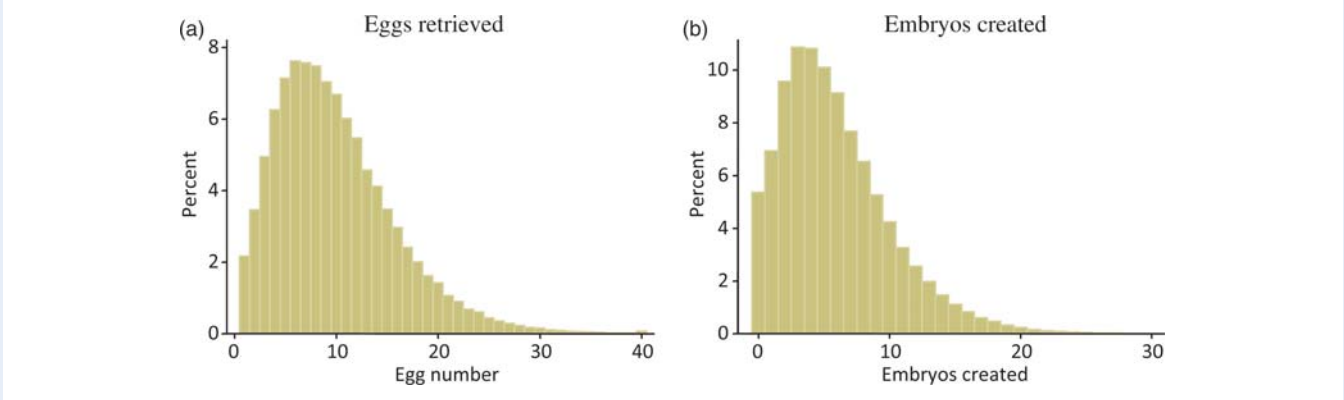

Figure 2 Number of eggs retrieved and embryos created.

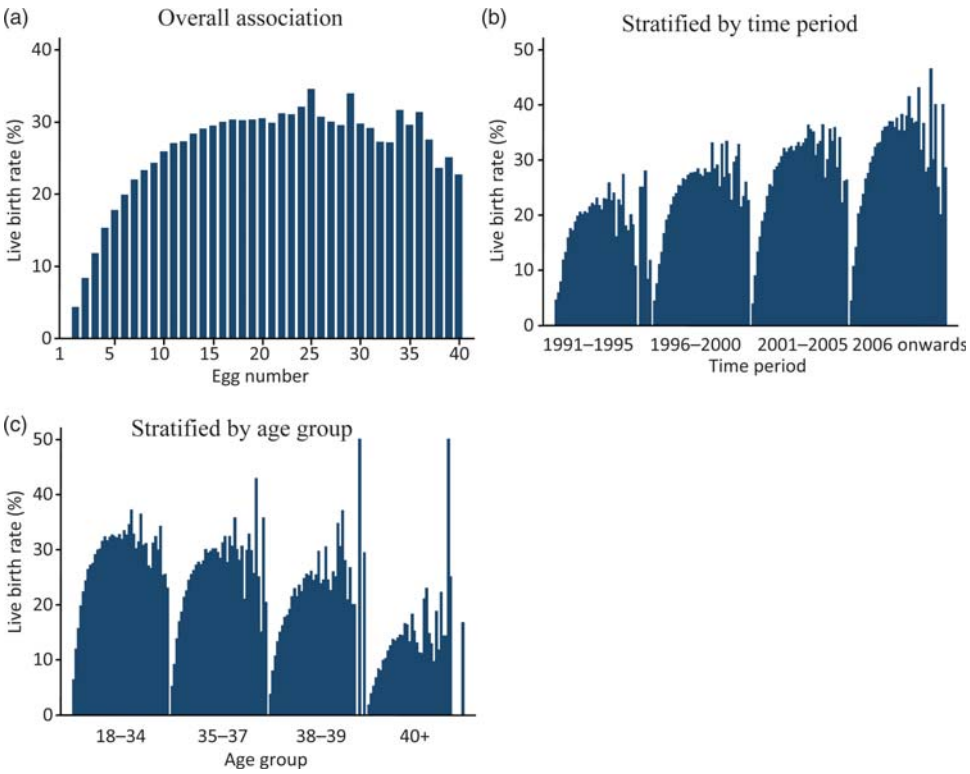

Figure 3 Association between egg number and live birth rate.

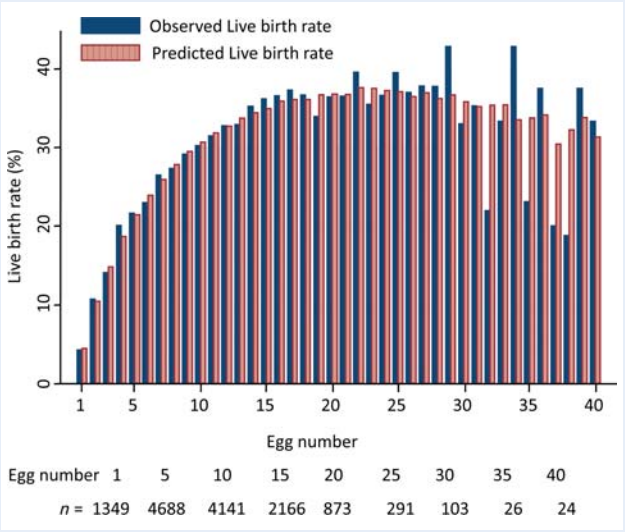

Figure 4 Observed versus predicted live birth rate in data from 2006 to 2007.

The predicted probability of live birth for a given number of eggs and age group is provided in Table II. This information is summarized in the nomogram (Fig. 5), which provides a graphic depiction for easy interpretation of the results.

Validation was performed on 17 366 IVF cycles and 4863 live births. Predictive ability of the model does not differ between the derivation and validation cohorts. Although the Hosmer–Lemeshow $\chi^2 = 16.3$ (df = 8, $P = 0.04$) is statistically significant due to the large sample size, the differences between predicted and observed live birth probabilities are clinically unimportant (Fig. 6). The c-index was 0.66 for the temporal validation cohort.

Discussion

Our results show a strong relationship between the number of eggs and the LBR in a fresh IVF cycle. The best chance of live birth was associated with the number of eggs of around 15 and showed a decline with >20 eggs. LBRs were seen to decline with advancing maternal age although a global increase over time was noted across all age groups.

We used the largest available clinical IVF database to assess the association between the number of eggs and live birth in a fresh IVF cycle. Although the clinical heterogeneity within the data set may be considered a drawback, such differences increase the generalizability of our findings. The model has been derived using more recent data (2006–2007) which closely represent current practice and validated using the most recent subset of IVF cycles within the cohort (2008) constituting a temporal external validation as current recommendations advocate.

Although the size of the database was large, we encountered problems with missing data and loss to follow-up; such data were excluded from the analysis. Data involving cycles where all embryos were frozen for reasons such as risk of ovarian hyperstimulation

Table II Predicted probabilities for live birth.

	18–34 years				35–37 years				38–39 years				40 years and over			
Eggs	*n*	Observed live birth (%)	Predicted live birth (%)	95%CI predicted (%)	*n*	Observed live birth (%)	Predicted live birth (%)	95%CI predicted (%)	*n*	Observed live birth (%)	Predicted live birth (%)	95%CI predicted (%)	*n*	Observed live birth (%)	Predicted live birth (%)	95%CI predicted (%)
1	253	8	7	7, 8	275	7	6	6, 7	280	5	4	4, 5	541	1	2	2, 3
2	540	17	16	15, 17	579	14	14	13, 14	509	9	9	9, 10	774	5	5	5, 5
3	819	21	22	21, 22	840	18	19	18, 19	718	12	13	13, 14	1002	6	7	7, 8
4	1221	29	26	25, 26	1091	22	22	22, 23	817	17	16	15, 17	1025	9	9	8, 9
5	1486	29	29	28, 29	1245	24	25	24, 26	899	18	18	17, 19	1058	11	10	10, 11
6	1684	30	31	30, 31	1298	27	27	26, 28	854	18	20	19, 21	980	9	11	11, 12
7	1809	35	33	32, 33	1321	29	29	28, 30	846	21	21	20, 22	901	11	12	11, 13
8	1904	34	34	34, 35	1278	29	30	30, 31	729	23	22	22, 23	771	11	13	12, 14
9	1898	35	36	35, 36	1207	31	31	31, 32	672	23	23	23, 24	627	15	14	13, 14
10	1805	36	37	36, 37	1168	31	33	32, 33	630	25	24	23, 25	538	14	14	13, 15
11	1795	36	38	37, 38	1035	34	33	33, 34	549	23	25	24, 26	466	17	15	14, 15
12	1639	38	38	38, 39	872	34	34	33, 35	474	26	26	25, 27	401	15	15	14, 16
13	1484	38	39	38, 40	703	34	35	34, 36	411	26	26	25, 27	298	16	15	15, 16
14	1291	40	40	39, 40	675	37	35	34, 36	329	26	27	26, 28	252	16	16	15, 17
15	1155	40	40	39, 41	526	41	36	35, 37	256	26	27	26, 28	229	17	16	15, 17
20	487	41	41	41, 42	219	36	37	36, 38	93	29	28	27, 29	74	18	17	16, 18
25	172	42	41	40, 43	63	43	37	36, 38	37	30	28	27, 30	19	26	17	16, 18
30	67	31	40	38, 42	20	50	36	33, 38	4	0	27	25, 29	12	25	16	14, 18
35	14	29	37	33, 41	7	29	33	29, 37	5	0	25	22, 28	0	–	15	13, 17
40	15	27	33	28, 40	7	43	30	24, 35	2	50	22	18, 27	0	–	13	11, 16

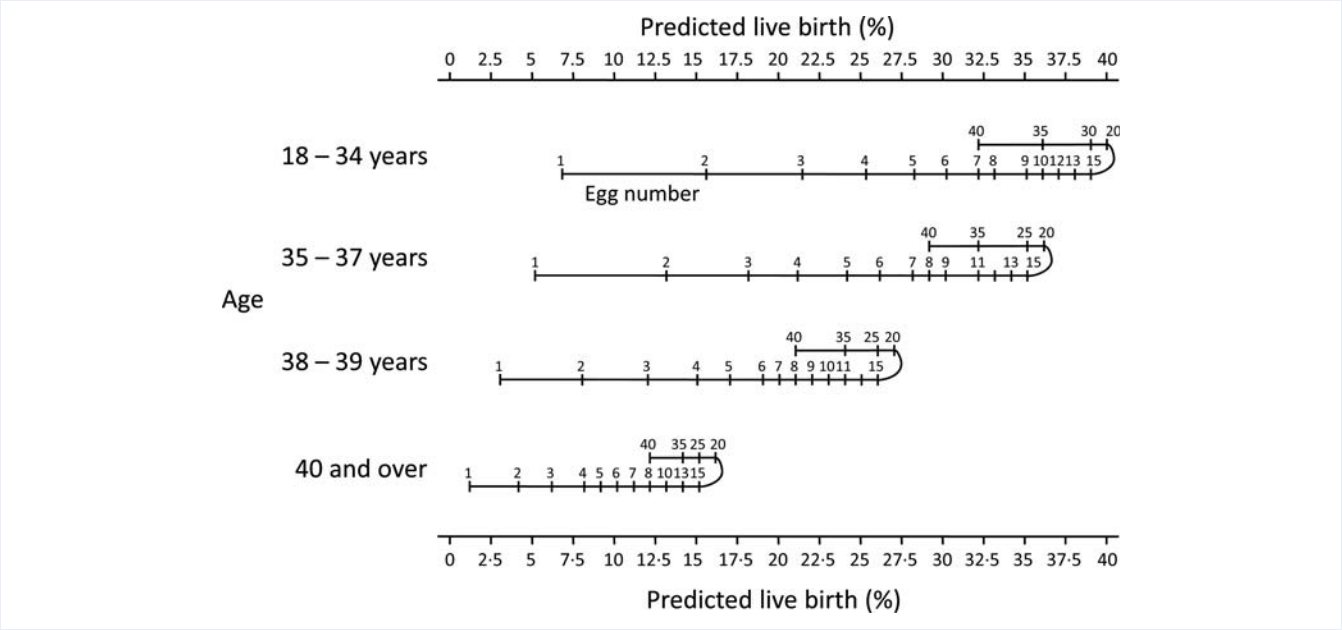

Figure 5 Nomogram to calculate predicted live birth probability given egg number and age.

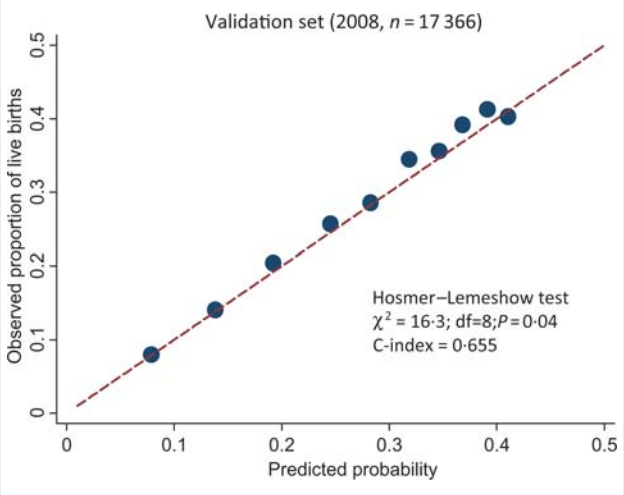

Figure 6 Calibration plot of the validation model. Circles indicate the observed proportion of live births per tenth of predicted probability. The dashed line represents perfect calibration.

syndrome (OHSS) also could not be analysed. Also, our study only analysed the outcome of fresh IVF cycles, and did not take into account the impact of frozen–thawed cycles on the cumulative LBR (due to data currently not being available as the current HFEA data set does not allow linkage of fresh and frozen cycles in the same woman). It is possible that the declining effect of higher number of eggs on the outcome of a fresh IVF cycle becomes attenuated by the increasing likelihood of a pregnancy in a subsequent frozen–thawed transfer cycle. The existing format of the anonymized data set precluded detailed exploration of age-related outcomes other than comparison of the existing age categories. This has certain drawbacks; for example, over half of all women were in the same age group (18–34 years). At the other end of the spectrum, all women over 40 years were treated as a homogeneous group although outcomes in older women change significantly with small increases in age, with LBRs of 11.9% in women aged 40–42 years falling to 3.4% in women aged 43–44 years (http://www.hfea.gov.uk/ivf-figures, HFEA authority). No information regarding type of stimulation or gonadotrophins used in IVF treatment was collected by the HFEA, and these data were therefore unavailable for analysis.

Previous studies looking at the relationship between the number of eggs and pregnancy rates have reported inconsistent results in showing that pregnancy rates increased with an increasing number of eggs (Meniru and Craft, 1997), best pregnancy rates being obtained with number of eggs of 10–15 (Kably Ambe *et al.*, 2008), or 7–16 (Molina Hita Ma. del M *et al.*, 2008). Furthermore, these studies involved small numbers and were reported from single centres, which limited their generalizability. Our study is the first to provide vital information on predicting the LBR on the basis of eggs retrieved in women of different age groups. The simplicity of the nomogram facilitates interpretation of this information by clinicians as well as couples seeking IVF treatment.

Knowledge of factors predicting IVF success is critical to patients and service providers in informing decisions to embark on IVF treatment and the choice of ovarian stimulation regimens. Such information is also helpful in counselling couples about deciding against further IVF treatment or plans to opt for donor eggs. To date, most clinical decisions on ovarian stimulation in IVF have been based on ovarian reserve tests which are good at predicting numbers of eggs retrieved but poor in terms of predicting live birth (Broekmans *et al.*, 2006; Broer *et al.*, 2009). By allowing clinicians to link the (predicted) number of eggs to live birth, the nomogram generated by this study is likely to facilitate use of these tests to optimize outcomes in IVF while preventing complications relating to production of an excessive number of eggs.

Our data suggest that around 15 eggs may be the optimal number to aim for in a fresh IVF cycle in order to maximize treatment success while minimizing the risk of OHSS which is associated with high number of eggs of >18 (Lyons *et al*., 1994; Verwoerd *et al*., 2008; Lee *et al*., 2010). The decline in the LBR observed with higher number of eggs could be due to the deleterious effect of the raised serum estradiol levels affecting embryo implantation (Valbuena *et al*., 2001; Mitwally *et al*., 2006; Joo *et al*., 2010). Even in cases where the aim is to freeze surplus embryos for future use, existing data suggest that the numbers of embryos frozen after a fresh IVF cycle are not enhanced by retrieving >18 eggs (Hamoda *et al*., 2010). On the other hand, there has been a recent trend towards mild ovarian stimulation in IVF with the emphasis on recovering fewer eggs than previously deemed optimal (Fauser *et al*., 2010). Our findings support the use of moderate stimulation protocols over either mild or aggressive stimulation protocols in IVF treatment.

The nomogram that we have established is the first of its kind that allows prediction of live birth for a given number of eggs and female age group. This is potentially valuable for patients and clinicians in planning IVF treatment protocols and counselling regarding the prognosis for a live birth occurrence, especially in women with either predicted or a previous poor ovarian response.

The relationship observed between the number of retrieved eggs and live birth in a fresh IVF cycle, across all female age groups, suggests that number of eggs is a reasonable surrogate outcome to use in IVF practice and research. Future research should focus on establishing the relationship between retrieved eggs and the cumulative LBR per IVF cycle by including the outcome following replacement of all frozen embryos generated from a single fresh IVF treatment.

Authors' roles

S.K.S. undertook the task of verifying and validating the HFEA data and contributed to writing the manuscript. V.R. undertook the task of verifying and validating the HFEA data. N.R.-F. contributed to writing the manuscript. S.B. contributed to writing the manuscript and appraised it critically for important intellectual content. J.Z. undertook the analysis of the data and contributed to writing the manuscript. A.C. conceived the idea and contributed to writing the manuscript.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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