Supplementary material for:

Population implications of cessation of IVF

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Data

Our analyses our based on our paper on "Live-birth rate associated with repeat in vitro fertilisation treatment cycles";[1] details on ethical approval, source of data, eligibility criteria and definitions are given in the published paper. For the purposes of developing the model we also included cycles from women who had already had an IVF live-birth and excluded oocyte retrievals occurring before a live-birth from an embryo replacement from an earlier retrieval. This resulted in a cohort of 158,197 women undergoing 271,438 ovarian stimulation cycles for IVF in the UK between January 1, 2003 and December 31, 2010, with follow-up until June 30, 2012.

Couple and treatment characteristics

The covariates included in the model were selected on the basis of previous publications showing that they were related to within-cycle live-birth rate,[2,3] and that they would be available before a treatment cycle, i.e. available at the time when most treatment decisions are typically made. These were: woman's age (in years), number of previous cycles of IVF, duration of infertility (in years attempting to have a live birth), previous IVF pregnancy or live birth, and cause of infertility (tubal, ovulatory, endometriosis, or male cause). The treatment characteristics were oocyte source (autologous or donor), sperm source (woman's partner or donor), and whether ICSI was performed.

Statistical model selection

Our estimates of the effect of age on within-cycle live-birth rate are derived from a prediction model for the number of cycles of IVF required before a live birth. This model was developed during the course of our research for our paper on "Live-birth rate associated with

repeat in vitro fertilisation treatment cycles",[1] but detail of this model did not appear in the published version.

We fitted logistic regression models for the effect of couple and treatment characteristics on within-cycle live-birth rate in UK (HFEA) data. We included a different intercept for each number of previous IVF cycles. This adjusts the model for the number of previous IVF cycles. It further has the advantage that it allowed us to model the number of IVF cycles required before a live birth, although this was only relevant to the published paper and not the current analysis.

We initially examined the univariable association of each covariate with within-cycle live-birth rate. Age and duration of infertility were considered as ordinal variables in the existing literature,[2-6] but both variables were measured continuously (in whole numbers of years) in the UK (HFEA) database. A nonlinear relationship between age, duration of infertility and live-birth rate has previously been shown.[3,6] Hence the shapes of the associations between delivery rate and age and duration of infertility were modelled with linear splines. A stepwise procedure was used to select knots from a list that included a knot at every different year. As there was of a differing association between age and live-birth rate for autologous and donor oocytes,[3,4] we included an interaction between age and oocyte source and allowed the stepwise procedure to choose potentially different knots for autologous and donor oocytes. Duration of infertility was missing in 3% of cycles. We overcame this by including an indicator for missingness as well as the spline model for the association between duration of infertility and delivery rate.

After selecting the shape of the associations of age and duration of infertility, we examined multivariable associations of all covariates with within-cycle live-birth rate. We then ran a backward stepwise procedure to remove non-significant associations with age, duration of infertility, and patient history. We explored the possibility of interactions between age and oocyte source, age and duration of infertility, sperm source and oocyte source, and sperm source, male cause and ICSI by including interactions terms in the regression. These interactions were explored because of their biological plausibility and evidence from previous publications of their existence in relation to live-birth rate.[3] All possible interactions between the age and duration of infertility splines included in the multivariable model were considered by a stepwise procedure. Finally, we ran a backward stepwise procedure to remove spurious interactions from the model. We included 3-way interactions whenever the final model selection contained all 3 relevant 2-way interactions. The stepwise regression procedures were based on the likelihood ratio test, and used p-value thresholds that were calculated, according to Bonferroni correction and the closed testing procedure,[7] to give a family-wise type I error of 5%.

Model details

We developed our model using the UK (HFEA) data for 271,438 ovarian stimulation cycles undertaken between January 1, 2003 and December 31, 2010 with follow-up to June 30, 2012. For autologous oocytes, the stepwise procedure selected a linear spline with knots (changes in gradient) at 26, 33, 36 and 40 years. For donor oocytes, there was no association between woman's age and delivery rate. For duration of infertility, the stepwise procedure selected a linear spline with a knot at 4 years. The interactions selected were between oocyte source and sperm source, and a 3-way interaction between sperm source, male cause of

infertility and ICSI. Multivariable associations in the model with interaction terms are shown in Table S1.

Since these data are from UK cycles initiated between 2003 and 2010 our model required recalibration for the US analysis of the effect of stopping IVF treatment. This is because overall IVF live-birth rates are likely to differ between the UK and US, and live-birth rates in both countries have increased since the data in our models were collected. Recalibration was based on the Centers for Disease Control and Prevention. 2017 Assisted Reproductive Technology Fertility Clinic Success Rates Report using 2017 as the most recent year for which complete data is available[8]. Age is grouped in the CDC data, so we identified a nominal age within each group to use for recalibration of the model. These nominal ages are shown in Table S2. We recalibrated the model by adding a constant to the model intercept, calculated such that the overall within-cycle live-birth rate (for all ages) predicted by the recalibrated model would be equal to the overall observed within-cycle live-birth rate. Table S2 shows that the recalibrated model underestimated the within-cycle live-birth rate for women aged less than 35 years and overestimated for all other age groups. However, a calibration regression showed no evidence of unacceptable calibration of the model (regression slope 1.125, [95% CI 0.782 to 1.467]). We estimated that the effect of miscalibration of this magnitude could change our estimated reduced number of live births by at most 31, 91 and 180 live births respectively for a one-month, three-month and six-month shutdown respectively, a maximum relative difference of 8%.

Assumptions of our analyses

The recalibration of our model makes several assumptions. We have used nominal ages (in the original model where age was measured as a number of years) to calibrate against age

groups (in the CDC data). This assumes an even distribution of ages within the age groups. This seems a reasonable approximation when age groups span only 2-3 years. We varied the nominal ages for the larger age groups, but the calibration did not appear to be sensitive to this choice (data not shown). We assumed that the decline in within-cycle live-birth rate with age is similar in both populations. When recalibrating our model, we did not detect any difference between the US in 2017 and the UK in 2003 to 2010 with follow-up to June 30, 2012. However, further validation of the model is required before it could be used to inform clinical practice or individual prognosis in either population. The original model is adjusted for other patient and treatment characteristics measured in the UK between 2003 and 2010. These are likely to differ in the US in 2017. However, our estimated reduction in within-cycle live-birth rates was calculated based on age alone, not these other patient and treatment characteristics. Although it is possible that the effect of age may depend on these other patient and treatment characteristics, this was not found in the development of our model as the odds ratios highlighted in Table S1 differed by less than 1% from those found in univariate analysis (data not shown).

Our estimation of the reduction in within-cycle live-birth rate associated with shutdown of IVF treatment also makes certain assumptions. In assessing one-month, three-month and six-month shutdowns, we have assumed that the shutdown lasts the same length of time across all clinics. It is likely that restrictions due to COVID-19 will start and stop at different times in different locations. Our calculations do not take into account the possibility of patients moving their treatment to clinics (potentially in other countries) not affected by the shutdown, but this seems unlikely due to travel restrictions. We have also assumed that the shutdown applies to all patients regardless of their age; if treatment is restricted to some age groups but not others, this will alter the estimated reduction in live births in the cohort. Finally, we have

assumed that the number and age-distribution of IVF cycles is comparable in 2020 and 2017. It is likely that the number of IVF patients has increased between 2017 and 2020 (at least prior to the outbreak of COVID-19) so we have potentially underestimated the reduction in number of live births due to shutdown.

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Competing interests

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References

1. Smith AD, Tilling K, Nelson SM, Lawlor DA. Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles. *JAMA.* 2015;314(24):2654-2662.
2. 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.
3. 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 Medicine 2011; 8:e1000386.
4. 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.
5. Malizia BA, Hacker MR, Pernzias AS. Cumulative live-birth rates after in vitro fertilization. N Engl J Med 2009; 360:236-43.
6. Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 1996; 348:1402-6.
7. Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. Biometrika 1976; 63:655-60.
8. Centers for Disease Control and Prevention. 2017 Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta (GA). US Dept of Health and Human Services; 2019.

Table S1

Associations between couple and treatment characteristics and per-cycle delivery rate from a model based on 271,438 IVF cycles undertaken by 158,197 women. Model adjusted for cycle number.

	Odds ratio (95% CI)	
Age and oocyte source		
Autologous oocytes, age 18	**1**	
Autologous oocytes, slope 18-26	**1.081 (1.057, 1.104)**	
Autologous oocytes, slope 26-33	**0.990 (0.984, 0.996)**	
Autologous oocytes, slope 33-36	**0.925 (0.916, 0.935)**	
Autologous oocytes, slope 36-40	**0.825 (0.817, 0.833)**	
Autologous oocytes, slope 40-53	**0.664 (0.648, 0.680)**	
Donor oocytes, age 21-55	**1.865 (1.576, 2.206)**	
Duration of infertility (with observed data)		
Missing	1	
Slope up to 4 years	0.945 (0.936, 0.953)	
4 years	0.963 (0.916, 1.012)	
Slope after 4 years	0.977 (0.974, 0.981)	
IVF history		
No previous IVF pregnancy	1	
Previous IVF pregnancy	1.584 (1.533, 1.636)	
Female causes of infertility (non-exclusive)		
Tubal	0.910 (0.889, 0.932)	
Ovulatory	1.032 (1.006, 1.060)	
Endometriosis	0.953 (0.919, 0.988)	
No cause above identified	1	
	No male cause of infertility identified	Male cause of infertility
Partner sperm, IVF only	1	0.647 (0.623, 0.673)
Partner sperm, IVF and ICSI	1.103 (1.074, 1.133)	1.137 (1.113, 1.161)
Donor sperm, IVF only	1.265 (1.145, 1.397)	1.583 (1.466, 1.710)
Donor sperm, IVF and ICSI	1.390 (1.247, 1.548)	1.610 (1.447, 1.791)
Donor oocytes and sperm	0.620 (0.508, 0.757)	

The section of the table in boldface was used to model the effects of age on within-cycle live-birth rate.

Table S2

Comparison of within-cycle live-birth rates in observed data (135,673 IVF cycles undertaken in the US in 2017) and estimated by a recalibrated model (originally based on 271,438 IVF cycles undertaken in the UK between 2003 and 2010).

Observed data						
Age group (years)	< 35	35-37	38-40	41-42	>42	All ages
Within-cycle live-birth rate	51.6%	37.5%	23.5%	11.8%	3.4%	34.4%
(95% CI)	(51.2, 52.0)	(36.9, 38.1)	(23.0, 24.0)	(11.3, 12.3)	(3.1, 3.7)	(34.1, 34.7)
Estimation based on recalibrated model						
Nominal age (years)	33	36	39	41.5	44	
Within-cycle live-birth rate	46.3%	40.6%	27.7%	14.6%	5.8%	34.4%
(95% CI)	(45.7, 46.9)	(39.9, 41.2)	(27.2, 28.2)	(14.2, 15.1)	(5.4, 6.3)	(34.0, 34.8)
Number of cycles (2017)	52,428	28,996	28,287	14,358	11,604	135,673

Supplemental Figure 1

Association between age, oocyte source, and cumulative live-birth rate, from a model based on 271,438 IVF cycles undertaken by 158,197 women in the UK between 2003 and 2010 with follow-up to June 2012. Baseline levels are recalibrated based on 135,673 IVF cycles undertaken in the US in 2017.