Original Investigation

Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles

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IMPORTANCE The likelihood of achieving a live birth with repeat in vitro fertilization (IVF) is unclear, yet treatment is commonly limited to 3 or 4 embryo transfers.

OBJECTIVE To determine the live-birth rate per initiated ovarian stimulation IVF cycle and with repeated cycles.

DESIGN, SETTING, AND PARTICIPANTS Prospective study of 156 947 UK women who received 257 398 IVF ovarian stimulation cycles between 2003 and 2010 and were followed up until June 2012.

EXPOSURES In vitro fertilization, with a cycle defined as an episode of ovarian stimulation and all subsequent separate fresh and frozen embryo transfers.

MAIN OUTCOMES AND MEASURES Live-birth rate per IVF cycle and the cumulative live-birth rates across all cycles in all women and by age and treatment type. Optimal, prognosis-adjusted, and conservative cumulative live-birth rates were estimated, reflecting 0%, 30%, and 100%, respectively, of women who discontinued due to poor prognosis and having a live-birth rate of 0 had they continued.

RESULTS Among the 156 947 women, the median age at start of treatment was 35 years (interquartile range, 32-38; range, 18-55), and the median duration of infertility for all 257 398 cycles was 4 years (interquartile range, 2-6; range, <1-29). In all women, the live-birth rate for the first cycle was 29.5% (95% CI, 29.3%-29.7%). This remained above 20% up to and including the fourth cycle. The cumulative prognosis-adjusted live-birth rate across all cycles continued to increase up to the ninth cycle, with 65.3% (95% CI, 64.8%-65.8%) of women achieving a live birth by the sixth cycle. In women younger than 40 years using their own oocytes, the live-birth rate for the first cycle was 32.3% (95% CI, 32.0%-32.5%) and remained above 20% up to and including the fourth cycle. Six cycles achieved a cumulative prognosis-adjusted live-birth rate of 68.4% (95% CI, 67.8%-68.9%). For women aged 40 to 42 years, the live-birth rate for the first cycle was 12.3% (95% CI, 11.8%-12.8%), with 6 cycles achieving a cumulative prognosis-adjusted live-birth rate of 31.5% (95% CI, 29.7%-33.3%). For women older than 42 years, all rates within each cycle were less than 4%. No age differential was observed among women using donor oocytes. Rates were lower for women with untreated male partner–related infertility compared with those with any other cause, but treatment with either intracytoplasmic sperm injection or sperm donation removed this difference.

CONCLUSIONS AND RELEVANCE Among women in the United Kingdom undergoing IVF, the cumulative prognosis-adjusted live-birth rate after 6 cycles was 65.3%, with variations by age and treatment type. These findings support the efficacy of extending the number of IVF cycles beyond 3 or 4.

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In vitro fertilization (IVF) is commonly stopped after 3 or 4 unsuccessful embryo transfers,[1,2] with 3 unsuccessful transfers labeled "repeat implantation failure."[3] This practice has been influenced by a study of 1328 embryo transfers undertaken 20 years ago, without use of intracytoplasmic sperm injection (ICSI), which reported a decline in live-birth rates after the fourth cycle.[4] With 1 exception,[5] previous studies of cumulative pregnancy or live-birth rates have been relatively small, with limited ability to precisely estimate cumulative success beyond 4 transfers.[4,6-9] Previous studies have defined a cycle of IVF as an embryo transfer.[5-9] Thus, each initiation of IVF with ovarian stimulation has been treated as several separate cycles whenever there has been a series of repeated embryo transfers. Because both the promotion of single embryo transfer and the effectiveness of freezing embryos have increased markedly over the last 10 to 15 years,[10-15] it has been suggested that IVF success should be calculated as the live-birth rate per initiated ovarian stimulation, including all subsequent separate fresh and frozen embryo transfers.[5,10-13]

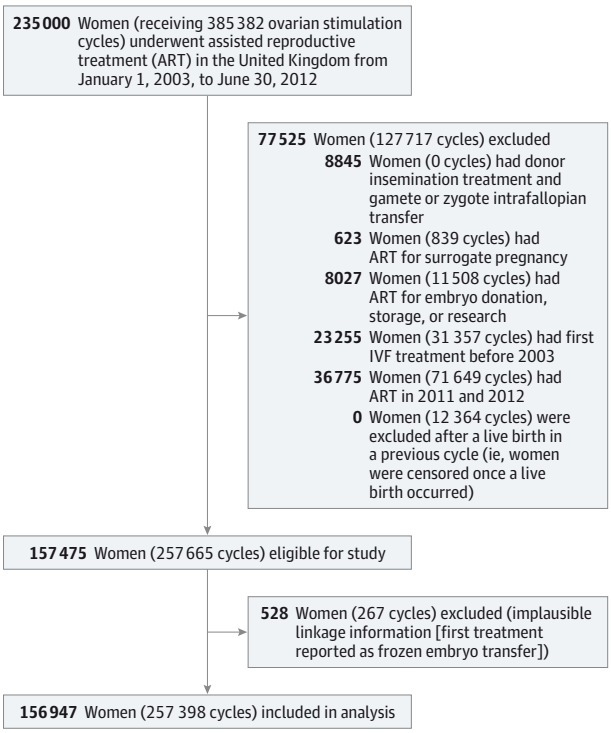
The aim of this study was to determine the extent to which repeat IVF cycles continue to increase the likelihood of a live birth, defining an IVF cycle as the initiation of treatment with ovarian stimulation and all resulting separate fresh or frozen embryo transfers; hereafter, we use the term *cycle* for this. Specific objectives were to determine (1) the live-birth rate within each cycle and the cumulative rate across all cycles, (2) how these varied by age and treatment type (use of donor oocyte, ICSI, or sperm donation), and (3) the association between oocyte yield in 1 cycle and live-birth rate in subsequent cycles.

Methods

Ethical approval for this study was provided by the UK Human Fertilisation and Embryology Authority (HFEA), which has statutory obligations to prospectively collect information on all assisted reproductive treatment (ART) in the United Kingdom. Women provided written consent for this information to be used in analyses, audits, and publications. The HFEA provided us with data on all ART events occurring in the United Kingdom between January 1, 2003, and June 30, 2012, with linkage of cycles to individual women and data on birth outcomes (**Figure 1**). Because all UK clinics, whether private or public, must provide information on any patients treated with ART, together with the outcomes of that treatment, to the HFEA, they are able to link cycles to individual women for all UK ART. We chose the 2003 start date to obtain a large cohort representative of contemporary treatment, and June 2012 was the latest date for which the HFEA could provide validated data. Because the live-birth outcome data were incomplete for cycles commencing between January 2011 and June 2012 (as many of these cycles were still continuing and births from them could occur after June 2012), we limited our potentially eligible cohort to ovarian stimulation cycles initiated between January 1, 2003, and December 31, 2010, with live-birth outcome data collected up to June 2012.

We excluded ART that was not IVF or was undertaken for the purpose of storage, donation, or surrogacy. We excluded women who had started IVF before 2003. As in other studies,[5-9] once a live birth occurred, women were censored from further analysis. To reflect clinical practice and allow comparisons with other studies,[4,5,7,9] we included all embryo transfers, whether the individual transfer was of 1 or more embryos.

Figure 1. Definition of Eligible and Analysis Cohort



IVF indicates in vitro fertilization.

Live birth was defined as an infant born alive after 24 weeks' gestation who survived longer than 1 month. The World Health Organization defines live birth as a birth showing any sign of life irrespective of gestational age. As in other studies,[5,15,16] we modified this definition to capture births that were likely to be viable. We defined an IVF cycle as the initiation of ovarian stimulation and all resulting separate fresh or frozen embryo transfers. The live-birth rate within a cycle was defined as the probability of a live birth from an ovarian stimulation encompassing all subsequent fresh and frozen embryo transfers from that stimulation. Thus, for those embarking on IVF, the live-birth rate within 1 cycle answers the question, "What is my chance of a live birth with 1 stimulation and retrieval of oocytes followed by as many subsequent separate embryo transfers as possible from that retrieval?" The cumulative live-birth rate at a given cycle was defined as the probability of a live birth from all cycles up to and including that cycle. This answers the question, "What is my total chance of a live birth with repeat ovarian stimulation and oocyte retrievals, together with the subsequent embryo transfers from each cycle, up to a given cycle number?"

Information on age, types of treatment (oocyte donation, sperm donation, and ICSI), oocyte yield, and other couple characteristics were obtained from the HFEA data set.

Statistical Methods

We calculated the live-birth rates within the first and subsequent cycles up to the ninth as the proportion of cycles resulting in a live birth, using a normal approximation to construct confidence intervals. We calculated estimates of cumulative live-birth rates up to the ninth cycle using the Kaplan-Meier method with Greenwood's approximation to calculate confidence intervals (eMethods in the Supplement).[17,18] We calculated 3 different estimates using different assumptions for women who discontinued IVF without a live birth (see below). We used a log-rank test[19] to compare the live-birth rate within each cycle and cumulatively across all cycles. The first set of comparisons was between woman's age and oocyte source category, and the second was between no male cause of infertility and male cause of infertility with and without treatment by ICSI or sperm donation. We assessed the relationship of oocyte yield in 1 cycle to live-birth rates in subsequent cycles in women younger than 40 years using their own oocytes, by calculating the within-cycle live-birth rates in the first, second, and third cycles by oocytes retrieved in the first cycle, and also calculating the within-cycle live-birth rates up to the fifth cycle by oocytes retrieved in the immediately preceding cycle.

Dealing With Discontinuation of IVF

Infertile couples discontinue IVF for a number of reasons, with a systematic review of patient perceptions concluding that the most common reasons were the physical or psychological burden of treatment, relationship problems, and personal problems.[20] In any study estimating cumulative live-birth rates, assumptions must be made about what the rate in those who discontinue would have been had they continued. To account for this, we calculated "optimal" and "conservative" estimates, which have been assessed in previous studies. In addition, we calculated a prognostic-adjusted estimate. The optimal estimate is based on the observed data, and while not always explicit in previous publications, this assumes that the cumulative live-birth rate in women who discontinue IVF without a live birth if they had continued would be equal to the rate in those who continue to have further cycles.[5] The conservative estimate assumes those who discontinue IVF would have had a subsequent live-birth rate of 0.[5] The true rate is thought to lie between these two.[7] The prognostic-adjusted estimate aims to obtain this more realistic value. It assumes that a fixed proportion of those who discontinue do so because of poor prognosis and that the live-birth rate in that proportion would have been 0, whereas for those who discontinue for other reasons, such as inability to pay, emotional distress, or (in our data set) emigration from the United Kingdom, it would have been similar to those who continue with treatment.

For the prognosis-adjusted estimate, we considered the woman's age at her first cycle and oocyte yield in the previous cycle to be the strongest prognostic factors, because these have been shown to be strongly related to live-birth success.[5,7,9,21,22] We checked that these were indicators of live birth and of discontinuation of treatment in our own data and compared other available characteristics between those who discontinued and continued treatment after 1 unsuccessful cycle. To obtain age-adjusted and oocyte yield-adjusted estimates, we calculated results for each age strata (18-34, 35-37, 38-39, 40-42, 43-44, 45-50, and ≥50 years) and for each possible oocyte yield in the previous cycle and then obtained an average, weighted by the numbers within each category in the first cycle. It was not possible to calculate age-adjusted estimates for the age-stratified analyses because there was too little age variation within the age strata. For any analyses that included women using donor oocytes, it was not possible to calculate rates adjusted for oocyte yield in the previous cycle as women using donor oocytes will not have an oocyte yield.

The age and previous oocyte yield–adjusted results suggested that 3% of those who discontinued IVF did so because of poor prognosis. However, to calculate a prognostic-adjusted cumulative live-birth rate, we assumed 30% of those who discontinued did so because of poor prognosis. We chose a value of 10× that suggested by our data to obtain a conservative prognostic-adjusted estimate. (Full details of how these estimates were calculated are provided in the eMethods in the Supplement.)

Because the average population live-birth success rate for a single embryo transfer is between 20% and 30% in high-income countries,[10-13] we considered 20% to be a benchmark for a good live-birth rate within a cycle. All analyses were undertaken in Stata version 13 MP2. Two-sided *P* values <.05 were considered to provide evidence against the null hypothesis.

Comparison With Live-Birth Rates for Those Not Receiving ART

We used data on pregnancy and pregnancy loss rates from published literature to estimate live-birth rates for women who conceive naturally.[23-25] Two prospective cohort studies of couples actively trying to conceive provided age-specific pregnancy rates attained within 12 menstrual cycles.[23,24] Live-birth rates were calculated assuming 20% of natural conceptions result in a pregnancy loss.[25]

Results

Following planned exclusions, the eligible cohort included 257 665 cycles in 157 475 women. For all analyses, we excluded women with missing linkage information or implausible linkage (ie, first IVF transfer being a frozen embryo transfer without preceding ovarian stimulation). This resulted in an analysis cohort of 257 398 cycles by 156 947 women (more than 99% of the eligible cohort; Figure 1). **Table 1** shows the characteristics of the cohort. Among the 156 947 women, the median age at start of treatment was 35 years (interquartile range, 32-38; range, 18-55), and the median duration of infertility for all 257 398 cycles was 4 years (interquartile range, 2-6; range, <1-29). eTable 1 in the Supplement shows characteristics by year of treatment. Because of the large sample size, there was statistical evidence of differences in all characteristics, but for most these were small and unlikely to be clinically important. For

example, median age of the women differed by 1 year, and median oocyte retrieval differed by 1 across the study period. Use of ICSI increased by 11% and transfer of single embryos by 17%, although the live-birth rate increased by just 2% across the study period.

Table 2 shows the live-birth rate within each cycle for the whole cohort. In all women, the live-birth rate for the first cycle was 29.5% (95% CI, 29.3%-29.7%). The live-birth rate within cycles remained above 20% for each cycle up to and including the fourth. After their first cycle, there were 110 614 women (70.5% of the analysis cohort) who did not have a live birth. Of these, 37 704 (34.1%) discontinued treatment and 72 910 (65.9%) had at least 1 more cycle. eTable 2 in the Supplement compares characteristics between these 2 groups. Although there was statistical evidence of differences for all characteristics, the actual differences were small.

The cumulative live-birth rate continued to increase up to the ninth cycle, with a cumulative prognosis-adjusted live-birth rate of 65.3% (95% CI, 64.8%-65.8%) by the sixth cycle (Table 2). The equivalent optimal (78.0% [95% CI, 77.3%-78.8%]) and age-adjusted (76.7% [95% CI, 76.0%-77.5%]) estimates for 6 cycles were similar, while the conservative estimate was 46.8% (95% CI, 46.5%-47.0%) (Table 2 and eFigure 1 in the Supplement).

Results varied by age and oocyte source (**Figure 2**, **Table 3**, and eTables 3 and 4 in the Supplement). In women who were younger than 40 years and using their own oocytes (133 379 women, 85% of the cohort), the live-birth rate for the first cycle was 32.3% (95% CI, 32.0%-32.5%). This remained above 20% up to and including the fourth cycle. The previous cycle oocyte yield-adjusted and optimal estimates were similar. Six cycles achieved cumulative live-birth rates of 68.4% (95% CI, 67.8%-68.9%), 80.3% (95% CI, 79.5%-81.0%), and 50.7% (95% CI, 50.5%-51.0%), for the prognostic-adjusted, optimal, and conservative estimates, respectively. For women aged 40 to 42 years, the live-birth rate for the first cycle was 12.3% (95% CI, 11.8%-12.8%), with 6 cycles achieving cumulative live-birth rates of 31.5% (95% CI, 29.7%-33.3%), 41.5% (95% CI, 38.0%-44.9%), and 19.2% (95% CI, 18.5%-19.8%) for prognostic-adjusted, optimal, and conservative estimates, respectively. For women older than 42 years, all rates within each cycle were less than 4% or based on too few live births to calculate confidence intervals.

Use of donor oocytes removed this age differential, as the log-rank test showed no evidence for different cumulative live-birth rates between age categories (eTable 3 in the Supplement). Irrespective of age, women using donor oocytes achieved live-birth rates within each cycle of 29.6% or greater for all cycles up to and including the ninth and a cumulative live-birth rate after 6 cycles of 86.7% (95% CI, 85.2%-88.3%), 91.7% (95% CI, 90.3%-93.1%), and 75.5% (95% CI, 74.0%-77.1%) for the prognostic-adjusted, optimal, and conservative estimates, respectively (eTable 4 in the Supplement).

Live-birth rates varied by male-partner cause infertility and its treatment (**Figure 3** and eTables 5 to 7 in the Supplement). Women whose infertility was due to a male-related cause and who were not treated with either ICSI or donor sperm had lower live-birth rates than those with a nonmale cause of infertility (eTables 3 and 5). Women with a male-partner cause of infertility who were treated with ICSI had

Table 1. Characteristics of the Analysis Cohort of 156 947 Women Commencing IVF Treatment for Infertility in the United Kingdom in 2003-2010 (With Outcomes Assessed up to June 2012)

Characteristic	No. (%)	
	For All Cycles Combined[a]	For First Cycle[b]
No. of women	156 947	156 947
Total No. of cycles		
1	93 494 (59.6)	
2	39 707 (25.3)	
3	15 507 (9.9)	
>3	8239 (5.2)	
No. of cycles	257 398	156 947
Live births (% per cycle)	70 093 (27.2)	46 333 (29.5)
Woman's age, median (IQR), y	35 (32-38)	35 (32-38)
Duration of infertility, y		
Median (IQR)	4 (2-6)	3 (2-5)
Missing duration data	11 165 (4.3)	6586 (4.0)
Causes of infertility (nonexclusive)		
Tubal	46 535 (18.1)	28 181 (18.0)
Ovulatory	34 473 (13.4)	21 582 (13.8)
Endometriosis	15 889 (6.2)	9654 (6.1)
Male-partner cause	105 014 (40.8)	63 023 (40.2)
No cause above reported (indicated the cause is clinically uncertain)	82 112 (31.9)	50 664 (32.3)
Treatment		
ICSI	123 009 (47.8)	68 608 (43.7)
Sperm donation	8067 (3.1)	4781 (3.05)
Oocyte donation	7223 (2.8)	3587 (2.3)
Oocytes retrieved (own), median (IQR), No.	9 (5-13)	9 (5-13)
Embryo transfer events per cycle		
No embryos transferred	31 738 (12.3)	20 794 (13.3)
Fresh embryo transfer only	199 713 (77.6)	119 462 (76.1)
Fresh and frozen embryo transfer	25 947 (10.1)	16 691 (10.6)
No. of embryo transfer events	257 581	157 043
No. of embryos transferred per embryo transfer event[c]		
1	44 330 (17.2)	29 942 (19.1)
2	201 888 (78.4)	122 483 (78.0)
3-4	11 363 (4.4)	4618 (3.0)

Abbreviations: ICSI, intracytoplasmic sperm injection; IQR, interquartile range; IVF, in vitro fertilization.

[a] The unit of analysis is cycle (with results the average across all cycles per woman).

[b] As this is just 1 cycle, the unit of analysis is the women at their first treatment cycle.

[c] As there are a variable number of transfer events per treatment cycle (which includes all subsequent fresh and frozen transfer events), the percentage is per number of transfer events (not per cycle).

Table 2. Live-Birth Rates Within Initiated Treatment Cycle and Cumulative Live-Birth Rates Across All Cycles for 156 947 Women Undergoing 257 398 Cycles of IVF[a]

Cycle No.	No. of Cycles	No. of Live Births	Live-Birth Rate Within Each Cycle, % (95% CI)	Cumulative Live-Birth Rates Across All Cycles, % (95% CI)			
				Optimal Estimate[b]	Age-Adjusted Estimate[c]	Prognostic-Adjusted Estimate[d]	Conservative Estimate[e]
1	156 947	46 333	29.5 (29.3-29.7)	29.5 (29.3-29.7)	29.5 (29.3-29.7)	29.5 (29.3-29.7)	29.5 (29.3-29.7)
2	63 453	15 825	24.9 (24.6-25.3)	47.1 (46.8-47.4)	46.7 (46.4-47.0)	45.1 (44.9-45.4)	40.5 (40.3-40.8)
3	23 746	5358	22.6 (22.0-23.1)	59.0 (58.7-59.4)	58.3 (57.9-58.6)	54.3 (54.0-54.6)	44.6 (44.4-44.9)
4	8239	1690	20.5 (19.6-21.4)	67.4 (67.0-67.9)	66.4 (66.0-66.9)	59.8 (59.4-60.1)	46.1 (45.8-46.3)
5	3012	553	18.4 (17.0-19.7)	73.4 (72.8-74.0)	72.2 (71.6-72.7)	63.1 (62.6-63.5)	46.6 (46.3-46.8)
6	1162	202	17.4 (15.2-19.6)	78.0 (77.3-78.8)	76.7 (76.0-77.5)	65.3 (64.8-65.8)	46.8 (46.5-47.0)
7	458	79	17.2 (13.8-20.7)	81.8 (80.8-82.8)	80.5 (79.5-81.5)	66.8 (66.2-67.4)	46.9 (46.7-47.2)
8	199	37	18.6 (13.2-24.0)	85.2 (83.9-86.5)	83.7 (82.4-85.0)	68.0 (67.3-68.7)	46.9 (46.7-47.2)
9	83	13	15.7 (7.8-23.5)	87.5 (85.9-89.1)	86.3 (84.7-87.9)	68.7 (68.0-69.5)	46.9 (46.7-47.2)

Abbreviation: IVF, in vitro fertilization.

[a] Note: it is not possible to calculate an oocyte-adjusted estimate for the whole cohort due to the presence of women using donor oocytes.

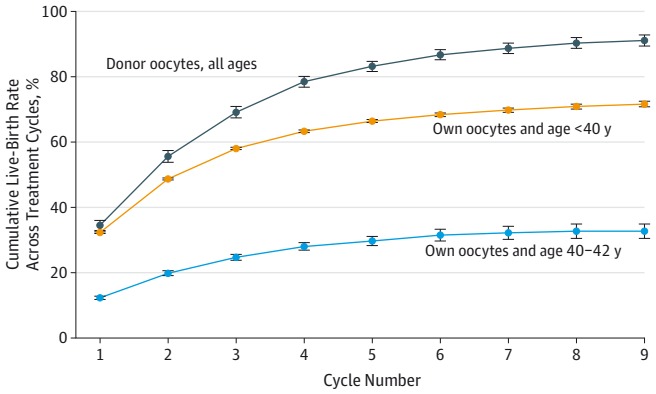
[b] Assumes that the cumulative live-birth rate for women who discontinue IVF without a live birth, if they had continued, would have been equal to the rate in women who continued to have further IVF. That is, it assumes that 0% of women who discontinued IVF did so because of poor prognosis that would have affected their live-birth success had they continued.

[c] Assumes that the cumulative live-birth rate for women who discontinued IVF, if they had continued, would have been equal to the rate in women who were the same age at the start of treatment and who continued to have further IVF. These results suggested approximately 3% of women who discontinued did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

[d] Assumes that 30% of women who discontinued IVF did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

[e] Assumes that the cumulative live-birth rate for all women who discontinued IVF would have been 0 had they continued. That is, it assumes that 100% of women who discontinued did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

Figure 2. Cumulative Live-Birth Rate Across All Initiated IVF Cycles by Age and Oocyte Source



No. of women									
Donor oocytes, all ages	3587	1636	939	554	287	126	53	27	8
Own oocytes and age <40 y	133 379	53 568	19 719	6641	2357	882	335	131	51
Own oocytes and age 40–42 y	15 561	6671	2579	884	301	130	60	36	20
Own oocytes and age >42 y	4420	1578	509	160	67	24	10	5	4

The prognosis-adjusted estimate of cumulative live-birth rate (ie, the rate shown on the y-axis is the likelihood of a live birth across all initiated cycles up to and including the numbers on the x-axis), with 95% confidence intervals (error bars). These are presented for women in 2 different age categories at the start of their first in vitro fertilization (IVF) treatment cycle (<40 years and 40-42 years; women in both of these categories used their own oocytes) and also in women who used donor oocytes (these women cover the full age range). Data for women older than 42 years at their first treatment cycle are not shown because rates were so low it would have been difficult to represent them on this same graph (full results for these women are shown in Table 3). The prognostic-adjusted estimate assumes that 30% of those who discontinued IVF did so because of poor prognosis and that the live-birth rate in that 30% would have been 0 had they continued. Analyses were completed for 156 947 women undergoing 257 398 cycles. Log-rank tests indicated a difference between the cumulative live-birth rates for all groups ($P < .001$ for all comparisons).

cumulative live-birth rates, after 6 cycles, of 71.3% (95% CI, 70.5%-72.1%), 82.2% (95% CI, 81.1%-83.4%), and 54.7% (95% CI, 54.3%-55.2%) using the prognostic-adjusted, optimal, and conservative estimates, respectively (eTable 6 in the Supplement). Equivalent results for those with male infertility treated with donor sperm were 81.2% (95% CI, 78.6%-83.9%), 90.2% (95% CI, 87.2%-93.1%), and 65.9% (95% CI, 63.9%-67.9%), respectively (eTable 7). Live-birth

Table 3. Live-Birth Rates Within Initiated Treatment Cycle and Cumulative Live-Birth Rates Across All Cycles for 153 360 Women Undergoing 250 175 Cycles of IVF Using Their Own Oocytes, Stratified by Age at First Ovarian Stimulation Cycle[a]

Cycle No.	No. of Cycles	No. of Live Births	Live-Birth Rate Within Each Cycle, % (95% CI)	Cumulative Live-Birth Rates Across All Cycles, % (95% CI)			
				Optimal Estimate[b]	Previous Oocyte Yield–Adjusted Estimate[c]	Prognostic-Adjusted Estimate[d]	Conservative Estimate[e]
Women Aged <40 Years							
1	133 379	43 019	32.3 (32.0-32.5)	32.3 (32.0-32.5)	32.3 (32.0-32.5)	32.3 (32.0-32.5)	32.3 (32.0-32.5)
2	53 568	14 532	27.1 (26.8-27.5)	50.6 (50.3-50.9)	50.7 (50.4-51.1)	48.7 (48.4-49.0)	44.3 (44.0-44.5)
3	19 719	4793	24.3 (23.7-24.9)	62.6 (62.3-63.0)	62.7 (62.3-63.1)	58.0 (57.7-58.4)	48.6 (48.4-48.9)
4	6641	1419	21.4 (20.4-22.4)	70.6 (70.1-71.1)	70.5 (70.1-71.0)	63.3 (62.9-63.7)	50.1 (49.8-50.3)
5	2357	449	19.0 (17.5-20.6)	76.2 (75.6-76.8)	76.0 (75.4-76.6)	66.4 (66.0-66.9)	50.6 (50.3-50.8)
6	882	150	17.0 (14.5-19.5)	80.3 (79.5-81.0)	80.1 (79.3-80.8)	68.4 (67.8-68.9)	50.7 (50.5-51.0)
7	335	58	17.3 (13.3-21.4)	83.7 (82.7-84.7)	83.4 (82.4-84.4)	69.8 (69.1-70.4)	50.8 (50.5-51.1)
8	131	25	19.1 (12.4-25.8)	86.8 (85.4-88.2)	86.5 (85.1-87.9)	70.9 (70.1-71.6)	50.9 (50.6-51.1)
9	51	10	19.6 (8.7-30.5)	89.4 (87.6-91.2)	88.8 (87.2-90.3)	71.6 (70.8-72.5)	50.9 (50.6-51.2)
Women Aged 40-42 Years							
1	15 561	1914	12.3 (11.8-12.8)	12.3 (11.8-12.8)	12.3 (11.8-12.8)	12.3 (11.8-12.8)	12.3 (11.8-12.8)
2	6671	671	10.1 (9.3-10.8)	21.1 (20.3-21.9)	20.8 (20.0-21.6)	19.8 (19.1-20.6)	16.8 (16.3-17.4)
3	2579	223	8.6 (7.6-9.7)	27.9 (26.8-29.1)	27.6 (26.5-28.7)	24.7 (23.8-25.6)	18.5 (17.8-19.1)
4	884	69	7.8 (6.0-9.6)	33.6 (31.9-35.2)	33.0 (31.4-34.7)	28.0 (26.9-29.2)	19.0 (18.4-19.6)
5	301	16	5.3 (2.8-7.9)	37.4 (34.8-39.4)	36.5 (34.3-38.8)	29.7 (28.3-31.1)	19.1 (18.5-19.8)
6	130	9	6.9 (2.6-11.3)	41.5 (38.0-44.9)	40.5 (37.3-43.8)	31.5 (29.7-33.3)	19.2 (18.6-19.8)
7	60	2	3.3[f]	43.4 (39.1-47.7)	42.4 (38.4-46.3)	32.2 (30.2-34.2)	19.2 (18.6-19.9)
8	36	1	2.8[f]	45.0 (39.8-50.1)	43.4 (39.1-47.6)	32.7 (30.5-34.9)	19.2 (18.6-19.9)
9	20	0	0.0[f]	45.0 (39.8-50.1)	43.4 (39.1-47.6)	32.7 (30.5-34.9)	19.2 (18.6-19.9)
Women Aged >42 Years							
1	4420	164	3.7 (3.2-4.3)	3.7 (3.2-4.3)	3.7 (3.2-4.3)	3.7 (3.2-4.3)	3.7 (3.2-4.3)
2	1578	52	3.3 (2.4-4.2)	6.9 (5.9-7.9)	6.9 (5.9-7.9)	6.3 (5.4-7.2)	4.9 (4.3-5.6)
3	509	17	3.3 (1.8-4.9)	10.0 (8.2-11.7)	9.8 (8.1-11.5)	8.3 (7.1-9.6)	5.4 (4.7-6.0)
4	160	2	1.3[f]	11.1 (8.8-13.4)	10.1 (8.5-11.8)	8.9 (7.4-10.5)	5.5 (4.8-6.2)
5	67	3	4.5[f]	15.1 (10.2-20.0)	14.2 (10.7-17.7)	10.7 (8.2-13.2)	5.5 (4.8-6.2)
6	24	0	0.0[f]	15.1 (10.2-20.0)	14.2 (10.7-17.7)	10.7 (8.2-13.2)	5.6 (4.9-6.3)
7	10	2	20.0[f]	32.1 (10.7-53.5)	22.3 (14.0-30.5)	15.9 (8.5-23.2)	5.6 (4.9-6.3)
8	5	0	0.0[f]	32.1 (10.7-53.5)	22.3 (14.0-30.5)	15.9 (8.5-23.2)	5.6 (4.9-6.3)
9	4	0	0.0[f]	32.1 (10.7-53.5)	22.3 (14.0-30.5)	15.9 (8.5-23.2)	5.6 (4.9-6.3)

Abbreviation: IVF, in vitro fertilization.

[a] Note: it is not possible to calculate an age-adjusted estimate; there is too little age variation within the age-stratified groups to further adjust for age.

[b] Assumes that the cumulative live-birth rate for women who discontinue IVF without a live birth, if they had continued, would have been equal to the rate in women who continued to have further IVF. That is, it assumes that 0% of women who discontinued IVF did so because of poor prognosis that would have affected their live-birth success had they continued.

[c] Assumes that the cumulative live-birth rate for women who discontinued IVF, if they had continued, would have been equal to the rate in women who had the same oocyte yield in the immediately previous ovarian stimulation treatment and who continued to have further IVF. These results suggested approximately 3% of women who discontinued did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

[d] Assumes that 30% of women who discontinued IVF did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

[e] Assumes that the cumulative live-birth rate for all women who discontinued IVF would have been 0 had they continued. That is, it assumes that 100% of women who discontinued did so because of poor prognosis and would have had a live-birth rate of 0 had they continued.

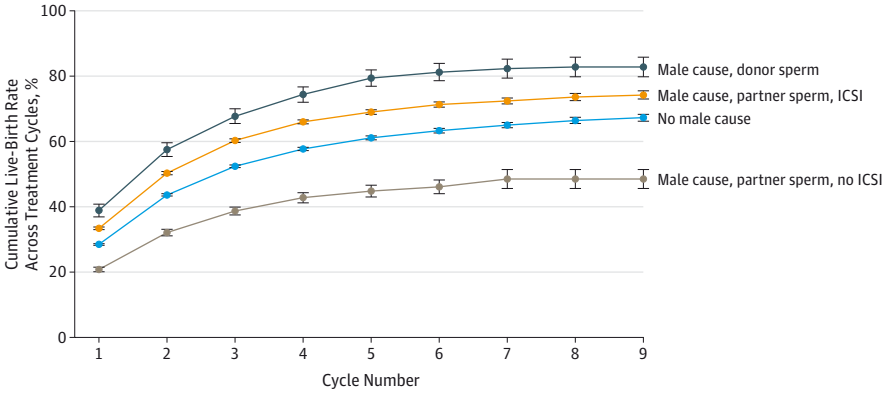
[f] There were <6 live births for these cycles; standard errors and hence confidence intervals could not be calculated.

rates in both of these groups were greater than for women with a nonmale cause of infertility (eTables 3 and 8 in the Supplement).

Figure 4 shows the live-birth rate within the first, second, and third cycles plotted against the number of oocytes retrieved in the first cycle in women younger than 40 years using their own oocytes. For those in whom no oocytes were retrieved in the first cycle, the live-birth rates in the second and third cycles were greater than 20%. The live-birth rates in the first, second, and third cycles continued to increase with increasing oocytes retrieved in the first cycle up to around 15 oocytes; thereafter, the curves flatten. Plotting the live-birth rate within any cycle against the number of oocytes retrieved in the previous cycle gave a similar pattern (eFigure 2 in the Supplement).

Using published data,[23-25] we estimated the live-birth rate for women conceiving naturally who had been trying for 12 menstrual cycles. This rate varied between 58% and 74%, depending on the woman's age and frequency of intercourse (eTable 9 in the Supplement). These estimates are based on

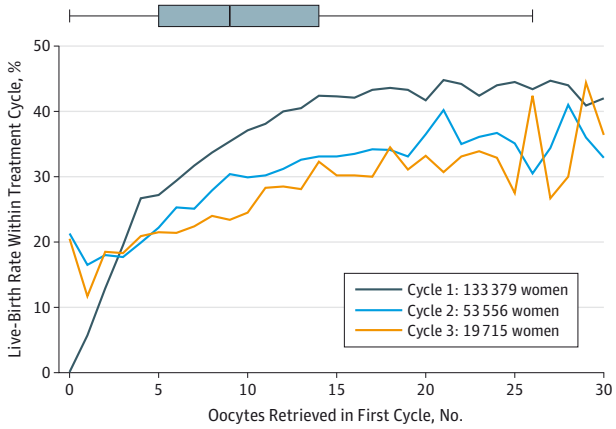
Figure 3. Cumulative Live-Birth Rate Across All Initiated IVF Cycles by ICSI and Sperm Donation



No. of women									
Male cause, donor sperm	2471	1079	420	177	84	25	10	8	5
Male cause, partner sperm, ICSI	48 016	21 006	8203	2911	1015	377	141	57	24
No male cause	93 924	37 161	13 645	4680	1765	690	277	119	51
Male cause, partner sperm, no ICSI	12 536	4207	1478	471	148	70	30	15	3

The prognosis-adjusted estimates of cumulative live-birth rates (ie, the rate shown on the y-axis is the likelihood of a live birth across all initiated cycles up to and including the numbers on the x-axis), with 95% confidence intervals (error bars). These are shown for couples without a male-partner cause of infertility, couples with a male cause who were not treated with intracytoplasmic sperm injection (ICSI) or sperm donation, those with a male cause who were treated with ICSI, and those with a male cause who used sperm donation. The prognostic-adjusted estimate assumes that 30% of those who discontinued in vitro fertilization (IVF) did so because of poor prognosis and that the live-birth rate in that 30% would have been 0 had they continued. Analyses were completed for 156 947 women undergoing 257 398 cycles. Log-rank tests indicated a difference between the cumulative live-birth rates for all groups ($P < .001$ for all comparisons).

Figure 4. Live-Birth Rate Within Each Single In Vitro Fertilization Treatment Cycle by Oocyte Retrieval in First Cycle



The live-birth rate within each individual first, second, and third treatment cycle (ie, for each curve, the rate on the y-axis is the rate for just that 1 treatment cycle) according to the number of oocytes retrieved in the first treatment cycle. Analyses are for 134 903 women younger than 40 years using their own oocytes. Box and whiskers indicate the central 95% of the distribution of oocytes retrieved in the first cycle, as well as the median and lower and upper quartiles.

studies that only included women younger than 40 years. Similar cumulative live-birth rates were achieved by the fifth or sixth cycle of IVF treatment in women of this age (Table 3); however, in these women, 5 cycles took a median of 2 years (interquartile range, 2-3).

Discussion

To our knowledge, this is the first study to have linked fresh and frozen embryo transfers to obtain estimates of live-birth rate within each IVF ovarian stimulation cycle and cumulative live-birth rates across repeated stimulation cycles. Despite a decline in the success rate within each cycle as the number of these increased, the cumulative rate across cycles increased up to the ninth in the whole cohort, women younger than 40 years (using their own oocytes), and women using donor oocytes (irrespective of age). They also increased up to the eighth or ninth cycle for women aged 40 to 42 years, although for women older than 42 years (using their own oocytes), the likelihood of success was low and the cumulative live-birth rate did not appear to clearly increase beyond the fourth or fifth cycle. For those women able to use donor oocytes, age was unrelated to success. In those for whom the cause of infertility was related to a male partner problem, treatment with ICSI or donor sperm made a marked difference in the likelihood of success, with cumulative rates increasing up to the eighth or ninth cycle, whereas without treatment rates were lower than for women with other causes of infertility. For women younger than 40 years with a low oocyte yield in a previous cycle, there was benefit in continuing with further cycles. We also found that women younger than 40 years could achieve cumulative live-birth rates after 5 or 6 cycles that were similar to published live-birth rates achieved naturally within 12 menstrual cycles.[23-25] It should be noted, however, that, in these women, 5 cycles took a median of 2 years.

Widespread adoption of single embryo transfer has reduced multiple pregnancies and adverse perinatal outcomes but has meant that the chance of a live birth from a single ovarian stimulation cycle is spread across multiple embryo transfers, which we have assessed here. Because this method of assessing IVF success combines all embryo transfer events after an ovulation stimulation into 1 analysis unit, we were unable to examine the effect of the number of embryos transferred per event. However, this method of assessing IVF success is increasingly recommended.[5,10-13] Our results show how success rates per embryo transfer event are misleadingly lower, compared with the rate within each ovarian stimulation cycle. We have previously shown, using unlinked data from the same population, that the number of embryos transferred in an embryo transfer event is associated with live-birth rate, with a difference of 9% in women younger than 40 years and 16% in those 40 years or older, comparing double with single embryo transfer.[15]

Despite the differences in the definition of cumulative success between our study and the previous largest study (from the United States), in which cumulative live-birth rates were estimated on the basis of each embryo transfer,[5] and differences in health systems between the United States and United Kingdom, both studies found age differences in rates and that the differences were removed with the use of donor oocytes. In the US study, women with a male partner cause of infertility had one of the highest cumulative live-birth rates per embryo transfer, but that study did not examine the effect of different treatments (ICSI or sperm donation), and it may be that all of those patients with male partner–cause infertility in the United States receive one of these treatments.

The key limitation of all studies looking at cumulative outcomes with repeat IVF is how patients who discontinue treatment are treated. As seen in our data and in previous studies,[5,7] the extremes of the optimal and conservative estimates often vary markedly; for example, in our data, the optimal and conservative estimates were 78.0% and 46.8%, respectively, for the whole cohort. This is because of the differences between these 2 estimates in assumptions made regarding what would have been the live-birth rate in those who discontinued IVF had they continued; for the optimal estimate, this is assumed to be the same as those who did continue, whereas for the conservative estimate it is assumed to be 0. We examined the likelihood that such discontinuation was due to poor prognosis based on age and previous cycle oocyte retrieval. These analyses suggested approximately 3% of those who discontinued did so because of poor prognosis. This small proportion was because although these 2 factors are important predictors of live birth, few women receiving IVF are older than 40 years (only 15% in our national population cohort), and most women have a high oocyte yield (median, 9 per cycle in our cohort). However, to account for other factors, such as pretreatment reproductive hormone levels, smoking, and body mass index, which have been linked to live-birth rates[7,22] but were not available in this study, we assumed a 30% discontinuation due to poor prognosis. Because of the legal requirement for all UK clinicians to provide data on all ART patients, the HFEA was able to link cycles to individual women even if they moved between clinics within the United Kingdom. However, treatment abroad would be absent from our data. A European study conducted 6 years ago found very few UK couples traveled for ART to 49 clinics in 6 (non-UK) European countries with high rates of cross-border patients.[26] We were only able to assess live birth as an outcome: future studies should also consider potential adverse effects of continued treatment, including ovarian hyperstimulation syndrome and possible increased risk of preterm birth, low birth weight, or congenital anomalies.[16,27,28]

For some couples, the emotional stress of repeat treatments may be undesirable, and the cost of a prolonged treatment course, with several repeat oocyte stimulation cycles, may be unsustainable for health services, insurers, or couples. However, we think the potential for success with further cycles should be discussed with couples. A cost-effectiveness analysis is beyond the scope of this study, and the difficulties of undertaking such analyses for IVF, in which decisions related to how one values a new life and whether "benefits" and "costs" for both parents and the child should be included, are well documented.[29] The costs of IVF treatment vary between countries, whether publicly or privately funded, and the treatment type used but are approximately $14 000 (equivalent of approximately £9000, €12 000) to $17 000 (equivalent of approximately £11 000, €15 000) per cycle.[1,29,30] These costs exclude assessment prior to starting IVF and are based on transfer of 1 fresh embryo. Assuming each additional frozen embryo transfer costs $4000 to $5000,[30] the cost per couple of continuing to 6 cycles, rather than having just 3, could be as much as $132 000 compared with $66 000 (assuming 1 fresh and 1 frozen transfer per cycle).

Conclusions

Among women in the United Kingdom undergoing IVF, the cumulative prognosis-adjusted live-birth rate after 6 cycles was 65.3%, with variations by age and treatment type. These findings support the efficacy of extending the number of IVF cycles beyond 3 or 4.

ARTICLE INFORMATION

Author Contributions: Drs Smith and Lawlor had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Nelson and Lawlor contributed equally to this work.
Study concept and design: Smith, Nelson, Lawlor.
Acquisition, analysis, or interpretation of data: Smith, Tilling, Nelson, Lawlor.
Drafting of the manuscript: Smith, Lawlor.
Critical revision of the manuscript for important intellectual content: Tilling, Nelson.
Statistical analysis: Smith.
Obtained funding: Nelson, Lawlor.
Study supervision: Tilling, Nelson, Lawlor.

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