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Live-birth rate associated with repeat in vitro fertilisation treatment cycles.

Andrew D.A.C. Smith, PhD[1,2], Kate Tilling, PhD[1,2], Scott M Nelson, PhD[3]*, Debbie A Lawlor, PhD[1,2]*

[1] Medical Research Council Integrative Epidemiology Unit at the University of Bristol, UK

[2] School of Social and Community Medicine, University of Bristol, UK

[3] School of Medicine, University of Glasgow, UK

* These authors made equal contributions.

Corresponding author:

DA Lawlor

School of Social and Community Medicine

University of Bristol

Oakfield House, Oakfield Grove

Clifton

Bristol

BS8 1BN

United Kingdom

d.a.lawlor@bristol.ac.uk

+44 (0)117 3310096

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Abstract

Importance: The likelihood of achieving a live-birth with repeat in-vitro fertilisation (IVF) is unclear, yet the number of treatment is commonly limited to three or four embryo transfers.

Objective: To determine the live-birth rate per initiated IVF cycle and with repeated cycles.

Design: Prospective study of 156,947 UK women who received 257,398 IVF treatment cycles between 2003 and 2010 and were followed until June 2012.

Main exposure: IVF, with a cycle defined as an episode of ovarian stimulation and all subsequent separate fresh and frozen embryo transfers.

Main Outcome(s): Live-birth rate per IVF cycle and the cumulative live-birth rate across all cycles in all women and by age and treatment type.

Results: 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 live-birth rate across all cycles continued to increase up to the ninth, with 78.0% (77.3, 78.8) of women achieving a live-birth by the sixth cycle. In women younger than 40 using their own oocytes, the live-birth rate for the first cycle was 32.3% (32.0, 32.5), and remained above 20% up to and including the fourth cycle. Six cycles achieved a cumulative live-birth rate of 80.3% (79.5, 81.0). For women aged 40-42, the live-birth rate for the first cycle was 12.3% (95%CI: 11.8, 12.8), with six cycles achieving a cumulative live-birth rate of 41.5% (38.0, 44.9). For women older than 42 years all rates within each cycle were less than 4%. Use of donor oocytes removed the age differential. Rates were lower in those with untreated male factor infertility compared to those with any other cause, but treatment with either intra-cytoplasmic sperm injection or sperm donation removed this difference.

Conclusions and relevance: Among women in the UK undergoing IVF, the cumulative live-birth rate after six cycles was 78.0%, with variations by age and treatment type. These findings support the efficacy of extending the number of IVF cycles beyond three or four.

Introduction

In-vitro fertilization (IVF) is commonly stopped after three or four unsuccessful embryo transfers,[1,2] with three unsuccessful transfers labelled 'repeat implantation failure'.[3] This practice has been influenced by a study of 1,328 embryo transfers undertaken twenty-years ago, without use of intra-cytoplasmic sperm injection (ICSI), which reported a decline in live-birth rates after the fourth cycle.[4] With one exception,[5] previous studies of cumulative pregnancy or live-birth rates have been relatively small, with limited ability to precisely estimate cumulative success beyond four transfers.[4,6-9] Previous studies have defined a cycle of IVF as an embryo transfer.[5-9] Thus, each initiation of IVF treatment has been treated as several separate cycles whenever there has been a series of repeated embryo transfers. Given the promotion of single embryo transfer and the effective freezing of embryos have increased markedly over the last 10-15 years,[10-15] it has been suggested that IVF success should be calculated as the live-birth rate per initiated ovarian stimulation treatment, 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: (i) the live-birth rate within each cycle, and the cumulative rate across all cycles; (ii) how these varied by age and treatment types (use of donor oocyte, ICSI or sperm donation); (iii) the association between oocyte yield in one cycle and live-birth rate in subsequent cycles; and (iv) to compare cumulative live-birth rates with IVF to published rates in women conceiving naturally.

Methods

Ethical approval for this study was provided by the UK Human Fertilisation and Embryology Authority (HFEA) who have statutory obligations to prospectively collect information on all assisted reproductive treatment (ART) in the UK. Women provided written consent for this information to be used in analyses, audit and publications. The HFEA provided us with data on all ART events occurring in the UK between 1st January 2003 and 30th June 2012, with linkage of cycles to individual women and data on birth outcomes. 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 in order 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 treatment initiated between 1st January 2003 and 31st December 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 treatment 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 one or more embryos.

Live-birth was defined as a baby born alive after 24 weeks gestation surviving more than one month. The World Health Organisation (WHO) define live-birth as a birth showing any sign of life irrespective of gestational age. As in other studies,[5, 15,16] we modified this to capture births that were likely to be viable. We defined an IVF cycle as the initiation of treatment with 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 treatment the live-birth rate within one cycle answers the question '*What is my chance of a live-birth with one 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 dataset.

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 the cumulative live-birth rate, up to the ninth cycle, using the Kaplan-Meier method with Greenwood's approximation to calculate confidence intervals (see online supplementary material for full details).[17,18] We compared the live-birth rate within each cycle and cumulatively across all cycles between age and treatment type categories using a log-rank test.[19] We assessed the relationship of oocyte yield in one cycle to live-birth rates in subsequent cycles in women younger than 40 years using their own oocytes, by calculating the within live-birth rate in the first, second, and third cycles by oocytes retrieved in the first cycle, and also calculating the within live-birth rate up to the fifth cycle by oocytes retrieved in the immediately preceding cycle.

Dealing with discontinuation of IVF

We calculated 'optimal', 'conservative' and 'prognostic-adjusted' estimates of the cumulative live-birth rate. The optimal estimate assumes the cumulative live-birth rate in women who discontinue treatment without a live-birth is equal to the rate in those who continue to have further cycles.[5] The conservative estimate assumes those who discontinue treatment have a subsequent live-birth rate of zero.[5] The true rate is thought to lie between these two extremes.[7] The prognostic-adjusted estimate aims to obtain this more realistic value. It assumes a fixed proportion of those who discontinue treatment do so because of poor prognosis and that the live-birth rate in that proportion will be zero, whereas for those who discontinue for other reasons, such as inability to pay, emotional distress or (in our dataset) emigration from the UK, the live-birth rate will be similar to those who continue with treatment.

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.[5,7,9,20,21] We checked that these were indicators of live-birth and of discontinuation of treatment in our own data, as well as comparing other available characteristics between those who discontinued and continued treatment after one unsuccessful cycle. To adjust for age and oocyte yield in the previous cycle we calculated results within categories and then obtained an average, weighted by the numbers within each category in the first cycle.

We used the adjusted live-birth rate to estimate the proportion of those who discontinued treatment because of poor prognosis. This provided an estimate of the proportion who discontinued because of poor prognosis of 3%. However, to calculate a prognostic-adjusted cumulative live-birth rate we assumed 30% of those who discontinued treatment did so because of poor prognosis. We chose a value of ten-times that suggested by our data to obtain a reasonably conservative prognostic-adjusted estimate. Full details of how all of the estimates were calculated are provided in online supplementary material.

As the average population live-birth success rate for a single embryo transfer is between 20-30% 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 < 0.05 were considered to provide evidence against the null hypothesis.

Comparison with live-birth rates in those not receiving ART

We used data from published literature to estimate live-birth rates in women who conceive naturally.[22-24] Full details of how we calculated these estimates are provided in online supplementary material.

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 (i.e. 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 at the first cycle and also for all cycles. **eTable 1** 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 one-year and median oocyte retrieval differed by one across the whole study period between 2003 and 2010. Use of ICSI increased by 11%, and transfer of single embryos by 17%, though the live-birth rate increased by just two-percent across the study period.

Table 2 shows the live-birth rate within each cycle and cumulatively across all cycles 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 one more cycle. **eTable 2** compares characteristics between these two groups. Although there was statistical evidence of differences for all characteristics the actual differences were small; e.g. women who discontinued treatment were one-year older and had median of one fewer oocytes retrieved per cycle. The proportion who used donor oocytes was higher in those who discontinued treatment (3.7% vs 1.3%). The age-adjusted and optimal cumulative live-birth rate estimates were similar (**Table 2 and eFigure 1**). **eFigure 2** shows the cumulative live-birth rates assuming 0% (equivalent to the optimal), 3% (as suggested by our analyses), 30% (used for our prognostic-adjusted estimate) and 100% (equivalent to the conservative) of those who discontinue treatment do so for poor prognosis. Six cycles achieved cumulative live-birth rates of 78.0% (77.3, 78.8), 46.8% (46.5, 47.0) and 65.3% (64.8, 65.8), by the optimal, conservative and prognostic-adjusted estimates, respectively (**Table 2**).

Results varied by age and oocyte source (**Figure 2**). 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% (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 (**Table 3**). Six cycles achieved cumulative live-birth rates of 80.3% (79.5 to 81.0), 50.7% (50.5, 51.0) and 68.4%, (67.8, 68.9), by the optimal, conservative and prognostic-adjusted estimate, respectively (**Table 3**). For women aged 40-42, the live-birth rate for the first cycle was 12.3% (11.8, 12.8), with six cycles achieving a cumulative live-birth rates of 41.5% (38.0, 44.9), 19.2% (18.5, 19.8) and 31.5% (29.7, 33.3), for optimal, conservative and prognostic-adjusted estimates, respectively (**eTable 3**). 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 (**eTable 4**). Use of donor oocytes removed the age differential ($p = 0.34$ for difference between women in the youngest and middle age categories using donor oocytes and $p = 0.89$ for difference between women in the middle and oldest categories). 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 six cycles of 91.7% (90.3, 93.1), 75.5% (74.0, 77.1) and 86.7% (85.2, 88.3), for the optimal, conservative and prognostic-adjusted estimates, respectively (**eTable5**).

Live-birth rates varied by male cause infertility and its treatment (**Figure 3 and eTables 6 to 9**). 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 non-male cause of infertility (**eTable 6** $p < 0.001$ for log-rank test). Those with a male cause of infertility who were treated with ICSI had cumulative live-birth rates, after six cycles, of 82.2% (81.1, 83.4), 54.7% (54.3, 55.2) and 71.3% (70.5, 72.1), using the optimal, conservative, and conservative prognostic-adjusted estimates, respectively (**eTable 7**). Equivalent results for those with male infertility treated with donor sperm were 90.2% (87.2, 93.1), 65.9% (63.9, 67.9) and 81.2% (78.6, 83.9), respectively (**eTable 8**). Live-birth rates in both of these groups were greater than in those with a non-male cause of infertility (**eTable 9**, $p < 0.001$ for both log-rank tests).

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 under 40 years of age 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 immediately previous cycle gave a similar pattern (**eFigure 3**).

Using published data[22-24] we estimated that the live-birth rate for women conceiving naturally, and who had been trying for 12 menstrual cycles, varied between 58% and 74% depending on the woman's age and frequency of intercourse (**eTable 10**). These estimates are based on studies that only included women younger than 40 years. Similar cumulative live-birth rates were achieved by the fourth or fifth cycle of IVF treatment in women of this age (**Table 3**), though, in these women, five cycles took a median of 2 years (1st, 3rd quartile: 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, those younger than 40 years (using their own oocytes) and those using donor oocytes (irrespective of age). They also increased up to the eighth or ninth in women aged 40-42, though for women older than 42 (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 prepared, and able, to use donor oocytes, age was unrelated to success. Similarly, 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 in those with other causes of infertility. In women under 40 years with a low oocyte yield in a previous cycle there was benefit in continuing with further cycles. We also found women under 40 years could achieve cumulative live-birth rates after four or five cycles that were similar to published live-birth rates achieved naturally within 12 menstrual cycles.[22-24] It should be noted, however, that, in these women, five 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. Since this method of assessing IVF success combines all embryo transfer events following an ovulation stimulation into one analysis unit, we were unable to examine the effect of the number of embryos transferred per event. However, the method of assessing IVF success that we have used is increasingly recommended,[5,10-13] as it reflects the reality of contemporary IVF treatment. Our results show how success rates per embryo transfer event are misleadingly lower, compared with the rate within each ovarian stimulation cycle. Furthermore, we have previously shown, using unlinked data from the same population, that the number of embryos transferred in one event has a relatively modest effect on live-birth rate, with a difference of 9% in women younger than 40 years and 16% in those aged 40 years or older, comparing double to single embryo transfer.[15]

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

The key limitation of all studies looking at cumulative outcomes with repeat IVF is how one treats those who discontinue treatment. We examined the likelihood that such discontinuation was due to poor prognosis based on age and previous cycle oocyte retrieval, both factors shown in previous studies to be important predictors of success,[5,7,9,20,21] and confirmed in our data to be related to live-births (**Figures 2 and 4**). These analyses suggested approximately 3% of those who discontinued did so because of poor prognosis. This small proportion was because although these two were important predictors of live-birth, the poor prognosis levels of these exposures were uncommon. Only 15% of women were 40-years or older and the median oocyte retrieval was 9 per cycle. However, to account for other factors, for example pre-treatment reproductive hormone levels, smoking and body mass index (BMI), which have been linked to live-birth success, [7,21] but that were not available in this study, we assumed a 30% discontinuation of treatment due to poor prognosis. Even assuming this much higher level of discontinuation, our results show high cumulative success rates, particularly in women under 40 years, with repeat ovarian stimulation up to the sixth such cycle. Because of the legal requirement for all UK clinicians to provide data on all ART patients, the HFEA were able to link cycles to individual women even if they move between clinics within the UK. However, treatment abroad would be absent from our data. A European study, conducted 6 years ago, found very few UK couples travelled for ART to 49 clinics in six (non-UK) European countries with high rates of cross-border patients.[27] We were only able to assess live-birth as an outcome: future studies should also consider potential adverse effects of continued treatment, including ovarian hyper-stimulation syndrome and possible increased risk of preterm birth, low birth weight or congenital anomalies.[16,25,26]

We acknowledge that 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. Though our results show that the median time to complete five ovarian stimulation treatments, with all subsequent embryo transfers is just 2-years. We feel the potential for success with further cycles should be discussed with couples. A cost-effectiveness analysis is beyond the scope of this paper, and the difficulties of undertaking such analyses for IVF treatment, 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.[28] The costs of IVF treatment vary between countries, whether publicly or privately funded, and the treatment type used, but are in the range of $14,000 (£9,000, €12,000) to $17,000 (£11,000, €15,000) per cycle.[1,28,29] These costs exclude assessment prior to starting treatment and are based on transfer of one fresh embryo. Assuming each addition frozen embryo transfer costs $4000 to $5000,[29] the cost per couple of continuing to six, rather than having just three cycles, could be as much as $132,000 compared to $66,000 (assuming one fresh and one frozen transfer per cycle).

Conclusions

Among women in the UK undergoing IVF, the cumulative live-birth rate continued to increase up to the ninth cycle for the whole cohort. The optimal, conservative and prognostic-adjusted cumulative live-birth rates after six cycles were 78.0%, 46.8% and 65.3%, respectively. Results varied by age and treatment type, with women under 40 years using their own oocytes, those using donor oocytes (irrespective of age) and those treated with ICSI or sperm donation for a male cause of infertility, having broadly similar results to those for the whole cohort. These findings support the efficacy of extending the number of IVF cycles beyond three or four.

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Author contributions: DAL and SMN designed the study, developed the aims and obtained data. All authors contributed to developing the statistical analysis plan. ADACS completed all statistical analyses. DAL and ADACS wrote the first draft of the paper and all authors contributed to interpreting results and making critical comments on subsequent paper drafts. DAL and ADACS had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Figure descriptive titles and legends

Figure 1: Definition of eligible and analysis cohort

Figure 2: Cumulative live-birth rate across all initiated IVF cycles by age and oocyte source.

The figure shows the optimal estimates of cumulative live-birth rates (i.e. 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. These are presented for women in two different age categories at the start of their first 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 aged over 42 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 eTable 4). Analyses were completed in 156,947 women undergoing 257,398 cycles. Log-rank tests indicated a difference between the cumulative live-births rates for all groups ($p < 0.001$ for all comparisons).

Figure 3: Cumulative live-birth rate across all initiated IVF cycles by ICSI and sperm donation.

The figure shows the optimal estimates of cumulative live-birth rates (i.e. 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. These are shown for couples without a male cause of infertility, couples with a male cause who were not treated with ICSI or sperm donation, those with a male cause who were treated with ICSI and those with a male cause who used sperm donation. Analyses were completed in 156,947 women undergoing 257,398 cycles. Log-rank tests indicated a difference between the cumulative live-births rates for all groups ($p < 0.001$ for all comparisons).

Figure 4: Live-birth rate within each single IVF treatment cycle by oocyte retrieval in first cycle.

The figure shows the live-birth rate within each individual first, second and third treatment cycle (i.e. for each line the rate on the y-axis is the rate for just that one treatment cycle), against the number of oocytes retrieved in the first treatment cycle (shown on the x-axis). Analyses are in 134,903 women aged less than 40 years and using their own oocytes. Box and whiskers show the central 95% of the distribution of oocytes retrieved in the first cycle, as well as the median and lower and upper quartiles.

Table 1: Characteristics of the analysis cohort of 156,947 women commencing IVF treatment for infertility in the UK in 2003-2010 (with outcomes assessed up to June 2012).

Characteristic	For all cycles combined[a]	For first cycle[b]
Number of women	156,947	156,947
Total number of cycles		
1	93,494 (59.6%)	
2	39,707 (25.3%)	
3	15,507 (9.9%)	
More than 3	8,239 (5.2%)	
Number of cycles	257,398	156,947
Live-births (% per cycle)	70,093 (27.2%)	46,333 (29.5%)
Woman's age (years)		
Median (1st quartile, 3rd quartile)	35 (32, 38)	35 (32, 38)
Duration of infertility (years)		
Median (1st quartile, 3rd quartile)	4 (2, 6)	3 (2, 5)
Missing	11,165 (4.3%)	6,586 (4.0%)
Causes of infertility (non-exclusive)		
Tubal	46,535 (18.1%)	28,181 (18.0%)
Ovulatory	34,473 (13.4%)	21,582 (13.8%)
Endometriosis	15,889 (6.2%)	9,654 (6.1%)
Male cause	105,014 (40.8%)	63,023 (40.2%)
Treated with ICSI	123,009 (47.8%)	68,608 (43.7%)
Treated with sperm donation	8,067 (3.1%)	4,781 (3.05%)
Treated with oocyte donation	7,223 (2.8%)	3,587 (2.3%)
Oocytes retrieved (own) Median (1st quartile, 3rd quartile)	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%)
Number of embryo transfer events	257,581	157,043
Number 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%)	4,618 (3.0%)

[a] The unit of analysis here is cycle (with results the average across all cycles per woman)
[b] As this is just one 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 % is per the number of transfer events (not per cycle)

Table 2: Within initiated treatment cycle live-birth rates and cumulative live-birth rate across all cycles in 156,947 women undergoing 257,398 cycles of IVF

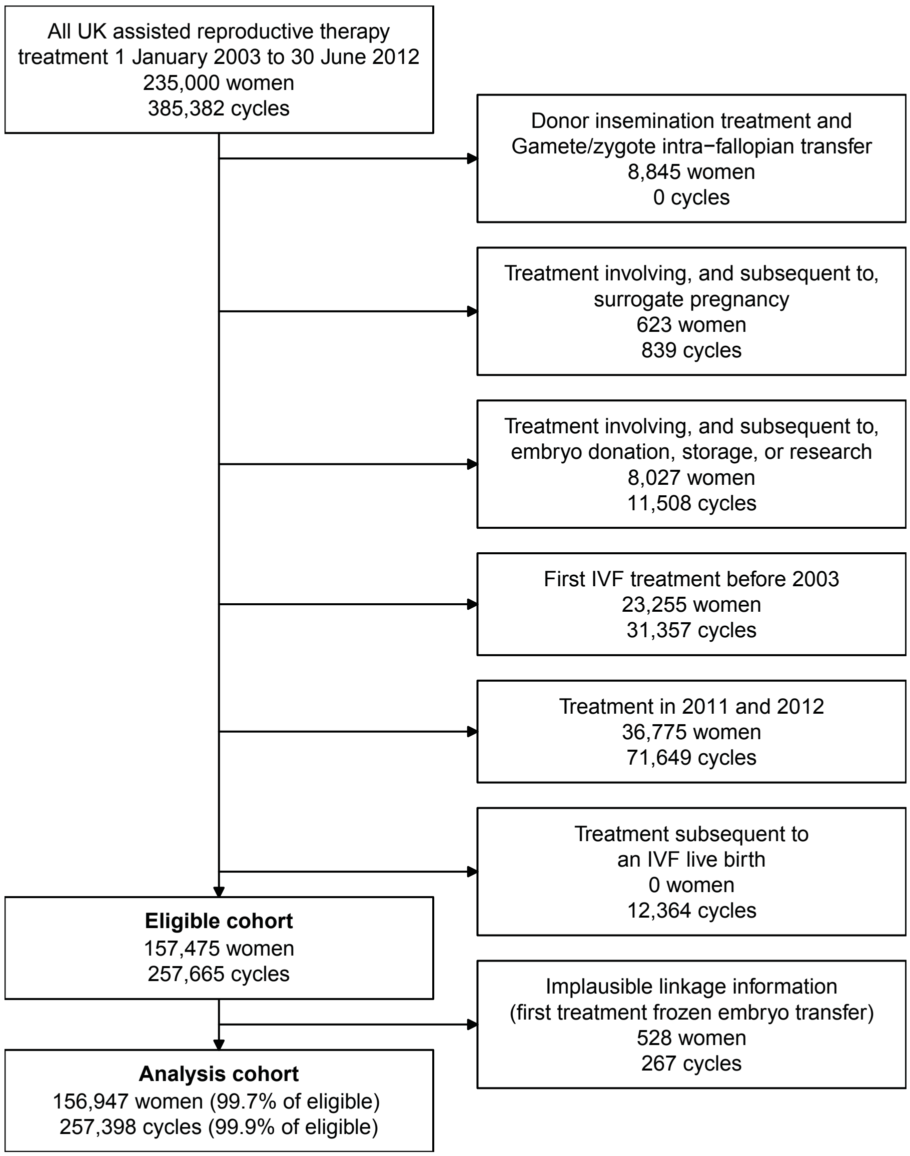
Cycle number	N Cycles	N live-births	Live-birth rate within each cycle % (95%CI)	Cumulative live-birth across all cycles using different estimates % (95%CI)			
				Optimal estimate	Conservative estimate	Age adjusted estimate	Prognostic adjusted estimate[a]
1st	156,947	46,333	29.5 (29.3, 29.7)	29.5 (29.3, 29.7)	29.5 (29.3, 29.7)	29.5 (29.3, 29.7)	29.5 (29.3, 29.7)
2nd	63,453	15,825	24.9 (24.6, 25.3)	47.1 (46.8, 47.4)	40.5 (40.3, 40.8)	46.7 (46.4, 47.0)	45.1 (44.9, 45.4)
3rd	23,746	5,358	22.6 (22.0, 23.1)	59.0 (58.7, 59.4)	44.6 (44.4, 44.9)	58.3 (57.9, 58.6)	54.3 (54.0, 54.6)
4th	8,239	1,690	20.5 (19.6, 21.4)	67.4 (67.0, 67.9)	46.1 (45.8, 46.3)	66.4 (66.0, 66.9)	59.8 (59.4, 60.1)
5th	3,012	553	18.4 (17.0, 19.7)	73.4 (72.8, 74.0)	46.6 (46.3, 46.8)	72.2 (71.6, 72.7)	63.1 (62.6, 63.5)
6th	1,162	202	17.4 (15.2, 19.6)	78.0 (77.3, 78.8)	46.8 (46.5, 47.0)	76.7 (76.0, 77.5)	65.3 (64.8, 65.8)
7th	458	79	17.2 (13.8, 20.7)	81.8 (80.8, 82.8)	46.9 (46.7, 47.2)	80.5 (79.5, 81.5)	66.8 (66.2, 67.4)
8th	199	37	18.6 (13.2, 24.0)	85.2 (83.9, 86.5)	46.9 (46.7, 47.2)	83.7 (82.4, 85.0)	68.0 (67.3, 68.7)
9th	83	13	15.7 (7.8, 23.5)	87.5 (85.9, 89.1)	46.9 (46.7, 47.2)	86.3 (84.7, 87.9)	68.7 (68.0, 69.5)

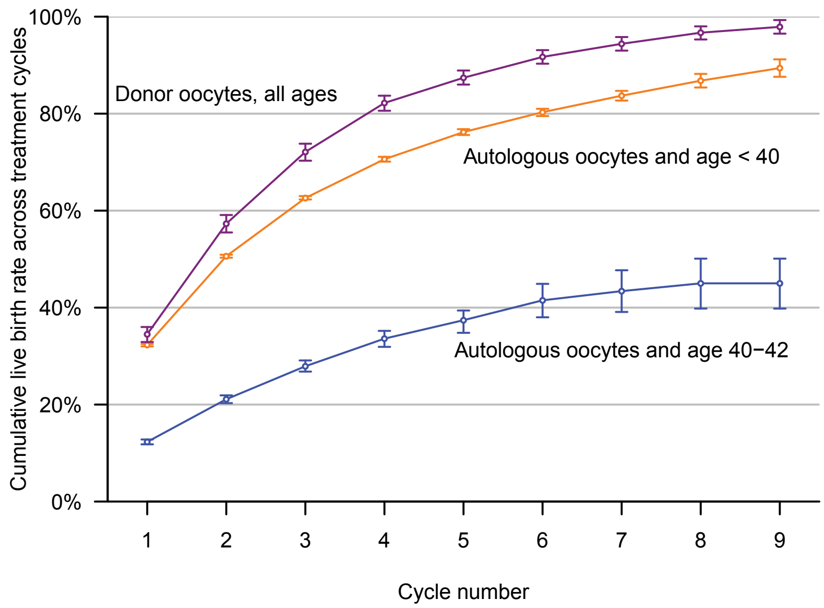
[a] In these estimates we assumed that 30% of women who were lost to follow-up did so because of poor prognosis; 30% is conservative since the proportions suggested by the results from age- adjusted results (shown in column 7) is approximate 3%.
Note it is not possible to calculate an oocyte-adjusted estimate for the whole cohort due to the presence of women using donor oocytes.

Table 3: Within initiated treatment cycle live-birth rates and cumulative live-birth rate across all cycles in 133,379 women, undergoing 217,113 cycles of IVF, who were younger than 40 years at their first treatment cycle and using their own oocytes.

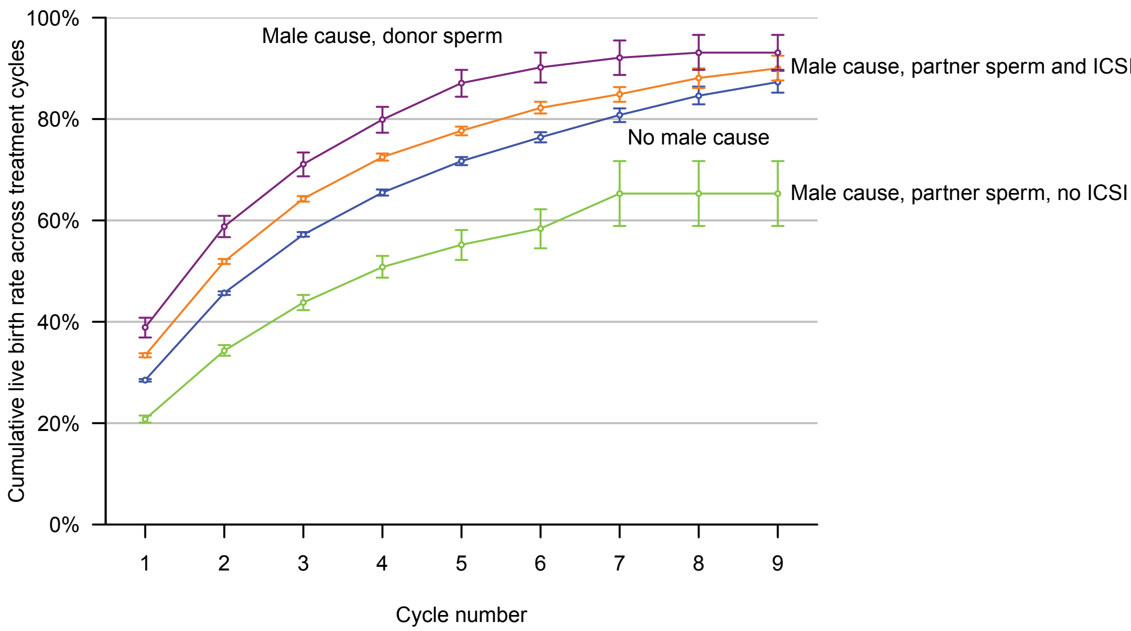
Cycle number	N Cycles	N live-births	Live-birth rate within each cycle % (95%CI)	Cumulative live-birth across all cycles using different estimates % (95%CI)			
				Optimal estimate	Conservative estimate	Previous oocyte yield-adjusted estimate	Prognostic adjusted estimate[a]
1st	133,379	43,019	32.3 (32.0, 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)
2nd	53,568	14,532	27.1 (26.8, 27.5)	50.6 (50.3, 50.9)	44.3 (44.0, 44.5)	50.7 (50.4, 51.1)	48.7 (48.4, 49.0)
3rd	19,719	4,793	24.3 (23.7, 24.9)	62.6 (62.3, 63.0)	48.6 (48.4, 48.9)	62.7 (62.3, 63.1)	58.0 (57.7, 58.4)
4th	6,641	1,419	21.4 (20.4, 22.4)	70.6 (70.1, 71.1)	50.1 (49.8, 50.3)	70.5 (70.1, 71.0)	63.3 (62.9, 63.7)
5th	2,357	449	19.0 (17.5, 20.6)	76.2 (75.6, 76.8)	50.6 (50.3, 50.8)	76.0 (75.4, 76.6)	66.4 (66.0, 66.9)
6th	882	150	17.0 (14.5, 19.5)	80.3 (79.5, 81.0)	50.7 (50.5, 51.0)	80.1 (79.3, 80.8)	68.4 (67.8, 68.9)
7th	335	58	17.3 (13.3, 21.4)	83.7 (82.7, 84.7)	50.8 (50.5, 51.1)	83.4 (82.4, 84.4)	69.8 (69.1, 70.4)
8th	131	25	19.1 (12.4, 25.8)	86.8 (85.4, 88.2)	50.9 (50.6, 51.1)	86.5 (85.1, 87.9)	70.9 (70.1, 71.6)
9th	51	10	19.6 (8.7, 30.5)	89.4 (87.6, 91.2)	50.9 (50.6, 51.2)	88.8 (87.2, 90.3)	71.6 (70.8, 72.5)

[a] In these estimates we assumed that 30% of women who were lost to follow-up did so because of poor prognosis; 30% is conservative since the proportions suggested by the results from previous oocyte yield-adjusted results (shown in column 7) is approximate 3%.
Note it is not possible to calculate an age-adjusted estimate in this group because it is already age stratified and there is too little age variation within this group to adjust for it.


All UK assisted reproductive therapy treatment 1 January 2003 to 30 June 2012
235,000 women
385,382 cycles
Donor insemination treatment and Gamete/zygote intra−fallopian transfer
8,845 women
0 cycles
Treatment involving, and subsequent to, surrogate pregnancy
623 women
839 cycles
Treatment involving, and subsequent to, embryo donation, storage, or research
8,027 women
11,508 cycles
First IVF treatment before 2003
23,255 women
31,357 cycles
Treatment in 2011 and 2012
36,775 women
71,649 cycles
Treatment subsequent to an IVF live birth
0 women
12,364 cycles
Eligible cohort
157,475 women
257,665 cycles
Implausible linkage information (first treatment frozen embryo transfer)
528 women
267 cycles
Analysis cohort
156,947 women (99.7% of eligible)
257,398 cycles (99.9% of eligible)

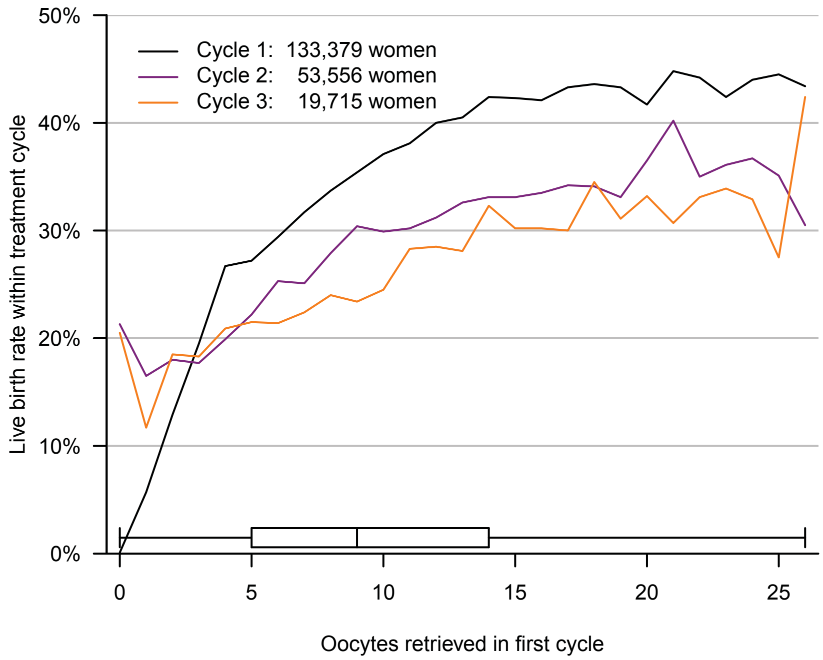


Number of women									
Autologous oocytes and age < 40	133,379	53,568	19,719	6,641	2,357	882	335	131	51
Autologous oocytes and age 40−42	15,561	6,671	2,579	884	301	130	60	36	20
Donor oocytes, all ages	3,587	1,636	939	554	287	126	53	27	8



Number of women

	1	2	3	4	5	6	7	8	9
No male cause	93,924	37,161	13,645	4,680	1,765	690	277	119	51
Male cause, partner sperm, no ICSI	12,536	4,207	1,478	471	148	70	30	15	3
Male cause, partner sperm and ICSI	48,016	21,006	8,203	2,911	1,015	377	141	57	24
Male cause, donor sperm	2,471	1,079	420	177	84	25	10	8	5


Cycle 1: 133,379 women
Cycle 2: 53,556 women
Cycle 3: 19,715 women
50%
40%
30%
20%
10%
0%
Live birth rate within treatment cycle
0
5
10
15
20
25
Oocytes retrieved in first cycle