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1 **Revision 2: 19th November 2015**

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

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10

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15

16 **Abstract**

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

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

20 **Design, Setting and Participants:** Prospective study of 156,947 UK women who received
21 257,398 IVF ovarian stimulation cycles between 2003 and 2010 and were followed until June
22 2012.

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

25 **Main Outcome(s):** Live-birth rate per IVF cycle and the cumulative live-birth rates across all
26 cycles in all women and by age and treatment type. Optimal, prognosis-adjusted and
27 conservative cumulative live-birth rates were estimated, reflecting 0%, 30% and 100% of
28 women discontinuing due to poor prognosis and having a live-birth rate of zero had they
29 continued.

30 **Results:** In all women the live-birth rate for the first cycle was 29.5% (95%CI: 29.3, 29.7).
31 This remained above 20% up to and including the fourth cycle. The cumulative prognosis-
32 adjusted live-birth rate across all cycles continued to increase up to the ninth, with 65.3%
33 (64.8, 65.8) of women achieving a live-birth by the sixth cycle. In women younger than 40
34 using their own oocytes, the live-birth rate for the first cycle was 32.3% (32.0, 32.5), and
35 remained above 20% up to and including the fourth cycle. Six cycles achieved a cumulative
36 prognosis-adjusted live-birth rate of 68.4% (67.8, 68.9). For women aged 40-42, the live-birth
37 rate for the first cycle was 12.3% (95%CI: 11.8, 12.8), with six cycles achieving a cumulative
38 prognosis-adjusted live-birth rate of 31.5% (29.7, 33.3). For women older than 42 years all
39 rates within each cycle were less than 4%. No age differential was observed among women
40 using donor oocytes. Rates were lower in those with untreated male factor infertility

41 compared to those with any other cause, but treatment with either intra-cytoplasmic sperm
42 injection or sperm donation removed this difference.

43 **Conclusions and relevance:** Among women in the UK undergoing IVF, the cumulative
44 prognosis-adjusted live-birth rate after six cycles was 65.3%, with variations by age and
45 treatment type. These findings support the efficacy of extending the number of IVF cycles
46 beyond three or four.

47

48 **Introduction**

49 In-vitro fertilization (IVF) is commonly stopped after three or four unsuccessful embryo
50 transfers,^{1,2} with three unsuccessful transfers labelled ‘repeat implantation failure’.³ This
51 practice has been influenced by a study of 1,328 embryo transfers undertaken twenty-years
52 ago, without use of intra-cytoplasmic sperm injection (ICSI), which reported a decline in
53 live-birth rates after the fourth cycle.⁴ With one exception,⁵ previous studies of cumulative
54 pregnancy or live-birth rates have been relatively small, with limited ability to precisely
55 estimate cumulative success beyond four transfers.^{4,6-9} Previous studies have defined a cycle
56 of IVF as an embryo transfer.⁵⁻⁹ Thus, each initiation of IVF with ovarian stimulation has
57 been treated as several separate cycles whenever there has been a series of repeated embryo
58 transfers. Given the promotion of single embryo transfer and the effective freezing of
59 embryos have increased markedly over the last 10-15 years,¹⁰⁻¹⁵ it has been suggested that
60 IVF success should be calculated as the live-birth rate per initiated ovarian stimulation,
61 including all subsequent separate fresh and frozen embryo transfers.^{5,10-13}

62

63 The aim of this study was to determine the extent to which repeat IVF cycles continue to
64 increase the likelihood of a live-birth, defining an IVF cycle as the initiation of treatment with
65 ovarian stimulation and all resulting separate fresh or frozen embryo transfers; hereafter we
66 use the term “cycle” for this. Specific objectives were to determine: (i) the live-birth rate
67 within each cycle, and the cumulative rate across all cycles; (ii) how these varied by age and
68 treatment types (use of donor oocyte, ICSI or sperm donation); and (iii) the association
69 between oocyte yield in one cycle and live-birth rate in subsequent cycles.

70

71 **Methods**

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

87

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

93

94 Live-birth was defined as an infant born alive after 24 weeks gestation surviving more than
95 one month. The World Health Organisation (WHO) define live-birth as a birth showing any
96 sign of life irrespective of gestational age. As in other studies,^{5, 15,16} we modified this to

97 capture births that were likely to be viable. We defined an IVF cycle as the initiation of
98 ovarian stimulation and all resulting separate fresh or frozen embryo transfers. The live-birth
99 rate within a cycle was defined as the probability of a live-birth from an ovarian stimulation
100 encompassing all subsequent fresh and frozen embryo transfers from that stimulation. Thus,
101 for those embarking on IVF the live-birth rate within one cycle answers the question ‘*What is*
102 *my chance of a live-birth with one stimulation and retrieval of oocytes followed by as many*
103 *subsequent separate embryo transfers as possible from that retrieval?*’ The cumulative live-
104 birth rate at a given cycle was defined as the probability of a live-birth from all cycles up to
105 and including that cycle. This answers the question ‘*What is my total chance of a live-birth*
106 *with repeat ovarian stimulation and oocyte retrievals, together with the subsequent embryo*
107 *transfers from each cycle, up to a given cycle number?*’.

108

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

111

112 ***Statistical methods***

113 We calculated the live-birth rates within the first and subsequent cycles up to the ninth, as the
114 proportion of cycles resulting in a live-birth, using a normal approximation to construct
115 confidence intervals. We calculated estimates of cumulative live-birth rates using different
116 assumptions of women who discontinue IVF without a live birth (see below), up to the ninth
117 cycle, using the Kaplan-Meier method with Greenwood’s approximation to calculate
118 confidence intervals (see online supplementary material for full details).^{17,18} We used a log-
119 rank test¹⁹ to compare the live-birth rate within each cycle and cumulatively across all cycles.
120 The first set of comparisons was between woman’s age and oocyte source category and the
121 second was between no male cause of infertility and male cause of infertility with and

122 without treatment by ICSI or sperm donation. We assessed the relationship of oocyte yield in
123 one cycle to live-birth rates in subsequent cycles in women younger than 40 years using their
124 own oocytes, by calculating the within live-birth rate in the first, second, and third cycles by
125 oocytes retrieved in the first cycle, and also calculating the within live-birth rate up to the
126 fifth cycle by oocytes retrieved in the immediately preceding cycle.

127

128 *Dealing with discontinuation of IVF*

129 Infertile couples discontinue IVF for a number of reasons, with a systematic review of patient
130 perceptions concluding that the commonest reasons were the physical and/or psychological
131 burden of treatment, relationship or personal problems.²⁰ In any study estimating cumulative
132 live-birth rates assumptions have to be made about what the rate in those who discontinue
133 would have been had they continued. To account for this we calculated ‘optimal’ and
134 ‘conservative’ estimates, which are the have been assessed in previous studies. In addition we
135 calculated a prognostic-adjusted estimate. The optimal estimate, is based on the observed
136 data, and whilst not always explicit in previous publications, this assumes that the cumulative
137 live-birth rate in women who discontinue IVF without a live-birth, if they had continued
138 would be equal to the rate in those who continue to have further cycles.⁵ The conservative
139 estimate assumes those who discontinue IVF would have had a subsequent live-birth rate of
140 zero.⁵ The true rate is thought to lie between these two.⁷ The prognostic-adjusted estimate
141 aims to obtain this more realistic value. It assumes a fixed proportion of those who
142 discontinue do so because of poor prognosis and that the live-birth rate in that proportion
143 would have been zero, whereas for those who discontinue for other reasons, such as inability
144 to pay, emotional distress or (in our dataset) emigration from the UK, it would have been
145 similar to those who continue with treatment.

146

147 For the prognosis-adjusted estimate we considered the woman's age at her first cycle and
148 oocyte yield in the previous cycle to be the strongest prognostic factors, because these have
149 been shown to be strongly related to live-birth success.^{5,7,9,21,22} We checked that these were
150 indicators of live-birth and of discontinuation of treatment in our own data, as well as
151 comparing other available characteristics between those who discontinued and continued
152 treatment after one unsuccessful cycle. To obtain age-adjusted and oocyte yield-adjusted
153 estimates we calculated results for each age strata (18-34, 35-37, 38-39, 40-42, 43-44, 45-50,
154 50+ years) and for each possible oocyte-yield in the previous cycle and then obtained an
155 average, weighted by the numbers within each category in the first cycle. It was not possible
156 to calculate an age-adjusted estimates for the age stratified analyses as there is too little age
157 variation within the age strata. For any analyses that include women using donor oocytes it is
158 not possible to calculate rates adjusted for oocyte yield in the previous cycle as women using
159 donor oocytes will not have an oocyte yield.

160

161 The age and previous oocyte yield adjusted results suggested that 3% of those who
162 discontinued IVF did so because of poor prognosis. However, to calculate a prognostic-
163 adjusted cumulative live-birth rate we assumed 30% of those who discontinued did so
164 because of poor prognosis. We chose a value of ten-times that suggested by our data to obtain
165 a conservative prognostic-adjusted estimate. Full details of how these estimates were
166 calculated are provided in online supplementary material.

167

168 As the average population live-birth success rate for a single embryo transfer is between 20-
169 30% in high income countries,¹⁰⁻¹³ we considered 20% to be a benchmark for a good live-
170 birth rate within a cycle. All analyses were undertaken in Stata version 13 MP2. Two-sided p-
171 values < 0.05 were considered to provide evidence against the null hypothesis.

172

173 ***Comparison with live-birth rates in those not receiving ART***

174 We used data on pregnancy and pregnancy loss rates from published literature to estimate
175 live-birth rates in women who conceive naturally.²³⁻²⁵⁴ Two prospective cohort studies of
176 couples actively trying to conceive provided age specific pregnancy rates attained within
177 twelve menstrual cycles.^{23,24} Live birth rates were calculated assuming 20% of natural
178 conceptions result in a pregnancy loss.²⁵

179

180 **Results**

181 Following planned exclusions the eligible cohort included 257,665 cycles in 157,475 women.
182 For all analyses we excluded women with missing linkage information or implausible linkage
183 (i.e. first IVF transfer being a frozen embryo transfer without preceding ovarian stimulation).
184 This resulted in an analysis cohort of 257,398 cycles by 156,947 women (more than 99% of
185 the eligible cohort; **Figure 1**). **Table 1** shows the characteristics of the cohort. **eTable 1**
186 shows characteristics by year of treatment. Because of the large sample size there was
187 statistical evidence of differences in all characteristics, but for most these were small and
188 unlikely to be clinically important. For example, median age of the women differed by one-
189 year and median oocyte retrieval differed by one across the study period. Use of ICSI
190 increased by 11%, and transfer of single embryos by 17%, though the live-birth rate increased
191 by just two-percent across the study period.

192

193 **Table 2** shows the live-birth rate within each cycle for the whole cohort. In all women the
194 live-birth rate for the first cycle was 29.5% (95%CI: 29.3, 29.7). The live-birth rate within
195 cycles remained above 20% for each cycle up to and including the fourth. After their first
196 cycle there were 110,614 women (70.5% of the analysis cohort) who did not have a live-

197 birth. Of these, 37,704 (34.1%) discontinued treatment and 72,910 (65.9%) had at least one
198 more cycle. **eTable 2** compares characteristics between these two groups. Although there was
199 statistical evidence of differences for all characteristics the actual differences were small.

200

201 The cumulative live-birth rate continued to increase up to the ninth cycle, with a cumulative
202 prognosis-adjusted live-birth rate of 65.3% (64.8, 65.8) by the sixth cycle (**Table 2**). The
203 equivalent optimal (78.0% (77.3, 78.8)) and age-adjusted (76.7% (76.0, 77.5)) estimates for
204 six cycles were similar, while the conservative estimate was 46.8% (46.5, 47.0) (**Table 2 and**
205 **eFigure 1**).

206

207 Results varied by age and oocyte source (**Figure 2, Table 3, eTables 3 and 4**). In women
208 who were younger than 40 years and using their own oocytes (133,379 women, 85% of the
209 cohort), the live-birth rate for the first cycle was 32.3% (32.0, 32.5). This remained above
210 20% up to and including the fourth cycle. The previous cycle oocyte-yield adjusted and
211 optimal estimates were similar. Six cycles achieved cumulative live-birth rates of 68.4%,
212 (67.8, 68.9), 80.3% (79.5 to 81.0) and 50.7% (50.5, 51.0), for the prognostic-adjusted,
213 optimal and conservative estimates, respectively. For women aged 40-42, the live-birth rate
214 for the first cycle was 12.3% (11.8, 12.8), with six cycles achieving a cumulative live-birth
215 rates of 31.5% (29.7, 33.3), 41.5% (38.0, 44.9), and 19.2% (18.5, 19.8) for prognostic-
216 adjusted, optimal and conservative estimates, respectively. For women older than 42 years all
217 rates within each cycle were less than 4% or based on too few live-births to calculate
218 confidence intervals.

219

220 Use of donor oocytes removed this age differential, as the log-rank test showed no evidence
221 for different cumulative live-birth rates between age categories (**eTable 3**). Irrespective of

222 age, women using donor oocytes achieved live-birth rates within each cycle of 29.6% or
223 greater for all cycles up to and including the ninth and a cumulative live-birth rate after six
224 cycles of 86.7% (85.2, 88.3), 91.7% (90.3, 93.1) and 75.5% (74.0, 77.1) for the prognostic-
225 adjusted, optimal and conservative estimates, respectively (**eTable 4**).

226

227 Live-birth rates varied by male cause infertility and its treatment (**Figure 3 and eTables 5 to**
228 **7**). Women whose infertility was due to a male related cause and who were not treated with
229 either ICSI or donor sperm had lower live-birth rates than those with a non-male cause of
230 infertility (**eTables 3 and 5**). Those with a male cause of infertility who were treated with
231 ICSI had cumulative live-birth rates, after six cycles, of 71.3% (70.5, 72.1), 82.2% (81.1,
232 83.4) and 54.7% (54.3, 55.2) using the prognostic-adjusted, optimal and conservative,
233 estimates, respectively (**eTable 6**). Equivalent results for those with male infertility treated
234 with donor sperm were 81.2% (78.6, 83.9), 90.2% (87.2, 93.1) and 65.9% (63.9, 67.9)
235 respectively (**eTable 7**). Live-birth rates in both of these groups were greater than in those
236 with a non-male cause of infertility (**eTables 3 and 8**).

237

238 **Figure 4** shows the live-birth rate within the first, second and third cycles plotted against the
239 number of oocytes retrieved in the first cycle in women under 40 years of age using their own
240 oocytes. For those in whom no oocytes were retrieved in the first cycle the live-birth rates in
241 the second and third cycles were greater than 20%. The live-birth rates in the first, second and
242 third cycles continued to increase with increasing oocytes retrieved in the first cycle up to
243 around 15 oocytes; thereafter the curves flatten. Plotting the live-birth rate within any cycle
244 against the number of oocytes retrieved in the previous cycle gave a similar pattern (**eFigure**
245 **2**).

246

247 Using published data²³⁻²⁵ we estimated that the live-birth rate for women conceiving
248 naturally, who had been trying for 12 menstrual cycles, varied between 58% and 74%
249 depending on the woman's age and frequency of intercourse (**eTable 9**). These estimates are
250 based on studies that only included women younger than 40. Similar cumulative live-birth
251 rates were achieved by the fifth or sixth cycle of IVF treatment in women of this age (**Table**
252 **3**), though, in these women, five cycles took a median of 2 years (1st, 3rd quartile: 2, 3).

253

254 **Discussion**

255 To our knowledge this is the first study to have linked fresh and frozen embryo transfers to
256 obtain estimates of live-birth rate within each IVF ovarian stimulation cycle and cumulative
257 live-birth rates across repeated stimulation cycles. Despite a decline in the success rate within
258 each cycle as the number of these increased, the cumulative rate across cycles increased up to
259 the ninth in the whole cohort, those younger than 40 (using their own oocytes) and those
260 using donor oocytes (irrespective of age). They also increased up to the eighth or ninth in
261 women aged 40-42, though for women older than 42 (using their own oocytes) the likelihood
262 of success was low and the cumulative live-birth rate did not appear to clearly increase
263 beyond the fourth or fifth cycle. For those women able to use donor oocytes, age was
264 unrelated to success. In those for whom the cause of infertility was related to a male partner
265 problem, treatment with ICSI or donor sperm made a marked difference in the likelihood of
266 success, with cumulative rates increasing up to the eighth or ninth cycle, whereas without
267 treatment rates were lower than in those with other causes of infertility. In women under 40
268 years with a low oocyte yield in a previous cycle there was benefit in continuing with further
269 cycles. We also found women under 40 years could achieve cumulative live-birth rates after
270 five or six cycles that were similar to published live-birth rates achieved naturally within 12

271 menstrual cycles.²³⁻²⁵ It should be noted, however, that, in these women, five cycles took a
272 median of 2 years.

273

274 Widespread adoption of single embryo transfer has reduced multiple pregnancies and adverse
275 perinatal outcomes, but has meant that the chance of a live-birth from a single ovarian
276 stimulation cycle is spread across multiple embryo transfers, which we have assessed here.
277 Since this method of assessing IVF success combines all embryo transfer events following an
278 ovulation stimulation into one analysis unit, we were unable to examine the effect of the
279 number of embryos transferred per event. However, this method of assessing IVF success is
280 increasingly recommended.^{5,10-13} Our results show how success rates per embryo transfer
281 event are misleadingly lower, compared with the rate within each ovarian stimulation cycle.
282 Furthermore, we have previously shown, using unlinked data from the same population, that
283 the number of embryos transferred in one event has a relatively modest effect on live-birth
284 rate, with a difference of 9% in women younger than 40 years and 16% in those aged 40
285 years or older, comparing double to single embryo transfer.¹⁵

286

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

295

296 The key limitation of all studies looking at cumulative outcomes with repeat IVF is how one
297 treats those who discontinue treatment. As seen in our data, and in previous studies,^{5,7} the
298 extremes of the optimal and conservative estimates often vary markedly, for example in our
299 data the optimal and conservative estimates were 78.0% and 46.8%, respectively, for the
300 whole cohort. This is because of the differences between these two, in what they assume
301 would have been the live-birth rate in those who discontinued IVF, had they continued; for
302 the optimal estimate this is assumed to be the same as those who did continue, whereas the
303 conservative estimate it is assumed to be zero. We examined the likelihood that such
304 discontinuation was due to poor prognosis based on age and previous cycle oocyte retrieval.
305 These analyses suggested approximately 3% of those who discontinued did so because of
306 poor prognosis. This small proportion was because although these two were important
307 predictors of live-birth, few women receiving IVF are older than 40 years (only 15% in our
308 national population cohort) and most women have a high oocyte yield (median 9 per cycle in
309 our cohort). However, to account for other factors, for example pre-treatment reproductive
310 hormone levels, smoking and body mass index (BMI), which have been linked to live-birth
311 success,^{7,22} but that were not available in this study, we assumed a 30% discontinuation due
312 to poor prognosis. Because of the legal requirement for all UK clinicians to provide data on
313 all ART patients, the HFEA were able to link cycles to individual women even if they moved
314 between clinics within the UK. However, treatment abroad would be absent from our data. A
315 European study, conducted 6 years ago, found very few UK couples travelled for ART to 49
316 clinics in six (non-UK) European countries with high rates of cross-border patients.²⁶ We
317 were only able to assess live-birth as an outcome: future studies should also consider
318 potential adverse effects of continued treatment, including ovarian hyper-stimulation
319 syndrome and possible increased risk of preterm birth, low birth weight or congenital
320 anomalies.^{16,27,28}

321

322 We acknowledge that for some couples the emotional stress of repeat treatments may be
323 undesirable and the cost of a prolonged treatment course, with several repeat oocyte
324 stimulation cycles, may be unsustainable for health services, insurers or couples. However,
325 we think the potential for success with further cycles should be discussed with couples. A
326 cost-effectiveness analysis is beyond the scope of this study, and the difficulties of
327 undertaking such analyses for IVF, in which decisions related to how one values a new life
328 and whether ‘benefits’ and ‘costs’ for both parents and the child should be included, are well-
329 documented.²⁹ The costs of IVF treatment vary between countries, whether publicly or
330 privately funded, and the treatment type used, but are in the range of \$14,000 (£9,000,
331 €12,000) to \$17,000 (£11,000, €15,000) per cycle.^{1,29,30} These costs exclude assessment prior
332 to starting IVF and are based on transfer of one fresh embryo. Assuming each additional frozen
333 embryo transfer costs \$4000 to \$5000,³⁰ the cost per couple of continuing to six, rather than
334 having just three cycles, could be as much as \$132,000 compared to \$66,000 (assuming one
335 fresh and one frozen transfer per cycle).

336

337 *Conclusions*

338 Among women in the UK undergoing IVF, the cumulative prognosis-adjusted live-birth rate
339 after six cycles was 65.3%, with variations by age and treatment type. These findings support
340 the efficacy of extending the number of IVF cycles beyond three or four.

341

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

358

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- 439

440 **Figure descriptive titles and legends**

441 **Figure 1: Definition of eligible and analysis cohort**

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

443 **source.**

444 The figure shows the prognosis-adjusted estimates of cumulative live-birth rates (i.e. the rate
445 (shown on the y-axis) is the likelihood of a live-birth across all initiated cycles up to and
446 including the numbers on the x-axis), with 95% confidence intervals. These are presented for
447 women in two different age categories at the start of their first IVF treatment cycle (< 40
448 years and 40-42 years; women in both of these categories used their own oocytes) and also in
449 women who used donor oocytes (these women cover the full age range). Data for women
450 aged over 42 at their first treatment cycle are not shown because rates were so low it would
451 have been difficult to represent them on this same graph (full results for these women are
452 shown in Table 3). The prognostic-adjusted estimate assumes that 30% of those who
453 discontinued IVF did so because of poor prognosis and that the live-birth rate in that 30%
454 would have been zero had they continued. Analyses were completed in 156,947 women
455 undergoing 257,398 cycles. Log-rank tests indicated a difference between the cumulative
456 live-births rates for all groups ($p < 0.001$ for all comparisons).

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

458 **donation.**

459 The figure shows the prognosis-adjusted estimates of cumulative live-birth rates (i.e. the rate
460 (shown on the y-axis) is the likelihood of a live-birth across all initiated cycles up to and
461 including the numbers on the x-axis), with 95% confidence intervals. These are shown for
462 couples without a male cause of infertility, couples with a male cause who were not treated
463 with ICSI or sperm donation, those with a male cause who were treated with ICSI and those
464 with a male cause who used sperm donation. The prognostic-adjusted estimate assumes that

465 30% of those who discontinued IVF did so because of poor prognosis and that the live-birth
466 rate in that 30% would have been zero had they continued. Analyses were completed in
467 156,947 women undergoing 257,398 cycles. Log-rank tests indicated a difference between
468 the cumulative live-births rates for all groups ($p < 0.001$ for all comparisons).

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

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

477

478 **Table 1: Characteristics of the analysis cohort of 156,947 women commencing IVF**
 479 **treatment for infertility in the UK in 2003-2010 (with outcomes assessed up to June**
 480 **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)	9 (5, 13)	9 (5, 13)
Median (1st quartile, 3rd quartile)		
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%)

481 ^a The unit of analysis here is cycle (with results the average across all cycles per woman)

482 ^b As this is just one cycle the unit of analysis is the women at their first treatment cycle

483 ^c As there are a variable number of transfer events per treatment cycle (which includes all
 484 subsequent fresh and frozen transfer events) the % is per the number of transfer events (not
 485 per cycle)

486 **Table 2: Within initiated treatment cycle live-birth rates and cumulative live-birth rate across all cycles in 156,947 women undergoing**
 487 **257,398 cycles of IVF**
 488

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 ^a	Age adjusted estimate ^b	Prognostic-adjusted estimate ^c	Conservative estimate ^d
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)	46.7 (46.4, 47.0)	45.1 (44.9, 45.4)	40.5 (40.3, 40.8)
3rd	23,746	5,358	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)
4th	8,239	1,690	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)
5th	3,012	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)
6th	1,162	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)
7th	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)
8th	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)
9th	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)

489 ^a The optimal estimate assumes that the cumulative live-birth rate in women who discontinue IVF without a live-birth, if they had continued,
 490 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
 491 so because of poor prognosis that would have affected their live-birth success had they continued.
 492
 493 ^b The age-adjusted estimate assumes that the cumulative live-birth rate in women who discontinued IVF, if they had continued, would have been
 494 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
 495 approximately 3% of women who discontinued did so because of poor prognosis and would have had a live-birth rate of zero, had they
 496 continued.
 497 ^c The prognostic-adjusted estimate assumes that 30% of women who discontinued IVF did so because of poor prognosis and would have had a
 498 live-birth rate of zero, had they continued.
 499 ^d The conservative estimate assumes that the cumulative live-birth rate in all women who discontinued IVF would have been zero, had they
 500 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
 501 zero, had they continued.
 502 Note it is not possible to calculate an oocyte-adjusted estimate for the whole cohort due to the presence of women using donor oocytes.

503
504
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Table 3: Within initiated treatment cycle live-birth rates and cumulative live-birth rate across all cycles in 153,360 women, undergoing 250,175 cycles of IVF using their own oocytes, stratified by age at first ovarian stimulation cycle.

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 ^a	Previous oocyte yield-adjusted estimate ^b	Prognostic-adjusted estimate ^c	Conservative estimate ^d
Aged less than 40 years							
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)	50.7 (50.4, 51.1)	48.7 (48.4, 49.0)	44.3 (44.0, 44.5)
3rd	19,719	4,793	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)
4th	6,641	1,419	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)
5th	2,357	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)
6th	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)
7th	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)
8th	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)
9th	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)
Aged 40 to 42 years							
1st	15,561	1,914	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)
2nd	6,671	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)
3rd	2,579	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)
4th	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)
5th	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)
6th	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)
7th	60	2	3.3 [†]	43.4 (39.1, 47.7)	42.4 (38.4, 46.3)	32.2 (30.2, 34.2)	19.2 (18.6, 19.9)
8th	36	1	2.8 [†]	45.0 (39.8, 50.1)	43.4 (39.1, 47.6)	32.7 (30.5, 34.9)	19.2 (18.6, 19.9)
9th	20	0	0.0 [†]	45.0 (39.8, 50.1)	43.4 (39.1, 47.6)	32.7 (30.5, 34.9)	19.2 (18.6, 19.9)
Aged more than 42 years							
1st	4,420	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)
2nd	1,578	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)
3rd	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)

4th	160	2	1·3 [†]	11·1 (8·8, 13·4)	10·1 (8·5, 11·8)	8·9 (7·4, 10·5)	5·5 (4·8, 6·2)
5th	67	3	4·5 [†]	15·1 (10·2, 20·0)	14·2 (10·7, 17·7)	10·7 (8·2, 13·2)	5·5 (4·8, 6·2)
6th	24	0	0·0 [†]	15·1 (10·2, 20·0)	14·2 (10·7, 17·7)	10·7 (8·2, 13·2)	5·6 (4·9, 6·3)
7th	10	2	20·0 [†]	32·1 (10·7, 53·5)	22·3 (14·0, 30·5)	15·9 (8·5, 23·2)	5·6 (4·9, 6·3)
8th	5	0	0·0 [†]	32·1 (10·7, 53·5)	22·3 (14·0, 30·5)	15·9 (8·5, 23·2)	5·6 (4·9, 6·3)
9th	4	0	0·0 [†]	32·1 (10·7, 53·5)	22·3 (14·0, 30·5)	15·9 (8·5, 23·2)	5·6 (4·9, 6·3)

506

507 ^a The optimal estimate assumes that the cumulative live-birth rate in women who discontinue IVF without a live-birth, if they had continued,
508 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
509 so because of poor prognosis that would have affected their live-birth success had they continued.

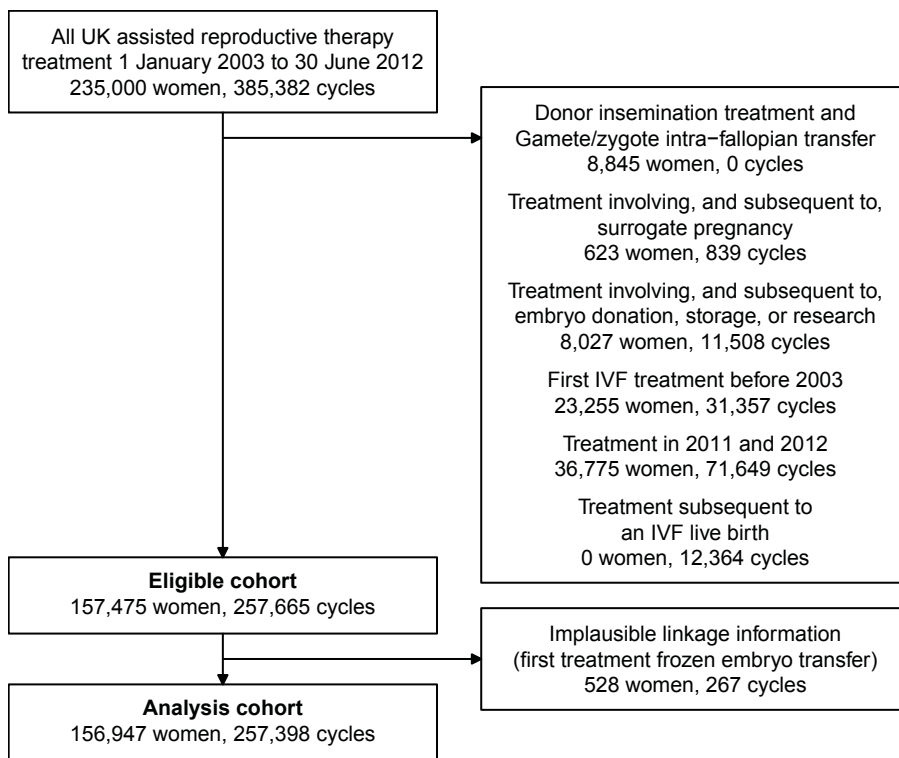
510 ^b The previous oocyte yeild-adjusted estimate assumes that the cumulative live-birth rate in women who discontinued IVF, if they had continued,
511 would have been equal to the rate in women who had the same oocyte yield in the immediately previous ovarian stimulation treatment, and who
512 continued to have further IVF. These results suggested approximately 3% of women who discontinued did so because of poor prognosis and
513 would have had a live-birth rate of zero, had they continued.

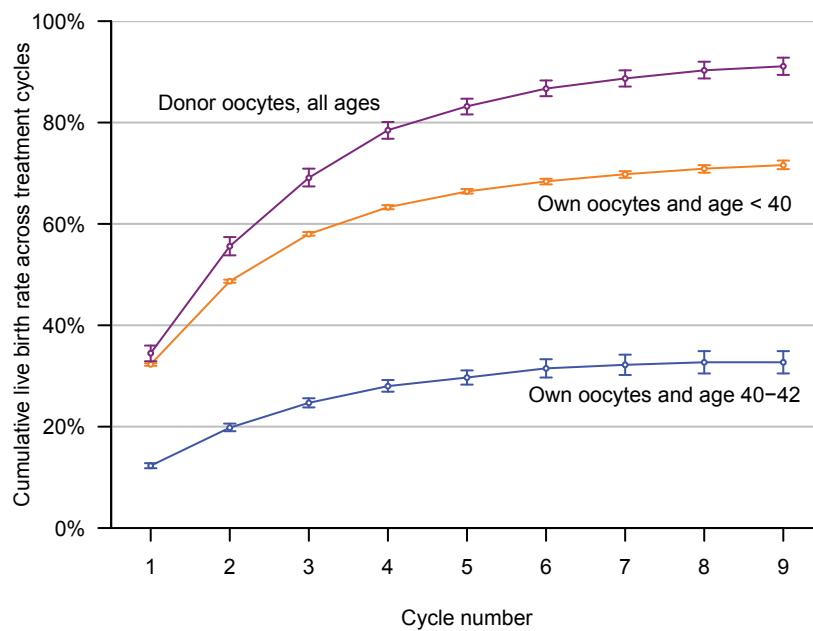
514 ^c The prognostic-adjusted estimate assumes that 30% of women who discontinued IVF did so because of poor prognosis and would have had a
515 live-birth rate of zero, had they continued.

516 ^d The conservative estimate assumes that the cumulative live-birth rate in all women who discontinued IVF would have been zero, had they
517 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
518 zero, had they continued.

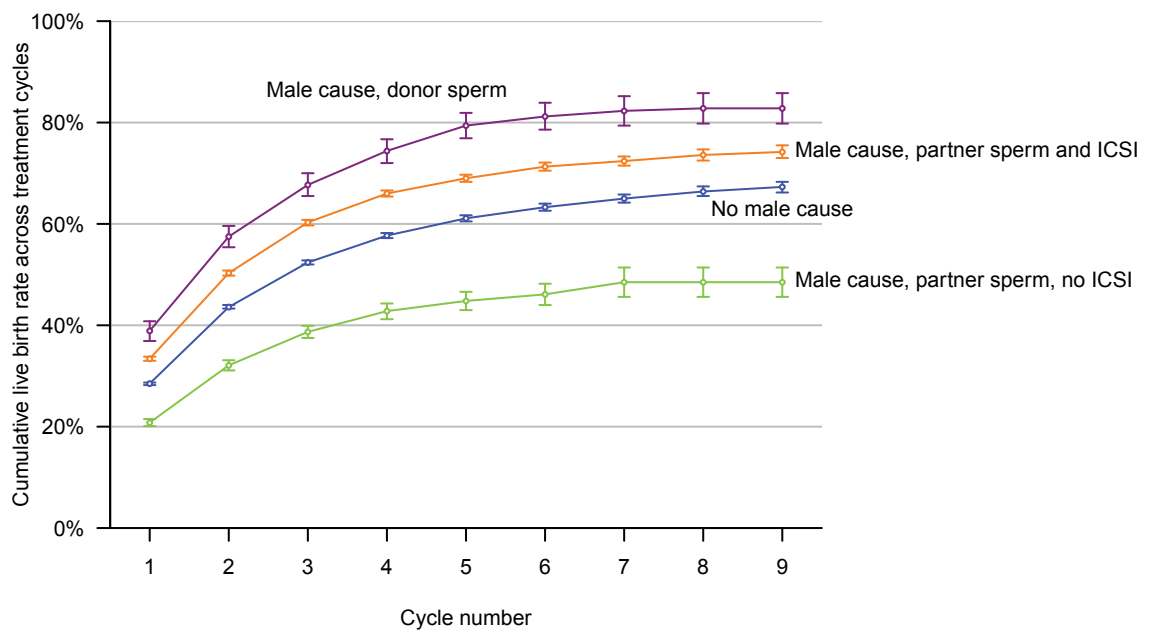
519 Note it is not possible to calculate an age-adjusted estimate these age stratified analyses and there is too little age variation within the ages
520 stratified groups to further adjust for age.

521 [†] These are cycles for which there was fewer than six live births and for these standard errors and hence confidence intervals could not be
522 calculated





Number of women	1	2	3	4	5	6	7	8	9
Own oocytes and age < 40	133,379	53,568	19,719	6,641	2,357	882	335	131	51
Own oocytes and age 40-42	15,561	6,671	2,579	884	301	130	60	36	20
Own oocytes and age > 42	4,420	1,578	509	160	67	24	10	5	4
Donor oocytes, all ages	3,587	1,636	939	554	287	126	53	27	8



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

