

1 **Treatment-independent live birth after in-vitro fertilisation: a**
2 **retrospective cohort study of 2,133 women**

3
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21 **Running title:** Treatment independent live birth after IVF

22

23 **Abstract**

24 **Study question:** What is the chance of a treatment-independent live birth following IVF
25 (including ICSI) treatment?

26 **Summary answer:** Over five years of follow-up, the treatment-independent live birth rate
27 was 17% in unsuccessfully treated women and 15% in those who had a live birth after IVF.

28 **What is known already:** A limited number of studies have investigated the chance of
29 treatment-independent conception following completion of IVF, but most of them have
30 been based on surveys with poor response rates and limited sample sizes.

31 **Study design, size, duration:** This is a population-based, retrospective cohort study of 2,133
32 women who received IVF treatment between 1998 and 2011 at a single regional IVF Unit
33 and were followed for a minimum of one year and maximum of 15 years after their last IVF
34 or ICSI treatment cycle.

35 **Participants/materials, setting, methods:** This study included all women, residing in the
36 North-East of Scotland, who attended the Aberdeen Fertility Clinic and received IVF
37 treatment between 1998 and 2011. Clinical and diagnostic information of all women were
38 linked with treatment and pregnancy outcome data. A total of 2,133 women were divided
39 into two groups: a) those who achieved a live birth following successful IVF or ICSI
40 treatment (n=1,060); and b) those in whom treatment was unsuccessful i.e. resulted in
41 either no pregnancy or pregnancy loss (n=1,073). The two groups were followed from the
42 date of the last embryo transfer until the first treatment-independent live birth or 31st
43 December 2012, whichever came first. The primary outcome was the treatment-
44 independent live birth rate at one, two and a half, five and ten years of follow up. Cox
45 regression was used to determine factors associated with treatment-independent live birth
46 in each group.

47 **Main results and the role of chance:** Within five years of follow up, the treatment-
48 independent live birth rate was 17% (95% CI, 15%-19%) among women whose IVF or ICSI
49 treatment was unsuccessful and 15% (95% CI, 12%-17%) among women whose treatment
50 resulted in live birth. In both groups, shorter duration of infertility, younger female age and
51 IVF as compared to ICSI were associated with a higher chance of achieving treatment-
52 independent live birth. Among unsuccessfully treated women, the chance of post-IVF live
53 birth was reduced in those with tubal factor infertility. Three or more previous IVF or ICSI
54 embryo transfers were associated with a lower chance of treatment-independent live birth
55 among successfully treated women.

56 **Limitations, reasons for caution:** The study was conducted in a single fertility centre, which
57 could compromise the generalisability of the findings. Moreover, data were unavailable on
58 the women's use of contraception or active attempts to get pregnant, both of which could
59 influence treatment-independent live birth rates.

60 **Wider implications of the findings:** This study provides a better understanding of the long-
61 term prognosis for treatment-independent live birth after completion of IVF or ICSI
62 treatment. The results will inform women of their chances of a treatment-independent live
63 birth following failed or successful treatment and the factors which are associated with it.

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68 **Trial registration number:** N/A

69 **Key words:** IVF/ICSI outcome, treatment independent live birth, infertility, live birth rate,
70 duration of infertility, female age

71 **Introduction**

72 Infertility affects around one in six couples in the UK (Oakley et al. 2008). Conventional in-
73 vitro insemination (IVF), as well as intracytoplasmic sperm injection (ICSI), are the
74 recommended treatments for women with prolonged unresolved infertility (National
75 Institute for Health and Clinical Excellence 2013). The number of cycles and embryo
76 transfers of IVF or ICSI treatment in the UK has increased almost three-fold over 20 years
77 from 18,304 in 1994 to 52,288 in 2014 (Human Fertilisation and Embryology Authority 2016,
78 Human Fertilisation and Embryology Authority 2007). While initially used to treat women
79 with tubal disease, the scope of IVF has expanded in the last two decades to embrace a
80 wider range of indications, including unexplained and mild male factor infertility where
81 there is no identified barrier to pregnancy (Kamphuis et al. 2014).

82 Although the success rate per cycle of IVF in the UK has doubled from 14% in 1994 to
83 around 27% in 2014 (Human Fertilisation and Embryology Authority 2007, Human
84 Fertilisation and Embryology Authority 2016), these figures show that the majority of
85 women still do not become pregnant after their first IVF or ICSI cycle (de Mouzon et al.
86 2010, Human Fertilisation and Embryology Authority 2016, McLernon et al. 2016). Most
87 discontinue treatment after their first attempt due to the psychological and physical burden
88 of treatment as well as financial constraints (Deka and Sarma 2010, Gautam 2010, Nandi et
89 al. 2014, McLernon et al. 2016). Although women who have no absolute barrier to
90 conception retain the ability to conceive on their own, many equate unsuccessful treatment
91 with the end of any hope of having a baby (Throsby 2002).

92 Few studies have reported treatment-independent live birth rates after IVF treatment and
93 explored factors associated with them. In a recent record-linkage cohort study of women
94 starting treatment with assisted reproductive technology (ART) and followed for up to 5

95 years, the rate of treatment-independent live births was 11% (Malchau et al. 2017). In a
96 French survey, about 17% and 24% of women achieved a spontaneous pregnancy following
97 either successful or unsuccessful IVF (Troude et al. 2012). Younger female age and shorter
98 infertility duration have been shown to be associated with treatment-independent live birth
99 (Shimizu et al. 1999, Hennelly et al. 2000, Osmanagaoglu et al. 2002, Brandes et al. 2010,
100 Khalili et al. 2012, Troude et al. 2012). Women with unexplained infertility had better
101 prognosis in comparison with those with other causes of infertility (Eijkemans et al. 2008,
102 Donckers et al. 2011). Many of these studies have relatively small sample sizes, a short
103 duration of follow-up or, in the case of surveys, poor response rates (Shimizu et al. 1999,
104 Osmanagaoglu et al. 2002, Cahill et al. 2005, Troude et al. 2016). As a result, it is difficult to
105 determine with any degree of accuracy, the chance of a treatment-independent pregnancy
106 or the clinical factors which affect this.

107 We conducted a population-based cohort study to determine the incidence of women who
108 had a treatment-independent live birth following: a) IVF or ICSI treatment which resulted in
109 a live birth (successful group) or b) IVF or ICSI treatment which did not result in a live birth
110 (unsuccessful group). We also aimed to identify factors in each group that were associated
111 with treatment-independent live birth.

112

113 **Methods**

114 ***Study population***

115 This population-based cohort study included all women residing in the North-East of
116 Scotland who were referred to Aberdeen Fertility Clinic for investigation and subsequently
117 received IVF (including ICSI) treatment at the Aberdeen Assisted Reproduction Unit between
118 January 1998 and December 2011. Aberdeen Assisted Reproduction Unit is the only centre

119 that provides private and NHS funded IVF treatment in the North-East Scotland region
120 (Grampian, Highlands, Orkney, and Shetland regions) (Pandey et al. 2014).

121 The following exclusion criteria were applied: a) women aged less than 18 or over 50 at the
122 beginning of their IVF treatment; b) women who underwent their first treatment before
123 January 1998 or after December 2011; c) women residing in the Orkney and Shetland
124 regions; and d) women who were treated using donor sperm, donor oocytes or surrogacy.

125 Of the 3091 women who underwent IVF or ICSI treatment in the Aberdeen Assisted
126 Reproduction Unit during the chosen time period, 2,133 were included in our study after
127 applying the exclusion criteria (see Figure 1).

128

129 ***Study groups and follow up***

130 The cohort of 2,133 women were divided into two groups: a “successfully treated group” of
131 1,060 women who had a live birth resulting from IVF treatment and an “unsuccessfully
132 treated group” of 1,073 women whose treatment did not result in a live birth. Women in
133 the first group were followed from treatment-dependent live birth until: treatment-
134 independent live birth, they returned to the clinic with a different male partner or 31st
135 December 2012, whichever came first. Women in the second group were followed from the
136 first menstrual cycle after unsuccessful IVF treatment until: treatment-independent live
137 birth, they returned to the clinic with a different male partner or 31st December 2012,
138 whichever came first.

139

140 ***Databases***

141 Aberdeen Fertility Centre database holds registration and demographic data of all infertile
142 women referred to the Aberdeen Assisted Reproduction Unit (Pandey et al. 2014). The

143 Assisted Reproduction Unit database, which contains treatment details, was record-linked
144 to the Aberdeen Fertility Centre database (Maheshwari et al. 2009). Diagnostic and
145 treatment data from both databases were also record-linked to the national Scottish
146 maternity admission database (SMR02). SMR02 stores maternity admission records which
147 provided the pregnancy outcomes for women in this study (Administrative Data Liaison
148 Service 2017). Live birth data was available until December 2012 meaning that all women
149 were followed for at least one year after their last embryo transfer. The final linked
150 anonymised data was stored on the dedicated secure Data Safe Haven (DaSH) University of
151 Aberdeen server with access restricted to named and approved researchers only.

152

153 ***Baseline characteristics***

154 Baseline characteristics of women at treatment dependent live birth (for the successful
155 group) or after their final IVF cycle (for the unsuccessful group) included female age (years),
156 the cause of infertility (categorised as male factor, unexplained infertility, tubal factor,
157 ovulatory disorder, more than one cause or other), number of fresh or frozen embryo
158 transfers conducted, duration of infertility (years), infertility type (primary versus secondary)
159 and treatment type (IVF or ICSI).

160

161 ***Outcome***

162 The primary outcome was the treatment-independent live birth rate at one, two and a half,
163 five and ten years of follow up. The final linked dataset enabled us to identify all treatment-
164 dependent and treatment-independent live births from the same woman. Gestational age
165 at birth, which was recorded in the national Scottish maternity admission database

166 (SMR02), was used to identify and code live births as treatment independent or treatment
167 dependent by comparing the estimated pregnancy dates to dates of embryo transfer.

168

169 ***Statistical analysis***

170 Descriptive statistics of women and treatment characteristics were calculated at the time of
171 treatment-dependent live birth (successful group) or after the last IVF cycle (unsuccessful
172 group). The frequency and percentage were used for categorical data and means and
173 standard deviations for normally distributed data. For skewed data, median and the 25th
174 and 75th percentiles were presented.

175

176 ***Treatment independent live birth***

177 We estimated the treatment independent live birth rate at one, two and a half, five and ten
178 years of follow up in both the “successful” and “unsuccessful” groups by fitting a Kaplan-
179 Meier curve for time to pregnancy and calculated the median follow up in both groups.

180

181 ***Factors associated with treatment independent live birth***

182 A multivariable Cox regression model was used per “successful” and “unsuccessful” group to
183 examine the association between baseline characteristics and time-to-treatment-
184 independent live birth. In addition to the baseline characteristics, the year of IVF treatment
185 was included to account for changes in policy and practice.

186 A backward stepwise selection technique was used with a decrease in Akaike’s Information
187 Criterion (AIC) when a variable was removed representing a better fit (Akaike, 1974).

188 Statistical software IBM SPSS statistics version 24 was used for data management and R

189 3.4.3 was used for data analysis.

190

191 *Missing data*

192 Approximately 3% of data on patient and/or treatment characteristics was missing. We
193 applied single imputation to account for this, including all mentioned baseline
194 characteristics and the cumulative hazard for pregnancy in the imputation model to account
195 for the time aspect in the data (White and Royston, 2009).

196

197 *Ethical approval*

198 The study was approved by the North of Scotland Research Ethics Committee (12/NS/0120).
199 Consent was not required from study participants as the final database did not contain
200 identifiable information.

201

202 *Results***203 *Characteristics of the study population***

204 Clinical characteristics of all women at the time of their last IVF cycle (unsuccessful group) or
205 after giving birth (successful group) are presented in Table I. Women whose treatment was
206 unsuccessful were older (mean of 35.7 versus 33.9 years) compared to women whose IVF
207 treatment was successful. The cause of infertility, number of embryo transfers and duration
208 of infertility (median of 5.1 years for the successful group and 5.3 years for the unsuccessful
209 group) were comparable across the two groups.

210

211 *Treatment-independent live birth*

212 Of the 1,073 unsuccessfully treated women, 185 had at least one subsequent treatment-
213 independent live birth over the maximum follow-up period of 15 years (Figure 2). The

214 median follow-up period was 6 years (2.16-10.5). Of the 1,060 successfully treated women,
215 151 had at least one treatment-independent live birth over the maximum follow-up period
216 of 15 years (Figure 2). The median follow-up time was 5.9 years (2.6-10).

217 The one-year Kaplan-Meier treatment-independent live birth rate was 10% (95% CI, 8%-
218 12%) among unsuccessfully treated women and 4% (95% CI, 3%-5%) among successfully
219 treated women (Figure 3). At two and a half years, these rates increased to 15% (95% CI,
220 12%-17%) and 11% (95% CI, 9%-13%) respectively. The five-year rates were 17% (95% CI,
221 15%-19%) and 15% (95% CI, 12%-17%), and the ten-year rates were 19% (95% CI, 16%-22%)
222 and 17% (95% CI, 14%-19%), respectively.

223

224 ***Predictive factors***

225 Factors associated with a treatment-independent live birth among successfully treated
226 women are shown in Table II as hazard ratios (HR) and 95% confidence intervals (CIs). The
227 multivariable analysis showed that the factors of an increased female age, increased
228 duration of infertility, two or three or more embryo transfers compared to one embryo
229 transfer and ICSI versus IVF treatment (HR: 0.62, 95%CI 0.44 to 0.88) were all associated
230 with a decrease in the chance of treatment-independent pregnancy.

231 Factors associated with a treatment-independent live birth among unsuccessfully treated
232 women are shown in Table III. The factors of an increased female age, increased duration of
233 infertility and ICSI versus IVF treatment (HR: 0.70, 95%CI 0.47 to 1.05) were associated with
234 a decrease in the chance of pregnancy. The cause of infertility was associated with the
235 chance of pregnancy with tubal factor having the worst prognosis (HR: 0.31, 95%CI 0.17 to
236 0.55) and ovulatory disorder having the best prognosis (HR: 1.11, 95%CI 0.64 to 1.94)
237 compared to male factor infertility as reference.

238

239 Discussion**240 *Principal findings***

241 Following unsuccessful IVF or ICSI treatment, approximately 15% (one in seven) women had
242 a treatment-independent pregnancy leading to live birth over two and a half years, rising to
243 17% (one in six) over five years. The corresponding figures in women who had an IVF or ICSI
244 live birth were slightly lower at 11% (one in nine) and 15% (one in seven) respectively. After
245 ten years, the percentage is very little more than that at five years. The Kaplan-Meier curve
246 indicated that for the group in which IVF was successful, the time to treatment independent
247 live birth was longer compared to women who were unsuccessful. This difference could be
248 explained by the fact that women who had the desired child through fertility treatment may
249 be less likely to try to get pregnant again soon after having a live birth and may have used
250 contraception for a period of time (Troude et al. 2012).

251 Increasing female age and duration of infertility were associated with a decreased chance of
252 treatment-independent live birth in both groups. Having more than one embryo transfer
253 and having received ICSI instead of IVF treatment lowered the chance of a treatment-
254 independent live birth among successfully treated women. Among unsuccessfully treated
255 women, the chance of post-IVF live birth was reduced in those with tubal factor infertility
256 and those who received ICSI treatment.

257

258 *Strengths and limitations*

259 At 2,133, the sample size for this population-based retrospective cohort study was
260 reasonably large compared to most studies which have examined treatment-independent
261 live birth after IVF and the follow up was long (Shimizu et al. 1999, Hennelly et al. 2000,

262 Osmanagaoglu et al. 2002, Cahill et al. 2005, Ludwig et al. 2008, Donckers et al. 2011, Khalili
263 et al. 2012, Pandey et al. 2014). Our sample is representative of the entire population as
264 there is only one IVF clinic in the region. Data used in this record-linkage study were
265 extracted from high quality and validated databases that have been successfully used in
266 previous studies (Maheshwari et al. 2009, Pandey et al. 2014, Rukuni et al. 2016). A further
267 strength of this study was the fact that our study was not reliant on telephone interviews or
268 postal questionnaires, minimising recall bias and overcoming problems relating to poor
269 response rates reported in some earlier studies (Shimizu et al. 1999, Hennelly et al. 2000,
270 Osmanagaoglu et al. 2002, Cahill et al. 2005, Khalili et al. 2012). Our population-based study
271 design allowed us to avoid the situation reported in a Danish study (Pinborg et al. 2009)
272 where non-response by women who failed to become pregnant led to overestimation of the
273 treatment-independent live birth rate by 5.3%.

274 The study has a number of limitations. A key drawback is the single-centre retrospective
275 design, which raises questions about generalisability. Although the majority of fertility clinics
276 in the UK have access to the same guidelines (NICE guidelines), the selection of candidates
277 and number of cycles could have been influenced by clinical judgment and patient
278 preferences (Kim et al. 2015). In addition, a multicentre study design with a higher number
279 of participants would have increased the sample size in the different subgroups which
280 would have allowed us to draw more accurate comparisons between causes of infertility.

281 Another factor which could limit the generalisability of our study to other populations is that
282 the population of the North East of Scotland is ethnically relatively homogeneous; the
283 majority of residents are Caucasians (Scottish Gov 2014).

284 A natural drawback associated with data from clinical databases is the fact that not all
285 desired covariates were available. For instance, data were unavailable on use of

286 contraception or active plans to get pregnant. A questionnaire-based study found that
287 10.9% of women following ICSI treatment had used contraception (Ludwig et al. 2008).
288 Exclusion of women who used active contraception following IVF, leaving a cohort of
289 women who remained actively trying for a second baby, might increase the proportion of
290 treatment-independent live births over the observation period. It is difficult to define a
291 timepoint such as the 'completion of IVF treatment' with certainty as we were unable to
292 distinguish between a treatment-independent conception that occurred between planned
293 IVF cycles and a conception that occurred after the couple decided not to have further IVF.
294 In addition, we lacked information on any pregnancy outcomes which may have occurred
295 outside Scotland and any IVF treatments which may have occurred outside the Grampian
296 region. It is possible that some women could have undergone treatment outside the region
297 and then returned to give birth. This would have been counted as a natural conception using
298 our databases. Finally, although we censored women if they came back with a different
299 partner during treatment cycles, we were not able to detect a change in partnership after
300 IVF treatment. We were also unable to account for dropout factors such as stress due to
301 failed IVF treatment.

302

303 ***Related literature***

304 Our treatment-independent live birth rate of 17% (one in six) over five years in
305 unsuccessfully treated women was higher than the 11.5% reported in a five-year follow-up
306 study in Belgium (Osmanagaoglu et al. 2002), 10% in a five-year cohort study in the
307 Netherlands (Brandes et al 2010), and the 12% observed by Troude et al (2016) in a French
308 cohort followed up for eight years. However, Troude et al (2012) reported a treatment
309 independent live birth rate of 24% among women unsuccessfully treated by IVF over an

310 average follow-up period of seven years which was longer than our median follow-up period
311 (Troude et al. 2012). Approximately 15% of successfully treated women in our study had a
312 treatment-independent live birth over five years. This figure is slightly lower than the 17% to
313 21% reported in the literature from France, Ireland and Japan (Shimizu et al. 1999, Hennelly
314 et al 2010, Troude et al. 2012) but higher than the 11.7% observed in a five-year follow-up
315 Danish study (Pinborg et al. 2009).

316 Recent publications have reported higher rates of treatment-independent live birth after IVF
317 treatment compared to older studies (Shimizu et al. 1999, Hennelly et al 2010, Troude et al.
318 2012). This is despite the increase in success rate of IVF treatment over the last few years
319 (Human Fertilisation and Embryology Authority 2007, Human Fertilisation and Embryology
320 Authority 2016). Increased availability of IVF and early access for women who have a
321 reasonably good chance of spontaneous pregnancy has been noted to lead to
322 overtreatment (Kamphuis et al. 2014, Marcus et al. 2016). A Danish study found that 9.1% of
323 patients on the waiting list for IVF had a treatment-independent live birth within one year
324 (Eijkemans et al. 2008). The median IVF cycle number in our study was two for
325 unsuccessfully treated women which was higher than the average number in the UK
326 (McLernon et al. 2016). This is probably due to the fact that during the study period, the
327 Scottish Government supported up to two complete cycles of IVF (before increasing it to
328 three rounds in 2017) (Fertility Fairness 2017).

329 Our study showed that the chance of having a treatment-independent live birth among both
330 successfully and unsuccessfully treated women decreased with increasing female age and
331 duration of infertility. Both of these factors have been identified as being associated with
332 treatment-independent live birth in previous studies (de La Rochebrochard et al. 2009,
333 Khalili et al. 2012, Walschaerts et al. 2012, Troude et al. 2016). In successfully treated

334 women, we observed a lower chance of treatment independent live birth in women who
335 received more than one cycle, in particular in women who received three cycles (or more), a
336 finding also previously demonstrated in a Danish prospective cohort study (Pinborg *et al.*,
337 2009).

338 In those who had unsuccessful IVF, women with ovulatory disorder had an increased chance
339 of treatment-independent live birth whilst those with tubal factor infertility had a decreased
340 chance of treatment-independent live birth. This has been previously reported in a
341 prospective cohort study (Donckers *et al.*, 2011) and is indicative of sporadic ovulation in
342 women with this diagnosis. ICSI was associated with a decreased chance of treatment-
343 independent live birth for both the successful and unsuccessful groups even after
344 accounting for cause of infertility. This finding could be due to the clinician choosing ICSI for
345 couples who have a relatively poor prognosis based on predictors unknown to us.

346

347 ***Wider implications of the findings***

348 This study provides a better understanding of the long-term prognosis of treatment-
349 independent live birth and associated factors of such an outcome. The results can provide
350 an indication to women, who remain childless after fertility treatment or who wish to have
351 another baby after successful IVF treatment, of their prognosis based on their
352 characteristics. Those counselling infertile women should include information about their
353 chance of natural conception at the end of fertility treatment, which starts to peak in the
354 first few years.

355

356 ***Conclusion***

357 We found that treatment-independent live birth after either successful or failed IVF or ICSI
358 treatment occurs in approximately one in six couples. This is more likely to occur in younger
359 women treated with IVF and who have been trying to conceive for a relatively short
360 duration. Our results will help clinicians to counsel infertile couples on the characteristics
361 associated with a live birth after a failed or successful IVF outcome.

362

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369 note searching.

370

371 **Authors' roles**

372 DJM, SB and YE designed the study. YE and RVE conducted the statistical analysis and
373 the literature search and wrote the article. All authors contributed intellectually to the
374 writing or revising of the manuscript and approved the final version.

375

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383

384 **Conflict of interest**

385 All authors have completed the ICMJE uniform disclosure form at
386 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
387 declare that there was no support from any organisation for the submitted work, no
388 financial relationships with any organisations that might have an interest in the submitted
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390 have influenced the submitted work.

391

392 **Figures**

393 **Figure 1.** Flow chart showing inclusion and exclusions before data analysis

394

395 **Figure 2.** Flow chart showing the number of women per group and resulting treatment
396 independent live births over the maximum follow-up period of 15 years

397

398 **Figure 3.** Cumulative treatment independent live birth rates over follow up from last IVF
399 cycle or live birth

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540 **Table 1 Characteristics of the women after treatment dependent live birth (successfully treated**
 541 **group) or after their last IVF cycle (unsuccessfully treated group)**

Characteristics	Successfully treated group n = 1060	Unsuccessfully treated group n = 1073
Mean (SD) female age (years)	33.9 (4.0)	35.7 (4.7)
Infertility type (primary versus secondary), n (%)	0 (0)	663 (61.8)
Cause of infertility, n (%)		
Male	383 (36.1)	329 (30.7)
Ovulatory	70 (6.6)	85 (7.9)
Unexplained	284 (26.8)	259 (24.1)
Tubal	179 (16.9)	228 (21.1)
Other/unknown	41 (3.9)	59 (5.5)
More than one cause	103 (9.7)	113 (10.5)
Infertility duration (median, 25th-75th)	5.1 (3.9-6.7)	5.3 (3.7-7.2)
Infertility duration, n (%)		
<3	99 (9.3)	140 (13.0)
3-6	607 (57.3)	512 (47.7)
>6	354 (33.4)	421 (39.2)
No. of embryo transfer episodes(median, 25th-75th)	2 (1-3)	2 (1-3)
No. of embryo transfer episodes, n (%)		
1	398 (37.5)	398 (37.1)
2	261 (24.3)	277 (25.8)
3	172 (16.0)	181 (16.9)
>3	229 (21.3)	217 (20.2)
Treatment type		
IVF (in vitro fertilization)	652 (61.5)	708 (65.4)
ICSI (intracytoplasmic sperm injection)	408 (38.5)	371 (34.6)

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543

544 **Table 2 Factors associated with treatment independent live birth over time in successfully treated**
 545 **women (n=1060)**

	Multivariable analysis with backward selection based on AIC		
	HR	95% CI	P value
Female age (per year ≤ 31)	0.92	0.84 to 1.01	0.10
Female age (per year >31)	0.89	0.77 to 1.02	0.09
Duration of infertility (per year)	0.89	0.83 to 0.97	0.006
Number of embryo transfer episodes			
1 ^a	1		
2	0.74	0.51 to 1.09	0.13
3	0.31	0.17 to 0.59	<0.001
>3	0.52	0.32 to 0.84	0.007
Type of treatment			
IVF ^a	1		
ICSI	0.62	0.44 to 0.88	0.007

546 ^a Used as a reference variable.

547 HR = hazard ratio; CI = confidence interval; BMI = body mass index; IVF = in vitro fertilisation; ICSI =
 548 intracytoplasmic sperm injection

549 Note: Female age was included in the model as two continuous linear terms, one for age up to 31
 550 and one for age over 31 years

551

552 **Table 3 Factors associated with treatment independent live birth over time in unsuccessfully**
 553 **treated women (n=1073)**

Multivariable analysis with backward selection based on AIC			
	HR	95% CI	P value
Female age (per year ≤ 31)	1.04	0.94 to 1.15	0.48
Female age (per year >31)	0.85	0.74 to 0.97	0.02
Duration of infertility (per year)	0.86	0.81 to 0.92	<0.001
Cause of infertility			
Male ^a	1		
Anovulation	1.11	0.64 to 1.94	0.71
Unexplained	1.08	0.70 to 1.67	0.74
Tubal	0.31	0.17 to 0.55	<0.001
Other	0.61	0.30 to 1.22	0.16
More than one cause	0.48	0.26 to 0.87	0.02
Type of treatment			
IVF ^a	1		
ICSI	0.70	0.47 to 1.05	0.08

554 ^a Used as a reference category.

555 HR = hazard ratio; CI = confidence interval; BMI = body mass index; IVF = in vitro fertilisation; ICSI =
 556 intracytoplasmic sperm injection

557 Note: Female age was included in the model as two continuous linear terms, one for age up to 31
 558 and one for age over 31 years

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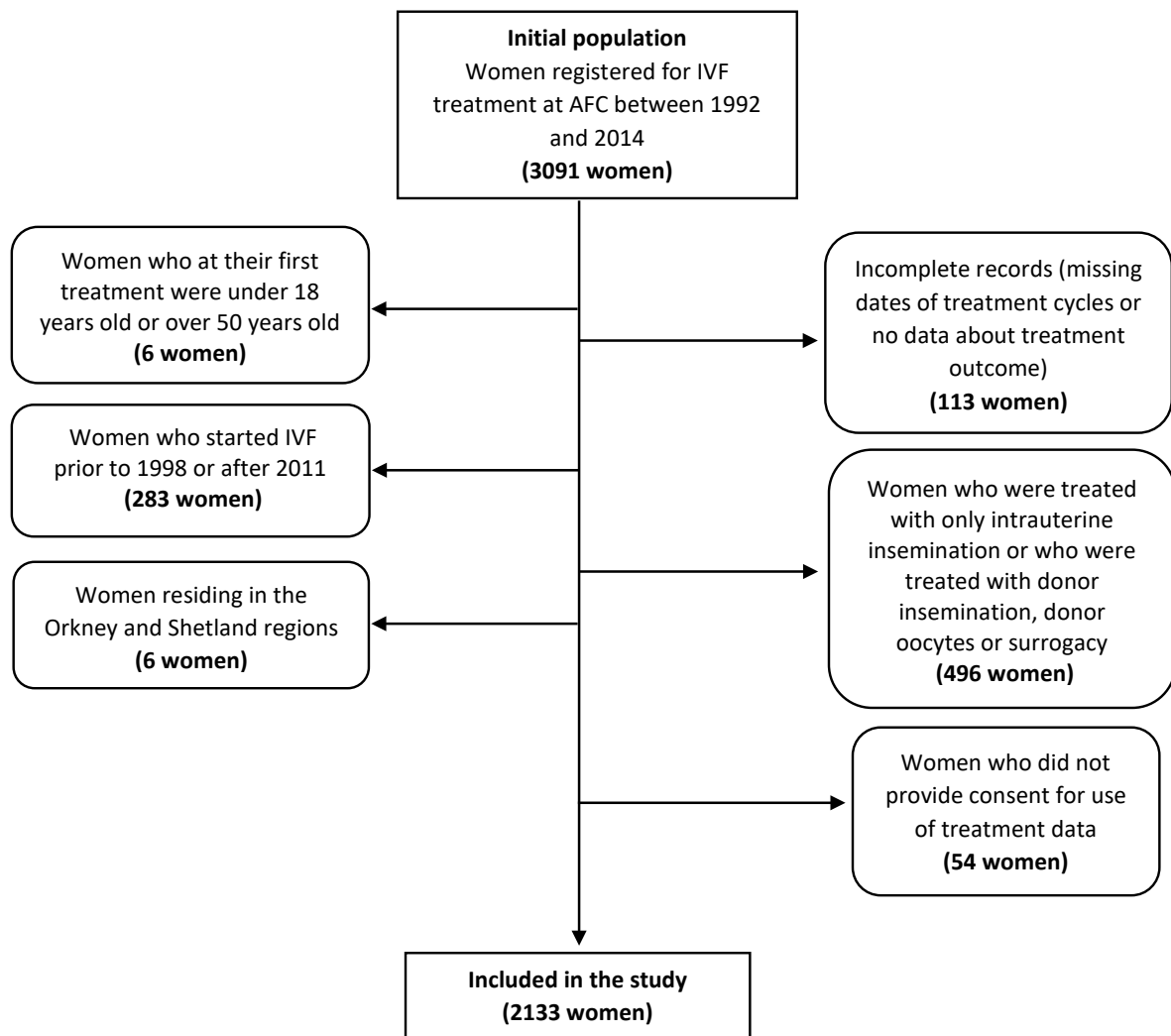
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Figure 1 Flow chart showing inclusion and exclusions before data analysis



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Figure 2 Flow chart showing the number of women per group and resulting treatment independent live births over the maximum follow-up period of 15 years

