

1 **Cost of fertility treatment and live birth outcome in women of different ages and BMI**

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22 **Running title: Cost of fertility treatment by age and BMI**

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26

27 **Abstract**

28 **Study question**

29 What is the impact of different age and BMI groups on total investigation and treatment costs in  
30 women attending a secondary/tertiary care fertility clinic?

31

32 **Summary answer**

33 Women in their early to mid-30s and women with normal BMI had higher cumulative investigation  
34 and treatment costs, but also higher probability of live birth.

35

36 **What is known already?**

37 Female age and BMI have been used as criteria for rationing publically funded fertility treatments.  
38 Population based data on the costs of investigating and treating infertility are lacking.

39

40 **Study design, size and duration**

41 A retrospective cohort study of 2463 women was conducted in a single secondary/tertiary care fertility  
42 clinic in Aberdeen, Scotland from 1998-2008.

43

44 **Participants/materials, setting, methods:**

45 Participants included all women living in a defined geographical area referred from primary care to a  
46 specialised fertility clinic over an 11 year period. Women were followed up for 5 years or until live  
47 birth if this occurred sooner. Mean discounted cumulative National Health Service costs (expressed in  
48 2010/2011 GBP) of fertility investigations, treatments (including all types of assisted reproduction)  
49 and pregnancy (including delivery episode) and neonatal admissions were calculated and summarised  
50 by age ( $\leq 30$ , 31-35, 36-40,  $> 40$  years) and BMI groupings ( $< 18.50$ , 18.50-24.99 (normal BMI), 25.00-  
51 29.99, 30.34.99,  $\geq 35.00$  kg/m<sup>2</sup>). Further multivariate modelling was carried out to estimate the impact  
52 of age and BMI on investigation and treatment costs and live birth outcome, adjusting for covariates  
53 predictive of the treatment pathway and live birth.

54

**55 Main results and the role of chance**

56 Of the 2463 women referred, 1258 (51.1%) had a live birth within 5 years, with 694 (55.1%) of these  
57 being natural conceptions. The live birth rate was highest among women in the youngest age group  
58 (64.3%), and lowest in those aged >40 years (13.4%). Overall live birth rates were generally lower in  
59 women with BMI >30 kg/m<sup>2</sup>. The total costs of investigations were generally highest among women  
60 younger than 30 years (£491 in those with normal BMI), whilst treatment costs tended to be higher in  
61 31-35 year olds (£1,840 in those with normal BMI). Multivariate modelling predicted a cost increase  
62 associated with treatment which was highest among women in the lowest BMI group (across all ages),  
63 and also highest among women aged 31-35 years. The increase in the predicted probability of live  
64 birth with exposure to treatment was consistent across age and BMI categories (~10%), except in the  
65 oldest age group where a slightly smaller increase in the probability of live birth was observed. The  
66 ratio of increased costs to the increased probability of live birth in women who were treated increased  
67 markedly in women over the age of 40 years, but tended to fall as BMI increased within all age groups.

68

**69 Limitations and reason for caution**

70 Our results, based on retrospective observational data from a single centre, have limited  
71 generalizability and are not free from clinician and clinic selection bias which can influence the choice  
72 of treatments as well as their costs.

73

**74 Wider implications of the findings**

75 Spontaneous live birth rates were particularly high in younger women with unexplained infertility,  
76 suggesting that expectant management is a reasonable option in this group. The policy of not over-  
77 investigating older women and offering early treatment where appropriate still incurred the highest  
78 costs per additional live birth associated with treatment, owing to the lower probability of treatment  
79 success. The increased additional cost for each live birth associated with treatment for women with

80 decreasing BMI across all age groups, suggests that it may be possible to identify a more targeted  
81 approach to treatment.

82

### 83 **Study funding/competing interest(s)**

84 This study was partly funded by an NHS endowment grant (Grant Number 12/48) and DM by a Chief  
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86

87 Key words: Fertility, Live Birth, Body Mass Index, Age, Costs

88

### 89 **Introduction**

90 Considerations of cost-effectiveness are increasingly influential in informing treatment decisions  
91 within the National Health Service (NHS) in the UK as well as in other health care settings across the  
92 world. Results of published studies showing that women who are older and heavier are less likely to  
93 achieve a pregnancy has led to rationing of access to publicly funded fertility treatment on the basis  
94 of age and BMI (National Collaborating Centre for Women's and Children's Health 2013). In addition,  
95 pregnant women who are obese have been shown to have a higher risk of fetal anomalies (Stothard  
96 et al 2009), operative deliveries (Poobalan et al 2009) and pregnancy complications, such as diabetes  
97 and hypertension (Cedergren 2004, Bhattacharya et al 2007), all of which can increase the cost of  
98 perinatal care (Denison et al 2014). Whilst a substantial amount of data have been published on the  
99 costs of IVF (National Collaborating Centre for Women's and Children's Health 2013), the literature  
100 contains very little on the cumulative costs of all fertility treatments and investigations (including IVF).  
101 There are also few studies which have been able to describe the cost of treatment independent and  
102 treatment dependent pregnancies and live births in couples with fertility problems. In the UK, the  
103 National Institute for Health and Care Excellence (NICE 2013), which has generated cost-effectiveness  
104 models to determine the criteria required for access to NHS funded IVF treatment, acknowledges the  
105 paucity of data in this field. A Dutch group used data from the literature to inform models on the  
106 cumulative costs and outcomes of ovulation induction, intrauterine insemination (IUI) and IVF with

107 respect to overweight and obese women (Koning et al 2010). However, to our knowledge, no previous  
108 study has used population based data to estimate the actual impact of current practice on the  
109 cumulative costs of both fertility investigations and treatment on women in different age and BMI  
110 categories. The aim of this study was to estimate the mean total health service costs of investigating  
111 and treating women with infertility living within a defined geographical area.

112

113

#### 114 **Methods**

115 Following approval from the North of Scotland Research Ethics Committee (10/S0802/57) and the  
116 relevant Caldicott Guardians, fertility and maternity data were obtained on all women residing in the  
117 Aberdeen City District who attended the Aberdeen Fertility Centre (AFC) for the first time between  
118 1998 and 2008. These two data sources were linked using unique identifiers.

119

120 The AFC is ideally placed to carry out such a study since it holds extensive electronic fertility and  
121 maternity records for all women in Aberdeen City district and has logged all fertility investigation and  
122 treatment events since 1991. Assessments and tests were performed according to evidence-based  
123 standard operating procedures of the AFC based on the NICE guidelines of management of infertility  
124 in the UK or, prior to this, Royal College Guidelines (Royal College of Obstetricians and Gynaecologists,  
125 1998). Details of the clinical protocols used in decision making at the AFC are included in the  
126 Supplementary Data. The Aberdeen Assisted Reproduction Unit Database (ARUD) holds details on all  
127 IVF events since 1998, and the Aberdeen Maternity and Neonatal Databank (AMND) has information  
128 on all pregnancies and deliveries occurring in Aberdeen City and district since 1950  
129 (<http://www.abdn.ac.uk/amnd/>). These databases have been used previously to assess the cost of IVF  
130 treatment in women in different age and BMI categories (Maheshwari et al 2009, 2010). In this study  
131 we used them to assess the costs and outcomes of all fertility investigations and treatments in a cohort  
132 of women referred from primary care to a specialised clinic.

133

134 Data were extracted on all women for a 5 year period or until the first live birth - if this occurred sooner  
135 - after an initial visit to the AFC. A 5 year period was chosen in order to factor in any waiting time  
136 between treatments and minimise loss to follow up. The AFC database provided baseline  
137 characteristics, outcomes of diagnostic tests, infertility diagnosis, and details of clomiphene citrate,  
138 gonadotrophin and intrauterine insemination (IUI) treatments. Details of IVF treatment were obtained  
139 from the ARUD. Data on on-going pregnancies, antenatal care, obstetric care and neonatal care were  
140 obtained from the AMND. The data were linked and anonymized by the University of Aberdeen data  
141 management team, using date of first attendance at the AFC clinic, date of birth, unit number, CHI  
142 (unique identification) number and partner's date of birth.

143

#### 144 *Inclusion criteria*

145 All women residing in Aberdeen City district (identified by their post codes) and attending AFC for the  
146 first time between 1998 and 2008 were eligible for inclusion. Those living outside Aberdeen City  
147 District were excluded as some of their maternity records were not recorded within the AMND.

148

#### 149 *Outcomes*

150 Our outcome measure, live birth, was considered to be treatment dependent if the antenatal booking  
151 date for the pregnancy was within 3 months of a treatment cycle reporting an outcome consistent  
152 with pregnancy. A live birth was considered to be treatment independent if there was no preceding  
153 treatment cycle or if the timing and/or reported outcome of the preceding treatment cycle was  
154 inconsistent with the recorded booking date for the live birth. As AFC is the only fertility centre in  
155 Aberdeen, all pregnancies in women who had no contact with AFC were deemed (in the absence of  
156 any further information) to be treatment independent (Thompson et al 2005).

157

#### 158 *Power Calculation*

159 Approximately 500 new couples from Aberdeen and its surrounding areas are seen in the AFC each  
160 year. As 50% of them are expected to be resident in Aberdeen City District, we anticipated a sample

161 size of approximately 2500 new couples over the study period. Assuming that the proportions of  
162 women in each BMI category were similar to those reported by our group in a previous study  
163 (Maheshwari et al, 2009), it was estimated that a sample of 2500 women would have more than 90%  
164 power to detect a difference in costs of one third of a standard deviation between the obese group  
165 (BMI  $\geq 30\text{kg/m}^2$ ) and the normal BMI group (18.5-24.9 $\text{kg/m}^2$ ).

166

#### 167 *Resource use and costs*

168 Costs to the health service were estimated using a combination of top-down (aggregated high level)  
169 and bottom-up (detailed micro-costing) approaches. Estimates of resource use inputs required for  
170 investigations and treatments were based on a combination of patient records (for certain quantities  
171 of consumable items), centre treatment and monitoring protocols, and the opinion of AFC clinicians.  
172 Resource items considered included staff time, consumables, capital equipment, overheads and  
173 space.

174

175 The unit costs to add to the resource use data were obtained from Aberdeen Assisted Reproduction  
176 Unit expenditure records for consumables. Staff time was valued using nationally available unit costs  
177 (per hour) incorporating gross salaries, employer superannuation and national insurance  
178 contributions, allocated overheads, and costs associated with the use of building space (Curtis 2011).  
179 These incorporate the annuitized cost of the resources invested in training health professionals (Curtis  
180 2011).

181

182 For capital equipment, an equivalent annual cost was calculated based on the purchase price and  
183 expected serviceable life span of each item, and this in turn was used to calculate an average cost per  
184 use based on estimated annual throughput. A discount rate of 3.5% was applied to capture the  
185 opportunity cost of investing in capital equipment. Discounting is performed in economic analyses to  
186 account for societal time preference so as to determine the net present value of costs in a common  
187 base year. Where use of space associated with a procedure was missing from the staff cost ready

188 reckoner, this was estimated using a unit cost per square metre for a new build, multiplied by the area  
189 of space used and annuitized over a 25 year period. Costs calculated are presented in Supplementary  
190 tables 1-6.

191  
192 For early treatment outcomes (biochemical pregnancy, ectopic pregnancy and miscarriage) the  
193 average unit costs of diagnosing and treating these events, as reported by Maheshwari et al (2010),  
194 were inflated to 2010/2011 values (Supplementary table 3). Antenatal care contacts, including clinic  
195 appointments, scans, blood tests, and hospital admissions were valued using readily available (top-  
196 down) unit costs based on financial returns data, as were neonatal admissions (ISD Scotland,  
197 <http://www.isdscotland.org/Health-Topics/Finance/Costs/File-Listings-2011.asp>) (Supplementary  
198 table 6).

199  
200 All the costs were expressed in 2010/2011 GBP and future costs (beyond year 1) were discounted at  
201 a rate of 3.5% per annum in line with HM Treasury recommendations and NICE (2013). Total costs  
202 were estimated for each individual by multiplying the numbers of different procedures reported by  
203 the estimated unit cost for each procedure, and then summing across all procedures.

204

## 205 **Statistical Methods**

206 Analyses were conducted using SPSS (version 18), STATA (version 12) and SAS (version 9.3).  
207 Characteristics of the women attending the fertility centre and treatments undertaken are reported  
208 by BMI group and for women whose BMI was missing. Comparison of baseline characteristics and  
209 treatments undertaken across BMI groups (<18.5kg/m<sup>2</sup>, 18.5-24.9kg/m<sup>2</sup>, 25-29.9kg/m<sup>2</sup>, 30-  
210 34.9kg/m<sup>2</sup> and ≥35 kg/m<sup>2</sup>) were made. Pearson's chi-squared test was used to test for an  
211 association between BMI group and each of the following variables: causes of infertility, the  
212 proportion of nulliparous women, smoking status, alcohol status, and each type of fertility treatment.  
213 The mean female age was compared between the BMI groups using analysis of variance, and the  
214 Kruskal Wallis test was used to compare duration of infertility between the BMI groups. The

215 proportion of missing data was documented and the characteristics of, and treatments given to,  
216 patients with complete data were compared to patients with missing data using similar tests as above.  
217 Clinical outcomes, mean discounted investigation costs, mean discounted treatment costs, mean  
218 discounted pregnancy, delivery and neonatal costs, number of women treated and the mean (SD)  
219 number of treatment cycles were presented by BMI and age groups ( $\leq 30$  years, 31 to 35 years, 36 to  
220 40 years,  $>40$  years).

221  
222 The impact of age and BMI on total fertility investigation and treatment costs and live birth was  
223 assessed using general linear regression. Pregnancy, delivery and neonatal costs were not included  
224 in this part of the analysis. These models were adjusted for exposure to fertility treatment (yes/no),  
225 primary versus secondary infertility, duration of infertility, year of registration and cause of infertility  
226 (including male factor, endometriosis, ovulatory, unexplained, tubal and other). With the exception  
227 of duration of infertility and year of registration, which were entered as covariates (i.e. linear effects),  
228 all predictors were fitted as factors (i.e. categorical effects). Interactions between the fertility  
229 treatment indicator and BMI category, and between the treatment indicator and age category, were  
230 also included in the model. A significant age (or BMI) treatment interaction would suggest that the  
231 effect of BMI (or age) category on cost/live birth differs between women who did and did not have  
232 treatment. Since they help to explain further variation, any significant interactions remained in the  
233 model. These models were used to predict costs and the probability of live birth by age and BMI  
234 groupings, with and without exposure to treatment. In this calculation, the results are expressed for  
235 a cohort of patients with unexplained infertility - a group where spontaneous or treatment  
236 independent pregnancies are more common than in other groups – with all other predictors held fixed  
237 at either their reference category or mean value.

238  
239 The 95% confidence intervals for the predicted probabilities and costs were calculated by drawing  
240 3000 random bootstrap samples from the dataset. For each bootstrapped sample we fitted the

241 models predicting cost and live birth, calculated the predicted costs and probabilities of live birth, and  
242 took the values at the 2.5th and 97.5th percentile as the lower and upper confidence limit respectively.

243

244 The above analysis was conducted using only patients with complete data. A multiple imputation  
245 process was performed to impute values for all predictors with missing information. This was  
246 performed using a combination of the Monte Carlo Markov Chain method and predicted mean  
247 matching regression (Rubin, 1987). Many other variables, aside from those used in the statistical  
248 modelling, were used to inform the imputation process. These included alcohol status, smoking  
249 status, parity, and number of cycles of different fertility treatments i.e. clomiphene citrate,  
250 gonadotrophin, IUI, donor insemination, fresh IVF and frozen IVF. The statistical analysis described  
251 above was performed for the imputed database.

252

## 253 **Results**

### 254 *Patient and treatment characteristics*

255 A total of 2463 women from the Aberdeen City District attended the fertility clinic at the AFC for the  
256 first time between 1998 and 2008. Of 1736 (70.5%) women whose BMI data were available, 56% had  
257 a normal BMI (i.e. 18.5-24.9kg/m<sup>2</sup>), 25% were overweight (i.e. 25-29.9kg/m<sup>2</sup>) and 16% were obese  
258 ( $\geq 30$  kg/m<sup>2</sup>). Table 1 shows the baseline characteristics of women in different BMI categories along  
259 with the treatments received. Women with a BMI  $< 18.5$  kg/m<sup>2</sup> were significantly younger than women  
260 with BMI in the normal range and women with BMI between 30 to 34.9 kg/m<sup>2</sup>. Over half of all women  
261 with BMI  $\geq 35$  kg/m<sup>2</sup> presented with anovulatory infertility whilst more women (36%) in the normal  
262 BMI group had unexplained infertility. Fewer women with BMI over 35 kg/m<sup>2</sup> underwent IVF/ICSI  
263 treatment as compared to women with lower BMIs. Women with missing BMI data were significantly  
264 older (33 versus 32 years of age), had more secondary infertility (55% versus 41%), smoked more (27%  
265 versus 22%) and had a higher percentage of tubal factor infertility (26% versus 17%) compared to  
266 women with complete data (Supplementary Table 7). A significantly lower proportion had anovulatory

267 (14% versus 23%) and unexplained (24% versus 31%) infertility. They also had less clomifene citrate  
268 (14% versus 21%), gonadotrophin (1% versus 3%), and IVF (29% versus 34%) treatment.

269

#### 270 *Live birth outcome*

271 Of all the women referred to AFC from primary care with a diagnosis of infertility during the study  
272 period, 1258 (51.1%) had a live birth within 5 years with 694 (55.1%) of these being treatment  
273 independent (spontaneous) conceptions. In those  $\leq 30$  years of age, 36.7% conceived spontaneously,  
274 compared to only 9.1% of women over the age of 40 years. Out of the 1211 (49.2%) women who  
275 received any treatment, 564 (46.6%) had a treatment dependent live birth while 164 (13.5%) had a  
276 subsequent spontaneous live birth. Out of the 1252 (50.8%) women who did not receive fertility  
277 treatment, 530 (42.3%) had a spontaneous live birth (Table 2). In women of all age groups,  
278 spontaneous conception rates were higher than those as a direct result of active treatment, but were  
279 not associated with BMI (Table 2).

280

#### 281 *Costs of investigation, treatment and pregnancy*

282 Table 3 highlights the mean investigation, fertility treatment and pregnancy costs by age and BMI  
283 group. Generally, the average cost of investigations tended to decrease with age and also tended to  
284 be lower in women classified as severely obese ( $\geq 35$ kg/m<sup>2</sup>). The average treatment costs generally  
285 appeared highest in women with normal BMI, except in the youngest age group. Average pregnancy  
286 and neonatal costs followed a similar pattern (reflecting the higher live birth rate in women with  
287 normal BMI) but in some age groups these costs were highest among women with BMI  $> 35$  kg/m<sup>2</sup>.  
288 The total costs of investigation and treatment were highest among women who were 30 years or  
289 younger, with BMI less than 25kg/m<sup>2</sup>.

290

291 Table 4 shows the number of women in different age and BMI groups who were investigated, along  
292 with the resulting costs. In comparison with younger women with normal BMI, fewer women who  
293 were older ( $> 40$  years) or heavier (BMI  $> 30$ kg/m<sup>2</sup>) underwent a laparoscopy, possibly due to concern

294 about increased surgical and anaesthetic risks. Cheaper investigations, such as blood tests (e.g. mid-  
295 luteal progesterone and other hormonal tests), were more frequent in the obese group up to the age  
296 of 40 years. With regards to fertility treatment (Table 5), fewer women in the older (and also the  
297 youngest) age groups, and in the higher BMI groups, received IVF treatment. By contrast, more women  
298 in the youngest age group (and within some age groupings the higher BMI groups) received treatment  
299 with clomifene citrate.

300

### 301 *Relationship between costs and age and BMI groups*

302 To further explore the relationship between costs of fertility investigation and treatment with age and  
303 BMI, we estimated these costs whilst adjusting for factors associated with the treatment pathway and  
304 treatment success. The modelling information (including the parameter estimates for the cost model)  
305 is contained in supplementary table S8. The parameter estimate for a particular factor affecting  
306 outcome is defined as the predicted increase in cost associated with a one unit increase in the value  
307 of that covariate.

308

309 The predicted costs from these adjusted analyses are presented in Table 6 for a cohort of women with  
310 unexplained infertility – a group without an absolute barrier to conception who would be expected to  
311 have a reasonable chance of treatment independent pregnancy. The results show a cost increase  
312 associated with treatment which is higher among women in the lowest BMI group (across all age  
313 groups), and also highest among women aged 31-35 years, followed by women aged 36-40 years  
314 (compared to women in the youngest and oldest age groups).

315

### 316 *Additional cost per additional live birth associated with treatment*

317 A similar approach also assessed the predicted probability of live birth. The live birth outcome model  
318 shows an uplift in the predicted probabilities of live birth with exposure to treatment, which is fairly  
319 consistent across age and BMI categories (~10%), except in the oldest age group where a slightly  
320 smaller increase in the probability of live birth is observed (see Table 6 and supplementary table S9).

321 Table 7 shows the difference in costs and the difference in the probability of live birth between treated  
322 and untreated couples with unexplained infertility across different BMI and age groups. The ratio of  
323 these two quantities represents the additional cost per additional live birth associated with fertility  
324 treatment. This ratio appears to be fairly consistent across the three youngest age groups. However,  
325 it is consistently higher in women over the age of forty than it is for women in the other age groups  
326 (across all BMI categories). For example, in women over 40 years of age with a BMI between 18.5 and  
327 25 kg/m<sup>2</sup>, the cost of an additional live birth with treatment was £32,785.52. For a woman aged 36 to  
328 40 years with similar BMI, the cost of an additional live birth with treatment was £24,249.10. A  
329 surprising finding is that this ratio tends to fall as BMI increases within all age groups. Similar findings  
330 were observed for the baseline risk predicted costs and live birth probabilities (see Supplementary  
331 Table S10).

332

333 In both models the year of registration was statistically significant meaning that the costs and live birth  
334 outcomes changed over time, as one may expect. To investigate this further we split the cohort into  
335 two time periods, i.e. 1998 to 2003 and 2004 to 2008, and refitted the models for each. Generally,  
336 there was little difference between the effects of age, BMI and treatment in the two models  
337 (supplementary Tables S11 and S12). For the cost model, the interaction between age and treatment  
338 status was not statistically significant for the earlier time period but was for the latter time period,  
339 with significantly less costs for treatment in women over 40 years.

340

341 Multiple imputation of missing data (mainly BMI) did not appear to alter the magnitude and direction  
342 of the results substantially (supplementary tables S13 and S14) but the inclusion of 947 extra patients  
343 increased the statistical power resulting in narrower confidence intervals and more highly significant  
344 parameter estimates. The predicted probabilities of live birth were generally slightly higher across all  
345 the age and BMI categories than those based on the analysis on the complete data (Supplementary  
346 Table S15). The predicted costs from the analysis with imputed data were also slightly higher for all  
347 age and BMI categories apart from the lowest BMI category which had lower estimates.

348

349 **Discussion**350 *Principal findings*

351 The results of this study show that within each age category, more women conceived spontaneously  
352 than as a result of fertility treatment. However, in women who received treatment, over 60% had a  
353 live birth either as a result of treatment (46.6%) or spontaneously at a later point in time (13.5%). Of  
354 those who did not receive treatment, 42.3% had a live birth. This explains why the increased predicted  
355 probability of live birth following treatment (versus no treatment) was higher across all age and BMI  
356 groups. The size of this increase was fairly consistent across BMI and age, although it fell substantially  
357 in women over the age of 40 years.

358

359 The cost of fertility investigations increased in line with BMI in normal BMI and overweight women,  
360 but was lower in women classified as obese ( $\geq 30\text{kg/m}^2$ ) and women  $>40$  years. Women with normal  
361 BMI who had the highest overall conception rate incurred the highest costs of treatment as well as  
362 pregnancy and neonatal costs. In contrast, older women ( $> 40$  years) and women in the high BMI  
363 groups were less likely to receive invasive investigations, such as laparoscopy, and expensive  
364 treatments such as IVF. Total costs were highest in women aged 30 years or less with a BMI less than  
365  $18.5\text{kg/m}^2$ . The overall probability of live birth tended to decrease with increasing BMI within each  
366 age group. The ratio of the predicted increase in costs to the predicted increase in the probability of  
367 live birth (with treatment) was consequently highest for women in the oldest age group ( $>40$  years),  
368 but tended to decrease with increasing BMI within each age group.

369

370 *Strengths and weaknesses of the study*

371 To our knowledge, this is the first study to explore the overall cost of providing fertility services to  
372 women of different ages and BMI groups, using direct health service costs and a relatively large sample  
373 of women. Whilst 29.5% of patients had missing BMI information, inclusion of data on these women  
374 using multiple imputation produced results which were similar to those where these were excluded.

375 As expected, several age and BMI group combinations were under-populated (as shown in Table 2)  
376 which may have introduced a level of uncertainty in the results for these groups. However, as the  
377 tests of model fit and residual plots were satisfactory, the impact on the final quality of this analysis is  
378 likely to be small. A key drawback of this study is the single centre retrospective design which made  
379 it impossible to adjust for clinician preference bias against planning investigations and treatment in  
380 older and heavier women which may have resulted in lower costs in these groups. However, due to  
381 the dominance of the non NHS private sector in fertility care and natural bias associated with under  
382 reporting of spontaneous pregnancy outcomes, it would be difficult to replicate this study in any other  
383 setting. Aberdeen is unique in being a city with a single NHS fertility clinic (which is also the only  
384 provider of IVF in the region) and an NHS maternity unit, with no provision of either service in the  
385 private sector. The live birth rates by age group in women who underwent IVF treatment at Aberdeen  
386 Fertility Centre in 2012 (33%, <35 years; 24%, 35-37 years; 19%, 38-39 years; 6%, >40 years) (see  
387 <http://www.aberdeenfertility.org.uk/success-rates/>) were reasonably similar to the national average  
388 for 2011 (32.2%, <35 years; 27.4%, 35-37 years; 19.9%, 38-39 years; 13.4%, 40-42 years; 5.1%, 43-44  
389 years; 0.8%, >44 years) (Human Fertilisation and Embryology Authority, 2013).

390

### 391 *Strengths and weaknesses in relation to other studies*

392 A relatively high rate of spontaneous conception in a cohort of infertile couples has been  
393 demonstrated previously, especially for unexplained infertility (Brandes 2011, Collins 1995). This  
394 finding was confirmed on a much larger population by our study which is one of very few in the  
395 literature to be able to analyse longitudinal data on a population based cohort due to the unique  
396 nature of local fertility services. Most clinic based fertility studies have a natural reporting bias in terms  
397 of not being able to follow up women who conceive without treatment, while population based  
398 surveys based on self-completion of questionnaires can suffer from recall bias in terms of details of  
399 diagnosis and treatment.

400

401 This is the first study to provide a comprehensive assessment of total NHS costs for the diagnosis,  
402 treatment and follow-on care after pregnancy in women with infertility. A previous study  
403 (Maheshwari et al, 2009) has investigated the impact of women's BMI on IVF costs but was unable to  
404 capture the total costs of fertility management. A subsequent study by Koning et al (2010) addressed  
405 the costs of fertility treatment in general for a hypothetical cohort of 1000 ovulatory and anovulatory  
406 women of different weight categories. That study did not account for other conditions, such as sperm  
407 dysfunction or tubal factor, and, in the absence of patient level data, relied on modelling techniques  
408 based on estimates published in the literature. Thus, it lacked precision and external validity due to its  
409 reliance on diverse sources of costs and outcomes reported in the literature over a long time period.  
410 In their model, Koning et al (2010) assumed that all overweight and obese women would follow the  
411 same pathway, although in actual fact, physician and patient choices can mean that this is not always  
412 the case. Studies on direct health service costs of IVF treatment in women in different age groups  
413 (Maheshwari et al 2009, Suchartwatnachai et al 2000) showed that the cost of live birth increased  
414 with age and was considerably higher in women over 40 years. This was in agreement with our findings  
415 though Suchartwatnachai et al, (2000) used charges rather than direct health service costs. Phillips et  
416 al (2000) has explored the costs of providing fertility treatment in women with different causes of  
417 infertility but none of the above mentioned studies has explored the costs of investigating infertile  
418 couples.

419

#### 420 *Meaning of the results*

421 Higher costs in younger women with normal BMI reflect prevailing practice based on expert guidance  
422 (Balen and Anderson 2007). Unlike overweight and obese women in whom invasive tests or treatment  
423 are conditional on weight loss, younger and leaner women are more likely to be considered to be fit  
424 for full investigation and eligible for a greater number of treatments. As fertility is known to decline  
425 with age, older women are either likely to be offered rapid access to IVF or discouraged from active  
426 treatment if the prognosis is expected to be very poor. Thus, they are less likely to undergo expensive  
427 tests of tubal evaluation which are unlikely to contribute to clinical decision making, or incur the costs

428 of IVF when the outcome is expected to be poor. In contrast, younger women may be offered a variety  
429 of treatments, such as IUI, before moving onto more definitive treatment like IVF which is often  
430 perceived as a last resort.

431 In terms of interpreting our results relating to costs and outcomes in older women, it is worth noting  
432 that women over 40 years were not eligible for NHS funded IVF during our study period. It is possible  
433 that our findings reflect the fact that only those deemed to have the best chance of conceiving (based  
434 on unobserved factors) decided to proceed with self-funded treatment. Younger women, who were  
435 more likely to receive NHS funded IVF had a better prognosis, but also a higher rate of multiples which  
436 contributed to increased combined pregnancy, delivery and neonatal costs. The finding that the  
437 additional cost per live birth (associated with fertility treatment) decreased with BMI within age  
438 groups could be explained by the association between BMI and certain types of infertility. For  
439 example, in comparison to women with a normal BMI, fewer women with polycystic ovary syndrome,  
440 who tend to have a higher BMI, are likely to need IVF as they can often be treated successfully with  
441 less costly alternatives such as ovulation induction.

442

443 Women with very low and very high BMI were younger at their first consultation, possibly because  
444 symptoms of anovulation, such as irregular or absent periods, prompted them to seek medical advice  
445 sooner.

446

447 Within each age category, spontaneous conception rates were higher than those associated with  
448 fertility treatment. This supports the results of recent studies which have shown that young women  
449 with unexplained infertility have a higher spontaneous conception rate and early treatment does not  
450 appear to necessarily improve their chances (Steures et al, 2006, Bhattacharya et al, 2008, Brandes et  
451 al, 2011, Kamphuis et al, 2014) in comparison with expectant management.

452

453 The additional cost per additional live birth with treatment was highest for women over 40 years of  
454 age, mainly due to the small increase in probability of treatment associated live-birth in this group.

455 This ratio showed a decreasing trend with rising BMI within all age groups, partly reflecting the fact  
456 that invasive and expensive investigations and treatments were more likely to be withheld in this  
457 group. Although local policy in keeping with British Fertility Society policy and practice guidelines  
458 (Balen and Anderson 2007) excluded women with BMI > 35kg/m<sup>2</sup> from IVF treatment, some of them  
459 had spontaneous pregnancies.

460

461 As changes in practice, clinical decision-making and resource use patterns are inevitable over the 11  
462 year study period, we fitted the models predicting costs and live birth separately for two time periods  
463 (1998 to 2003 and 2004 to 2008) as a *post hoc* analysis. We found that for the first half of the study  
464 period there were no significant differences in total investigation and treatment costs across age  
465 groups in those treated and not treated. However, during the second half, women aged 31 to 35 years  
466 who received treatment incurred significantly higher costs than those in other age groups whilst  
467 treated women over 40 years incurred significantly lower costs. This suggests that early targeted  
468 delivery of IVF treatment to older women with a better prognosis may have become more frequent in  
469 more recent years.

470

#### 471 *Implications for clinicians and policy makers*

472 The fact that treatment independent conception rates were higher than those associated with active  
473 treatment in the different age groups and predictably highest in younger women with unexplained  
474 infertility suggests that expectant management is a reasonable option in this group. However, it  
475 should be noted that the presence of other unmeasured patient and clinician factors may mean that  
476 for some of these patients, being treated is the better option. This study demonstrates that our  
477 current approach of not over investigating women over 40 years of age and offering assisted  
478 reproduction where appropriate, still incurred the highest costs per additional live birth. We advise  
479 further research to investigate cost-effectiveness of treatment in this group before making firm  
480 recommendations for clinicians and policy makers. In women between the ages of 31 and 35 years in

481 whom treatment associated cost per additional live birth were highest, there may be scope to improve  
482 the targeting of treatment strategies.

483

#### 484 *Unanswered questions and future research*

485 Further research is needed to explore more efficient pathways of investigating and treating fertility  
486 problems in younger women. This can be facilitated by developing more accurate prediction models  
487 for spontaneous pregnancy which would allow a more targeted approach towards identifying who  
488 would benefit from early investigation and treatment. As the additional benefit of treatment versus  
489 no treatment in women over 40 was modest, it is worth exploring the cost effectiveness of treating  
490 women in this age group.

491

#### 492 **Conclusion**

493 Over half of all women with fertility problems conceive within 5 years of referral to secondary care  
494 and over a quarter conceive spontaneously. Women with normal BMI and those who are younger  
495 tend to incur higher NHS costs as they are more likely to receive a greater array of investigations and  
496 treatment, despite having a greater chance of treatment independent pregnancies. The additional  
497 cost per additional live birth associated with treatment rises with decreasing BMI in women of all age  
498 groups, suggesting that it may be possible to identify a more targeted approach to the provision of  
499 treatment in women with normal BMI. Future research should focus on efforts to develop better  
500 prediction models for spontaneous pregnancy and the assessment of more tailored treatment  
501 pathways based on such models.

502

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509

#### 510 **Author's Roles**

511 SP, GS and SB conceived the project and designed it with input from JM and SW. DM designed the  
512 statistical analysis plan and analysed the data. SP and DM entered and cleaned the data and wrote  
513 the first draft. All authors contributed to the interpretation of the results and the final draft. GS  
514 designed the health economic methods and interpreted the results of the health economic analysis.  
515 Finally, both SP and DM contributed equally as authors in conducting the project and writing the  
516 paper.

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#### 520 **Conflict of interest**

521 All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)  
522 (available on request from the corresponding author) and there are no conflicting interests.

523

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