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

2

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

23

24

25 †The authors consider that the first two authors should be regarded as joint First Authors

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 (≤ 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, ≥ 35.00 kg/m²). 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/m². 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
85 Scientist Office Postdoctoral Fellowship (Ref PDF/12/06). There are no conflicts of interest to declare.

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 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/m², 18.5-24.9kg/m², 25-29.9kg/m², 30-
210 34.9kg/m² and ≥35 kg/m²) 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 (≤ 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/m²), 25% were overweight (i.e. 25-29.9kg/m²) and 16% were obese
258 (≥ 30 kg/m²). 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/m² were significantly younger than women
260 with BMI in the normal range and women with BMI between 30 to 34.9 kg/m². Over half of all women
261 with BMI ≥ 35 kg/m² presented with anovulatory infertility whilst more women (36%) in the normal
262 BMI group had unexplained infertility. Fewer women with BMI over 35 kg/m² 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 ≤ 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 (≥ 35 kg/m²). 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/m².
288 The total costs of investigation and treatment were highest among women who were 30 years or
289 younger, with BMI less than 25kg/m².

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/m²) 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/m², 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 18.5kg/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/m² 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
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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
522 (available on request from the corresponding author) and there are no conflicting interests.

523

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