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Is intrauterine insemination with ovarian stimulation effective in couples with unexplained subfertility?

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1 **Is intrauterine insemination with ovarian stimulation effective**
2 **in couples with unexplained subfertility?**

3

4 **Running title:** Effectiveness of IUI with ovarian stimulation

5

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21 **Extended abstract**

22

23 **Study question:** Does starting intrauterine insemination with ovarian stimulation (IUI-OS) within
24 one and a half years after completion of the fertility workup increase ongoing pregnancy rates
25 compared to expectant management in couples with unexplained subfertility?

26

27 **Summary answer:** IUI-OS is associated with higher chances of ongoing pregnancy compared
28 to expectant management in unexplained subfertile couples, specifically those with poor
29 prognoses of natural conception i.e. <15% over 6 months or <25% over one year.

30

31 **What is known already:** IUI-OS is often the first-line treatment for couples with unexplained
32 subfertility. Two randomised controlled trials compared IUI-OS to expectant management using
33 different thresholds for the prognosis of natural conception as inclusion criteria and found
34 conflicting results. A cohort of couples with unexplained subfertility exposed to expectant
35 management and IUI-OS offers an opportunity to determine the chances of conception after both
36 strategies and to evaluate whether the effect of IUI-OS depends on a couple's prognosis of
37 natural conception.

38

39 **Study design, size, duration:** A prospective cohort study on couples with unexplained or mild
40 male subfertility who could start IUI-OS at any point after completion of the fertility workup,
41 recruited in 7 Dutch centres between January 2002 and February 2004. Decisions regarding
42 treatment were subject to local protocols, the judgement of the clinician and the wishes of the
43 couple. Couples with bilateral tubal occlusion, anovulation, or a total motile sperm count $<1 \times 10^6$
44 were excluded. Follow up was censored at the start of IVF, after the last IUI cycle or at last
45 contact and truncated at a maximum of one and a half years after the fertility workup.

46

47 **Participants/materials, setting, methods:** The endpoint was time to conception leading to an
48 ongoing pregnancy. We used the sequential Cox approach comparing in each month ongoing
49 pregnancy rates over the next 6 months of couples who started IUI-OS to couples who did not.
50 We calculated the prognosis of natural conception for individual couples, updated this over
51 consecutive failed cycles and evaluated whether prognosis modified the effect of starting IUI-OS.
52 We corrected for known predictors of conception using inverse probability weighting.

53
54 **Main results and the role of chance:** Data from 1896 couples were available. There were 800
55 couples whom had at least one IUI-OS cycle within one and a half years post fertility workup of
56 whom 142 couples conceived (rate: 0.50 per couple per year, median follow up 4 months). The
57 median period between fertility workup completion and starting IUI-OS was 6.5 months. Out of
58 1096 untreated couples, 386 conceived naturally (rate: 0.31 per couple per year, median follow
59 up 7 months).

60 Starting IUI-OS was associated with a higher chance of ongoing pregnancy by a pooled, overall
61 hazard ratio of 1.96 (95%CI: 1.47-2.62) compared to expectant management. The effect of
62 treatment was modified by a couple's prognosis of achieving natural conception ($p=0.01$), with
63 poorer prognoses or additional failed natural cycles being associated with a stronger effect of
64 treatment. The predicted 6-month ongoing pregnancy rate for a couple with a prognosis of 25%
65 at completion of the fertility workup over the next 6 cycles (approximately 40% over one year)
66 was 25% (95%CI: 21-28%) for expectant management and 24% (95%CI: 9-36%) when starting
67 IUI-OS directly. For a couple with a prognosis of 15% (25% over one year), these predicted rates
68 were 17% (95%CI: 15-19%) for expectant management and 24% (95%CI: 15-32%) for starting
69 IUI-OS.

70
71 **Limitations, reasons for caution:** The effect estimates are based on a prospective cohort
72 followed up for one and a half years after completion of the fertility workup. Although we

73 balanced the known predictors of conception between treated and untreated couples using
74 inverse probability weighting, observational data may be subject to residual confounding. The
75 results need to be confirmed in external datasets.

76

77 **Wider implications of the findings:** These results explain the discrepancies between previous
78 trials that compared IUI-OS to expectant management, but further studies are required to
79 establish the threshold at which IUI-OS is (cost-)effective.

80

81 **Study funding/competing interest(s):** This study was facilitated by grant 945/12/002 from
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85 HROpen. The other authors have no conflicts of interest.

86

87 **Keywords**

88 Intrauterine insemination; unexplained subfertility; prospective cohort; time-varying treatment;
89 sequential Cox model

90 **Introduction**

91 Couples who have been trying to conceive for at least 12 months and whose fertility workup fails
92 to reveal any abnormalities are considered to have unexplained subfertility (Aboulghar *et al.*,
93 2009; Brandes *et al.*, 2010). IUI is often used as first-line treatment in these couples, especially
94 in combination with ovarian stimulation (OS), since it is less invasive and less costly than IVF
95 (Tjon-Kon-Fat *et al.*, 2015), despite conflicting evidence from randomised controlled trials
96 regarding the effectiveness of IUI-OS. The two trials that compared IUI-OS to expectant
97 management used different thresholds for the prognosis of natural conception as inclusion
98 criteria. In women with an intermediate prognosis to conceive naturally i.e. an estimated
99 probability between 30% and 40% to conceive within 12 months leading to live birth, IUI-OS was
100 not more effective than expectant management (Steures *et al.*, 2006). In women with a poor
101 prognosis i.e. <30% over 12 months, IUI-OS resulted in more live births than expectant
102 management (Farquhar *et al.*, 2018).

103 The results of these two trials suggest that IUI-OS might be effective in couples with a
104 poor prognosis, whereas it might be ineffective in couples with better prognoses. For example,
105 couples who have been trying to conceive for a longer period of time and where the female
106 partner is older and/or nulliparous might derive greater benefit from treatment (McLernon *et al.*,
107 2014). However, these two trial results cannot be taken as definite evidence that we should treat
108 all couples with a poor prognosis of natural conception. Other -unmeasured- differences
109 between the two trials could also explain the different results. The hypothesis that the prognostic
110 profile of a couple determines the benefit of IUI-OS thus needs to be addressed directly in a
111 single population that is heterogeneous in terms of their prognosis of natural conception.
112 Knowledge on who is more likely to conceive with IUI-OS is critical in informing clinical decision
113 making and avoids unnecessary treatment in some while ensuring early and appropriate access
114 to active treatment in others.

115 The aim of this study was to determine the chances of conception after expectant management
116 or starting IUI-OS in a cohort of unexplained subfertile couples that included couples who
117 followed both strategies.

118

119

120 **Materials and Methods**

121

122 *Patient selection*

123 Couples were selected from a prospective cohort recruited across 38 hospitals in The
124 Netherlands between January 2002 and February 2004, the detailed protocol for which has been
125 described elsewhere (van der Steeg *et al.*, 2007). The purpose of recruiting this cohort was to
126 validate the Hunault model to predict the chances of natural conception leading to live birth
127 (Hunault *et al.*, 2004). In 7 of these 38 centres, data on IUI cycles was also recorded and used to
128 validate a prediction model for chances of ongoing pregnancy per IUI cycle (Steures *et al.*, 2004;
129 Custers *et al.*, 2007). IVF pregnancy outcome data were not routinely collected but starting dates
130 of IVF treatment were known. Couples from the 7 centres that recorded IUI data were included
131 in the current study.

132 We defined subfertility as couples trying to conceive for at least 12 months (Habbema *et al.*,
133 2004; Gnoth *et al.*, 2005). Selected subfertile couples had regular menstrual cycles (cycle length
134 between 23 and 35 days), at least one patent fallopian tube if hysterosalpingography,
135 laparoscopy or transvaginal hydrolaparoscopy was performed and a total motile sperm count > 1
136 x 10⁶.

137 Women were evaluated for tubal patency according to the Dutch national guidelines and
138 protocols from 2002 to 2004 recommending the chlamydia antibody test (CAT) as the first-line
139 test (NVOG, 2004). In women who were CAT negative, invasive diagnostic testing was usually
140 refrained from, thus limiting tubal patency testing to the CAT (Broeze *et al.*, 2011). Women who

141 tested positive on the CAT, or if their history indicated a high risk of tubal pathology, were
142 subsequently tested with hysterosalpingography, transvaginal hydrolaparoscopy or laparoscopy.
143 Decisions regarding treatment - IUI, IVF or expectant management - were made according to
144 local protocols and subject to the judgement of the clinician and the wishes of the couple.
145 Expectant management was defined as no intervention or monitoring aside from the advice to
146 have intercourse. Eighty-three percent of couples who received IUI used stimulation in at least
147 one cycle and treatment was considered IUI-OS. The IUI protocols have been described in more
148 detail elsewhere (Custers *et al.*, 2007).

149

150 *Follow up and outcome definitions*

151 For the follow up of selected couples, we distinguished between time spent pursuing expectant
152 management and time spent receiving IUI-OS cycles. The start of the IUI period was defined as
153 the first day of menstruation before the first IUI cycle. The end of the IUI period was defined as
154 the first day of menstruation before the last IUI cycle. With this definition, and because natural
155 conceptions after unsuccessful IUI cycles were not recorded, all pregnancies in the IUI period
156 resulted from IUI. The start of expectant management coincided with the completion of the
157 fertility workup and ended at the last date of contact, first day of last menstruation before starting
158 IUI or IVF or, in case they conceived naturally, the first day of the last menstruation before
159 conceiving. We visualised the transition from expectant management to IUI-OS in the cohort by
160 counting the number of couples in both groups over follow up.

161 The endpoint was ongoing pregnancy, defined as the presence of foetal cardiac activity at
162 transvaginal sonography at a gestational age of at least 12 weeks (van der Steeg *et al.*, 2007).
163 Couples who miscarried before 12 weeks were not censored since they could still achieve
164 ongoing pregnancy in subsequent cycles after their miscarriage. If no ongoing pregnancy
165 occurred, we censored follow up at the end of expectant management or, if treated, at the end of
166 the IUI period.

167

168 *Cumulative pregnancy rates over multiple IUI cycles*

169 We opted for the Sequential Cox approach to be able to compare treated and untreated couples
170 over multiple cycles after starting treatment, not only directly after completion of the fertility
171 workup but also if they started later (Gran *et al.*, 2010).

172 In this approach, we derived multiple datasets from the cohort in which couples started IUI-OS at
173 approximately the same point in time and compared them to couples undergoing expectant
174 management at that time, mimicking hypothetical randomised controlled trials (Gran *et al.*,
175 2010). At completion of the fertility workup and each consecutive month thereafter, i.e. the
176 landmark time points, we constructed such a new mimicked trial from our data in which we
177 included all couples who remained in the cohort i.e. couples who had not conceived and who
178 were not lost to follow up before that point. In these 'trial' sets spanning 6 months, we
179 considered couples as treated if they started IUI-OS early i.e. within one month after the
180 landmark time point. Couples who started IUI-OS within the 6 month window of a trial, but later
181 than one month after the landmark time point, were 'artificially censored' at the time of starting
182 IUI-OS to retain a treatment group that all started at approximately the same time. This way,
183 couples were not included in a single group throughout the study. Instead, couples who started
184 IUI-OS were analysed as controls (under expectant management) in the trials preceding the
185 month in which they started IUI-OS, at which point they were analysed over cumulative
186 treatment cycles as part of the treated (IUI-OS) group in the mimicked trial that started that
187 month.

188 The maximum follow up period of 18 months after the fertility workup was chosen because of the
189 small numbers of couples starting treatment thereafter. Thus, we derived trial datasets from
190 landmark time point 0 i.e. the fertility workup until the final landmark time point at 12 months after
191 the workup, sliding forward in intervals of one month, resulting in a total of 13 mimicked trials.

192

193 *Adjusting for patient characteristics that differed between treated and untreated couples*

194 To balance treated, untreated, artificially censored and uncensored couples in important
195 predictors of conception, we applied iterative inverse probability weighting (Austin, 2011; van der
196 Wal, 2011; Austin and Stuart, 2015). Details on how we derived the weights to adjust for these
197 differences are given in the **Supplementary Material**. The patient characteristics we chose to
198 balance were: female age, duration of subfertility, primary or secondary subfertility, total motile
199 sperm count, referral status, presence of one-sided tubal pathology and fertility clinic (Hunault *et*
200 *al.*, 2004; van Eekelen *et al.*, 2017a). We calculated the mean weight, which is ideally around 1 to
201 avoid inflating the effective sample size (Cole and Hernan, 2008).

202
203 We assessed the degree of balance in patient characteristics before and after weighting using the
204 standardized mean difference between the treated and untreated group. A lower standardized
205 mean difference between groups represents better balance and a value below 0.10 generally
206 indicates no important difference (Austin, 2011; Austin and Stuart, 2015).

207
208 *Statistical analysis*

209 We analysed the weighted datasets using a pooled Cox proportional hazards model with IUI-OS
210 or expectant management as a treatment covariate. We calculated an overall hazard ratio by
211 stratifying on all 13 mimicked trials. We used a robust sandwich variance estimator to adjust
212 precision measures since couples can be included in multiple trials (Wei *et al.*, 1989). Using the
213 pooled Cox model, we predicted the probability of conception over 6 months when couples start
214 IUI-OS immediately after completion of the fertility workup or when they remain on expectant
215 management.

216
217 *Modification of the estimated effect of IUI-OS by the prognosis of natural conception*

218 To address whether the effect of starting IUI-OS depends on the decreasing prognosis of natural
219 conception of the individual couple, we added a treatment-by-prognosis interaction term to the
220 model. We calculated a time-updated prognosis of natural conception over the next 6 cycles at
221 the start of each mimicked trial dataset by using the dynamic prediction model that comprises
222 female age, duration of subfertility, primary or secondary subfertility, percentage of progressive
223 motile sperm and referral by a general practitioner or specialist (van Eekelen *et al.*, 2017a). The
224 prognosis for a couple is thus not one fixed value throughout the study, but decreases after
225 consecutive failed natural cycles. We included the complementary log-log of this updated
226 prognosis as a main effect, the main effect for treatment and the treatment-by-prognosis
227 interaction effect in the pooled Cox model. The weighting procedure was adjusted slightly for this
228 analysis (VanderWeele, 2009) because the difference in prognosis between groups was adjusted
229 for by adding it to the model as a main effect (see also **Supplementary Material**).

230 For three hypothetical couples, we visually depicted the relationship between their
231 worsening prognoses and the accompanying 6-month cumulative predicted probability of
232 conception following expectant management or starting IUI-OS, shown as treatment is initiated
233 later. The first example is a couple referred by their general practitioner, where the female partner
234 is nulliparous and 32 years old, the couple has 1 year of subfertility at the time of completion of
235 the fertility workup and the semen analysis showed 37% progressively motile sperm. In this case,
236 the estimated prognosis of natural conception over the next 6 cycles is 25%. A second couple with
237 the same characteristics except for a 2 year duration of subfertility at the completion of the fertility
238 workup has a prognosis of 20% while a third couple with the same characteristics but for a 3.5
239 year duration of subfertility has a prognosis of 15%. At the time of the completion of their fertility
240 workup, these couples have prognoses of 25%, 20% and 15% respectively over 6 cycles, which
241 translates to approximately 40%, 32% and 25% respectively over 13 cycles i.e. one year (van
242 Eekelen *et al.*, 2017a).

243 If these three hypothetical couples should fail to conceive naturally over the course of one year
244 after completion of the fertility workup i.e. if they would 'enter' the latest mimicked trial, their
245 prognoses over the next 6 cycles decrease to 13%, 10% and 7% respectively.

246 Estimated cumulative probabilities of ongoing pregnancy from this model are derived from the
247 separate mimicked trials that all have different observed conception rates, thus predictions may
248 fluctuate. We considered an absolute difference of more than 5% between point estimates of the
249 cumulative ongoing pregnancy rates, estimated at the completion of the fertility workup, to signify
250 a benefit of IUI-OS.

251
252 In addition to the impact of prognosis or a failure to conceive in consecutive natural cycles on the
253 effect of treatment, we modelled if the effect of IUI-OS depends on the time of initiation of treatment
254 by adding an additional interaction between treatment and landmark time point to the pooled Cox
255 model already including treatment, prognosis and the treatment-by-prognosis interaction. We also
256 added a three-way interaction between treatment, prognosis and landmark time point to the
257 previous model to see if the effect modification of prognosis on IUI-OS changed over mimicked
258 trials i.e. when starting treatment later.

259 As a sensitivity analysis, we tested whether couples with mild male subfertility had more or less
260 benefit from IUI-OS compared to couples that did not have mild male subfertility. We classified
261 couples as having mild male subfertility when they had a total motile count between 1 and 10×10^6 ,
262 then tested the hypothesis by fitting a Cox model including treatment, the mild male subfertility
263 classification and their interaction.

264
265 We used Akaike's Information Criterion (AIC) and Wald tests for the interaction terms to determine
266 whether including the interactions resulted in a better fit of the model to the data (Akaike, 1974).

267

268 *Missing data*

269 Missing data were accounted for using multiple imputation in a previous study, creating ten
270 imputation sets (van Eekelen *et al.*, 2017a). In total, only 1.3% of patient characteristic data used
271 for this study were missing and we chose to use one randomly selected imputation set for our
272 analyses.

273
274 All statistical analyses were performed using R version 3.3.2 ²²²²(R Core Team (2013). R: A
275 language and environment for statistical computing. R Foundation for Statistical Computing,
276 Vienna, Austria. <http://www.R-project.org/>) using the *survival*, *dynpred* and *CreateTableOne*
277 packages.

278

279

280 **Results**

281 From the 7860 couples included in the initial cohort, we selected 1896 couples for analysis
282 (Figure 1).

283 Of these, 800 couples had at least one IUI cycle within one and a half years after the workup for
284 a total of 3119 cycles (**Table I**) following which 142 couples conceived leading to ongoing
285 pregnancy (rate: 0.50 per couple per year over a median follow up for IUI of 4 months). Out of
286 1096 untreated couples followed up for one and a half years after the fertility workup, 386
287 conceived naturally leading to ongoing pregnancy (rate: 0.31 per couple per year over a median
288 follow up of 7 months). Among couples who remained on expectant management, there were 5
289 multiple pregnancies, 68 women miscarried and 7 had an ectopic pregnancy. Among couples
290 treated with IUI-OS, there were 16 multiple pregnancies, 35 women miscarried and 7 women
291 had an ectopic pregnancy.

292

293 Out of 800 couples who underwent IUI-OS, 64 started treatment directly after completion of the
294 fertility workup and 736 had a prior period of expectant management after completion of their

295 fertility workup. The median period between completion of the fertility workup and starting IUI-OS
296 was 6.5 months. In 57% of IUI cycles, recombinant gonadotrophins were used, in 24% no
297 medication was used, in 9% clomiphene citrate was used and in 7% urinary gonadotrophins
298 were used. In 3% of cycles, another type of drug was used or data were missing. Two hundred
299 and sixty eight couples (14%) received IVF as their first treatment, with a median period of
300 expectant management of one year between completion of the fertility workup and the start of
301 IVF.

302 We depicted the number of couples currently in the expectant management or IUI-OS group
303 over time in **Figure 2**. Until ten months after the fertility workup, there was a steady increase in
304 the number of couples who were currently in a treatment pathway, after which this number
305 declined again.

306
307 The baseline characteristics for couples who eventually received at least one cycle of IUI-OS
308 within one and a half years after the fertility workup or who remained untreated are summarized
309 in **Table I**. Treated couples more often had primary subfertility (70% versus 60%) and were more
310 often tested for tubal patency using laparoscopy, hysterosalpingography or transvaginal
311 hydrolaparoscopy (55% versus 39%) compared to couples that were not treated. Female age,
312 on average 32.1 years old (SD: 4.4) and median duration of subfertility of 1.6 years (5th-95th
313 percentile: 1.0-4.7), both at completion of the fertility workup, were similar between groups.

314 In the weighted trial datasets, the standardized mean differences between treated and untreated
315 couples were below 0.10 for all characteristics, indicating that the two groups were well balanced
316 in terms of prognostic factors after weighting. The mean weight used in the pooled dataset was
317 1.00, indicating that weights are stable and do not artificially inflate sample size.

318

319 *Effect estimates of IUI-OS*

320 Starting IUI-OS was associated with increased ongoing pregnancy rates compared to expectant
321 management as shown by an estimated hazard ratio of 1.96 (95%CI: 1.47-2.62), pooling all 13
322 mimicked, weighted trials running over 6 months.

323 The predicted probability that a couple would conceive over the course of 6 months of expectant
324 management after the fertility workup was 17% (95%CI: 16-19%). If the couple started IUI-OS
325 directly after completion of the fertility workup, their estimated probability of conception was 31%
326 (23-38%) over that same period.

327

328 The relative effect of IUI-OS depended on the prognosis of natural conception ($p=0.01$).

329 The relationship between prognosis and the estimated treatment effect as time progresses is
330 visualised in **Figure 3**, in which estimated 6-month cumulative probabilities of conception with
331 and without starting IUI-OS are shown for three different example couples with a prognosis to
332 conceive naturally at completion of the fertility workup over the next 6 cycles of 25% (**A**), 20%
333 (**B**) or 15% (**C**), which were updated over time when these couples fail consecutive natural
334 cycles and start treatment later.

335 The absolute cumulative predicted probability to conceive over 6 months after starting IUI-OS
336 was stable at around 24%, regardless of the prognosis at completion of the workup or the time
337 thereafter when a couple would start, which leads to larger differences between IUI-OS and
338 expectant management for couples at lower prognoses of natural conception and/or for couples
339 after additional failed natural cycles, both on absolute and relative scale.

340 It follows from **Figure 3** that a couple who has tried to conceive for 3.5 years post fertility work
341 up with a prognosis of 15% over the next 6 months (approximately 25% over one year) has a
342 higher predicted probability when starting treatment directly after completion of the fertility
343 workup compared to expectant management, whereas a couple who tried to conceive for 1 year
344 with a prognosis of 25% (approximately 40% over one year) does not.

345

346 Apart from the influence of decreasing prognosis over time, we found no evidence that the
347 relative effect of IUI-OS changed as treatment was started later ($p=0.38$) nor that the
348 dependency of the relative effect of IUI-OS on prognosis additionally depended on when
349 treatment was started ($p=0.66$). We found no evidence for a difference in the benefit of IUI-OS
350 between couples with or without mild male subfertility ($p=0.75$).

351

352

353 **Discussion**

354 In couples with unexplained subfertility, starting IUI-OS within one and a half years after
355 completion of the fertility workup was associated with increased ongoing pregnancy rates over 6
356 months compared to expectant management. The estimated benefit of treatment depended on
357 the prognosis of natural conception, not only expressed at the time of completion of the fertility
358 workup but also after additional failed natural cycles.

359

360 Our study has a number of strengths. First, the chosen study design represents the best
361 possible design for an observational study, being less subject to selection bias than a
362 comparison of separate cohorts since unexplained subfertile couples that will eventually be
363 treated or not were both sampled using a prospective approach and followed up thereafter
364 (Aboulghar *et al.*, 2009; McLernon *et al.*, 2014; van Eekelen *et al.*, 2017b). In addition, we were
365 able to adjust for differences in prognostic factors between treated and untreated couples and
366 the relatively large sample size and long follow up meant we were able to study whether the
367 prognosis of natural conception influences the effect of IUI, an approach aimed to improve the
368 management of unexplained subfertile couples and to explain the discrepancies between
369 existing trials.

370 Second, data collection took place before the current Dutch clinical guideline for fertility
371 recommending the application of the prediction model for natural conception leading to live birth

372 by Hunault *et al.* to decide on treatment (NVOG, 2010). Because decisions regarding treatment
373 were not clear-cut at the time, this led to considerable variation in observed time points when
374 couples started IUI and ensured that most couples would be eligible for treatment, reducing
375 confounding by indication.

376 Third, we defined the IUI period as the time between the first and last cycle, even when
377 treatment cycles were not consecutive, which is a realistic measure of the actual time that
378 couples spend in an IUI program. This allowed comparison with expectant management on the
379 same axis representing 'real' calendar time and allows our results to be easily interpreted (Daya,
380 2005).

381 Fourth, we focused on the clinical question on what would occur when treatment would
382 be started at a given time point and applied methodology that matched this question. When
383 analysing the data using a regular Cox approach with a time-varying covariate for treatment, the
384 couples currently undergoing IUI at a certain point in time consist of couples who just started and
385 couples who already failed several cycles, such that the resulting estimate would be different
386 from 'starting IUI' and more difficult to interpret (Gran *et al.*, 2010).

387
388 Our study also has some limitations. An adequately powered, randomised controlled trial offers
389 the best way of evaluating the effectiveness of IUI-OS compared to expectant management; our
390 observational study following a cohort of couples after both strategies is a less robust design
391 because treatment was not randomly allocated, which means that treated and untreated couples
392 might differ on important factors related to conception. We tried to balance these factors in both
393 groups using (iterative) inverse probability weighting. Nevertheless, our results could still be
394 influenced by unmeasured factors related to conception i.e. residual confounding. However, the
395 advantage of using observational data on couples with a wide range of prognoses of natural
396 conception was that we could directly address the hypothesis regarding the influence of
397 prognosis on the relative effect of IUI-OS. Addressing this hypothesis with an experimental

398 design would require the unfeasible, inefficient and indirect approach of conducting multiple
399 smaller, separate trials applying different inclusion criteria.

400 The primary outcome was ongoing pregnancy since following couples for live birth
401 increases logistical efforts that the study budget did not allow for. In addition, following couples
402 for live birth increases the likelihood of loss-to-follow-up. Ongoing pregnancy is generally
403 considered an appropriate and efficient proxy for live birth in clinical research: approximately
404 95% of ongoing pregnancies lead to live birth (Clarke *et al.*, 2010; Braakhekke *et al.*, 2014).

405 54% of couples only received a CAT and not a visual test for tubal patency. It is unlikely
406 that this has led to clinically relevant differences in tubal pathology between treated and
407 untreated couples because the decision to initiate IUI-OS was taken in the absence of visual
408 confirmation of tubal patency and thus, any difference is likely due to chance.

409 We lacked the sample size to accurately estimate interactions between all separate
410 patient characteristics female age, duration of subfertility etc. and IUI-OS to further individualize
411 treatment effects. Instead, we opted for the summary score in terms of an estimated prognosis
412 such that only one additional parameter was required (Dahabreh *et al.*, 2016) and updated this
413 over time using our previously developed dynamic model for natural conception to determine
414 when a couple would benefit from starting treatment (van Eekelen *et al.*, 2017a).

415
416 Our findings add context to the apparent discrepancies between the two randomised controlled
417 trials that compared IUI-OS to expectant management (Steures *et al.*, 2006; Farquhar *et al.*,
418 2018). Steures *et al.* included 253 couples with an intermediate prognosis for natural conception
419 i.e. 30% to 40% as calculated by the Hunault model and found a risk ratio of 0.85 (95%CI: 0.63-
420 1.10) for ongoing pregnancy after IUI-OS compared to expectant management over the course
421 of 6 months. The pragmatic TUI trial by Farquhar *et al.* included 201 couples with a prognosis
422 <30% and found a beneficial effect of IUI-OS compared to expectant management by a risk ratio
423 of 3.41 (95%CI: 1.71-6.79). Couples in the latter study had a much worse prognosis of natural

424 conception compared to the first; mostly due to an average duration of subfertility of 3.6 years
425 that was almost double the average duration in the trial by Steures *et al.* and in the present
426 study. Our finding that the benefit of IUI-OS is larger in couples with poorer prognoses of natural
427 conception, both on relative and absolute scale, may primarily explain and support the difference
428 in results.

429
430 Couples with a prognosis of natural conception of 25% over 6 months (approximately 40% over
431 one year) or higher were not expected to benefit from IUI-OS. For couples with a prognosis
432 around 20% over 6 months (approximately 32% over one year), it was uncertain if we can
433 expect a clinically relevant benefit of IUI-OS. Couples with a prognosis of 15% over 6 months
434 (approximately 25% over one year) or lower were expected to benefit from IUI-OS as the
435 absolute difference in pregnancy rates was more than 5%.

436 Since IUI-OS is invasive, expensive and associated with potential disadvantages such as
437 ovarian hyperstimulation or multiple pregnancies (Rooney and Domar, 2016), we believe that
438 counselling couples should involve a discussion about their prognosis when following alternative
439 treatment scenarios so that they are able to make an informed choice. These results, in
440 combination with the prognosis of natural conception derived from a prediction model (van
441 Eekelen *et al.*, 2017a), can be used to attain that goal.

442 Because confidence intervals around the predicted pregnancy rates after IUI-OS for a given
443 prognosis were broad in the current study, the results need to be interpreted with caution and
444 replicated in further research.

445

446 **Conclusion**

447 Within one and a half years post fertility workup, starting IUI-OS is associated with higher
448 chances of conception in couples with unexplained subfertility and a poor prognosis for natural
449 conception i.e. <15% over 6 months or <25% over one year. Our results explain the

450 discrepancies between two trials that compared IUI-OS to expectant management using
451 different inclusion criteria for the prognosis of natural conception. These results may be used in
452 counselling couples with unexplained subfertility. Future studies should focus on establishing the
453 threshold for the prognosis of natural conception at which IUI-OS is deemed (cost-)effective.

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459

460 **Authors' roles:**

461 NvG, PS, FvdV and MJE conceived the study. PS and IMC collected and cleaned the data. RvE,
462 MJE and NvG designed the statistical analysis plan. RvE analysed the data. RvE and NvG
463 drafted the manuscript. All authors contributed critical revision to the paper and approved the
464 final manuscript.

465

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470

471 **Conflicts of Interest**

472 BWM reports consultancy for ObsEva, Merck and Guerbet. SB reports acting as Editor-in-Chief
473 of HROpen. The other authors have no conflicts of interest.

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590

591 **Figure legends**

592

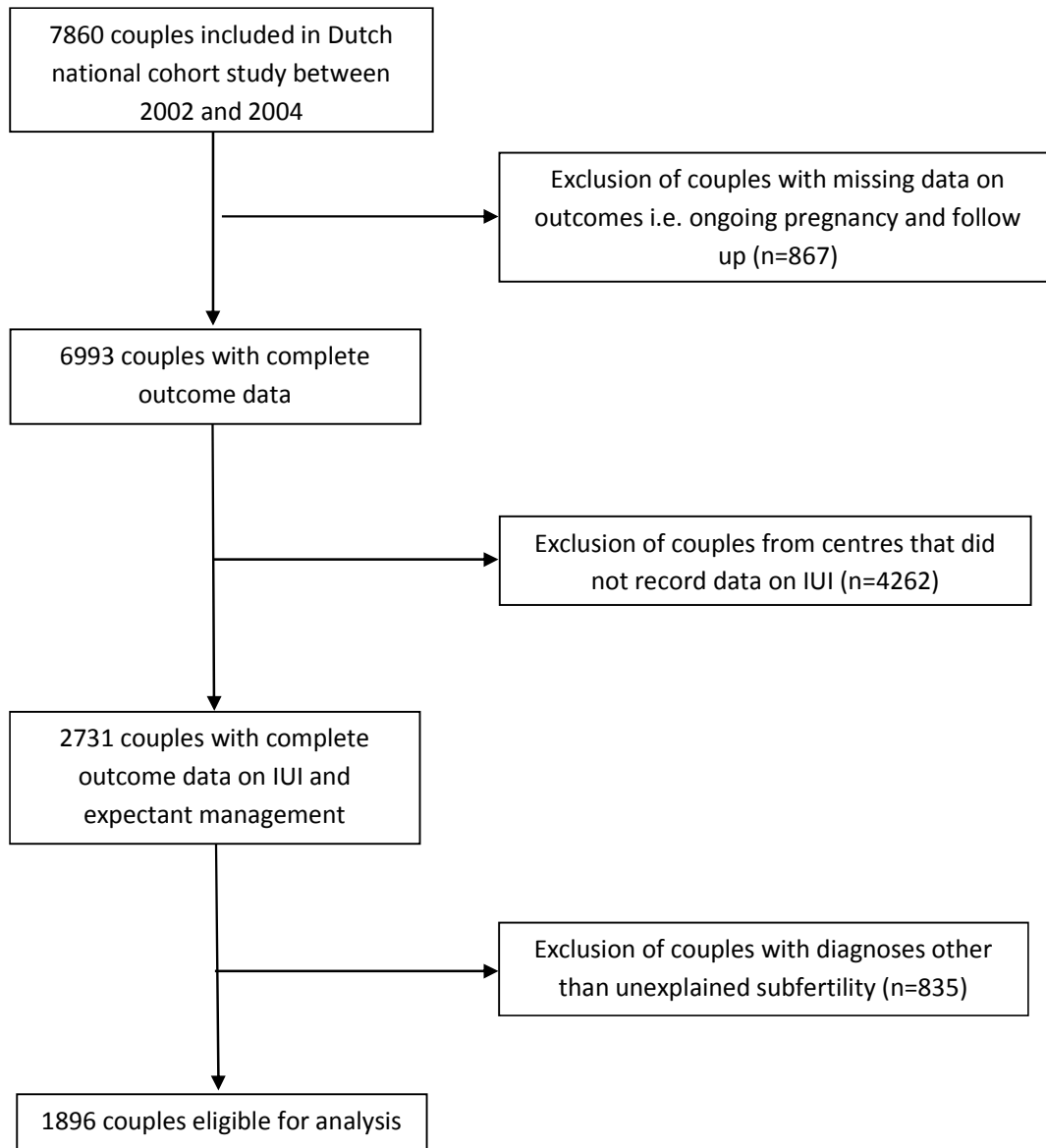
593 **Figure 1** Flow chart of couples from the cohort who were included in the analysis.

594

595 **Figure 2** Number of couples currently on treatment or not as time progresses, depicted in the
596 original dataset (n=1896) before the sequential Cox procedure.

597

598 **Figure 3** The association between the predicted prognosis of natural conception and the
599 estimated benefit of starting IUI-OS. This is shown as cumulative probabilities over 6 months (y-
600 axis) when starting IUI-OS or not at different time points after completion of the fertility workup
601 (x-axis) for three example couples that have three different prognoses at the workup completion:
602 25% (panel A), 20% (panel B) or 15% (panel C). The prognosis was calculated over 6 cycles
603 and updated after additional failed natural cycles. Grey bands represent 95% confidence limits.

Figure 1. Flowchart

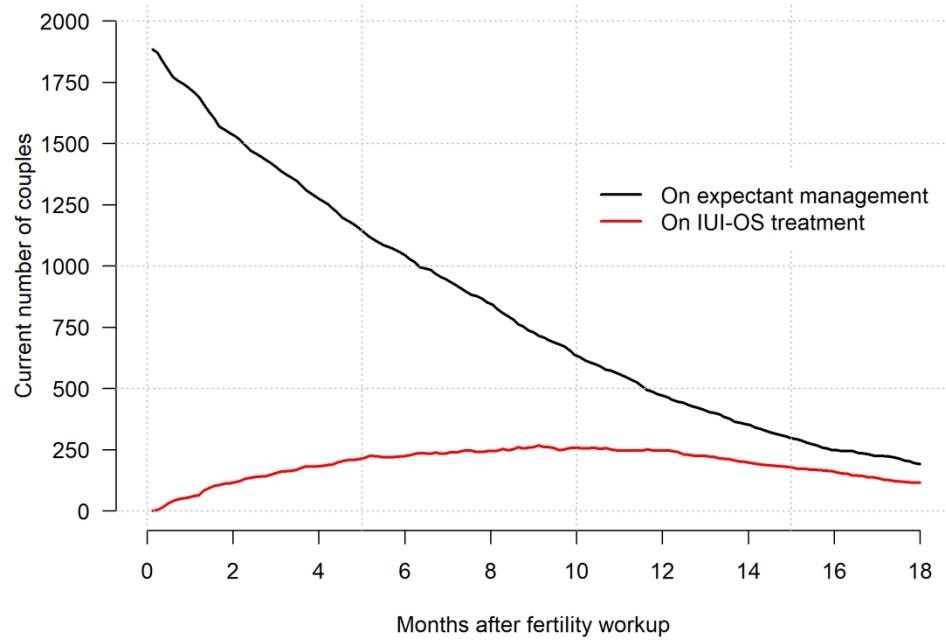


Figure 2. Number of couples currently on treatment or not as time progresses, depicted from the original dataset (n=1896) before the sequential Cox procedure

190x147mm (300 x 300 DPI)

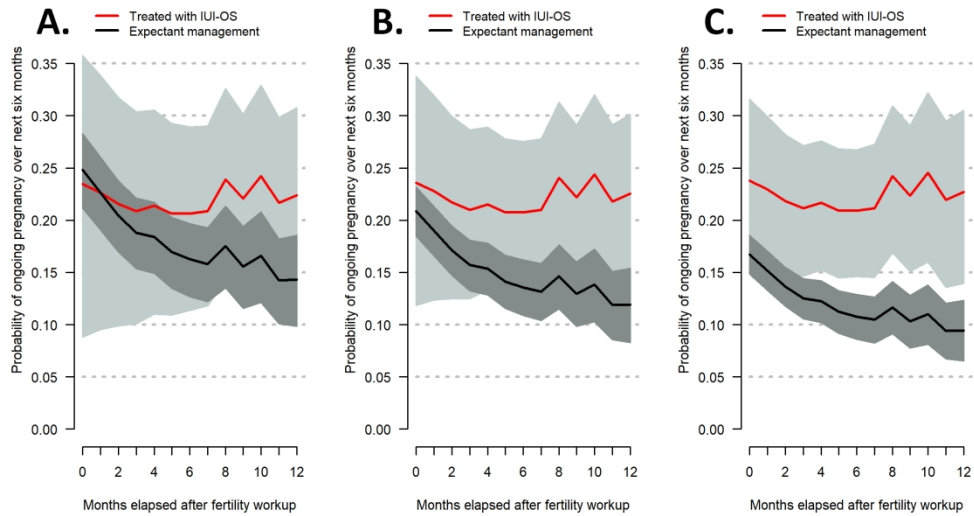


Figure 3. Association between the predicted prognosis of natural conception and the estimated benefit of IUI-OS, shown as cumulative probabilities over 6 months when starting IUI-OS or not for three different couples' prognoses at completion of the fertility workup: 25% (A), 20% (B) or 15% (C). The prognosis was calculated over 6 cycles and updated after additional failed natural cycles.

634x340mm (96 x 96 DPI)

Table I. Baseline characteristics of patients in the original dataset at completion of the fertility workup (n=1896) and the total number of IUI cycles they underwent. Data are mean or median (5th-95th percentile) or n (%).

	Couples who remained on expectant management (n=1096)	Couples who received at least one IUI cycle within one and a half years (n=800)
Female age at workup (years)	32.2 (24.0-39.4)	32.0 (25.3-38.6)
Duration of subfertility at workup (years, median)	1.6 (1.0-4.9)	1.6 (1.0-4.5)
Primary subfertility (versus secondary)	659 (60%)	558 (70%)
Total motile sperm count (in millions)	72 (2-240)	62 (3-205)
Tubal pathology		
Only CAT performed	667 (61%)	363 (45%)
Invasive testing ^a conducted:		
Both fallopian tubes functional	359 (33%)	380 (48%)
One-sided tubal occlusion	70 (6%)	57 (7%)
Ob/Gyn referral (versus GP referral)	125 (11%)	67 (8%)
Number of IUI cycles		
Cycle 1	-	800 (100%)
Cycle 2	-	673 (84%)
Cycle 3	-	561 (70%)
Cycle 4	-	431 (54%)
Cycle 5	-	355 (44%)
Cycle 6	-	272 (34%)
Cycles 7-13	-	27 (3%)

CAT, chlamydia antibody test; Ob/Gyn, gynaecologist; GP, general practitioner

^ahysterosalpingography, transvaginal hydrolaparoscopy or laparoscopy

1 **Supplementary material. Details regarding the weighing procedure**
2

3 In our iterative inverse probability weighting (IIPW) algorithm per trial, we started the iterative
4 process by first calculating the proportion of treated and untreated couples. We then divided
5 this by the predicted chance for individual couples of being treated or untreated based on
6 their characteristics, estimated by a logistic regression model in every trial dataset (Cole and
7 Hernan, 2008; Austin and Stuart, 2015). The result from this division, a weight for individual
8 couples, gives an indication how likely this couple was to have their observed treatment
9 status and if they should have an increased or decreased influence on the analysis relative
10 to other couples. After obtaining the weights in the first iteration, we applied the resulting
11 weights on the trial dataset in the second iteration, derived new weights in the same manner
12 on the weighted dataset, multiplied the old and the new weights and repeated the process
13 until all measured predictors were balanced between treated and untreated couples (Austin,
14 2011; van der Wal, 2011). In addition, a second criterion was that the set of weights should
15 balance measured predictors between artificially censored and uncensored couples as well,
16 for which we used a separate logistic regression model predicting censoring, which modified
17 the same set of weights.

18 We used a maximum of 2000 iterations per mimicked trial dataset. Weights were truncated
19 at the 1st and 99th percentile between iterations to remove extreme values and multiplied
20 with the inverse of the mean weight to center the weights around 1 (van der Wal, 2011). The
21 criterion for stopping the IIPW process was when the variance of the natural log of newly
22 derived weights, for both treatment initiators and censoring, were below 1×10^{-7} , indicating
23 that all new weights are 1 representing no further confounding present in the weighted
24 dataset (van der Wal, 2011), or when the maximum number of iterations was reached. The
25 algorithm is summarized in the **Explanatory Figure**.

26 We calculated the mean weight of the final set, which is ideally around 1 to avoid inflating the
27 effective sample size (Cole and Hernan, 2008).

28 We applied the above algorithm in every mimicked trial using the following predictive patient
 29 characteristics: female age, duration of subfertility, primary or secondary subfertility, total
 30 motile sperm count, referral status, one-sided tubal pathology and fertility clinic. If weights
 31 did not converge in a landmark, if they were highly unstable (i.e. no treated couples left in
 32 the trial dataset) or if there was residual imbalance in terms of a standardized mean
 33 difference above 0.1, weights were re-estimated for that landmark without the location
 34 variable.

35

36 For the secondary analysis investigating whether the prognosis of natural conception
 37 influences the estimated relative effect of IUI-OS, we calculated a different set of weights
 38 using female age, duration of subfertility, primary or secondary subfertility, total motile sperm
 39 count and referral status in the first (numerator) and divided the resulting probability this time
 40 by the probability from a second (denominator) model containing the same variables plus
 41 one-sided tubal pathology and fertility clinic. This was because balance in tubal pathology
 42 and clinic between groups was desired, but not for the other mentioned variables, since we
 43 already accounted for these in the outcome (Cox) model via the summary measure
 44 prognosis plus the interaction between prognosis and IUI-OS (vanderWeele, 2009).

45

46 **Explanatory Figure**

Iterative inverse probability weighting

