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External validation of a dynamic prediction model for repeated predictions of natural conception over time

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1 **External validation of a dynamic prediction model for**
2 **repeated predictions of natural conception over time**

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18 **Running title:** External validation of a dynamic prediction model

19

20 **Abstract**

21

22 **STUDY QUESTION:** How well does a previously developed dynamic prediction model
23 perform in an external, geographical validation in terms of predicting the chances of natural
24 conception at various points in time?

25

26 **SUMMARY ANSWER:** The dynamic prediction model performs well in an external validation
27 on a Scottish cohort.

28

29 **WHAT IS KNOWN ALREADY:** Prediction models provide information that can aid evidence-
30 based management of unexplained subfertile couples. We developed a dynamic prediction
31 model for natural conception (van Eekelen model) that is able to update predictions of natural
32 conception when couples return to their clinician after a period of unsuccessful expectant
33 management. It is not known how well this model performs in an external population.

34

35 **STUDY DESIGN, SIZE, DURATION:** A record-linked registry study including the long-term
36 follow up of all couples who were considered unexplained subfertile following a fertility work
37 up at a Scottish fertility clinic between 1998 and 2011. Couples with anovulation, uni/bilateral
38 tubal occlusion, mild/severe endometriosis or impaired semen quality according to World
39 Health Organization criteria were excluded.

40

41 **PARTICIPANTS/MATERIALS, SETTING, METHODS:** The endpoint was time to natural
42 conception, leading to an ongoing pregnancy (defined as reaching a gestational age of at
43 least 12 weeks). Follow up was censored at the start of treatment, at the change of partner or
44 at the end of study (31st of March, 2012). The performance of the van Eekelen model was

45 evaluated in terms of calibration and discrimination at various points in time. Additionally, we
46 assessed the clinical utility of the model in terms of the range of the calculated predictions.

47

48 **MAIN RESULTS AND THE ROLE OF CHANCE:** Of a total of 1203 couples with a median
49 follow up of 1 year and 3 months after the fertility workup, 398 (33%) couples conceived
50 naturally leading to an ongoing pregnancy. Using the dynamic prediction model, the mean
51 probability of natural conception over the course of the first year after the fertility workup was
52 estimated at 25% (observed: 23%). After 0.5 year, 1 year and 1.5 years of expectant
53 management after completion of the fertility workup, the average probability of conceiving
54 naturally over the next year was estimated at 18% (observed: 15%), 14% (observed: 14%)
55 and 12% (observed: 12%).

56 Calibration plots showed good agreement between predicted chances and the observed
57 fraction of ongoing pregnancy within risk groups. Discrimination was moderate with c
58 statistics similar to those in the internal validation, ranging from 0.60 to 0.64. The range of
59 predicted chances was sufficiently wide to distinguish between couples having a good and
60 poor prognosis with a minimum of zero at all times and a maximum of 55% over the first year
61 after the workup, which decreased to maxima of 43% after 0.5 years, 34% after 1 year and
62 29% after 1.5 years after the fertility workup.

63

64 **LIMITATIONS, REASONS FOR CAUTION:** The model slightly overestimated the chances of
65 conception by approximately 2 to 3 percentage points on group level in the first year post
66 fertility workup and after 0.5 years of expectant management, respectively. This is likely
67 attributable to the fact that the exact dates of completion of the fertility workup for couples
68 were missing and had to be estimated.

69

70 **WIDER IMPLICATIONS OF THE FINDINGS:** The van Eekelen model is a valid and robust
71 tool that is ready to use in clinical practice to counsel couples with unexplained subfertility on

72 their individualised chances of natural conception at various points in time, notably when
73 couples return to the clinic after a period of unsuccessful expectant management.

74

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78

79 **Keywords**

80 Natural conception; expectant management; prognosis; prediction model; dynamic prediction;

81 retrospective cohort

82 **Introduction**

83 Approximately 10% of all couples who wish to have a child do not conceive within the first
84 year of trying (Gnoth *et al.*, 2003; Wang *et al.*, 2003). For approximately half of these
85 couples, no clear barrier for conception can be found during the workup and these couples
86 are considered unexplained subfertile (Aboulghar *et al.*, 2009; Brandes *et al.*, 2010). It is
87 unclear whether these couples should start with ART; firstly, since observational studies
88 report that 18% to 38% of unexplained subfertile couples will conceive naturally in the year
89 after the fertility workup (Hunault *et al.*, 2004; van der Steeg *et al.*, 2007; van Eekelen *et al.*,
90 2017a) and secondly, since there remains uncertainty regarding the effectiveness of ART for
91 unexplained subfertile couples (Pandian *et al.*, 2015; Tjon-Kon-Fat *et al.*, 2016; Veltman-
92 Verhulst *et al.*, 2016; van Eekelen *et al.*, 2017b).

93 In the absence of clear evidence on the management of unexplained subfertile couples and
94 when to offer ART, an enticing option is to calculate chances of natural conception and to
95 base counselling on this estimated prognosis (van Eekelen *et al.*, 2017b). Fundamental to
96 this approach is to identify couples that are expected to benefit from treatment and those
97 who are not. In clinical practice, this would imply that couples with a good prognosis to
98 conceive naturally are advised to continue to try and become pregnant by sexual intercourse,
99 while couples with an unfavourable prognosis are advised to start ART. Several prediction
100 models for natural conception have been published of which the model by Hunault *et al.*, that
101 calculates a prognosis of conception leading to live birth over the first year after completion
102 of the fertility workup, has been externally validated and subsequently implemented in the
103 national guidelines and clinical practice in the Netherlands (Hunault *et al.*, 2004; van der
104 Steeg *et al.*, 2007; Leushuis *et al.*, 2009; NVOG, 2010). A practical drawback of the Hunault
105 model is that it cannot give a prediction at later time points when couples who continued
106 expectant management after the fertility workup but did not conceive, return to the clinic. This
107 is because applying the Hunault model at later time points leads to overestimation due to the
108 selection of less fertile couples over time that is not incorporated in the Hunault model (van
109 Eekelen *et al.*, 2017b).

110 Van Eekelen *et al.* recently developed a dynamic prediction model that accommodates the
111 need for repeated predictions (van Eekelen *et al.*, 2017a). This model comprises the clinical
112 factors female age, duration of subfertility (both at completion of the fertility workup),
113 percentage of progressively motile sperm, primary or secondary subfertility and being
114 referred to the fertility clinic by a general practitioner or a specialist. In addition to these
115 factors, the model uses as input the number of menstrual cycles that have passed since
116 completion of the fertility workup, with zero cycles denoting the prediction is made
117 immediately after the workup. The output is the predicted probability to conceive naturally in
118 the following cycle, leading to ongoing pregnancy, which can be extended to predict over any
119 given number of cycles with a maximum of 2.5 years after the workup (approximately 28-34
120 cycles). When couples return after a period of expectant management, the number of cycles
121 that have passed since the workup can be changed to update the predicted probability over
122 subsequent cycles.

123 The model developed by van Eekelen *et al.* showed promising results in the internal
124 validation, but this in itself is insufficient to advise clinical implementation since models tend
125 to perform better in the cohort they were developed on than in another cohort in which the
126 model may be applied (Steyerberg, 2009).

127 The aim of this study was to externally validate the van Eekelen model on a large cohort that
128 followed couples for natural conception after registration in the fertility clinic of the Grampian
129 region of Scotland, UK. This is the largest contemporary cohort following couples for natural
130 conception, aside from the Dutch cohort on which the dynamic model was developed.

131

132

133 **Materials and Methods**

134 We included couples diagnosed with unexplained subfertility residing in the Grampian region
135 of Scotland who registered with the Aberdeen Fertility Centre (AFC) from 1998 to 2011
136 (Pandey *et al.*, 2014). Only patients from the Grampian region visiting the AFC were selected
137 because there is no other fertility clinic in the region and it was considered important to have

138 a complete overview of a couple's trajectory after the fertility workup, which includes
139 treatment information. We combined the AFC registration database with three other data
140 sources using record-linkage to get the complete follow up for couples from the registration
141 at the AFC until ongoing pregnancy, treatment or end of study, which was the 31st of March,
142 2012.

143 The AFC database comprises patient characteristics and diagnostic information. Data entry
144 in the AFC database is validated and checked by regular case note audits. First, we record-
145 linked couples registered in the AFC database to the centre's Assisted Reproduction Unit
146 database which contained dates when treatment was started.

147 Second, we identified natural conceptions leading to an ongoing pregnancy by record-linkage
148 of the AFC database with the Aberdeen Maternity and Neonatal Databank, which contained
149 gestational age, outcome and delivery date of (early) pregnancies for all women residing in
150 Aberdeen City District. Third, we performed record-linkage with the national Scottish
151 Morbidity Records Maternity database for identifying gestational age, outcome and delivery
152 date of (early) pregnancies for women who delivered elsewhere in Scotland.

153 The Data Management Team of the University of Aberdeen created a new pseudonomised
154 identifier for all women by using the Community Health Index identifier. This new study-
155 specific identifier cannot be used to trace back to individuals and was then used by author
156 DJM to record-link the databases within the Grampian Data Safe Haven environment. This
157 process was carried out according to the Standard Operating Procedures of the Data
158 Management Team, University of Aberdeen. The resulting linked dataset was thus a
159 combination of these four data sources.

160 Ethical approval was provided by the North of Scotland Research Ethics Committee
161 (reference: 12/NS/0120). Access to the Aberdeen Fertility Clinic and the Assisted
162 Reproduction Unit databases was approved by the Aberdeen Fertility Databases Steering
163 Committee. Access to the Aberdeen Maternity and Neonatal Databank was approved by the
164 Aberdeen Maternity and Neonatal Database Steering Committee. Access to the Scottish

165 Morbidity Records Maternity database was approved by the Privacy Advisory Committee of
166 Information Services Division Scotland.
167 We defined unexplained subfertility as couples who tried to conceive for more than 50 weeks
168 before the fertility workup was completed and who had no obvious barriers to conception in
169 terms of uni- or bilateral tubal occlusion, anovulation, mild- or severe endometriosis
170 according to the revised American Society for Reproductive Medicine (ASRM) score (ASRM,
171 1997) or impaired semen quality according to World Health Organization (WHO) criteria
172 (WHO, 1999; WHO, 2010). We used the gestational age at birth or early pregnancy outcome
173 to derive the date of conception and included only pregnancies in the analysis that occurred
174 after registration of the couple at the clinic and that were ongoing, defined as reaching a
175 gestational age of at least 12 weeks. Time to conception was censored at the date of start of
176 IUI, start of IVF, when the woman returned to the fertility centre with a different male partner
177 or at the end of study.

178

179 *Missing data*

180 The date of completion of the fertility workup was not reported in the AFC database. The van
181 Eekelen model uses this date as the starting point of follow up, i.e. the time point from which
182 onwards the model can be used to estimate a prognosis. The date of registration and the
183 diagnosis category were available in the database. Judging from local protocols, we
184 assumed there were 3 months in between registration and completion of the fertility workup
185 for all couples. In a sensitivity analysis, we repeated the validation study assuming 1.5
186 months or 4.5 months between registration and completion of the fertility workup for all
187 couples.

188 Menstrual cycle length is used to determine the number of elapsed menstrual cycles since
189 the fertility workup when updating predictions using the dynamic prediction model. Cycle
190 length was not recorded in the AFC database and we therefore assumed an average cycle
191 length of 28 days for all women.

192 Data on outcomes or at least one prognostic factor were missing for approximately 4% of
193 couples; 0.5% on pregnancy or follow up, 0.5% on female age, 2.3% on duration of
194 subfertility, 0.5% on primary or secondary subfertility, 1.9% on the percentage of progressive
195 motile sperm and 0.5% on referral status. We had no reason to believe that couples with
196 missing data differed systematically from couples with complete data and we analysed
197 couples for which data was complete.

198

199 *Analysis*

200 We calculated the predicted probabilities of natural conception over 1 year for all couples in
201 the validation cohort using the formula in the Appendix of the paper by van Eekelen *et al* (van
202 Eekelen *et al.*, 2017a). To test the model's ability to not only predict after the completion of
203 the fertility workup, but also when a couple returns after an unsuccessful period of expectant
204 management, we calculated the prognosis at four time points: directly after completion of the
205 workup, after 0.5 year, 1 year and after 1.5 years of expectant management. We evaluated
206 model performance in terms of calibration, i.e. the degree of agreement between observed
207 and predicted natural conception rates, and discrimination, i.e. the ability of the dynamic
208 prediction model to distinguish between couples who do conceive and couples who do not
209 conceive.

210

211 To assess calibration, we first explored whether the overall prediction of the model was
212 correct by comparing the average predicted probability over a time period with the observed
213 conception rate over that same time period. This is referred to as calibration-in-the-large and
214 assesses whether the model systematically under- or overestimates the observed conception
215 rate (Steyerberg, 2009).

216 Second, we assessed whether the effects of patient characteristics were estimated
217 correctly in three ways: by visuals using calibration plots for risk groups, by calibration within
218 groups with similar patient characteristics and by calculating a calibration slope. For the
219 calibration plots we ordered the predicted probabilities of couples and divided them in risk

220 groups with similar predictions ($n=135$ per risk group). We compared the mean predicted
221 chances within these groups with the corresponding observed fraction of ongoing pregnancy
222 as estimated by the Kaplan-Meier method. We visualized the observed fractions and
223 predicted probabilities per risk group in plots and tabulated the absolute differences. In the
224 plots, the 45 degree line indicates what would be a perfect agreement between the observed
225 fraction and average predicted probability within a risk group.

226 We repeated the calibration procedure but instead of grouping based on predicted risks, we
227 grouped couples based on having similar patient characteristics. We again compared the
228 mean predicted chances within these groups with the corresponding observed fraction of
229 ongoing pregnancy as estimated by the Kaplan-Meier method and tabulated the results.
230 To calculate the calibration slope, we used the prognostic index (i.e. the sum of the
231 multiplication between all patient characteristics and the coefficients from the model) as an
232 explanatory variable in a Cox model for each of the four evaluated time periods (van
233 Houwelingen, 2000). Ideally, the calibration slope is unity i.e. 1, indicating that the strength of
234 the patient characteristics in the evaluated model perfectly matches the validation data.

235 Third, we used a recalibration procedure as an alternative way to assess the
236 systematic under- or overestimation (calibration-in-the-large) and the strength of the patient
237 characteristics (calibration slope) in the model. We did this by using the same coefficients for
238 the patient characteristics as reported by van Eekelen et al. to calculate a prognostic index,
239 but re-estimated the other parameters of the beta-geometric model in the validation dataset
240 (Bongaarts, 1975; Weinberg and Gladen, 1986). The recalibration model re-estimates three
241 parameters, which we compared to those in the van Eekelen model and tested for the
242 difference between the two using independent samples z-tests. Systematic under- or
243 overestimation was assessed by comparing the intercept and the variance parameters. The
244 intercept parameter indicates the estimated pregnancy chances in the first cycle after the
245 fertility workup and the variance parameter indicates how fast the estimated chances
246 decrease over consecutive failed natural cycles. Similarity in strength of the patient

247 characteristics was assessed by again calculating a calibration slope parameter, which would
248 ideally be 1.

249

250 We assessed discrimination by calculating Harrel's c statistic at the four time points, which
251 we compared to those found at internal validation (Harrell *et al.*, 1996).

252 Finally, we explored the range of predicted probabilities at the four time points to see if they
253 facilitate meaningful prognostic stratification of couples (Coppus *et al.*, 2009).

254 All analyses were conducted in R version 3.4.3 and RStudio (R Core Team, 2013). A p value
255 below 0.05 was considered statistically significant.

256

257

258 **Results**

259 Data of 1203 couples were included (Fig. 1). The baseline characteristics of the couples are
260 shown in Table I.

261 In total, 398 (33%) couples conceived naturally, leading to an ongoing pregnancy. The
262 median follow up was 1 year and 3 months after completion of the workup (average follow up
263 2 years and 6 months). The observed rates of natural conception up to 2.5 years are
264 depicted in Fig. 2 (upper panel). For couples who did not yet conceive after 0.5 year, 1 year
265 or 1.5 years after completion of the fertility workup, the observed rates of natural conception
266 over the following year are depicted in Fig. 2 (lower panel). The mean probability of natural
267 conception as predicted by the dynamic model over the course of the first year after the
268 fertility workup was 25% while the observed fraction was 23% (95%CI 20-25). For couples
269 who did not conceive after 0.5 years, after 1 year and after 1.5 years of expectant
270 management, the mean estimated probability of conceiving over the course of the following
271 year was estimated at 18%, 14% and 12%. The observed rates were 15% (13-18%), 14%
272 (11-17%) and 12% (9-15%) for these three time periods, respectively (Fig. 2, lower panel).
273 Except for the second period during which the model slightly overestimated the pregnancy
274 chances by 3 percentage points, the mean predicted probabilities fell within their respective

275 confidence limits of the observed rates, indicating good agreement between the average
276 prediction rendered by the dynamic model and the corresponding observed rate of natural
277 conception.

278

279 The calibration plots for the four time periods are presented in Fig. 3. The dynamic prediction
280 model was well calibrated based on the upward trends observed in the four plots, indicating
281 that higher predicted probabilities correspond to higher observed rates, and the CIs from the
282 observed rates which all but one cover the ideal 45 degree line. The second calibration plot
283 starting at 0.5 years after the fertility workup showed a slight overestimation since all points
284 are below the 45 degree line. The absolute differences between observed fractions and
285 predicted probabilities of natural conception within risk groups are shown in Table II. This
286 was on average 2.8 percentage points and 9.6 at the highest.

287 The results for the calibration grouping couples by similar characteristics are shown in
288 Supplementary Data I. Results were similar to those in the calibration using risk groups, with
289 a slight overestimation in the time periods right after completion of the fertility workup and
290 after 0.5 years of expectant management.

291 The calibration slopes using Cox models were 0.86, 1.01, 1.01 and 0.62 for the four time
292 periods, respectively. None of the corresponding p-values were below 0.05, indicating no
293 statistical evidence for under- or overfitting.

294 In the recalibration model, the intercept and variance parameters were similar to those
295 reported by van Eekelen *et al.* ($p=0.69$ and $p=0.29$ for the difference, respectively), indicating
296 similar underlying chances of pregnancy in the first cycle after the workup and a similar
297 decrease in chances as time progresses. The slope was 0.90 ($p=0.37$), indicating a similar
298 strength of patient characteristics in the validation cohort and no significant difference from 1.

299

300 The discriminative ability of the model in the validation cohort was moderate and similar to
301 that in the Dutch development cohort, ranging over time from a c statistic of 0.61 (95%CI
302 0.57-0.64) in the first year, 0.62 (95% CI 0.58-0.67) from 0.5 years, 0.63 (95% CI 0.57-0.69)

303 from 1 year, to 0.60 (95% CI 0.52-0.67) for 1.5 years after completion of the fertility workup,
304 all for conceiving in the following year. The c statistics were around 0.61 for all four time
305 periods and seemed stable over time.

306

307 The range of predictions varied between 0 and 55% over the course of the first year after the
308 fertility workup. After 0.5 years, 1 year and 1.5 years of expectant management the ranges
309 narrowed to 0 to 43%, 0 to 34% and 0 to 29% respectively, all over the course of the
310 following year, facilitating a distinction between couples with a good or poor prognosis.

311

312 *Sensitivity analyses*

313 Results from the two sensitivity analyses are reported online as supplementary data. The
314 analysis where we assumed 1.5 months between registration and completion of the fertility
315 workup showed a very good performance of the dynamic prediction model (Supplementary
316 Table SI, Supplementary Figs. S1 and S2). The analysis assuming 4.5 months between
317 registration and completion of the fertility workup showed similar results to the primary
318 analysis but with slightly more overestimation of chances by the model (Supplementary
319 Table SII, Supplementary Figs. S3 and S4).

320

321

322 **Discussion**

323 We conducted an external, geographical validation of the van Eekelen model that can be
324 used for repeated predictions of natural conception when couples return to the clinic after
325 unsuccessful expectant management. The model performed well in a Scottish cohort of
326 couples with unexplained subfertility that visited a fertility clinic and the model is expected to
327 be generalizable to other fertility centres and countries where the procedure of managing
328 unexplained subfertile couples is comparable to the Netherlands and the UK. In addition, the
329 predicted probabilities varied sufficiently to aid in distinguishing between couples with a good
330 and poor prognosis in terms of natural conception.

331

332 The data from the AFC was of high quality, registering every unexplained subfertile couple in
333 the Grampian region. All natural conceptions leading to ongoing pregnancy, including after
334 miscarriages and other early pregnancy outcomes, were found using data linkage with
335 maternity records. Indications for the fertility workup and definitions of censoring and
336 prognostic characteristics in the Scottish cohort were very similar to the Dutch cohort, aiding
337 comparability (van Eekelen *et al.*, 2017a).

338 The model was well calibrated, which we consider of higher importance than
339 discrimination since the c statistic can be expected to be moderate due to the limited range
340 of predicted chances in fertility (Mol *et al.*, 2005; Cook, 2007). This restricts the maximum
341 possible c statistic, even if a model were to produce perfect predictions. Recalibration, in
342 which one or more parameters of the prediction model are updated to accommodate better
343 predictions in a different country or clinical setting, was not necessary since the recalibration
344 model showed similar values for all parameters as observed in the development cohort.

345

346 The main limitation to our study was missing data in terms of dates of completion of the
347 fertility workup and menstrual cycle lengths. Menstrual cycle length was not considered very
348 influential since the estimations of the number of cycles per individual are reasonable
349 approximations due to the narrow range of possible cycle lengths in our selection of
350 unexplained subfertile couples, but we did have to make strong assumptions about the date
351 of completion of the fertility workup. We assumed 3 months between registration and
352 completion of the fertility workup, which resulted in ongoing pregnancies before 3 months
353 after registration being excluded. The 'starting' moment of follow up thus differed from the
354 Dutch development cohort since in the latter, the date of last tubal test was used as the end
355 of the workup. Some Dutch clinics did not conduct a visual test of tubal patency, i.e.
356 laparoscopy or hysterosalpingography after a negative result for the chlamydia antibody test.
357 In those Dutch clinics, the workup was thus considered as complete earlier after registration
358 compared to the AFC where visual tests of tubal patency are part of the standard protocol.

359 This may have led to the observed slight overestimation in the first year after the fertility
360 workup and after 0.5 years of expectant management but, despite these differences, the
361 dynamic model was still able to estimate a prognosis that was reasonably accurate on cohort
362 and risk group level. The results from the sensitivity analysis assuming 1.5 months between
363 registration and completion of the fertility workup were very good because the resulting
364 population more closely resembled that of the Dutch development cohort in which the same
365 average duration was observed between registration and the workup completion.
366 Accordingly, in the analysis assuming 4.5 months between registration and completion of the
367 fertility workup, the performance of the dynamic model was poorer because the populations
368 differed more due to additional selection that occurred.

369

370 The dynamic model is able to reassess the chance of natural conception after any given
371 period of expectant management from the completion of the fertility workup onwards. For
372 example, a couple with 1 year secondary subfertility is referred by a general practitioner to
373 the fertility clinic of which the woman is 33 years old at the completion of the fertility workup
374 and the man has 40% progressive motile sperm. Applying our model gives a predicted 38%
375 chance of natural conception over the first year after the workup and they might be advised
376 expectant management. When the couple returns to the clinic after 10 unsuccessful
377 months/cycles, reapplying the model yields 25% chance over the following year, which is a
378 realistic decrease given they have tried for an additional 10 months. This could be a reason
379 to consider starting treatment.

380

381 Both the Hunault model and the dynamic model performed well in external validations,
382 indicating that the added value of the dynamic model lies in the ability to update predictions
383 at later time points (van Eekelen *et al.*, 2017a). This provides clinicians and patients with
384 information regarding their prognosis of natural conception not only right after completion of
385 the fertility workup, but also when the couple returns after an additional, unsuccessful period
386 of expectant management, thus aiding in making clinical decisions at multiple time points

387 throughout a couple's trajectory. The ability to update predictions also aids in studies which
388 include the prognosis of natural conception as an in- or exclusion criterion, since the
389 prognosis of couples who return after unsuccessful expectant management can be updated
390 accurately, leading to the desired homogeneity of the study sample (van den Boogaard *et al.*,
391 2014). The dynamic model is flexible and can be used to predict over any desired number of
392 menstrual cycles, for instance when the couple is interested in time periods shorter or longer
393 than 1 year. In short, the dynamic model has a wider clinical applicability than the Hunault
394 model and should be the model of choice.

395

396 **Conclusion**

397 The van Eekelen model is a valid and robust tool that is ready to use in clinical practice to
398 counsel couples with unexplained subfertility on their individualised chances of natural
399 conception at various points in time, notably when couples return to the clinic after a period
400 of unsuccessful expectant management.

401

402 **Supplementary data**

403 Supplementary data are available at *Human Reproduction* online.

404

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413 queries.

414

415 **Authors' roles**

416 NvG, MDJ, BS, FvdV, MvW and MJE conceived the study. MDJ performed the data linkage,
417 storage in the Safe Haven and cleaned the data. RvE, NvG and MJE designed the statistical
418 analysis plan. RvE, MDJ and NvG analysed the data. RvE drafted the manuscript. All authors
419 contributed critical revision to the paper and approved the final manuscript.

420

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427

428 **Conflicts of interest**

429 None.

430 **References**

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526

527 **FIGURE LEGENDS**

528

529 **Figure 1** Flow chart of couples with unexplained subfertility who were considered for
530 inclusion in the external validation.

531

532 **Figure 2** Cumulative chances of natural conception leading to ongoing pregnancy.
533 Cumulative chances after completion of fertility workup (upper panel) and updated chances
534 of natural conception over the course of 1 year at completion of the fertility workup or 0.5
535 years, 1 year and 1.5 years thereafter (lower panel) in the validation cohort.

536 Percentages are Kaplan-Meier estimates of the observed fraction of natural conception
537 leading to ongoing pregnancy.

538

539 **Figure 3** Calibration of the predictions of the dynamic prediction model: predicted versus
540 observed 1 year natural conception rates at four fixed time points.

541

542 **Supplementary Figure S1** Cumulative chances of natural conception leading to ongoing
543 pregnancy after completion of fertility workup (upper panel) and updated chances of natural
544 conception over the course of 1 year at completion of the fertility workup or 0.5 years, 1 year
545 and 1.5 years thereafter (lower panel) in the validation cohort. Percentages are Kaplan-Meier
546 estimates of the observed fraction of natural conception leading to ongoing pregnancy. Data
547 analysis assumed 1.5 months between registration at the Aberdeen Fertility Clinic and
548 completion of the fertility workup (n=1261).

549

550 **Supplementary Figure S2** Calibration of the predictions of the dynamic prediction model:
551 predicted versus observed 1 year natural conception rates at four fixed time points. Data
552 analysis assumed 1.5 months between registration at the Aberdeen Fertility Clinic and
553 completion of the fertility workup (n=1261).

554

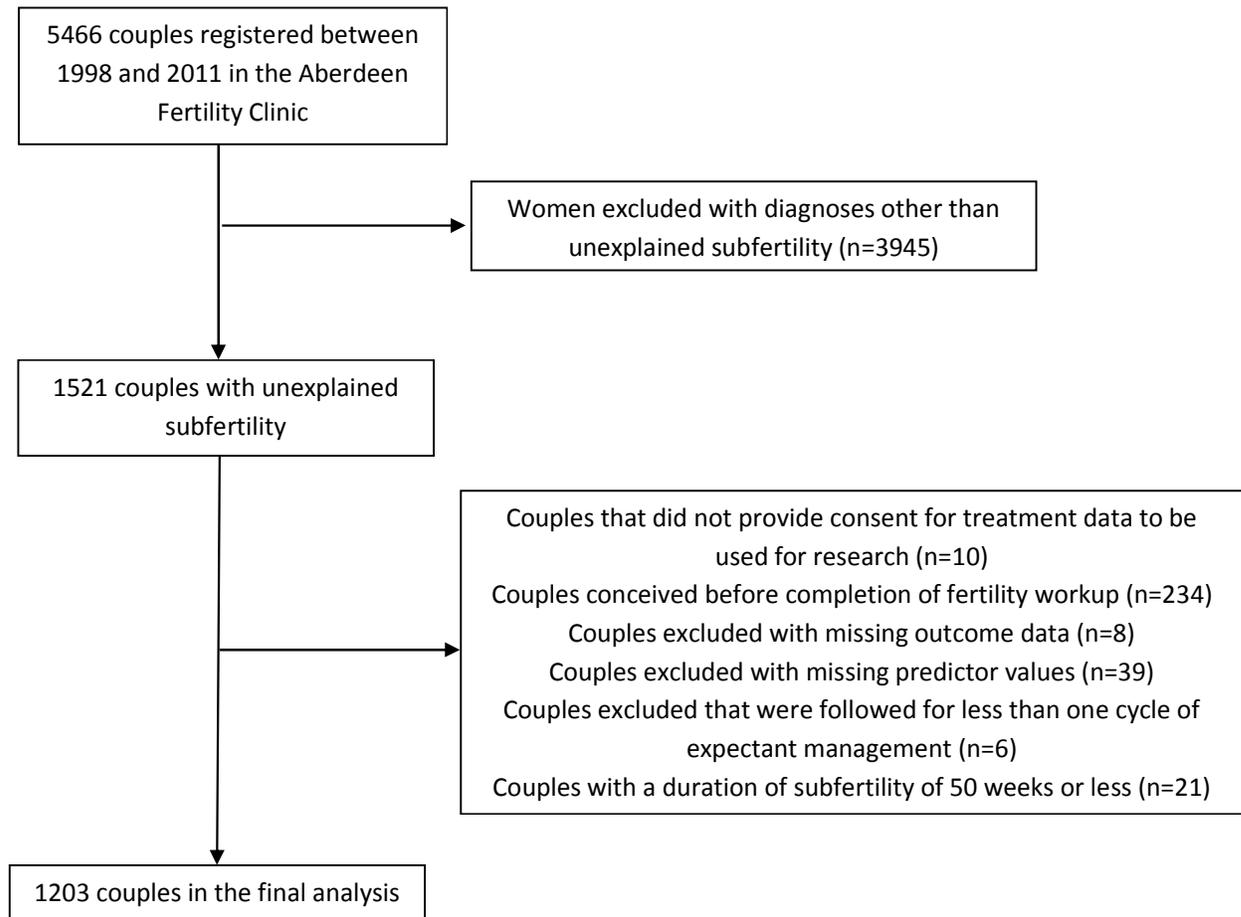
555 **Supplementary Figure S3** Cumulative chances of natural conception leading to ongoing
556 pregnancy after completion of fertility workup (upper panel) and updated chances of natural
557 conception over the course of 1 year at completion of the fertility workup or 0.5 years, 1 year
558 and 1.5 years thereafter (lower panel) in the validation cohort. Percentages are Kaplan-Meier
559 estimates of the observed fraction of natural conception leading to ongoing pregnancy. Data
560 analysis assumed 4.5 months between registration at the Aberdeen Fertility Clinic and
561 completion of the fertility workup (n=1123).

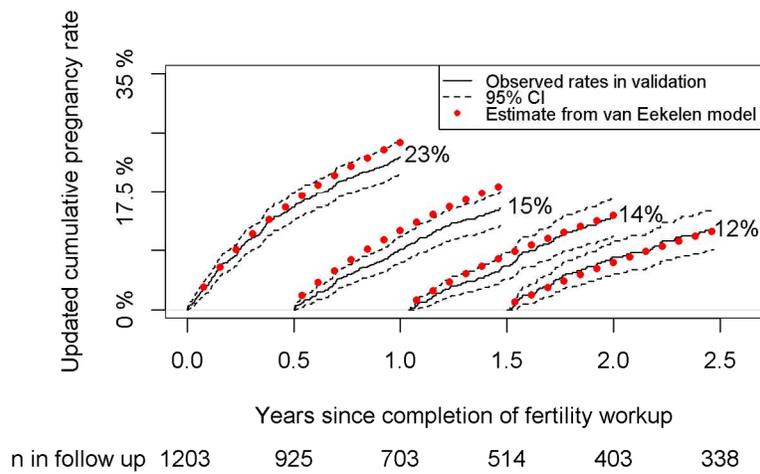
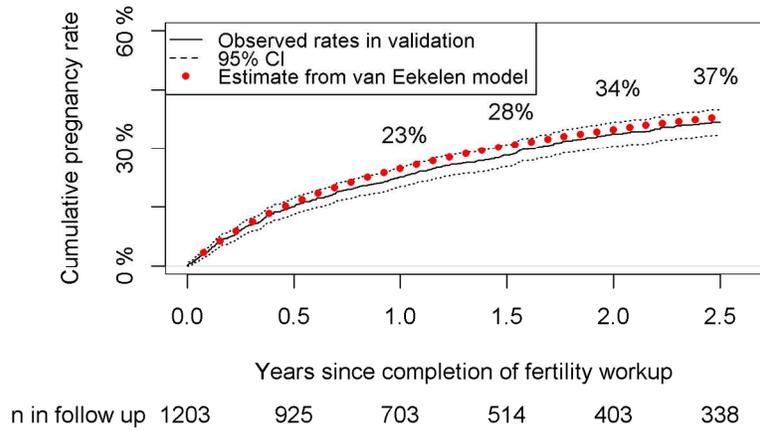
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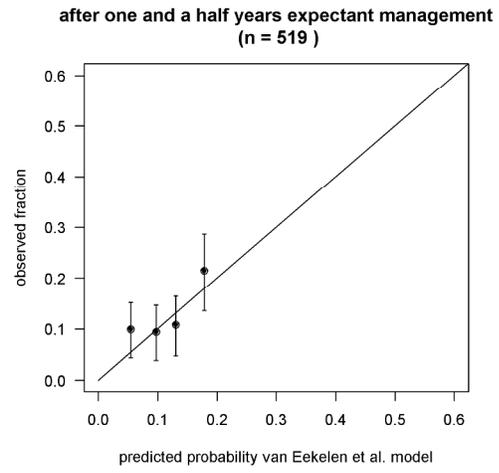
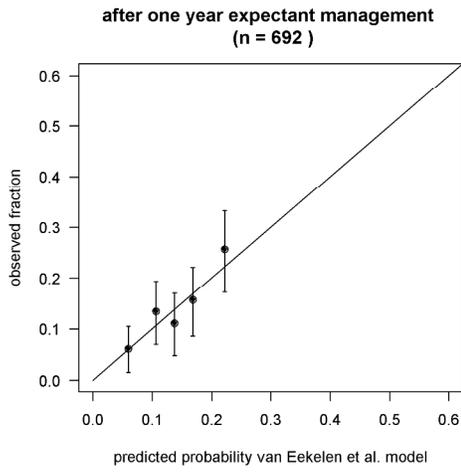
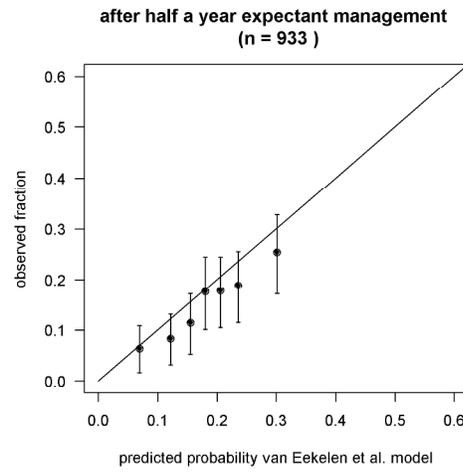
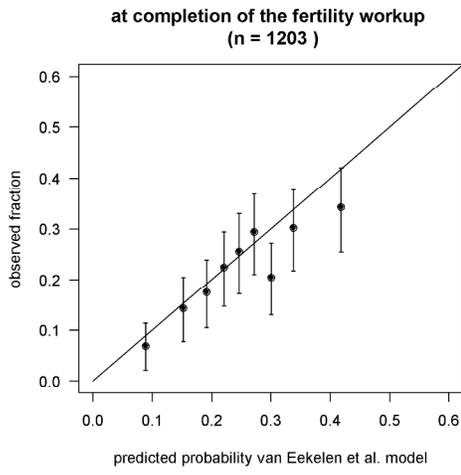
564 **Supplementary Figure S4** Calibration of the predictions of the dynamic prediction model:
565 predicted versus observed 1 year natural conception rates at four fixed time points. Data

566 analysis assumed 4.5 months between registration at the Aberdeen Fertility Clinic and
567 completion of the fertility workup (n=1123).

Figure 1.



160x220mm (300 x 300 DPI)



228x228mm (300 x 300 DPI)

Table I Baseline characteristics at completion of the fertility workup.

n = 1203	Mean or n	5th – 95th percentile or %
Female age, in years	33.3	25 - 41
Duration of subfertility, in years	2.7	1.3 - 5.6
Primary female subfertility	697	58%
Percentage of progressive motile sperm	51	24 - 76
Referral by secondary care	84	7%

Table II Calibration of the dynamic prediction model by risk groups.

	Mean difference	Max difference	Number of risk groups
After completion of workup	3.2	9.6	9
After 0.5 year EM	3.0	4.7	7
After 1 year EM	2.1	3.5	5
After 1.5 years EM	2.7	4.5	4
Total	2.8	9.6	25

Data are the mean and maximum of the absolute differences (in percentage points) between predicted and observed 1 year natural conception rates per risk group of n=135, stratified by the elapsed period of expectant management (EM).

Supplementary Data

Calibration per strata of patient characteristics.

Analyses were conducted for all four time periods in the primary scenario with 3 months between registration and completion of fertility workup.

Time period 1: after completion of the fertility workup

Female age:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 28 years [25.4, n=155]	33	30 (22-37)
28-32 years [29.3, n=336]	29	26 (21-30)
32-35 years [33.2, n=261]	24	23 (17-28)
> 35 years [38.3, n=451]	19	18 (14-21)

Duration of subfertility:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
1 - 1.5 years [1.3, n=227]	30	26 (20-32)
1.5-2 years [1.8, n=262]	29	26 (21-32)
2-3 years [2.4, n=393]	25	24 (20-29)
> 3 years [4.7, n=321]	16	14 (10-19)

Percentage of progressive motile sperm:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 35% [26, n=220]	21	18 (13-23)
35-50% [43, n=376]	24	23 (19-28)
50-65% [58, n=366]	26	23 (18-27)
> 65% [73, n=241]	28	26 (19-31)

Primary or secondary subfertility:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
Primary [n=697]	23	20 (17-23)
Secondary [n=506]	28	26 (22-30)

Referral by general practitioner (GP) or specialist/gynaecologist:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
GP [n=1119]	26	23 (20-25)
Specialist/gynaecologist	13	20 (10-29)

[n=84]		
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Time period 2: after 0.5 years of expectant management

Female age:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 28 years [25.4, n=117]	24	22 (13-29)
28-32 years [29.9, n=262]	22	18 (12-22)
32-35 years [33.2, n=205]	17	16 (11-22)
> 35 years [38.3, n=349]	14	11 (7-14)

Duration of subfertility:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
1 - 1.5 years [1.3, n=170]	23	18 (12-24)
1.5-2 years [1.8, n=204]	22	19 (13-25)
2-3 years [2.4, n=309]	19	17 (13-22)
> 3 years [4.7, n=250]	12	8 (4-11)

Percentage of progressive motile sperm:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 35% [26, n=176]	15	14 (8-20)
35-50% [43, n=282]	18	14 (9-18)
50-65% [58, n=291]	19	16 (11-20)
> 65% [73, n=184]	21	18 (12-24)

Primary or secondary subfertility:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
Primary [n=550]	17	14 (11-17)
Secondary [n=383]	20	17 (13-21)

Referral by general practitioner (GP) or specialist/gynaecologist:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
GP [n=867]	19	15 (13-18)
Specialist/gynaecologist [n=66]	10	14 (4-23)

Time period 3: after 1 year of expectant management

Female age:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 28 years [25.4, n=92]	19	24 (14-34)
28-32 years [29.9, n=189]	17	19 (12-25)
32-35 years [33.2, n=154]	14	15 (8-21)
> 35 years [38.5, n=257]	10	7 (4-10)

Duration of subfertility:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
1 - 1.5 years [1.3, n=129]	18	16 (9-23)
1.5-2 years [1.8, n=150]	17	20 (12-27)
2-3 years [2.4, n=223]	14	15 (9-20)
> 3 years [4.8, n=190]	9	9 (5-14)

Percentage of progressive motile sperm:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 35% [26, n=137]	12	16 (9-22)
35-50% [43, n=208]	14	14 (8-19)
50-65% [58, n=211]	15	14 (9-19)
> 65% [73, n=136]	15	15 (8-21)

Primary or secondary subfertility:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
Primary [n=402]	13	15 (11-19)
Secondary [n=290]	15	13 (9-17)

Referral by general practitioner (GP) or specialist/gynaecologist:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
GP [n=645]	14	15 (12-18)
Specialist/gynaecologist [n=47]	7	11 (1-20)

Time period 4: after 1.5 years of expectant management

Female age:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 28 years [25.3, n=69]	16	21 (10-30)
28-32 years [29.9, n=143]	14	21 (13-28)
32-35 years [33.2, n=107]	11	11 (4-17)
> 35 years [38.8, n=200]	9	6 (2-9)

Duration of subfertility:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
1 - 1.5 years [1.3, n=93]	15	10 (3-16)
1.5-2 years [1.8, n=104]	14	19 (11-26)
2-3 years [2.4, n=172]	12	12 (6-17)
> 3 years [4.8, n=150]	8	12 (6-17)

Percentage of progressive motile sperm:

Category [mean, n]	Predicted probability in %	Observed fraction in % (95%CI)
<= 35% [25, n=95]	10	14 (6-21)
35-50% [43, n=161]	12	13 (7-19)
50-65% [58, n=161]	12	14 (8-19)
> 65% [73, n=102]	13	11 (4-17)

Primary or secondary subfertility:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
Primary [n=286]	11	14 (9-18)
Secondary [n=233]	13	12 (7-16)

Referral by general practitioner (GP) or specialist/gynaecologist:

Category [n]	Predicted probability in %	Observed fraction in % (95%CI)
GP [n=485]	12	13 (9-16)
Specialist/gynaecologist [n=34]	6	16 (2-29)

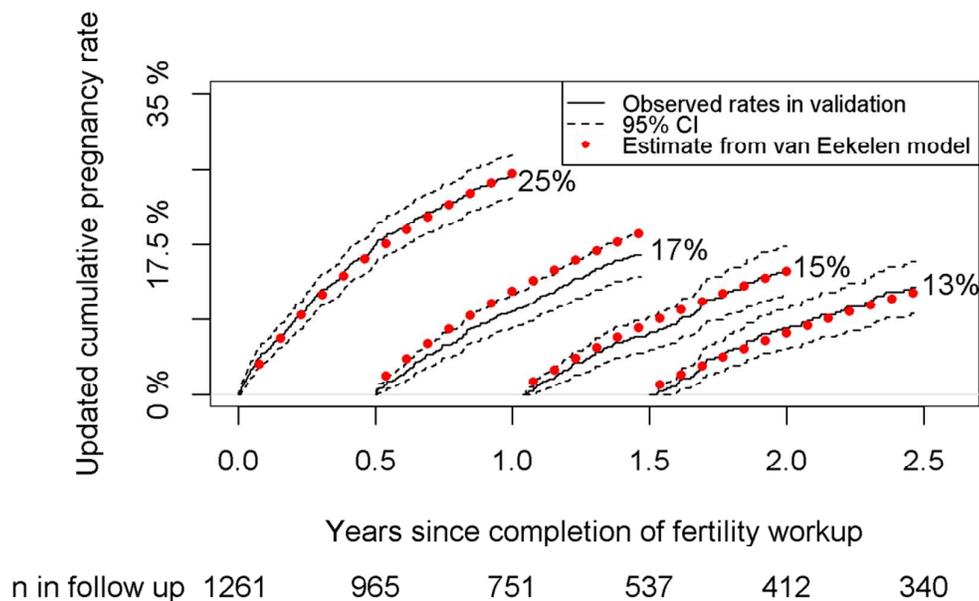
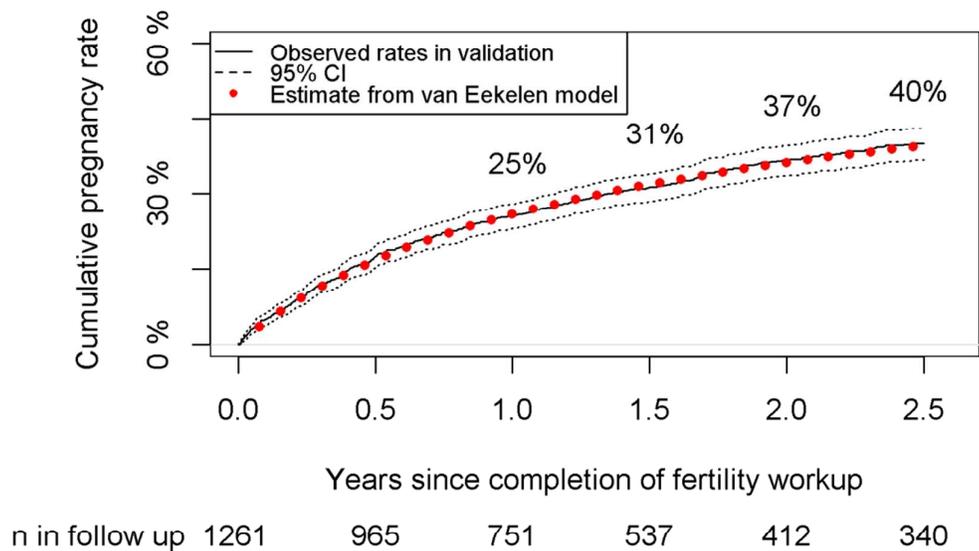
1 **Supplementary Table SI** Calibration of the dynamic prediction model by risk groups.*
 2

	mean difference	max difference	number of risk groups
After completion of workup	1.9	5.3	9
After 0.5 years EM	1.7	3.4	7
After 1 year EM	1.8	3.0	5
After 1.5 years EM	2.9	4.0	4
Total	2.1	5.3	25

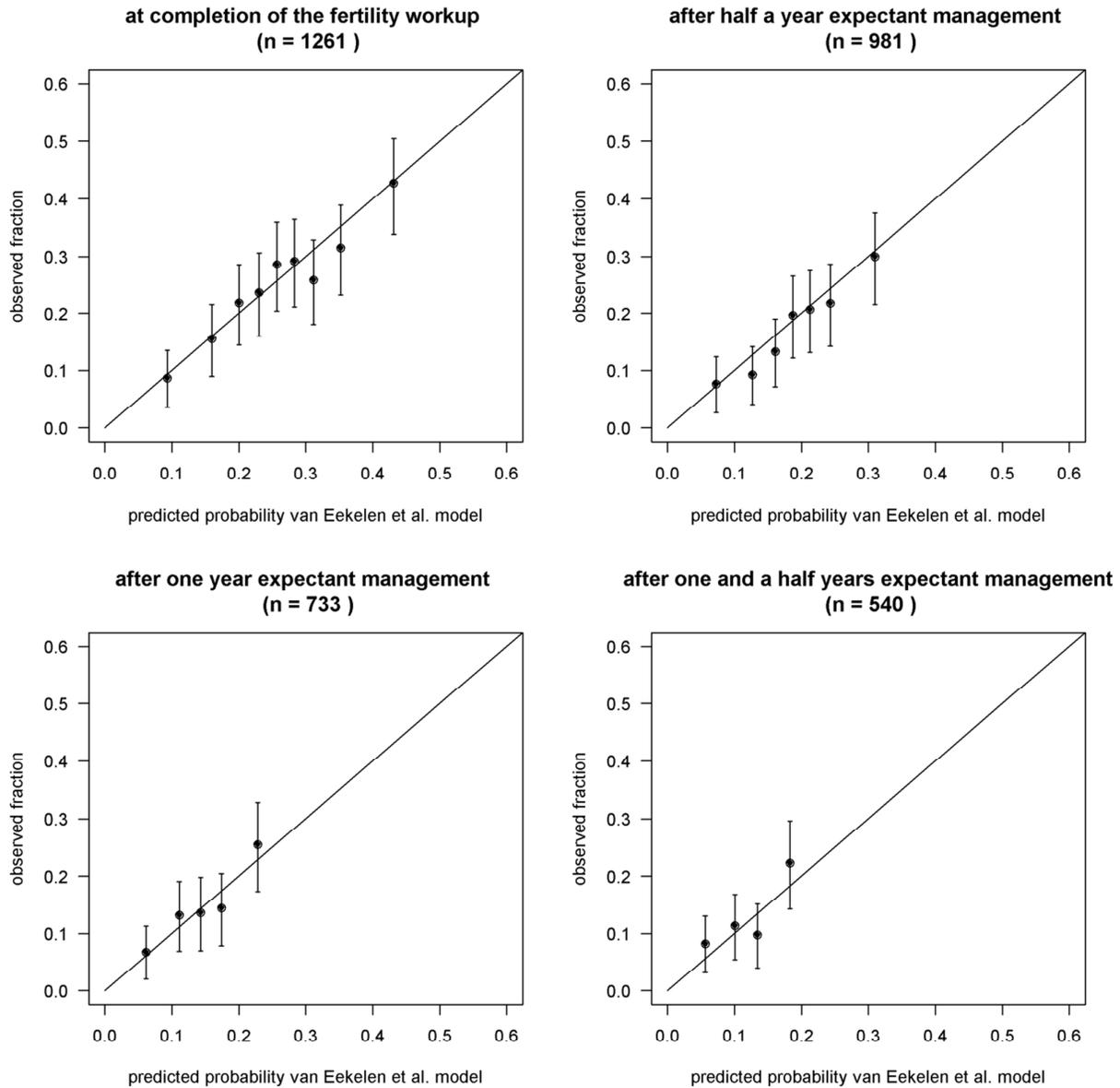
3 *Assuming 1.5 months between registration at the Aberdeen Fertility Clinic and completion of
 4 the fertility workup (n=1261).

5 Data are the mean and maximum of the absolute differences (in percentage points) between
 6 predicted and observed 1 year natural conception rates per risk group of n=135, stratified by
 7 the elapsed period of expectant management (EM).

8 **Supplementary Figure S1** Cumulative chances of natural conception leading to ongoing
 9 pregnancy after completion of fertility workup (upper panel) and updated chances of natural
 10 conception over the course of 1 year at completion of the fertility workup or 0.5 years, 1 year
 11 and 1.5 years thereafter (lower panel) in the validation cohort. Percentages are Kaplan-Meier
 12 estimates of the observed fraction of natural conception leading to ongoing pregnancy. Data
 13 analysis assumed 1.5 months between registration at the Aberdeen Fertility Clinic and
 14 completion of the fertility workup (n=1261).
 15



16 **Supplementary Figure S2** Calibration of the predictions of the dynamic prediction model:
17 predicted versus observed 1 year natural conception rates at four fixed time points. Data
18 analysis assumed 1.5 months between registration at the Aberdeen Fertility Clinic and
19 completion of the fertility workup (n=1261).
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22

23 **Supplementary Table SII** Calibration of the dynamic prediction model by risk groups.*
 24

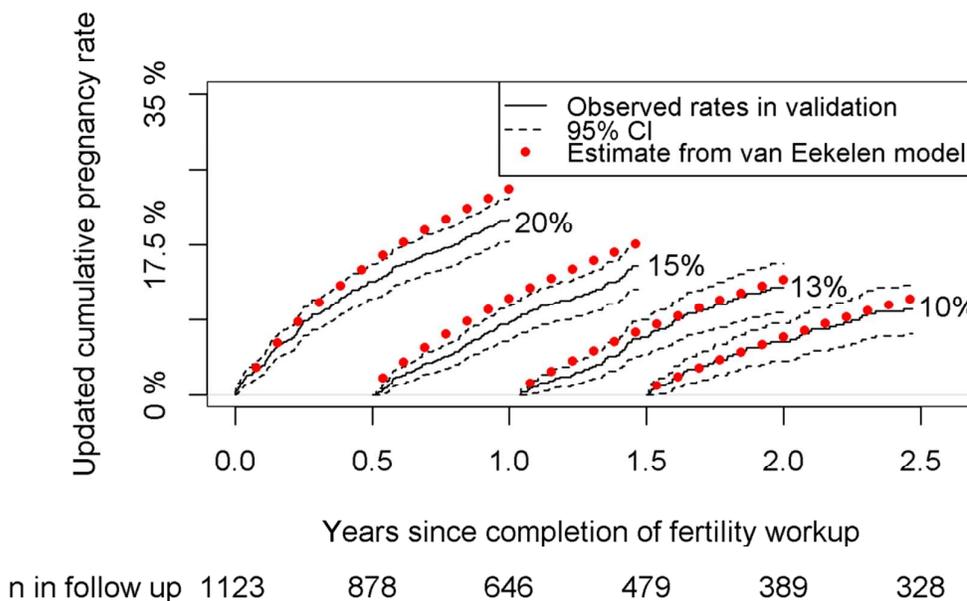
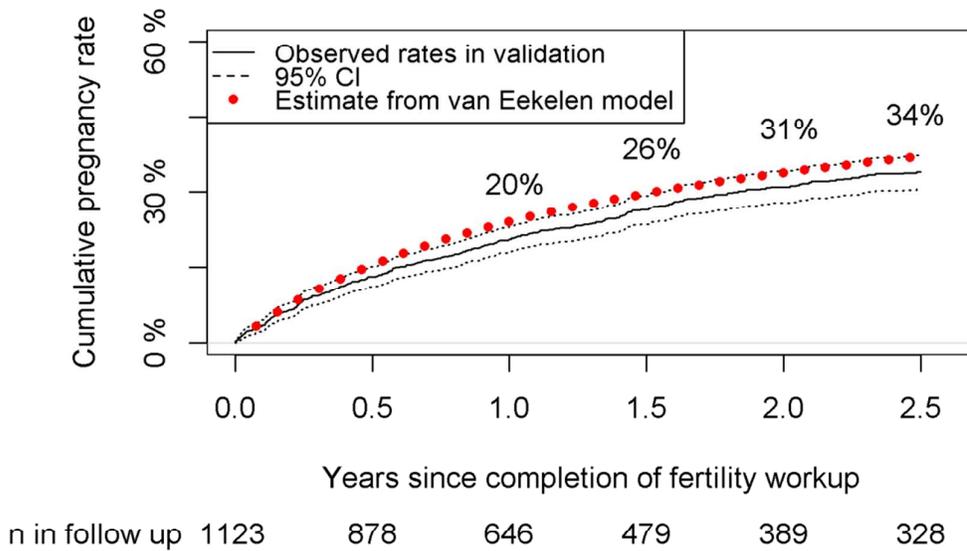
	mean difference	max difference	number of risk groups
After completion of workup	3.9	11.1	8
After half a year EM	1.9	5.8	7
After one year EM	2.6	4.3	5
After one and a half years EM	2.3	3.3	4
Total	2.7	11.1	24

25 *Data analysis assumed 4.5 months between registration at the Aberdeen Fertility Clinic and
 26 completion of the fertility workup (n=1123).

27 Data are the mean and maximum of the absolute differences (in percentage points) between
 28 predicted and observed 1 year natural conception rates per risk group of n=135, stratified by
 29 the elapsed period of expectant management (EM).

30 **Supplementary Figure S3** Cumulative chances of natural conception leading to ongoing
 31 pregnancy after completion of fertility workup (upper panel) and updated chances of natural
 32 conception over the course of 1 year at completion of the fertility workup or 0.5 years, 1 year
 33 and 1.5 years thereafter (lower panel) in the validation cohort. Percentages are Kaplan-Meier
 34 estimates of the observed fraction of natural conception leading to ongoing pregnancy. Data
 35 analysis assumed 4.5 months between registration at the Aberdeen Fertility Clinic and
 36 completion of the fertility workup (n=1123).
 37

38
 39



40 **Supplementary Figure S4** Calibration of the predictions of the dynamic prediction model:
41 predicted versus observed 1 year natural conception rates at four fixed time points. Data
42 analysis assumed 4.5 months between registration at the Aberdeen Fertility Clinic and
43 completion of the fertility workup (n=1123).
44

