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Gonadotrophins versus clomifene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomifene failure (M-OVIN)

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Published in:
LANCET

DOI:
[10.1016/S0140-6736\(17\)33308-1](https://doi.org/10.1016/S0140-6736(17)33308-1)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Weiss, N. S., Nahuis, M. J., Bordewijk, E., Oosterhuis, J. E., Smeenk, J. M. J., Hoek, A., ... van Wely, M. (2018). Gonadotrophins versus clomifene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomifene failure (M-OVIN): A randomised, two-by-two factorial trial. *LANCET*, 391(10122), 758-765. [https://doi.org/10.1016/S0140-6736\(17\)33308-1](https://doi.org/10.1016/S0140-6736(17)33308-1)

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1 Gonadotrophins versus clomiphene citrate with or
2 without intrauterine insemination in women with
3 normogonadotropic anovulation and clomiphene failure: a
4 randomized, two-by-two factorial trial.

5
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39 **SUMMARY**

40 **Background:**

41 Clomiphene citrate (CC) is in many countries the treatment of first choice in women with
42 normogonadotropic anovulation. If these women ovulate but do not conceive after several cycles with
43 CC, medication is usually switched to gonadotrophins, with or without intrauterine insemination (IUI).
44 We aimed to assess whether switching to gonadotrophins is more effective than continuing CC, and
45 whether IUI is more effective than intercourse.

46

47 **Methods:**

48 We performed a two-by-two factorial multicenter randomized clinical trial including women with
49 normogonadotropic anovulation not pregnant after six ovulatory cycles with CC (NTR1449). Women
50 were randomized using a central password protected internet-based randomization program to six
51 cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC
52 plus IUI or six cycles with CC plus intercourse. CC dosages varied from 50 to 150 mg daily orally and
53 gonadotrophin starting dose was 50 or 75 IU daily subcutaneously.
54 Primary outcome was conception leading to live birth within eight months after randomization. Primary
55 analysis was by intention to treat. We made two comparisons, one in which gonadotrophins was
56 compared to CC and one in which IUI was compared to intercourse.

57

58 **Findings:**

59 Between December 8th 2008 and December 16th 2015 we randomized 666 women to gonadotrophins/IUI
60 (N=166), gonadotrophins/intercourse (N=165), CC/IUI (N=163), or CC/intercourse (N=172).
61 Women allocated to gonadotrophins had more live births than those allocated to CC (167 of 327 women
62 [51·5%] vs. 138 of 334 [41·3%], (RR 1·24 (95% CI 1·05-1·46), p = 0·0124). Addition of IUI did not increase

63 live births compared to intercourse (161 of 327 women [49·2%] vs. 144 of 334 [43·1%], RR 1·14 (95% CI
64 0·97-1·35), p = 0·1152).

65 Multiple pregnancy rates for the two comparisons were low and not different.

66 There were three adverse events: one child with congenital abnormalities, one immature delivery due to
67 cervical insufficiency, and one stillbirth.

68

69 **Interpretation:** In women with normogonadotropic anovulation and CC failure, a switch of treatment to
70 gonadotrophins increases chances of live birth over treatment with CC, while we could not prove that
71 addition of IUI does so.

72

73 **Funding:** This trial was funded by the Netherlands Organization for Health Research and Development.
74 (80-82310-97-12067).

75

76 **Key words:** ovulation induction, anovulation, clomiphene citrate (failure), gonadotrophins, IUI, PCOS

77

78

79

80 **Research in context panel**

81 **Evidence before this study**

82 *A comprehensive literature search using PubMed was done on September 15th 2008 before the trial*
83 *started to identify all previous studies investigating women with clomiphene failure. Search terms*
84 *included “ovulation induction”, “polycystic ovary syndrome”, “clomiphene citrate” (CC), “*
85 *gonadotrophins”, and “IUI”. We only identified non-randomized studies indicating that continued*
86 *treatment with CC and a treatment switch to gonadotrophins are both effective options for these women.*
87 *If IUI increases pregnancy rates in women with CC failure is unknown.*
88 *We wanted to investigate if, in women who have failed to conceive after six ovulatory cycles with CC,*
89 *ovulation induction with gonadotrophins leads to more live birth rates than continued ovulation induction*
90 *with CC and if IUI gives more live births than intercourse.*

91

92 **Added value of this study**

93 *The M-OVIN (Modified ovulation induction) study compared in anovulatory women with CC failure two*
94 *types of medication as well as addition of IUI with intercourse. We found that a switch to gonadotrophins*
95 *significantly increases the live birth rate as compared to continued treatment with CC and that the*
96 *addition of IUI to gonadotrophins or CC seems not to increase live birth rates in women who are*
97 *anovulatory.*

98

99 **Implications of all the available evidence**

100 *Our findings imply that, for normogonadotropic anovulatory women with CC failure who wish to conceive,*
101 *continued treatment with CC or a treatment switch to gonadotrophins are both effective options in terms*
102 *of live birth rates whereas we could not prove this for IUI. The choice between CC and gonadotrophins*
103 *should be made based on women’s preferences, costs and, reimbursement. Considering recent*
104 *randomized research suggesting that letrozole gives higher live birth rates than CC in the first six cycles,*
105 *we suggest that future research establishes if continuing letrozole is also effective and safe if women*
106 *have not conceived within the first six months of treatment.*

107 **INTRODUCTION**

108 Women with normogonadotropic anovulation have absent or irregular ovulation due to hypothalamic-
109 pituitary-ovarian dysfunction associated with normal levels of endogenous estradiol.¹ In these women
110 wishing to conceive, Clomiphene Citrate (CC) has long been used as a first-line ovulation induction
111 agent.^{2,3} Systematic reviews and meta-analyses show that CC is an effective primary treatment option in
112 therapy-naive women with normogonadotropic anovulation and polycystic ovary syndrome (PCOS).⁴⁻⁶
113 Although ovulation is restored in ~75% of women starting ovulation induction with CC, six months of
114 treatment leads to conception in only about half of these women.^{5,7} Women not conceiving after six
115 ovulatory cycles are defined as having CC failure.⁸ The National Institute for Health and Care Excellence
116 (NICE) guideline recommends not to extend treatment with CC for more than six cycles, but this
117 recommendation is not underpinned by any evidence.⁹ In daily practice, these women usually switch to
118 ovulation induction with gonadotrophins and intra-uterine insemination (IUI) is often initiated instead of
119 relying on regular intercourse.¹⁰ However, the effectiveness of a switch to gonadotrophins and IUI
120 compared to continued treatment with CC has never been studied in randomized clinical trials.

121 We therefore conducted a randomized clinical trial to compare, in women who had six ovulatory cycles
122 with CC but did not conceive, the effectiveness of a switch to gonadotrophins as compared to continued
123 treatment with CC and the effectiveness of adding IUI to either CC or gonadotrophins.

124

125 **METHODS**

126 **Study design**

127 The M-OVIN (Modified ovulation induction) study was a multicenter randomized clinical trial performed
128 in 48 Dutch hospitals within the infrastructure of the Dutch Consortium for Healthcare Evaluation and
129 Research in Obstetrics and Gynaecology (www.studies-obsgyn.nl).

130 The study was granted approval by the Medical Ethical Committee of the Medical Spectrum Twente
131 Enschede (The Netherlands) and from the Central Committee on Research involving Human Subjects
132 (CCMO), The Netherlands (References P08-40 and Eudract number 2008-006171-73). The board of
133 directors of each of the participating centers approved local execution of the study.

134 The protocol was published previously¹¹ and the study is registered in the Netherlands Trial Register
135 (NTR1449). Two major adjustments to the protocol were made: The first, in April 2014, regarded a
136 change in the primary outcome from ‘ongoing pregnancy’ to ‘live birth’. The second regarded the
137 sample size which is specified in addendum 2. Both adjustments were approved by the Medical Ethical
138 Committee.

139

140 **Randomization and masking**

141 Eligible women were informed about the study in or immediately after their sixth treatment cycle either
142 by their doctor or by a dedicated research nurse. After written informed consent women were
143 randomized using a central password protected internet-based randomization program. The
144 randomization list had been prepared by an independent statistician with a variable block size with a
145 maximum block size of 8. There was no masking.

146 We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation
147 induction with gonadotrophins versus continuing CC and IUI versus intercourse. Women were randomly

148 assigned to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six
149 cycles with CC plus IUI, or six cycles with CC plus intercourse.

150

151 **Study population**

152 Subfertile women \geq 18 years with WHO type II anovulation (menstrual cycle > 35 days,
153 normogonadotropic, normo-oestrogenic, oligo-anovulation or anovulation), who had been ovulatory for
154 six cycles on CC treatment, with a maximum of 150 mg daily for five days, but who had not conceived,
155 were eligible for the trial. Presence of ovulation was assessed by a basal temperature curve, midluteal
156 progesterone (> 16 nmol/l), detection of a urinary Luteinizing Hormone (LH) surge or transvaginal
157 sonography, depending on the local protocol. All women had undergone a basic fertility work-up
158 including a semen analysis and endocrinological screening to rule out hyperprolactinemia and
159 uncorrected thyroid dysfunction. Couples with male subfertility could not participate. Women with
160 abnormal prolactin (0.05-0.80 IU/l) or thyroid-stimulating hormone (0.4-4.0 mU/l) were also not eligible.
161 Tubal pathology had to be ruled out by either a negative Chlamydia antibody titer (CAT) or
162 hysterosalpingography, transvaginal hydrolaparoscopy, or diagnostic laparoscopy showing at least one
163 patent Fallopian tube. Women with side effects in previous CC cycles were also not eligible.

164

165 **Interventions**

166 In women allocated to ovulation induction with gonadotrophins, a transvaginal ultrasound was usually
167 performed on the third day of a menstrual bleeding and medication was started on that same day, but
168 women were allowed to start medication up to day five . Treatment was not started if ultrasound
169 showed ovarian cysts >25 mm in mean diameter. According to local protocol, urinary or recombinant
170 gonadotrophins were used with a starting dose of 50 or 75 IU daily. Follicular growth was strictly

171 monitored by transvaginal ultrasound and we aimed for mono-follicular growth. If \geq four dominant
172 follicles (≥ 18 mm) developed, the cycle was cancelled i.e. couples were advised not to have intercourse
173 and the planned IUI was not performed. When at least one follicle with a diameter of ≥ 16 mm was
174 present, ovulation was triggered with 5.000 IU or 10.000 IU of human chorionic gonadotrophin (hCG).
175 In women allocated to ovulation induction with CC started on the third to fifth day of a menstrual
176 bleeding, in the same dosage as used in the last ovulatory cycle, varying between 50 mg and 150 mg
177 daily, for five days. Ovulation was monitored by a basal temperature curve, midluteal progesterone ($>$
178 16nmol/l), a urinary LH surge or transvaginal ultrasound, depending on the local protocol. The women
179 undergoing ovulation induction with CC with IUI underwent monitoring by ultrasound, the other women
180 were usually monitored by basal temperature curve, mid luteal progesterone measurement or urinary
181 LH surge. In case of ovulation not followed by pregnancy, women continued taking the same dose of CC
182 until pregnancy occurred, or until the end of the study eight months after randomization. If ovulation did
183 not occur, the dosage was increased in increments of 50 mg to maximum of 150 mg daily in the next
184 cycles.
185 In couples allocated to IUI, semen samples were processed within one hour of ejaculation according to
186 the local protocol and women were inseminated 36 to 40 hours after hCG injection. IUI was performed
187 once per cycle.

188

189 **Follow up**

190 Follow-up started at the day of randomization and ended on the first day of the last menstruation before
191 a positive pregnancy test within six treatment cycles or at eight months after randomization, whatever
192 came first. If pregnant, women underwent an ultrasound at 7 and 11 weeks of gestation and were

193 followed to delivery of their baby. If they miscarried or had an ectopic pregnancy within eight months
194 after randomization, couples were advised to continue their allocated treatment.
195 Data were collected by trained research nurses and doctors. They used a structured case record form
196 (CRF) to register the actual interventions, the reproductive outcomes, the occurrence of gestational
197 diabetes, hypertensive disorders, stillbirths, preterm labour, and fetal birth weight as well as the course
198 and outcome of subsequent pregnancies. If the women's medical records did not suffice in giving the
199 necessary information, women were contacted by telephone to ask about their outcomes.

200

201 **Withdrawal of individual patients**

202 We expected not all couples to complete the eight months of treatment as drop-outs represent normal
203 patient flow, particularly in this protocol in which they already had six ovulatory treatment cycles before
204 inclusion. Women who dropped out of the study were managed according to their preferences.

205

206 **Outcome measures**

207 The primary outcome measure was conception leading to live birth within eight months after
208 randomization defined as any baby born alive after a gestational age beyond 24 weeks. Secondary
209 outcome measures were ongoing pregnancy, multiple pregnancy, miscarriage (defined as loss of an
210 intrauterine pregnancy confirmed by ultrasound or histological examination before the 20th week of
211 pregnancy), ectopic pregnancy, time from randomization to the birth of a live child, fetal birth weight
212 and pregnancy complications i.e. hypertensive disorders, gestational diabetes and preterm labour.¹¹ We
213 did not monitor adverse drug events as these are already widely known for both types of medication.

214 We do not report on all outcomes mentioned in the statistical analysis plan (addendum 3) here.
215 Outcomes like clinical pregnancy rate, ovulation rate and gestational age will be reported elsewhere.

216

217 **Sample size calculation**

218 When we first planned our study, we designed the trial as a two-by-two factorial superiority trial. After
219 recruiting 136 women, we received governmental funding that allowed enlargement of our trial. To
220 evaluate if either switching to ovulation induction with gonadotrophins or addition of IUI would increase
221 the live birth rate from 40% to 55%,^{12,13} we needed to include 600 women (alpha of 5% and a power of
222 88% at three degrees of freedom). We decided to include a total of 660 women since 10% of women
223 became pregnant after randomization but before starting the trial. With these 660 women we would
224 have sufficient power to find a difference in live birth rate for the two comparisons that we have made.
225 A detailed description of all steps in establishing the sample size is provided in addendum 2. A statistical
226 analysis plan (addendum 3) was established prior to data lock.

227

228 **Statistical analysis**

229 The primary analysis was on an intention to treat basis. For the live birth rates and other binary outcome
230 measures, we calculated absolute risks, relative risks and 95% confidence intervals. Chi-square test
231 statistics were used to assess statistical significance.
232 We reported categorical data as absolute numbers and percentages. We summarized normally
233 distributed continuous variables as means with standard deviations, and non-normally distributed

234 continuous variables as medians with interquartile ranges. We formally tested for interaction between
235 the two comparisons.

236

237 We constructed Kaplan-Meier curves for time to conception leading to live birth for gonadotrophins
238 versus CC, for IUI versus intercourse and for all four treatment arms separately. They were compared
239 with a log-rank test. Two-sided P values of less than 0.05 were considered to indicate statistical
240 significance.

241 We assessed whether there was interaction between treatment effect and Body Mass Index (BMI) at cut-
242 off at 25kg/m² as this was the mean BMI of our population.

243 We also performed a per protocol analysis in which we only included women that were treated
244 according to the predefined protocol. SPSS software (version 23.0; IBM Corp., USA) was used for
245 statistical analysis.

246

247 **Study oversight and role of the funding source**

248 This trial was partially funded by the Netherlands Organization for Health Research and Development
249 (ZonMw). (Health Care Efficiency Research; projectnumber : 80-82310-97-12067). The funder had no
250 involvement in data collection, analysis or interpretation, and had no role in the writing of this
251 manuscript or the decision to submit for publication. The corresponding author confirms to have had full
252 access to all the data in the study and had final responsibility for the decision to submit for publication.

253

254 **RESULTS**

255 Between December 8th 2008 and December 16th 2015, we randomized 666 women. 166 women were
256 allocated to ovulation induction with gonadotrophins combined with IUI, 165 to ovulation induction with
257 gonadotrophins, 163 to ovulation induction with CC combined with IUI, and 172 to continued ovulation

258 induction with CC (Fig I). We excluded five women from analysis since they were randomized despite not
259 fulfilling the inclusion criteria. None of these women became pregnant. The baseline characteristics were
260 comparable across the four groups (Table I).

261 Women allocated to gonadotrophins with IUI underwent 540 cycles, women allocated to gonadotrophins
262 underwent 570 cycles, women allocated to CC with IUI underwent 612 cycles and women allocated to CC
263 underwent 681 cycles. Of these cycles respectively 65 (12%) and 61 (11%) were cancelled in the
264 gonadotrophins with IUI and gonadotrophins only arm. Of these cancelled cycles 35 (28%) were due to
265 anovulation, the other cycles were cancelled because of multiple follicular growth. (Table II).

266

267 **Outcomes**

268 Women allocated to gonadotrophins had significantly more live births than women allocated to CC (167
269 of 327 women [51.5%] vs. 138 of 334 [41.3%], (RR 1.24 (95% CI 1.05-1.46), $p = 0.0124$), absolute
270 difference 10.2% (95% CI 2.4-17.9) Table III)). The mean time to conception leading to a live birth was 5
271 months (95% CI 4.7-5.4) following gonadotrophins and 5.5 months (95% CI 5.1-5.8) following CC (log rank
272 test, $p=0.028$, Fig II)). There were seven women (2%) allocated to gonadotrophins who conceived a twin
273 pregnancy versus eight women (2%) allocated to CC (RR 0.89 (95% CI 0.33-2.4), $p = 0.8262$), absolute
274 difference 0%).

275 Women allocated to IUI had more live births than women allocated to intercourse, but this difference
276 was not statistically different (161 of 327 women [49.2%] vs. 144 of 334 [43.1%], RR 1.14 (95% CI 0.97-
277 1.35), $p = 0.1152$), absolute difference 6.1% (95% CI -1.71 - 13.8) Table III). The mean time to conception
278 leading to a live birth was 5.2 months (95% CI 4.8-5.5) with IUI and 5.3 months (95% CI 5.0-5.7) with
279 intercourse (log rank test, $p=0.27$ Fig II)). There were 11 twin pregnancies after IUI (3%) and four after
280 intercourse (1%) (RR 2.8 (95% CI 0.90-8.7), $p = 0.0743$), absolute difference 2.0%). There were no high
281 order pregnancies.

282 The number of miscarriages was higher after treatment with gonadotrophins (n=24, 7%) than after CC
283 (n=11, 3%) (RR 2.2 (95% CI 1.11-4.5), p = 0.0243), absolute difference 4.0%). Ectopic pregnancies were
284 comparable between all groups. We found no differences in mean birth weights and pregnancy
285 complications (Table III).

286 No interaction was seen between the two comparisons (p = 0.932). Also, there was no interaction of
287 BMI and treatment effect for both comparisons.

288
289 We included 563 women in the per protocol analysis. We found more live births after gonadotrophins
290 compared to CC: 123/279 women (44.1%) after gonadotrophins versus 90/284 (31.6%) after CC (RR 1.38
291 (95% CI 1.11-1.72), p = 0.0027), absolute difference 12.5%). Addition of IUI did not increase live births
292 compared to intercourse: 113/277 women (40.8%) after IUI versus 100/286 (35.0%) women after
293 intercourse (RR 1.17 (95% CI 0.94-1.44), p = 0.1548), absolute difference 12.5%).

294
295 There were three adverse events: one woman treated with CC conceived a child with congenital
296 abnormalities resulting in second trimester pregnancy termination, one woman treated with
297 gonadotrophins with IUI delivered at a gestational age of 20 weeks due to cervical insufficiency, and one
298 woman treated with CC suffered a stillbirth at a gestational age of 19 weeks.

299

Table I. Baseline characteristics of the participating couples*

	Gonadotrophins + IUI n = 164	Gonadotrophins n = 163	CC + IUI n = 163	CC n = 171
Mean female age (years)	29.5 ± 3.7	29.9 ± 3.7	30.0 ± 3.6	29.9 ± 4.0
Ethnicity				
Caucasian	131 (85)	134 (88)	133 (86)	141 (89)
Non-Caucasian	24 (15)	18 (12)	21 (14)	18 (11)
Mean BMI **	25.4 ± 5.1	25.6 ± 5.6	25.0 ± 4.9	25.4 ± 5.0
BMI >25.0	76 (46)	81 (49)	64 (39)	81 (47)
Current smoking status	29 (18)	20 (12)	22 (13)	22 (13)
Diagnosis diabetes	1	1	3	2
Previous live birth	32 (20)	35 (21)	36 (22)	34 (20)
Mean duration of subfertility (months)	26.3 ± 14.9	24.5 ± 12.5	24.5 ± 15.5	25.9 ± 19.0
Cycle pattern prior to treatment #				
Amenorrhea	124 (76)	125 (77)	115 (71)	120 (70)
Oligomenorrhea	21 (13)	25 (15)	27 (16)	32 (19)
Unknown	19 (11)	13 (8)	21 (13)	19 (11)
Median TMC *10 ⁶	52 (20-106)	43 (16-113)	53 (15-132)	38 (16-99)
Polycystic ovaries on ultrasound ##	110 (67)	103 (63)	109 (67)	117 (68)
Mean serum biochemical values				
FSH (IU/L)	5.7 ± 2.1	5.7 ± 1.7	6.2 ± 2.2	6.0 ± 2.2
LH (IU/L)	9.7 ± 7.4	10.6 ± 7.8	10.6 ± 7.6	10.9 ± 10.8
Estrogen (pmol/L)	255 ± 295	239 ± 217	201 ± 159	271 ± 460
Total testosterone (nmol/L)	1.6 ± 1.7	1.6 ± 2.0	1.8 ± 2.2	1.8 ± 1.8

* Data are n (%), mean (SD) or median (IQR). There were no significant differences (P<0.05) between the four groups in any of the baseline characteristics.

**BMI = the body-mass index which is the weight in kilograms divided by the square of height in meter. BMI was missing for 24 women; data were imputed by using multiple imputation.

amenorrhea: absence of menstrual bleeding for >6 months. Oligomenorrhea: irregular menstrual bleedings with intervals of >35 days but ≤6 months

Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter

IUI = intrauterine insemination

CC = clomiphene citrate

CAT = chlamydia antibody test

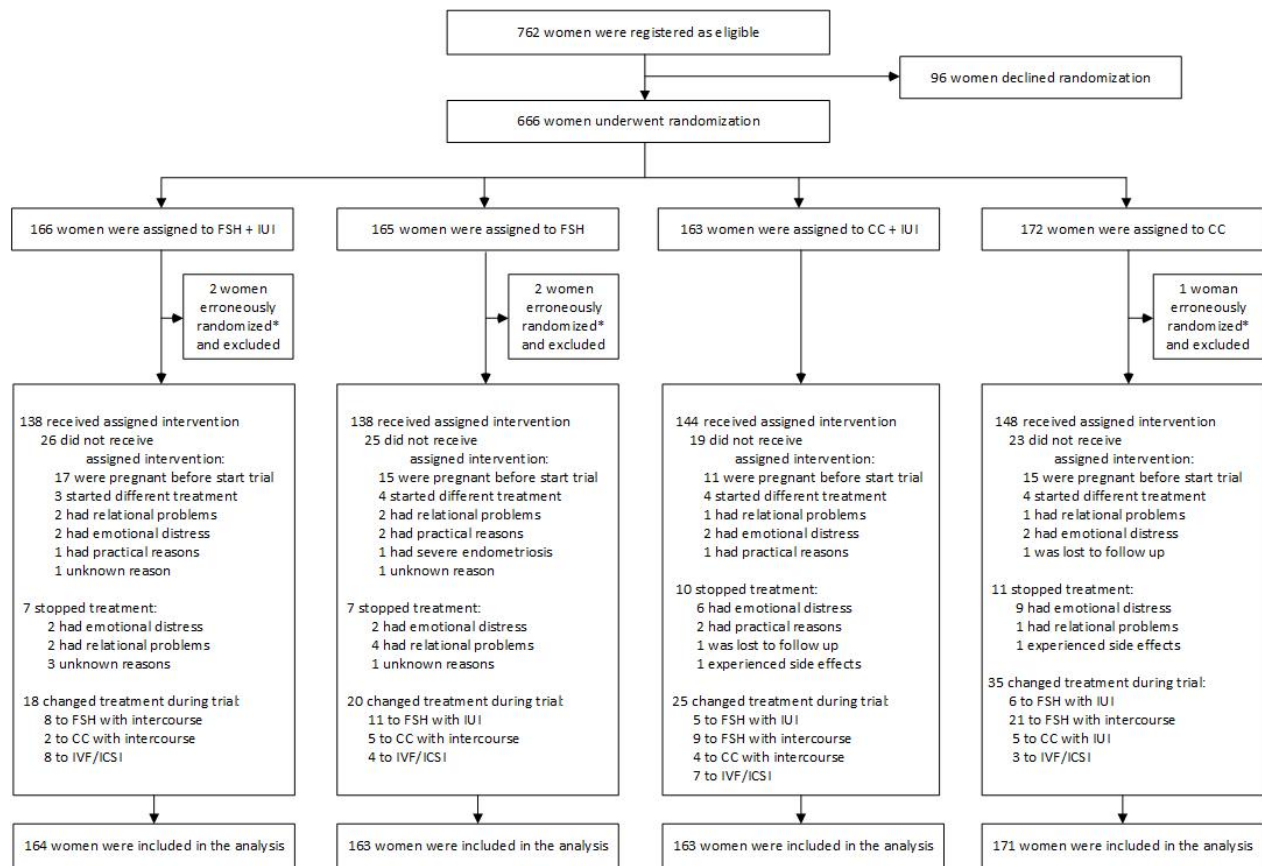
TMC = total motile sperm count

FSH = follicle stimulating hormone

LH = luteinizing hormone

Figure I. Study flow chart (Fig 1 has been uploaded in its original format)

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FSH = Follicle stimulating hormone = gonadotrophins

CC = clomiphene citrate

IUI = intrauterine insemination

*2 women had thyroid disease, 1 woman had bilateral tubal pathology, 1 male partner had azoospermia, 1 woman only had 2 cycles with CC before randomization

Table II. Cycle results*

	Gonadotrophins + IUI n=164	Gonadotrophins n=163	CC + IUI n=163	CC n=171
Total nr of cycles	540	570	612	681
Mean nr of cycles per woman	3.3 ± 2.0	3.5 ± 2.1	3.8 ± 1.8	4.0 ± 1.9
Mean nr of IUIs per woman	3.2 ± 2.2	0.04 ± 0.3	3.5 ± 2.2	0.05 ± 0.4
Total nr of cancelled cycles	65 (12)	61 (11)	4**	2**
Total units of gonadotrophins per woman	2594 ± 2439	2640 ± 2577	153 ± 823**	223 ± 823**
Total mg of CC per woman	4.5 ± 43.4 #	18.2 ± 128 #	1401 ± 1152	1255 ± 1139

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* Data are n (%) or mean (SD)

**After switching to gonadotrophins

After switching to CC

CC = clomiphene citrate

IUI = intrauterine insemination

332 **Table III. Primary and secondary outcomes***

	Gonadotrophins + IUI n = 164	Gonadotrophins n = 163	CC + IUI n = 163	CC n = 171	Gonadotrophins vs CC RR (95% CI)	Gonadotrophins vs CC P value	IUI vs I RR
Live birth	89 (54.3)	78 (47.9)	72 (44.2)	66 (38.6)	1.24 (1.05-1.46)	0.0124	1.1
Ongoing pregnancy	90 (54.9)	80 (49.1)	72 (44.2)	66 (38.6)	1.26 (1.07-1.48)	0.0063	1.1
Multiple pregnancy** per woman	4 (2.4)	3 (1.8)	7 (4.3)	1 (0.6)	0.89 (0.33-2.4)	0.82	2.8
Miscarriages per woman	15 (9.1)	9 (5.5)	8 (4.9)	3 (1.8)	2.2 (1.11-4.5)	0.02	1.9
Ectopic pregnancy per woman	1 (0.6)	1 (0.6)	3 (1.8)	1 (0.6)	#		#
Mean birth weight (g)	3279 ± 695	3302 ± 769	3178 ± 714	3408 ± 491		0.96	
Pregnancy complications							#
• Hypertensive disorders	4 (2)	6 (4)	5 (2)	2 (1)	#		
• Gestational diabetes	3 (2)	5 (3)	3 (2)	3 (2)			
• Preterm labour	6 (4)	2 (1)	0	1 (1)			

333 *Data are n (%) or mean ± SD

334 ** All multiple pregnancies were twin pregnancies

335 # No RR was calculated as the proportions are low.

336 IUI Intrauterine insemination

337 CC clomiphene citrate

338

339 **Figure II. Time to conception leading to live birth for the comparison gonadotrophins versus CC, and IUI versus intercourse**

340 **Fig II was uploaded in separate files.**

341

342 **DISCUSSION**

343 In this multicenter randomized trial, we found that, among normogonadotropic anovulatory women not
344 pregnant after six ovulatory cycles with CC, a switch to gonadotrophins with strict cycle monitoring
345 increased the live birth rate as compared to continued treatment with CC, while we could not prove this
346 for the addition of IUI. All four treatment arms resulted in acceptable pregnancy rates and low
347 complication rates.

348 A strength of our study is the two-by-two factorial design. This design allowed us to dissect the effect of
349 gonadotrophins and CC and to establish that IUI does not increase the chances of pregnancy compared
350 to intercourse, although there was a tendency towards higher live birth rates after the fourth IUI-cycle.
351 The per protocol analysis limited to women that received the allocated treatment did not alter these
352 results suggesting that the treatment switches did not have a large effect on live birth chances. A
353 weakness may be that we allowed participating hospitals to use their local protocols for ovulation
354 induction and IUI. On the other hand, this pragmatic approach might increase the generalizability of the
355 results. Plausible biological explanations for the finding of gonadotrophins giving more live births than CC
356 may be the following. First, treatment with gonadotrophins requires strict cycle monitoring whereas
357 treatment with CC does not. Therefore, women treated with gonadotrophins have more specific
358 knowledge on the timing of their ovulation which may lead to a better timing of their intercourse.
359 Second, CC is supposed to have negative effects on the endometrium, but studies examining this effect
360 in relation to pregnancy rates show conflicting results¹⁴⁻¹⁶. Third, CC possibly induces cervical factor
361 subfertility by influencing the cervical mucus.¹⁷⁻¹⁹

362 We do not know whether the differential monitoring in the women that underwent ovulation induction
363 with CC has had impact on the outcomes, but it is not something we expect. The addition of IUI where
364 monitoring was more strict did not result in significantly higher pregnancy chances. We believe one of

365 the merits of our study is that even with minimal monitoring good results can be obtained with
366 continued ovulation induction with CC.

367 We found a small, not statistically significant effect of IUI on live birth rates which seemed to increase
368 after cycle four. Apparently, IUI does not contribute to pregnancy chances in women with anovulatory
369 subfertility but, once the ovulation disorder has been resolved by either gonadotropins or CC and
370 conception does not occur, IUI may make a difference. These women could be considered to have
371 unexplained subfertility in whom IUI is standard treatment.

372 We found 4% multiple pregnancies after gonadotrophins versus 6% after CC which can be explained by
373 the very purpose of ovulation induction in women with anovulation which is to induce mono-follicular
374 growth with low doses of gonadotrophins.^{9,11}

375 There has traditionally there been reluctance in continuing treatment with CC because of safety issues.⁹
376 Of note, direct evidence that cancer risks are increased after six cycles of CC is lacking.

377 Women treated with gonadotrophins had more miscarriages than women treated with CC. Our study
378 was not powered to detect a difference in miscarriage rate, hence this finding needs to be confirmed in
379 future studies. We found only one second trimester miscarriage in the whole study population, which is
380 very low and in contrast to the miscarriage rate seen after IVF in a fresh transfer cycle in women with
381 PCOS.²⁰ This is probably due to the fact that ovulation induction aims folliculogenesis of one follicle
382 contrast to superovulation in IVF, resulting in a thinner endometrium in ovulation induction. .

383 The cumulative live birth rate after CC in cycles 7 to 12 is comparable with a previous observational
384 study.²¹ Similarly, the cumulative live birth rate after gonadotrophins is in line with a previous
385 prospective cohort study.⁸ This underpins the reliability of our results.

386 Recent randomized trials and network meta-analyses reported letrozole to be superior to CC in
387 establishing live births.^{6,22} We therefore suggest that future research establishes if letrozole is also
388 effective and safe if women have not conceived within the first six months of treatment. Based on our
389 current finding that continued treatment with CC is effective, one might hypothesize even higher live
390 birth rates for continued treatment with letrozole. We therefore suggest to evaluate letrozole in similar
391 settings.

392 Our results can be used by couples treated with first line ovulatory drugs who weigh the pros and cons of
393 switching to gonadotrophins and addition of IUI. CC is known to cause more side effects than
394 gonadotrophins, while gonadotrophins imply daily injections combined with ultrasound monitoring of
395 follicular development and are more expensive.²³ A recently performed patient preference study on
396 women with anovulation wishing to conceive showed that just over half of these women chooses
397 treatment with the least medical interference and lowest burden whereas under 50% prefers a
398 treatment with the highest success rates regardless of the burden.²⁴ We planned a cost-effectiveness
399 analyses which will be reported elsewhere.

400 Our study shows that subfertile women with anovulation who are treated with CC or gonadotrophins
401 with or without IUI reach acceptable pregnancy rates and low complication rates as they continue to
402 conceive even until their 12th treatment cycle. This means that switching to IVF after six failed ovulation
403 induction cycles is not necessary in contrast to the recommendation of the NICE guideline in unexplained
404 subfertility. The choice between these alternatives should therefore be made based on couples
405 preferences, costs, and reimbursement.

406

407 **ACKNOWLEDGMENTS**

408 We thank all couples that participated in the trial, the hospitals and their staff, the research nurses and
409 the staff of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology
410 for logistic support and the staff of the Clinical Research Unit of the Academic Medical Center,
411 Amsterdam for their help with the randomization program and the online database.

412

413 **AUTHORS' ROLES**

414 MJN, JO, PGH, FvdV, BWM and MvW designed the trial. NSW and MJN were the trial coordinators. NSW
415 and MvW performed the statistical analyses. NSW was in charge of drafting the manuscript. PGH, FvdV,
416 BWM and MvW participated in the analysis, manuscript drafting and supervision of the work. All authors
417 acquired the data from the participating centers, provided critical discussion and contributed in the
418 preparation of the manuscript.

419 MvW is corresponding author and confirms to have had full access to all the data in the study and had
420 final responsibility for the decision to submit for publication.

421

422 **FUNDING**

423 This trial was funded by the Netherlands Organization for Health Research and Development (ZonMw).
424 (Health Care Efficiency Research; projectnumber : 80-82310-97-12067) . The Eudract number for this trial
425 is 2008-006171-73. The Sponsor's Protocol Code Number is P08-40.

426

427 **CONFLICT OF INTEREST**

428 BWM is supported by a NHMRC Practitioner Fellowship (GNT1082548)

429 BWM reports consultancy for Merck, ObsEva and Guerbet.

430 The department of Obstetrics and Gynecology of the UMCG receives an unrestricted educational grant of
431 Ferring Pharmaceutical BV The Netherlands.

432 IvR reports personal fees from Advisory Board Ferring, from null, outside the submitted work.

433 CL reports grants from Ferring N.V. and Merck N.V., outside the submitted work.

434 JS reports grants and personal fees from Ferring, grants and personal fees from Merck Serono, personal

435 fees from TEVA, outside the submitted work

436

437 **ADDENDUM 1: Trial Protocol**

438 **ADDENDUM 2: Sample size calculation**

439 **ADDENDUM 3: Statistical analysis plan (SAP)**

440

441

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497 Accepted for publication in *Human Reproduction Open Access*. Date of acceptance: oct 2017; 2017.
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