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ORIGINAL ARTICLE *Infertility*

Long-term outcomes of switching to gonadotrophins versus continuing with clomiphene citrate, with or without intrauterine insemination, in women with normogonadotropic anovulation and clomiphene failure: follow-up study of a factorial randomized clinical trial

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STUDY QUESTION: What are the long-term outcomes after allocation to use of gonadotrophins versus clomiphene citrate (CC) with or without IUI in women with normogonadotropic anovulation and clomiphene failure?

SUMMARY ANSWER: About four in five women with normogonadotropic anovulation and CC failure had a live birth, with no evidence of a difference in pregnancy outcomes between the allocated groups.

WHAT IS KNOWN ALREADY: CC has long been used as first line treatment for ovulation induction in women with normogonadotropic anovulation. Between 2009 and 2015, a two-by-two factorial multicentre randomized clinical trial in 666 women with normogonadotropic anovulation and six cycles of CC failure was performed (M-ovin trial). This study compared a switch to gonadotrophins with continued treatment with CC for another six cycles, with or without IUI within 8 months. Switching to gonadotrophins increased the chance of conception leading to live birth by 11% over continued treatment with CC after six failed ovulatory cycles, at a cost of €15 258 per additional live birth. The addition of IUI did not significantly increase live birth rates.

STUDY DESIGN, SIZE, DURATION: In order to investigate the long-term outcomes of switching to gonadotrophins versus continuing treatment with CC, and undergoing IUI versus continuing with intercourse, we conducted a follow-up study. The study population comprised all women who participated in the M-ovin trial.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The participating women were asked to complete a web-based questionnaire. The primary outcome of this study was cumulative live birth. Secondary outcomes included clinical pregnancies, multiple pregnancies, miscarriage, stillbirth, ectopic pregnancy, fertility treatments, neonatal outcomes and pregnancy complications.

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[‡]M-ovin study group members are listed in the Appendix.

MAIN RESULTS AND THE ROLE OF CHANCE: We approached 564 women (85%), of whom 374 (66%) responded (184 allocated to gonadotrophins; 190 to CC). After a median follow-up time of 8 years, 154 women in the gonadotrophin group had a live birth (83.7%) versus 150 women in the CC group (78.9%) (relative risk (RR) 1.06, 95% CI 0.96–1.17). A second live birth occurred in 85 of 184 women (49.0%) in the gonadotrophin group and in 85 of 190 women (44.7%) in the CC group (RR 1.03, 95% CI 0.83–1.29). Women allocated to gonadotrophins had a third live birth in 6 of 184 women (3.3%) and women allocated to CC had a third live birth in 14 of 190 women (7.4%). There were respectively 12 and 11 twins in the gonadotrophin and CC groups. The use of fertility treatments in the follow-up period was comparable between both groups. In the IUI group, a first live birth occurred in 158 of 192 women (82.3%) and while in the intercourse group, 146 of 182 women (80.2%) reached at least one live birth (RR: 1.03 95% CI 0.93–1.13; 2.13%, 95% CI −5.95, 10.21).

LIMITATIONS, REASONS FOR CAUTION: We have complete follow-up results for 57% of the women.
There were 185 women who did not respond to the questionnaire, while 102 women had not been approached due to missing contact details. Five women had not started the original trial.

WIDER IMPLICATIONS OF THE FINDINGS: Women with normogonadotropic anovulation and CC failure have a high chance of reaching at least one live birth. In terms of pregnancy rates, the long-term differences between initially switching to gonadotrophins are small compared to continuing treatment with CC.

STUDY FUNDING/COMPETING INTEREST(S): The original study received funding from the Dutch Organization for Health Research and Development (ZonMw number: 80-82310-97-12067). A.H. reports consultancy for development and implementation of a lifestyle App, MyFertiCoach, developed by Ferring Pharmaceutical Company. M.G. receives unrestricted grants for scientific research and education from Ferring, Merck and Guerbet. B.W.M. is supported by an NHMRC Investigatorgrant (GNT1176437). B.W.M. reports consultancy for ObsEva and Merck and travel support from Merck. All other authors have nothing to declare.

TRIAL REGISTRATION NUMBER: This follow-up study was registered in the OSF Register, https://osf.io/pf24m. The original M-ovin trial was registered in the Netherlands Trial Register, number NTR1449.

Key words: PCOS / ovulation induction / gonadotrophins / clomiphene citrate / cumulative live birth

Introduction

Most women failing to achieve a pregnancy due to anovulation have WHO type II normogonadotropic anovulation. With a prevalence of 8–13%, it is a common hormonal condition in women of reproductive age and most of these women have polycystic ovary syndrome (Teede *et al.*, 2018).

In these women, ovulation induction with clomiphene citrate (CC) or letrozole is the first-line treatment. While CC has been used for decades, letrozole (used off-label) has recently been shown to be superior over CC. In 60–85% of women, ovulation induction with CC restores ovulation. Women on CC who have not conceived after six ovulatory cycles are defined as having CC failure. In these women, gonadotrophins could be used as second-line ovulation-induction treatment (moderate quality of evidence) (Teede *et al.*, 2018; Costello *et al.*, 2019a,b).

Between 2009 and 2015, we conducted a two-by-two factorial multicentre randomized clinical trial (RCT) (Nahuis *et al.*, 2013; Weiss *et al.*, 2018), in which 666 women with normogonadotropic anovulation and CC failure were included. In this RCT, a switch to gonadotrophins was compared with continued treatment with CC for another six cycles, while the addition of IUI was also evaluated. The cumulative live birth rate was 52% after switching to gonadotrophins and in 41% after continuing ovulation induction with CC (relative risk (RR) 1.24; 95% CI 1.05–1.46, $P = 0.012$). The addition of IUI did not significantly increase the live birth rate (RR 1.14; 95% CI 0.97–1.35, $P = 0.1152$). The cost-effectiveness analyses showed that the extra costs of having one additional live birth in women treated with gonadotrophins compared with CC were €15 258 (95% CI €8721 to €63 654) (Bordewijk *et al.*, 2019). The treatment effect was specifically present in women with a thin endometrium at the initial CC treatment (Bordewijk *et al.*, 2020).

The original trial included six ovulation induction cycles within 8 months. More knowledge on subsequent treatment decisions and success rates, in such a well-mapped population, is relevant for patients, gynaecologists, fertility doctors and policymakers. Patients would like more information on their chances over time to fulfil their child-wish, doctors would like to inform their patients better and policymakers need such information to make a realistic profile for budget impact analysis.

The aim of the present study was to investigate the long-term reproductive outcomes in terms of the long-term cumulative chance of delivering at least one live birth in women who were originally allocated to gonadotrophins or CC.

Materials and methods

Study design and participants

This study is a follow-up study of the M-ovin trial, a two-by-two factorial RCT in 48 Dutch hospitals that compared live birth rates after ovulation induction with gonadotrophins or CC, with or without IUI, in normogonadotropic anovulatory women with CC failure. Between December 2009 and December 2015, a total of 666 women were included. Subfertile women of at least 18 years of age with normogonadotropic anovulation who had been ovulatory for six cycles on CC, but who had not conceived, were eligible for the trial. Couples with severe male subfertility or double-sided tubal pathology were not eligible.

After written informed consent, women were randomly allocated to six cycles of gonadotrophins plus IUI, six cycles of gonadotrophins plus intercourse, six cycles of CC plus IUI or six cycles of CC plus

intercourse on a 1:1:1:1 basis. We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing CC, and IUI versus intercourse. The primary outcome measure was conception leading to live birth within 8 months after randomization. A live birth was defined as any baby born alive after a gestational age beyond 24 weeks. During the study, the data were collected by research nurses and after the last live birth, we closed the database. We performed a cost-effectiveness analysis alongside the study. Further details about the study design, sample size calculation, study procedures and outcomes have been described previously (Nahuis *et al.*, 2013; Weiss *et al.*, 2018).

All previously included women, for whom we had contact details, were asked by e-mail to participate in this follow-up study. They were all asked for informed consent and they received a digital questionnaire. The first contact was made by the principal investigators or representatives of the centres where the women were included. Women who did not respond were sent a second e-mail, followed by telephone contact. Collection of the follow-up data occurred between 02 December 2020 and 18 March 2022.

Questionnaire

The web-based questionnaire included topics about pregnancies, fertility treatments and neonatal outcomes. We collected data on all pregnancies that occurred within the follow-up period, including live birth, multiple pregnancies, miscarriages, stillbirth and ectopic pregnancies. We also asked whether these pregnancies had occurred by natural conception, with or without ovulation induction (CC and FSH, with or without IUI), by any form of ART (IVF, ICSI, frozen embryo transfer), by ovarian drilling or by other possible methods.

Outcomes

The primary outcome of this study was cumulative first live birth (defined as any baby born alive after 24 weeks amenorrhea). Secondary outcomes were second live birth, third or more live births, clinical pregnancies, multiple pregnancies, miscarriage (all pregnancy losses until 20 weeks of gestation), stillbirth (all pregnancy losses after 20 weeks of gestation), ectopic pregnancy (defined as a pregnancy in which implantation takes place outside the uterine cavity), neonatal outcomes (such as foetal birthweight) and pregnancy complications. We used the consensus definitions as established by the *Core Outcome Measure for Infertility Trials* (COMMIT) initiative (Duffy *et al.*, 2020).

Data handing

The data on fertility treatments, pregnancies, miscarriages and neonatal outcomes were retrieved via the web-based questionnaire device LimeSurvey (Version 2.6.7). This data were collected in the LimeSurvey web-based case record form and later transferred to an SPSS file. Data handling was performed with a coded set, with the participant code only available to members of the study group and research nurse of the participating hospitals.

Statistical analysis

We compared the outcomes after follow-up according to the randomization groups, i.e. gonadotrophins versus CC and IUI versus intercourse.

Cumulative live birth was expressed as a RR and risk difference (RD). Analyses for first, second and third live birth were performed for the women participating in the follow-up study. We calculated a hazard rate (with corresponding 95% confidence intervals (CI)), while including all women participating in the original trial and plotted Kaplan–Meier curves to visualize live birth rate over time. Analyses of first live birth were performed in the intention-to-treat (ITT) population. Analyses for second and third live birth were performed only in the women participating in the follow-up study.

Twin pregnancies, miscarriages, still birth and ectopic pregnancies were presented descriptively in the text.

For a subgroup analysis, we calculated the relative risk and 95% CI of live birth for gonadotropins versus CC at endometrial thickness (EMT) values below and above an EMT of 7 mm.

To assess whether non-response bias may have affected results, we compared responders and non-responder baseline and live birth outcomes within the original RCT.

The analyses were performed using SPSS software (version 26.0; IBM Corp., USA).

Ethical considerations

The M-ovin trial was registered in the Netherlands Trial Register, number NTR1449, and approved by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and by the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of the participating centres approved local execution of the study. Informed consent was obtained and included permission to investigate long-term outcomes. For this follow-up study, the Medical Ethical Committee of the Amsterdam UMC, location AMC, approved and provided a non-WMO statement on 22 October 2020 (MEC no. 20.508). This study was registered in the OSF Register, https://osf.io/pf24m.

Results

Between 8 December 2008 and 16 December 2015, 666 women had been randomized to receive an additional six cycles with a change to gonadotrophins (N = 331) or additional six cycles continuing with CC (N = 335). During the trial, five women did not start treatment such that a total of 661 women were eligible for this follow-up study. Between December 2020 and March 2022, we approached 564 women (85%), of whom 374 (66%) (184 allocated to gonadotrophins; 190 to CC) responded and completed the follow-up questionnaire. We had no follow-up data for 287 women (43%): 185 (28%) women were contacted but did not return the questionnaire, while 102 (15%) women were not approached due to missing contact details (n = 95) or non-participation at a local hospital (n = 7).

Median follow-up time was 98 months (min 75 months; max 154 months) in the women allocated to gonadotrophins and 99 months (min 75 months; max 159 months) in the women allocated to CC. The mean age at follow-up was 37.7 (SD 4.0) in the gonadotrophin arm and 38.0 (SD 3.8) in the CC arm. Other baseline characteristics are described in Tables I and II.

The flow chart with first cumulative live birth number is shown in Fig. 1A. Second and third cumulative births are shown in Fig. 1B.

First cumulative live birth

Among the 374 women, treatment with gonadotrophins resulted in a live birth in 154 of 184 women (83.7%) and treatment with CC resulted in a live birth in 150 of 190 women (78.9%) (RR: 1.06, 95% CI 0.96–1.17; RD 4.75%, 95% CI −3.13 to 12.63). Time to conception leading to a live birth is depicted in Fig. 2. Including all 661 women, the hazard rate for live birth was 1.20 (95% CI 0.99–1.44). For the 374 women who participated in the follow-up period, the hazard rate for live birth was 1.14 (95% CI 0.91–1.43). Figure 2A shows live birth over time for the complete population; the median time to conception leading to a first live birth was 6.7 months (95% CI 5.08–8.26) following gonadotrophins and 10.2 months (95% CI 7.76–12.62) following CC (log rank $P = 0.058$). Figure 2B shows live birth over time for the follow-up population; the median time to conception leading to a first live birth was 8.09 months (95% CI 4.61–11.47) following gonadotrophins and 10.68 months (95% CI 7.59–13.76) following CC (log rank $P = 0.24$).

We found no interaction between insemination method (IUI or intercourse) and treatment (gonadotrophins or CC) on live birth ($P = 0.91$).

Table III shows all fertility treatments that resulted in a first live birth. In the gonadotrophin group, 11 of the 154 live births (7.1%) during follow-up were conceived by natural conception and in the CC group, 15 of the 150 (10.0%) during follow-up were conceived by natural conception.

Second, third and fourth cumulative live birth after inclusion

Among the 374 women, a second live birth occurred in 85 of 184 women (46.2%) in the gonadotrophin group and in 85 of 190 women (44.7%) in the CC group (RR 1.03, 95% CI 0.83–1.29; RD 1.46%, 95% CI −8.63 to 11.55) (Fig. 1B). We found no interaction between insemination method (IUI or intercourse) and treatment (gonadotrophins or CC) on a second live birth ($P = 0.84$). In the gonadotrophin group, 47 of the 85 live births were conceived by natural conception and in the CC group, 44 of the 85 were conceived by natural conception.

Six of 184 women (3.3%) delivered a third child in the gonadotrophin group and 14 of 190 women (7.4%) delivered a third child in the CC group. In the gonadotrophin group, 4 of the 6 live births were conceived by natural conception and in the CC group, all of the 14 live births were conceived by natural conception.

One woman in the gonadotrophin group had a fourth live birth. Table IV shows the fertility treatment that resulted in a second, third or fourth live birth.

Twin pregnancies

Twin pregnancies occurred in 12 women (7.9%) allocated to gonadotrophins: 4 within the study period of 8 months after randomization and 8 women during follow-up. Of the women allocated to CC, 11 women had a twin pregnancy (7.4%): 4 within the study period and 7 women during follow-up. Of these 23 twin pregnancies, 19 resulted in a live birth, 3 miscarried and 1 was a vanishing twin of which the remaining singleton was delivered.

Table I Baseline characteristics of the participating couples: gonadotrophins vs CC.

	Gonadotrophins (N = 184)	CC (N = 190)
Age of women (years)	29.6 (3.6)	29.8 (3.6)
Ethnicity		
White	164 (89%)	170 (89%)
Non-white	12 (7%)	13 (7%)
BMI (kg/m^2)	25.5 (5.3)	24.9 (4.6)
BMI > 25.0 kg/m^2	87 (47%)	74 (39%)
Current smoker	27 (15%)	22 (12%)
Diabetes	1 (0.5%)	3 (1.6%)
Previous livebirth	33 (18%)	36 (19%)
Duration of subfertility (months)	23.1 (11.5)	24.3 (17.4)
Cycle pattern before treatment†		
Amenorrhoea	30 (16%)	34 (18%)
Oligomenorrhoea	138 (75%)	133 (70%)
Unknown	16 (9%)	23 (12%)
TMC (×10^6)	109 (177)	81 (110)
Polycystic ovaries on ultrasound‡	122 (66%)	137 (72%)

Data are mean (SD) or n (%).CC, clomiphene citrate; TMC, total motile sperm count.
†Amenorrhoea: absence of menstrual bleeding for >6 months. Oligomenorrhoea: 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.

Table II Baseline characteristics of the participating couples: IUI vs intercourse.

	IUI (N = 192)	Intercourse (N = 182)
Age of women (years)	29.6 (3.7)	29.9 (3.6)
Ethnicity		
White	171 (89%)	163 (90%)
Non-white	13 (7%)	12 (7%)
BMI (kg/m^2)	24.9 (5.0)	25.5 (5.0)
BMI > 25.0 kg/m^2	74 (39%)	87 (48%)
Current smoker	28 (15%)	21 (12%)
Diabetes	1 (0.5%)	3 (1.6%)
Previous livebirth	33 (17%)	32 (18%)
Duration of subfertility (months)	22.9 (11.4)	24.6 (17.6)
Cycle pattern before treatment†		
Amenorrhoea	32 (17%)	32 (18%)
Oligomenorrhoea	140 (73%)	131 (72%)
Unknown	20 (10%)	19 (10%)
TMC (×10^6)	111 (171)	77 (115)
Polycystic ovaries on ultrasound‡	132 (69%)	127 (70%)

Data are mean (SD) or n (%). TMC, total motile sperm count.
†Amenorrhoea: absence of menstrual bleeding for >6 months. Oligomenorrhoea: 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.

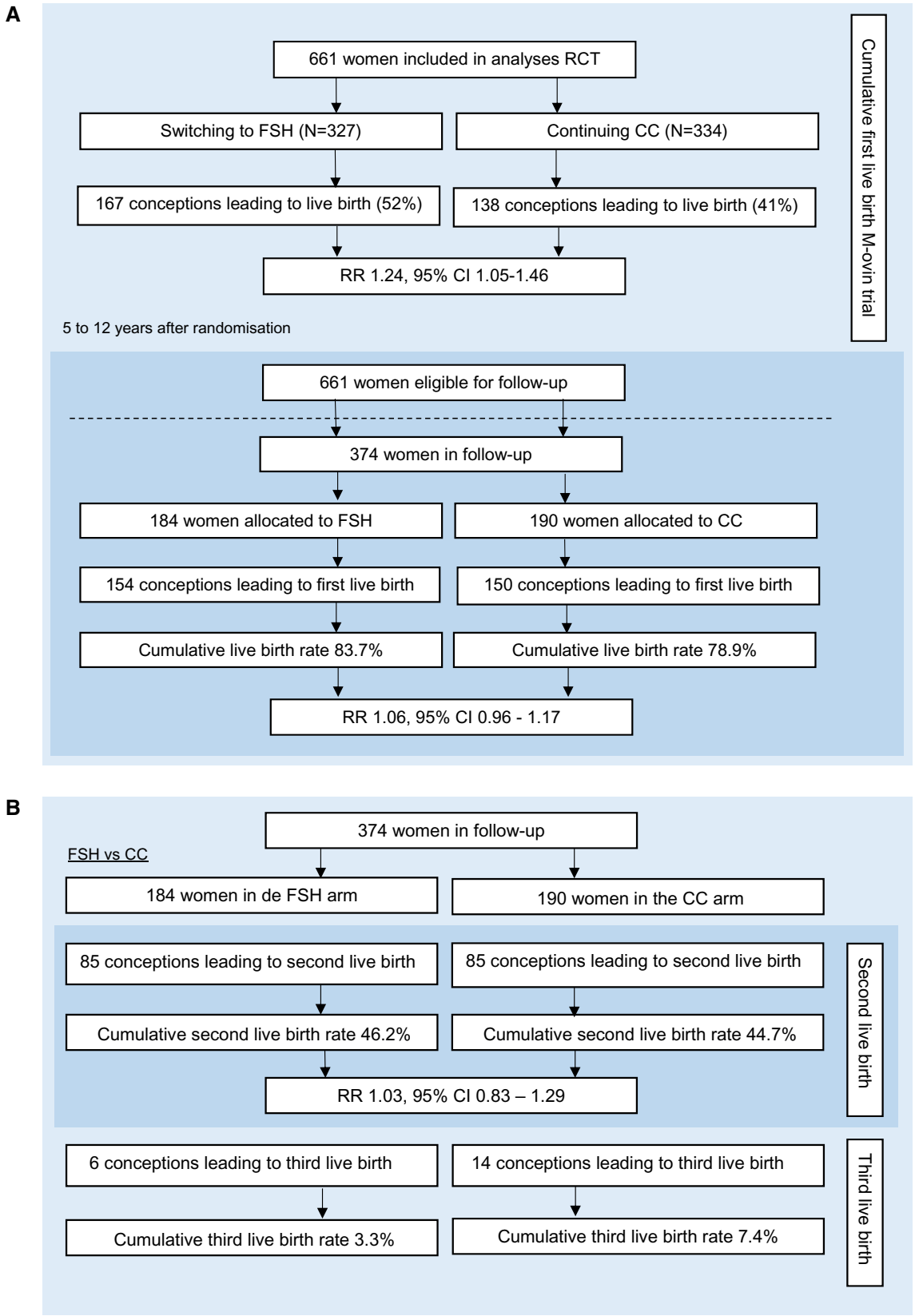

Figure 1. Flowcharts of pregnancy outcomes. (**A**) Outcomes of the first pregnancy leading to a live birth. (**B**) Outcomes of the second and third pregnancy leading to a live birth.

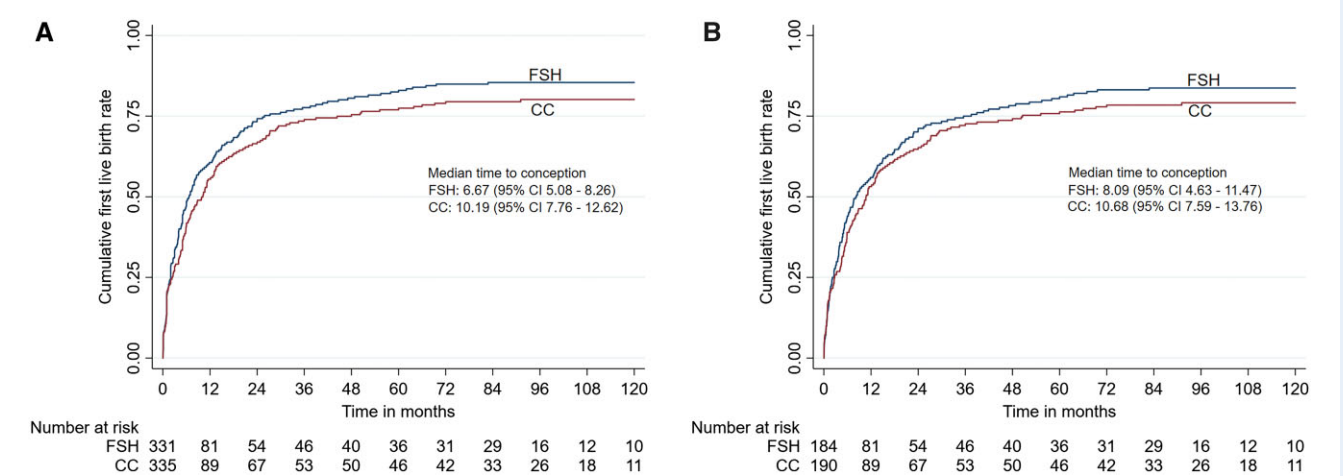

Figure 2. Time to conception leading to a live birth. (**A**) Cumulative livebirths for the first live birth, gonadotrophins versus clomiphene citrate, including all women from the primary RCT and follow-up period (log rank $P = 0.058$). (**B**) Cumulative livebirths for the first live birth, gonadotrophins versus clomiphene citrate, including women in the follow-up period (log rank $P = 0.240$).

Table III Period of first live birth and fertility treatments for first live birth.

First live birth		Gonadotrophins (N = 184)	CC (N = 190)
M-ovin trial (≤8 months)		92 (50.0)	78 (41.0)
	Natural conception	2 (1.1)	2 (1.1)
	CC	1 (0.5)	70 (36.8)
	Gonadotrophins	89 (48.4)	5 (2.6)
	IVF/ICSI	0 (0)	1 (0.5)
	Laparoscopic drilling	0 (0)	0 (0)
Follow-up (>8 months)		62 (33.7)	72 (37.9)
	Natural conception	11 (6.0)	15 (7.9)
	CC	3 (1.6)	6 (3.2)
	Gonadotrophins	19 (10.3)	23 (12.1)
	IVF/ICSI	26 (14.1)	26 (13.7)
	Laparoscopic drilling	1 (0.5)	0 (0)
	Unknown	2 (1.1)	2 (1.1)
Prior to the study[†]		5 (2.7)	9 (4.7)
No first live birth		27 (14.7)	33 (17.4)

Data are n (%).
[†]These women did not conceive during and after the study period but had at least one live birth prior to the study.

Miscarriage, stillbirth and ectopic pregnancy

Of the women allocated to gonadotrophins, 14 women had a miscarriage within the study period of 8 months after randomization and 63 (47 women) miscarriages occurred during follow-up. Over the follow-up period, in total, 52 women had at least one miscarriage (28.3%).

Of the women allocated to CC, 9 women had a miscarriage within the study period of 8 months after randomization and 58 (39 women) miscarriages occurred during follow-up. In total, 45 women had at least one miscarriage (23.7%).

Before the Movin study, 25 women had a miscarriage allocated to gonadotrophins (13.6%) and 24 women allocated to CC (12.6%).

In the gonadotrophin group, three women had a stillbirth (1.6%); one within the study period of 8 months after randomization and two women during follow-up (one conceived with gonadotrophins and one with gonadotrophins and IUI). One pregnancy was preterm terminated

Table IV Fertility treatments* for second and third live birth.

		Gonadotrophins (N = 184)	CC (N = 190)
Second live birth		85 (46.2)	85 (44.7)
	Natural conception	47 (25.5)	44 (23.2)
	CC	5 (2.7)	13 (6.8)
	CC + IUI	1 (0.5)	5 (2.6)
	Gonadotrophins	6 (3.3)	2 (1.1)
	Gonadotrophins + IUI	10 (5.4)	6 (3.2)
	IVF	10 (5.4)	8 (4.2)
	ICSI	5 (2.7)	7 (3.7)
	Laparoscopic drilling	0 (0)	0 (0)
	Unknown	1 (0.5)	2 (1.1)
Third live birth		6 (3.3)	14 (7.4)
	Natural conception	5 (2.7)	14 (7.4)
	Gonadotrophins + IUI	1 (0.5)	0 (0)
Fourth live birth		1 (0.5)	0 (0)
	Natural conception	1 (0.5)	0 (0)

Data are mean n (%).
*Women had more fertility treatments, but these ended not in a pregnancy or in a miscarriage and are not noted in this table.

due to congenital abnormalities (conceived with gonadotrophins). One woman allocated to gonadotrophins, but conceived just before randomization with CC had a still birth.

In the CC group, one woman had a stillbirth (0.5%), which had happened during follow-up (conceived with IVF).

In the gonadotrophin group, four women had an ectopic pregnancy (2.2%); one within the study period of 8 months after randomization and three women during follow-up (conceived naturally, with CC and one with gonadotrophins).

In the CC group, four women had an ectopic pregnancy (2.1%); one within the study period of 8 months after randomization and three women during follow-up (one conceived with CC and two with IVF).

IUI versus intercourse

Among the 374 women, a first live birth was reached in 158 of 192 women (82.3%) in the IUI group and in 146 of 182 women (80.2%) who continued with intercourse (RR: 1.03 95% CI 0.93–1.13; 2.13%, 95% CI −5.95, 10.21).

A second live birth occurred in 84 of 192 women (43.8%) in the IUI group and in 86 of 182 women (47.3%) in the intercourse group (RR 0.93 95% CI 0.74–1.16; RD −3.50%, 95% CI −13.59 to 6.59). Ten of 182 women delivered a third child in the IUI group and 10 of 172 women delivered a third child in the intercourse group. One woman in the IUI group had a fourth live birth.

Subgroup analysis: thin versus thick endometrium

The EMT in the sixth ovulatory cycle before randomization was available in 235 women (116 allocated to gonadotropins and 119 allocated to CC) participating in this follow-up study. There were 90 women (38%) who had an EMT of ≤7 mm and 145 women (62%) who had an EMT >7 mm.

Among the women with an EMT ≤7 mm, 39 of 41 women (95%) in the gonadotrophin group and 39 of 49 women (80%) in the CC group had at least one live birth (RR 1.20, 95% CI 1.02–1.40). Among the women with an EMT >7 mm, 59 of 75 women (79%) in the gonadotrophin group, and 55 of 70 women (79%) in the CC group (RR 1.00, 95% CI 0.84–1.19) had at least one live birth.

Non-responders

The 287 women from whom we failed to retrieve follow-up data had a similar mean age and BMI at start of the MOVIN trial as responders (see Supplementary Table SI). Of these non-responders, 136 women (47%) had a live birth after 8 months of randomization in the original RCT. The live birth rate during the trial was 45% for responders.

Discussion

In the original MOVIN study in women with normogonadotropic anovulation and CC failure, switching to treatment with gonadotrophins resulted in a 11% higher live birth rate than continuing with CC. In this follow-up study, we found that within a median follow-up time of 98 months (8.2 years), 8 out of 10 women had at least one live birth. At long-term follow-up, there were 4.8% more first live births in the group originally allocated to gonadotrophins, but this difference was no longer statistically significant. The median time to conception leading to a first live birth was 6.7 months following gonadotrophins and 10.2 months following CC for the entire population. The use of fertility treatments in the follow-up period (i.e. after the study period) was comparable between the two groups. Use of IUI or intercourse was not associated with cumulative live birth rate and there was no

interaction. Respectively, 46% and 45% of the women in the gonadotrophins and CC groups had a second live birth. More than half of the second live births were conceived in a natural cycle in both groups. The use of fertility treatments in the follow-up period was also comparable between the two groups for the second and third live birth. Women with a mid-cycle EMT ≤7 mm in the sixth ovulatory cycle with CC before randomization seem to have a higher first live birth rate if they were in the gonadotrophins group compared to the CC group, respectively 95% versus 80%. Amongst the women with an EMT >7 mm, the live birth rates were 79% in both groups.

A strength of this follow-up study is that our analyses are based on a strong and balanced two-by-two factorial RCT design.

Certain shortcomings should also be acknowledged. The main limitation is that we had no follow-up data for 43% (N = 287) of the women participating in the randomized controlled trial, such that selection bias could not be excluded. Of 287 women who did not participate in the follow-up, we know that 135 had a first live birth in the Movin study. On the other hand, these women had similar baseline profiles and live birth rates in the initial MOVIN trial were even slightly higher. In view of this, the population included in this study appears representative of the whole population.

For women with CC failure who had switched to gonadotrophins, our study found a cumulative live birth rate of 51% after 8 months and 83.7% after a follow-up period of 8.2 years. A previous follow-up cohort found a cumulative live birth rate of 50% (42 out of 84 women) after a follow-up period of 2 years. The lower live birth rate was likely due to the inclusion of both women with CC failure and women who did not ovulate after thee cycles of CC (Eijkemans *et al.*, 2003).

The results of our study suggest that the live birth rate in the gonadotrophins and CC groups are comparable over a longer period. This seems to be particularly true when the EMT is above 7 mm, as was also previously shown for the pre follow-up data (Bordewijk *et al.*, 2020). The original trial showed that women with normogonadotropic anovulation and CC failure had significantly more live births if they switched to gonadotrophins in comparison to continuing treatment with CC for another six cycles at costs of €15 258 for one extra live birth (Weiss *et al.*, 2018; Bordewijk *et al.*, 2019). Since the long-term cumulative live birth rates are comparable in both arms, continuing treatment after six cycles of CC treatment is likely to reduce costs in the long run as well and will also reduce the use of injections and may therefore reduce the treatment burden in women. The majority of the women who delivered their first live born, conceived with a fertility treatment. Almost half of all women in both the gonadotrophin and CC arm delivered a second child. In both arms, approximately 52–55% of the women conceived their second live birth in a natural cycle. This difference might be explained by a restored hormone balance due to ageing in women with normogonadotropic anovulation (Elting *et al.*, 2000).

We hypothesized that the women in the CC arm who did not conceive during the trial would first use gonadotrophins before switching to IVF, whereas the women who did not conceive in the gonadotrophin arm would start with IVF directly after six cycles of gonadotrophins. This hypothesis was rejected in this study since 25 women in the gonadotrophins group and 26 in the CC group conceived with IVF or ICSI.

Nowadays, letrozole, an aromatase inhibitor, is considered as a more effective first line medication for ovulation induction. It would be of interest to compare continuous letrozole with gonadotrophins and evaluate both short and long-term outcomes.

In conclusion, our results show that differences in the long-term cumulative live birth rates in women with normogonadotropic anovulation and CC failure are small when comparing those who switched to gonadotrophins and those who continued with CC. Women with normogonadotropic anovulation and CC failure have a high chance of reaching at least one live birth. The continued and repeated use of CC has been shown to reduce costs (Bordewijk *et al.*, 2019) and remains a good first alternative to more invasive and expensive treatments.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Authors' roles

T.I.J. and E.M.B. took the lead in writing the article. T.I.J., E.M.B. and M.v.W. performed the analyses. T.I.J. and E.M.B. were in charge of collecting the data. N.S.W., T.d.V., M.N., A.H., M.G., B.W.M. and M.v.W. helped with interpreting the outcomes of the data and reviewed the article. All authors read, edited and approved the final article.

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Conflict of interest

A.H. reports consultancy for development and implementation of a lifestyle App, MyFertiCoach, developed by Ferring Pharmaceutical Company. M.G. receives unrestricted grants for scientific research and education from Ferring, Merck and Guerbet. B.W.M. is supported by a NHMRC Investigatorgrant (GNT1176437). B.W.M. reports consultancy for ObsEva and Merck and travel support from Merck. All other authors have nothing to declare.

Appendix

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