Clomiphene Citrate in PCOS

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Gonadotrophins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure (M-OVIN): a randomized, two-by-two factorial trial

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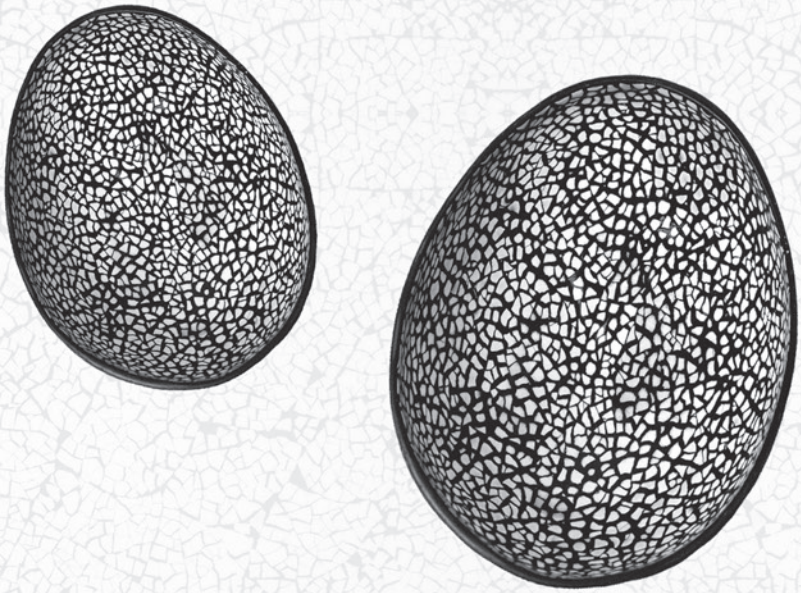

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SUMMARY

Background: In many countries, clomifene citrate is the treatment of first choice in women with normogonadotropic anovulation (ie, absent or irregular ovulation). If these women ovulate but do not conceive after several cycles with clomifene citrate, medication is usually switched to gonadotrophins, with or without intrauterine insemination. We aimed to assess whether switching to gonadotrophins is more effective than continuing clomifene citrate, and whether intrauterine insemination is more effective than intercourse.

Methods: In this two-by-two factorial multicentre randomised clinical trial, we recruited women aged 18 years and older with normogonadotropic anovulation not pregnant after six ovulatory cycles of clomifene citrate (maximum of 150 mg daily for 5 days) from 48 Dutch hospitals. Women were randomly assigned using a central password protected internet-based randomisation programme to receive six cycles with gonadotrophins plus intrauterine insemination, six cycles with gonadotrophins plus intercourse, six cycles with clomifene citrate plus intrauterine insemination, or six cycles with clomifene citrate plus intercourse. Clomifene citrate dosages varied from 50 to 150 mg daily orally and gonadotrophin starting dose was 50 or 75 IU daily subcutaneously. The primary outcome was conception leading to livebirth within 8 months after randomisation defined as any baby born alive after a gestational age beyond 24 weeks. Primary analysis was by intention to treat. We made two comparisons, one in which gonadotrophins were compared with clomifene citrate and one in which intrauterine insemination was compared with intercourse. This completed study is registered with the Netherlands Trial Register, number NTR1449.

Findings: Between Dec 8, 2008, and Dec 16, 2015, we randomly assigned 666 women to gonadotrophins and intrauterine insemination (n=166), gonadotrophins and intercourse (n=165), clomifene citrate and intrauterine insemination (n=163), or clomifene citrate and intercourse (n=172). Women allocated to gonadotrophins had more livebirths than those allocated to clomifene citrate (167 [52%] of 327 women vs 138 [41%] of 334 women, relative risk [RR] 1·24 [95% CI 1·05–1·46]; p=0·0124). Addition of intrauterine insemination did not increase livebirths compared with intercourse (161 [49%] vs 144 [43%], RR 1·14 [95% CI 0·97–1·35]; p=0·1152). Multiple pregnancy rates for the two comparisons were low and not different. There were three adverse events: one child with congenital abnormalities and one stillbirth in two women treated with clomifene citrate, and one immature delivery due to cervical insufficiency in a woman treated with gonadotrophins.

Interpretation: In women with normogonadotropic anovulation and clomifene citrate failure, a switch of treatment to gonadotrophins increased the chance of livebirth over treatment with clomifene citrate; there was no evidence that addition of intrauterine insemination does so.

Trial registration: NTR1449

Funding: The Netherlands Organisation for Health Research and Development (ZonMw).

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed on Sept 15, 2008, before the trial started to identify all previous studies investigating women with clomifene failure with the following search terms: "ovulation induction", "polycystic ovary syndrome", "clomiphene citrate" (CC), "gonadotrophins", and "intrauterine insemination".

We identified only non-randomised studies suggesting that continued treatment with clomifene citrate and a treatment switch to gonadotrophins were both effective options for these women. Whether intrauterine insemination increases pregnancy rates in women with clomifene citrate failure is unknown.

In view of this research gap, we aimed to assess whether, in women who have failed to conceive after six ovulatory cycles with clomifene citrate, ovulation induction with gonadotrophins leads to higher livebirth rates than continued ovulation induction with clomifene citrate and whether intrauterine insemination leads to more livebirths than intercourse.

Added value of this study

The M-OVIN (Modified Ovulation Induction) study compared in anovulatory women with clomifene citrate failure two types of medication as well as addition of intrauterine insemination with intercourse. We found that a switch to gonadotrophins significantly increased the livebirth rate compared with continued treatment with clomifene citrate and that the addition of intrauterine insemination to gonadotrophins or clomifene citrate did not increase livebirth rates.

Implications of all the available evidence

Our findings imply that, for normogonadotropic anovulatory women with clomifene citrate failure who wish to conceive, continued treatment with clomifene citrate or a treatment switch to gonadotrophins are both effective options in terms of livebirth rates, whereas we could not prove this for intrauterine insemination. The choice between clomifene citrate and gonadotrophins should be made based on women's preferences, costs, and reimbursement. Considering recent randomised research suggesting that letrozole gives higher livebirth rates than clomifene citrate in the first six cycles, future research should establish whether continuing letrozole is also effective and safe if women have not conceived within the first 6 months of treatment.

INTRODUCTION

Women with normogonadotropic anovulation have absent or irregular ovulation due to hypothalamic-pituitary-ovarian dysfunction associated with normal concentrations of endogenous oestradiol.[1] In these women wishing to conceive, clomifene citrate has long been used as a first-line ovulation induction agent.[2,3] Findings of systematic reviews and meta-analyses have shown that clomifene citrate is an effective primary treatment option in therapynaive women with normogonadotropic anovulation and polycystic ovary syndrome.[4–6] Although ovulation is restored in about 75% of women starting ovulation induction with clomifene citrate, 6 months of treatment leads to conception in only about half of these women.[5,7] Women not conceiving after six ovulatory cycles are defined as having clomifene citrate failure.[8] The National Institute for Health and Care Excellence (NICE) guideline recommends not to extend treatment with clomifene citrate for more than six cycles, but this recommendation is not underpinned by any evidence.[9] In daily practice, these women usually switch to ovulation induction with gonadotrophins and intrauterine insemination is often initiated instead of relying on regular intercourse.[10] However, the effectiveness of a switch to gonadotrophins and intrauterine insemination compared with continued treatment with clomifene citrate has never been studied in randomised clinical trials.

To address this research gap, we aimed to compare, in women who had six ovulatory cycles with clomifene citrate but did not conceive, the effectiveness of a switch to gonadotrophins compared with continued treatment with clomifene citrate and the effectiveness of adding intrauterine insemination to either clomifene citrate or gonadotrophins.

METHODS

Study design and participants

The Modified Ovulation Induction (M-OVIN) study was a multicentre randomised clinical trial done in 48 Dutch hospitals within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. Eligible women were subfertile, aged 18 years and older with WHO type II anovulation (menstrual cycle >35 days, normogonadotropic, normo-oestrogenic, oligo-anovulation or anovulation), and had been ovulatory for six cycles on clomifene citrate treatment, with a maximum of 150 mg daily for 5 days, but had not conceived. Presence of ovulation was assessed by a basal body temperature curve, midluteal progesterone (>16 nmol/L), detection of a urinary luteinising hormone surge, or transvaginal sonography, depending on the local protocol. All women had undergone a basic fertility work-up including a semen analysis and endocrinology screening to rule out hyperprolactinaemia and uncorrected thyroid dysfunction. Couples with male subfertility could not participate. Women with abnormal

prolactin (0·05–0·80 IU/L) or thyroid-stimulating hormone (0·4–4·0 mU/L) were also not eligible. Tubal pathology had to be ruled out by either a negative Chlamydia antibody titre (CAT) or hysterosalpingography, transvaginal hydrolaparoscopy, or diagnostic laparoscopy showing at least one patent fallopian tube. Women with side-effects in previous clomifene citrate cycles were also not eligible. All women provided written informed consent.
The study was granted approval by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of each of the participating centres approved local execution of the study. The protocol was published previously.[11]
Two major adjustments to the protocol were made: in April, 2014, a change was made to the primary outcome from "ongoing pregnancy" to "livebirth". The second regarded the sample size. Both adjustments were approved by the Medical Ethical Committee.

Randomisation and masking

Eligible women were informed about the study during or immediately after their sixth treatment cycle either by their doctor or by a dedicated research nurse. Women were randomly assigned using a central password protected internet based randomisation program. The randomisation list had been prepared by an independent statistician with a variable block size and a maximum block size of 8. There was no masking.
We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing clomifene citrate and intrauterine insemination versus intercourse. Women were randomly assigned to six cycles with gonadotrophins plus intrauterine insemination, six cycles with gonadotrophins plus intercourse, six cycles with clomifene citrate plus intrauterine insemination, or six cycles with clomifene citrate plus intercourse.

Procedures

In women allocated to ovulation induction with gonadotrophins, a transvaginal ultrasound was usually done on the third day of a menstrual bleed and medication was started on that same day, but women were allowed to start medication up to day 5. Treatment was not started if ultrasound showed ovarian cysts bigger than 25 mm in mean diameter. According to local protocol, urinary or recombinant gonadotrophins were used with a starting dose of 50 or 75 IU daily. Follicular growth was strictly monitored by transvaginal ultrasound and we aimed for mono-follicular growth. When at least one follicle with a diameter of at least 16 mm was present, ovulation was triggered with 5000 IU or 10 000 IU of human chorionic gonadotrophin. If four or more dominant follicles (≥18 mm) developed, the cycle was cancelled - ie, couples were advised not to have intercourse and the planned intrauterine insemination was not done. In women allocated to intrauterine insemination,

semen samples were processed within 1 h of ejaculation according to the local protocol and women were inseminated 36–40 h after human chorionic gonadotrophin injection. Intrauterine insemination was done once per cycle.

In women allocated to ovulation induction with clomifene citrate, treatment was started on the third to fifth day of a menstrual bleed, in the same dosage as used in the last ovulatory cycle, varying between 50 mg and 150 mg daily, for 5 days. Ovulation was monitored by a basal body temperature curve, midluteal progesterone (>16 nmol/L), a urinary lutenising hormone surge, or transvaginal ultrasound, depending on the local protocol. Women undergoing ovulation induction with clomifene citrate plus intrauterine insemination were monitored by ultrasound; women assigned to clomifene citrate with intercourse were usually monitored by basal body temperature curve, midluteal progesterone measurement, or urinary lutenising hormone surge. In case of ovulation not followed by pregnancy, women continued taking the same dose of clomifene citrate until pregnancy occurred, or until the end of the study (8 months after randomisation). If ovulation did not occur, the dosage was increased in increments of 50 mg to a maximum of 150 mg daily in the next cycles.

Follow-up started at the day of randomisation and ended on the first day of the last menstruation before a positive pregnancy test within six treatment cycles or at 8 months after randomisation, whichever came first. If pregnant, women had an ultrasound at 7 and 11 weeks of gestation and were followed up until delivery of their baby. If they miscarried or had an ectopic pregnancy within 8 months after randomisation, couples were advised to continue their allocated treatment.

Data were collected by trained research nurses and doctors. They used a structured case record form to register the actual interventions, the reproductive outcomes, the occurrence of gestational diabetes, hypertensive disorders, stillbirths, preterm labour, and fetal birthweight as well as the course and outcome of subsequent pregnancies. If the women's medical records did not give the necessary information, women were contacted by telephone to ask about their outcomes.

We expected some couples to drop out of the study as per usual clinical practice, particularly in this protocol in which women had already had six ovulatory treatment cycles before inclusion. Women who dropped out of the study were managed according to their preferences.

Outcomes

The primary outcome measure was conception leading to livebirth within 8 months after randomisation, defined as any baby born alive with a gestational age beyond 24 weeks. Secondary outcome measures were ongoing pregnancy, multiple pregnancy, miscarriage (defined as loss of an intrauterine pregnancy confirmed by ultrasound or histological examination before the 20th week of pregnancy), ectopic pregnancy, time from randomisation to the birth of a live child, fetal birthweight, and pregnancy complications -

ie, hypertensive disorders, gestational diabetes, and preterm labour.[11] We did not monitor adverse drug events because these are already widely known for both types of medication. We do not report on all outcomes mentioned in the statistical analysis plan here. Outcomes such as clinical pregnancy rate, ovulation rate, and gestational age will be reported elsewhere.

Statistical analysis

When we first planned our study, we designed the trial as a two-by-two factorial superiority trial. After recruiting 136 women, we received governmental funding that allowed enlargement of our trial. To assess whether either switching to ovulation induction with gonadotrophins or addition of intrauterine insemination would increase the livebirth rate from 40% to 55%,[12,13] we needed to include 600 women (alpha of 5% and a power of 88% at three degrees of freedom). We decided to include a total of 660 women because 10% of women became pregnant after randomisation but before starting the trial. With these 660 women we would have sufficient power to find a difference in livebirth rate for the two comparisons that we have made. A detailed description of all steps in establishing the sample size is provided in the appendix. A statistical analysis plan was established before data lock.

The primary analysis was on an intention-to-treat basis. For the livebirth rates and other binary outcome measures, we calculated absolute risks, relative risks, and 95% confidence intervals. Chi-square test statistics were used to assess statistical significance. We reported categorical data as absolute numbers and percentages. We summarised normally distributed continuous variables as means with standard deviations, and non-normally distributed continuous variables as medians with IQRs. We formally tested for interaction between the two comparisons. We constructed Kaplan-Meier curves for time to conception leading to livebirth for gonadotrophins versus clomifene citrate, for intrauterine insemination versus intercourse, and for all four treatment arms separately. They were compared with a log-rank test. Two-sided p values of less than 0·05 were considered to indicate statistical significance. We assessed whether there was interaction between treatment effect and body-mass index (BMI) at cut-off of 25 kg/m^2 as this was the mean BMI of our population. We also did a per-protocol analysis in which we only included women that were treated according to the predefined protocol. SPSS software (version 23.0; IBM Corp, USA) was used for statistical analysis.

This study is registered with the Netherlands Trial Register, number NTR1449.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between Dec 8, 2008, and Dec 16, 2015, 762 women were registered as eligible. 96 women declined randomisation and 666 were randomly assigned. 166 women were allocated to ovulation induction with gonadotrophins combined with intrauterine insemination, 165 to ovulation induction with gonadotrophins, 163 to ovulation induction with clomifene citrate combined with intrauterine insemination, and 172 to continued ovulation induction with clomifene citrate (figure 1). We excluded five women after randomisation because they did not fulfil the inclusion criteria. None of these women became pregnant. The baseline characteristics were similar across the four groups (table 1).

Table I . Baseline characteristics of the participating couples.

	Gonado-trophins + IUI **n = 164**	**Gonado-trophins + intercourse** **n = 163**	**CC + IUI** **n = 163**	**CC + inter-course** **n = 171**
Age of women (years)	29·5 ± 3·7	29·9 ± 3·7	30·0 ± 3·6	29·9 ± 4·0
Ethnicity				
White	131 (85%)	134 (88%)	133 (86%)	141 (89%)
Non-white	24 (15%)	18 (12%)	21 (14%)	18 (11%)
BMI (kg/m^2)*	25·4 ± 5·1	25·6 ± 5·6	25·0 ± 4·9	25·4 ± 5·0
BMI >25.0 kg/m^2	76 (46%)	81 (49%)	64 (39%)	81 (47%)
Current smoker	29 (18%)	20 (12%)	22 (13%)	22 (13%)
Diabetes	1	1	3	2
Previous livebirth	32 (20%)	35 (21%)	36 (22%)	34 (20%)
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 mean (SD), n (%) or median (IQR). BMI = body-mass index. TMC = total motile sperm count. FSH = follicle stimulating hormone. LH = luteinizing hormone. CC = clomiphene citrate. IUI = intrauterine insemination.
*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

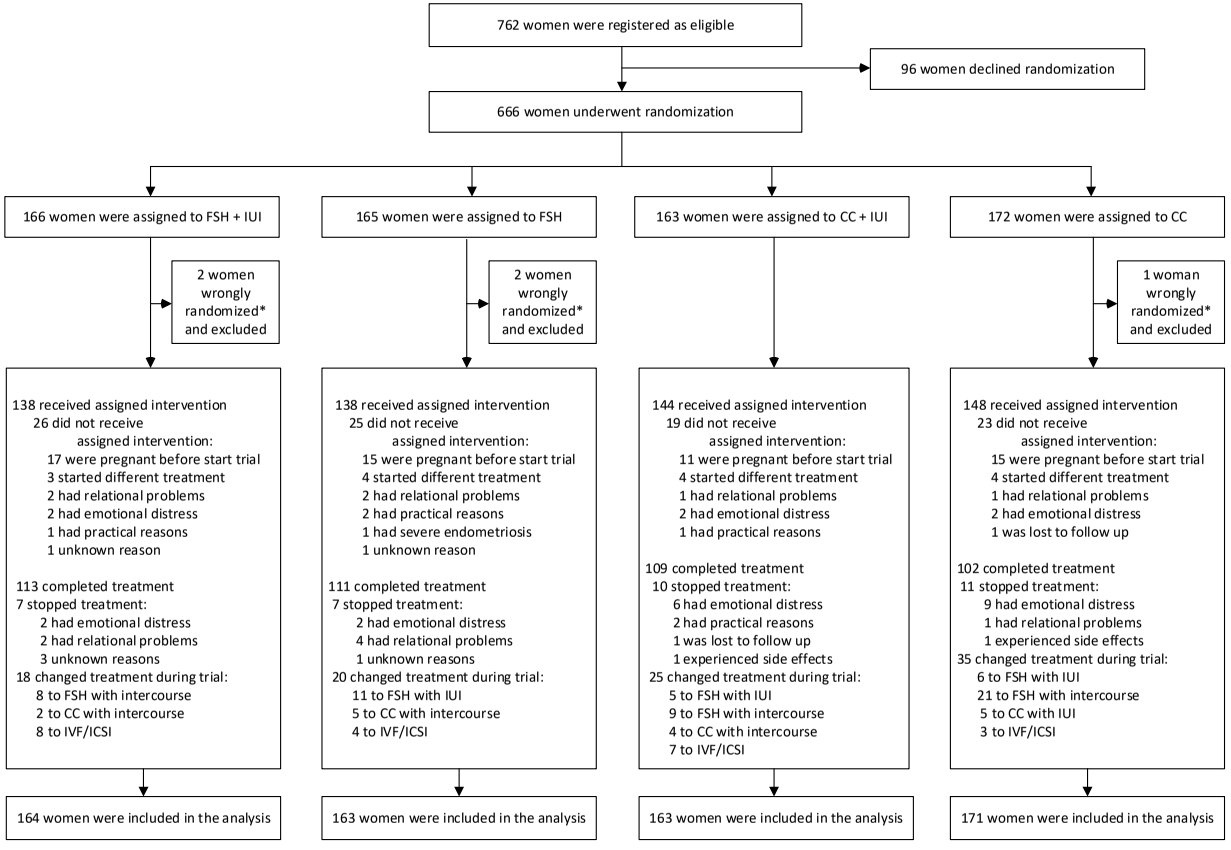

Figure 1. Trial profile

FSH = follicle stimulating hormone. CC = clomifene citrate. IUI = intrauterine insemination. IVF = in vitro fertilization. ICSI = intracytoplasmatic sperm injection. *2 women had thyroid disease, 1 woman had bilateral tubal pathology, 1 male partner had azoospermia, 1 woman only had two cycles with clomifene citrate before randomisation.

Table II. Cycle results

	Gonado-trophins + IUI n=164	Gonado-trophins + intercourse n=163	CC + IUI n=163	CC + intercourse 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

Data are n (%) or mean (SD)
*After switching to gonadotrophins
# After switching to CC
CC = clomiphene citrate. IUI = intrauterine insemination

Women allocated to gonadotrophins with intrauterine insemination underwent 540 cycles, women allocated to gonadotrophins only underwent 570 cycles, women allocated to clomifene citrate with intrauterine insemination underwent 612 cycles, and women allocated to clomifene citrate only underwent 681 cycles. Of these cycles, 65 (12%) were cancelled in the gonadotrophins with intrauterine insemination group and 61 (11%) in the gonadotrophins only group. Of these cancelled cycles, 35 (28%) were due to anovulation; the other cycles were cancelled because of multiple follicular growth (table 2).

Women allocated to gonadotrophins had significantly more livebirths than women allocated to clomifene citrate (167 [52%] of 327 women vs 138 [41%] of 334, relative risk [RR] 1·24 [95% CI 1·05–1·46]; p=0·0124; absolute difference 10·2% [95% CI 2·4–17·9]; table 3). The mean time to conception leading to a livebirth was 5 months (95% CI 4·7–5·4) following gonadotrophins and 5·5 months (5·1–5·8) following clomifene citrate (log-rank test; p=0·028; figure 2). Seven women (2%) allocated to gonadotrophins conceived a twin pregnancy versus eight women (2%) allocated to clomifene citrate (RR 0·89 [95% CI 0·33–2·4]; p=0·8262; absolute difference 0%).

Women allocated to intrauterine insemination had more livebirths than women allocated to intercourse, but this difference was not statistically different (161 [49%] of 327 women vs 144 [43%] of 334 women, RR 1·14 [95% CI 0·97–1·35]; p=0·1152; absolute difference 6·1% [95% CI –1·71 to 13·8; table 3). The mean time to conception leading to a livebirth was 5·2 months (95% CI 4·8–5·5) with intrauterine insemination and 5·3 months (5·0–5·7) with intercourse (log-rank test; p=0·27; figure 2).There were 11 (3%) twin pregnancies after intrauterine insemination and four (1%) after intercourse (RR 2·8 [95% CI 0·90–8·7]; p=0·0743; absolute difference 2·0%). There were no high order pregnancies.

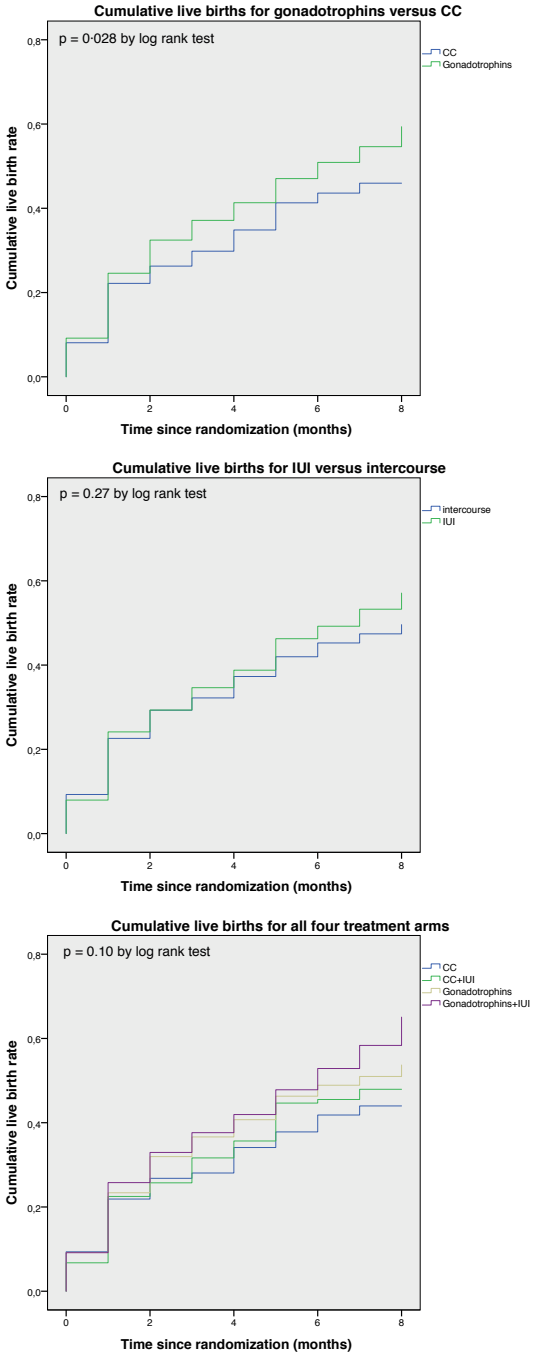

Figure 2. Time to conception leading to livebirth for the comparison gonadotrophins versus clomifene citrate, and intrauterine insemination versus intercourse.

Table III. Primary and secondary outcomes

	Gonado-trophins + IUI n = 164	Gonado-trophins n = 163	CC + IUI n = 163	CC n = 171	Gonado-trophins vs CC RR (95% CI)	Gonado-trophins vs CC P value	IUI vs intercourse RR (95% CI)	IUI vs intercourse P value
Livebirth	89 (54·3%)	78 (47·9%)	72 (44·2%)	66 (38·6%)	1·24 (1·05-1·46)	0·0124	1·14 (0·97-1·35)	0.12
Ongoing pregnancy	90 (54·9%)	80 (49·1%)	72 (44·2%)	66 (38·6%)	1·26 (1·07-1·48)	0·0063	1·14 (0·97-1·34)	0.13
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 (0·90-8·7)	0.07
Miscarriages per woman	15 (9·1%)	9 (5·5%)	8 (4·9%)	3 (1·8%)	2·2 (1·11-4·5)	0·02	1·96 (0·99-3·9)	0·05
Ectopic pregnancy per woman	1 (0·6%)	1 (0·6%)	3 (1·8%)	1 (0·6%)	*		*	
Birth weight (g)	3279 ± 695	3302 ± 769	3178 ± 714	3408 ± 491		0·96		0·14
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%)				

Data are n (%) or mean ± SD unless otherwise stated. All multiple pregnancies were twin pregnancies.
RR = relative risk. * No RR was calculated as the proportions are low.

The number of miscarriages was higher after treatment with gonadotrophins (n=24 [7%]) than after clomifene citrate (n=11 [3%]; RR 2·2 [95% CI 1·11–4·5]; p=0·0243; absolute difference 4·0%). The number of ectopic pregnancies was similar between all groups. We found no differences in mean birthweights and pregnancy complications (table 3). We noted no interaction between the two comparisons (p=0·932). Also, there was no interaction of BMI and treatment effect for both comparisons.

We included 563 women in the per-protocol analysis. We noted more livebirths after gonadotrophins compared with clomifene citrate (123 [44%] of 279 women after gonadotrophins vs 90 [32%] of 284 women after clomifene citrate, RR 1·38 [95% CI 1·11–1·72]; p=0·0027; absolute difference 13%). Addition of intrauterine insemination did not increase livebirths compared with intercourse: 113 (41%) of 277 women had a livebirth after intrauterine insemination versus 100 (35%) of 286 women after intercourse (RR 1·17 [95% CI 0·94–1·44]; p=0·1548; absolute difference 13%).

There were three adverse events: one woman treated with clomifene citrate conceived a child with congenital abnormalities resulting in second trimester pregnancy termination, one woman treated with gonadotrophins with intrauterine insemination delivered at a gestational age of 20 weeks due to cervical insufficiency, and one woman treated with clomifene citrate had a stillbirth at a gestational age of 19 weeks.

DISCUSSION

In this multicentre randomised trial, we found that, among normogonadotropic anovulatory women not pregnant after six ovulatory cycles with clomifene citrate, a switch to gonadotrophins with strict cycle monitoring increased the livebirth rate compared with continued treatment with clomifene citrate. The addition of intrauterine insemination did not increase livebirth rates. All four treatment groups resulted in acceptable pregnancy rates and low complication rates.

A strength of our study is the two-by-two factorial design. This design allowed us to dissect the effect of gonadotrophins and clomifene citrate and of intrauterine insemination versus intercourse. The per-protocol analysis limited to women that received the allocated treatment did not alter our results, suggesting that the treatment switches did not have a large effect on livebirth chances. A weakness could be that we allowed participating hospitals to use their local protocols for ovulation induction and intrauterine insemination. Alternatively, this pragmatic approach might increase the generalisability of the results. Plausible biological explanations for the finding of more livebirths with gonadotrophins than clomifene citrate may be the following. First, treatment with gonadotrophins requires strict cycle monitoring whereas treatment with clomifene citrate does not. Therefore, women given gonadotrophins have more specific knowledge on the timing of their

ovulation, which might lead to a better timing of their intercourse. Second, clomifene citrate might have negative effects on the endometrium; however, studies assessing this effect in relation to pregnancy rates show conflicting results.[14–16] Third, clomifene citrate might induce cervical factor subfertility by influencing the cervical mucus.[17–19]

We do not know whether the differential monitoring in the women that underwent ovulation induction with clomifene citrate affected the outcomes, but it is not something we expect. The addition of intrauterine insemination, in which monitoring was more strict, did not result in significantly higher pregnancy chances. We believe one of the merits of our study is that even with minimal monitoring good results can be obtained with continued ovulation induction with clomifene citrate.

We found a small, not statistically significant effect of intrauterine insemination on livebirth rates. Apparently, intrauterine insemination does not contribute to pregnancy chances in women with anovulatory subfertility. We reported 4% multiple pregnancies after gonadotrophins versus 6% after clomifene citrate, which can be explained by the very purpose of ovulation induction in women with anovulation, which is to induce mono-follicular growth with low doses of gonadotrophins.[9,11] There has traditionally been reluctance to continue treatment with clomifene citrate because of safety issues.[9] However, direct evidence that cancer risks are increased after six cycles of clomifene citrate is lacking. In our study, women given gonadotrophins had more miscarriages than women given clomifene citrate. Our study was not powered to detect a difference in miscarriage rate, hence this finding needs to be confirmed in future studies. We recorded only one second trimester miscarriage in the whole study population, which is very low and in contrast to the miscarriage rate seen after in-vitro fertilisation in a fresh transfer cycle in women with polycystic ovary syndrome.[20] This is probably due to the fact that ovulation induction aims to generate only one follicle in contrast to superovulation in in-vitro fertilisation, resulting in a thinner endometrium in ovulation induction. The cumulative livebirth rate after clomifene citrate in cycles 7–12 is similar to a previous observational study.[21] Similarly, the cumulative livebirth rate after gonadotrophins is in line with a previous prospective cohort study.[8] This underpins the reliability of our results.

Recent randomised trials and network meta-analyses reported that letrozole is associated with higher livebirth rates compared with clomifene citrate.[6,22] We therefore suggest that future research should aim to establish whether letrozole is also effective and safe if women have not conceived within the first 6 months of treatment. Based on our current finding that continued treatment with clomifene citrate is effective, one might hypothesise even higher livebirth rates for continued treatment with letrozole.

Our results can be used by couples treated with first-line ovulatory drugs who weigh the pros and cons of switching to gonadotrophins and addition of intrauterine insemination. Clomiphene citrate is known to cause more side-effects than gonadotrophins, whereas

gonadotrophins necessitate daily injections combined with ultrasound monitoring of follicular development and are more expensive.[23] Findings of a recent patient preference study of women with anovulation wishing to conceive showed that just over half of these women chose treatment with the least medical interference and lowest burden whereas less than 50% preferred a treatment with the highest success rates irrespective of the burden.[24] To evaluate cost differences we have planned a cost-effectiveness analysis that will be reported elsewhere.

Our study shows that subfertile women with anovulation who are given clomifene citrate or gonadotrophins with or without intrauterine insemination reach acceptable pregnancy rates and low complication rates even until their 12th treatment cycle. This means that, in contrast to the recommendation of the NICE guideline for unexplained subfertility, switching to in-vitro fertilisation after six failed ovulation induction cycles is not necessary. The choice between these alternatives should therefore be made based on couples' preferences, costs, and reimbursement.

DECELERATIONS OF INTEREST

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