


Expectant management versus IUI in unexplained subfertility and a poor pregnancy prognosis (EXIUI study): a randomized controlled trial

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STUDY QUESTION: For couples with unexplained subfertility and a poor prognosis for natural conception, is 6 months expectant management (EM) inferior to IUI with ovarian stimulation (IUI-OS), in terms of live births?

SUMMARY ANSWER: In couples with unexplained subfertility and a poor prognosis for natural conception, 6 months of EM is inferior compared to IUI-OS in terms of live births.

WHAT IS KNOWN ALREADY: Couples with unexplained subfertility and a poor prognosis are often treated with IUI-OS. In couples with unexplained subfertility and a relatively good prognosis for natural conception (>30% in 12 months), IUI-OS does not increase the live birth rate as compared to 6 months of EM. However, in couples with a poor prognosis for natural conception (<30% in 12 months), the effectiveness of IUI-OS is uncertain.

STUDY DESIGN, SIZE, DURATION: We performed a non-inferiority multicentre randomized controlled trial within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. We intended to include 1091 couples within 3 years. The couples were allocated in a 1:1 ratio to 6 months EM or 6 months IUI-OS with either clomiphene citrate or gonadotrophins.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We studied heterosexual couples with unexplained subfertility and a poor prognosis for natural conception (<30% in 12 months). The primary outcome was ongoing pregnancy leading to a live birth. Non-inferiority would be shown if the lower limit of the one-sided 90% risk difference (RD) CI was less than minus 7% compared to an expected live birth rate of 30% following IUI-OS. We calculated RD, relative risks (RRs) with 90% CI and a corresponding hazard rate for live birth over time based on intention-to-treat and per-protocol (PP) analysis.

MAIN RESULTS AND THE ROLE OF CHANCE: Between October 2016 and September 2020, we allocated 92 couples to EM and 86 to IUI-OS. The trial was halted pre-maturely owing to slow inclusion. Mean female age was 34 years, median duration of subfertility was 21 months. Couples allocated to EM had a lower live birth rate than couples allocated to IUI-OS (12/92 (13%) in the EM group versus 28/86 (33%) in the IUI-OS group; RR 0.40 90% CI 0.24 to 0.67). This corresponds to an absolute RD of minus 20%; 90% CI: -30% to -9%. The hazard ratio for live birth over time was 0.36 (95% CI 0.18 to 0.70). In the PP analysis, live births rates were 8 of 70 women (11%) in the EM group versus 26 of 73 women (36%) in the IUI-OS group (RR 0.32, 90% CI 0.18 to 0.59; RD -24%, 90% CI -36% to -13%) in line with inferiority of EM.

LIMITATIONS, REASONS FOR CAUTION: Our trial did not reach the planned sample size, therefore the results are limited by the number of participants.

WIDER IMPLICATIONS OF THE FINDINGS: This study confirms the results of a previous trial that in couples with unexplained subfertility and a poor prognosis for natural conception, EM is inferior to IUI-OS.

STUDY FUNDING/COMPETING INTEREST(S): The trial was supported by a grant of the SEENEZ healthcare initiative. The subsidizing parties were The Dutch Organisation for Health Research and Development (ZonMW 837004023, www.zonmw.nl) and the umbrella organization of 10 health insurers in The Netherlands. E.R.G. receives personal fees from Titus Health care outside the submitted work. M.G. declares unrestricted research and educational grants from Guerbet, Merck and Ferring not related to the presented work, paid to their institution VU medical centre. A.B.H. reports receiving travel and speakers fees from Nordic Pharma and Merck and he is member of the Nordic Pharma ANGEL group and of the Safety Monitoring Board of Womed. C.B.L. reports speakers fee from Inmed and Yingming, and his department receives research grants from Ferring, Merck and Guerbet paid to VU medical centre. B.W.J.M. is supported by a NHMRC Investigator grant (GNT1176437) and reports consultancy for ObsEva and Merck. M.v.W. received a grant from the Netherlands Organisation for Health Research and Development ZonMW (80-8520098-91072). F.M. received two grants from the Netherlands Organisation for Health Research and Development ZonMW (NTR 5599 and NTR 6590). The other authors report no competing interest.

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Introduction

Unexplained subfertility is diagnosed in couples who are unable to conceive after 12 months of unprotected intercourse, and where routine fertility investigations show no abnormalities (Smith *et al.*, 2003). Such couples are often treated with IUI with ovarian stimulation (IUI-OS), which aims to increase the pregnancy rates compared to natural conception. In this situation, models that predict the chance of natural conception can be used to differentiate between couples that have favourable chances for natural conception (score $\geq 30\%$ for successful conception in the next 12 months) and those that have poor prospects (score $< 30\%$). The model of Hunault, for example, is an externally validated and relatively simple synthesis model that includes female age, duration of subfertility, sperm motility, a previous pregnancy and referral status (Hunault *et al.*, 2004; van der Steeg *et al.*, 2007).

In couples with unexplained subfertility and good prospects for natural conception, six cycles of IUI-OS do not result in a higher live birth rate than expectant management (EM) (Steures *et al.*, 2006). However, the effectiveness of IUI-OS compared to EM in couples with unexplained subfertility and a poor prognosis is uncertain. Two meta-analysis, both authorized by Cochrane, showed insufficient data whether treatment with IUI-OS leads to higher live birth rates compared to EM (Wang *et al.*, 2019; Ayeleke *et al.*, 2020).

Since IUI-OS treatment increased the risk of a multiple pregnancies and generates financial costs, there should be good evidence that

IUI-OS is effective (van Eekelen *et al.*, 2021). A recent randomized controlled trial (RCT) showed that in couples with a poor prognosis for natural conception IUI-OS increases live birth rates (Farquhar *et al.*, 2018). Since in this study, the median duration of subfertility was almost 4 years, the generalizability of these findings to all couples is limited, and these findings need confirmation. Meanwhile, IUI-OS is standard practice and the first choice of treatment in many areas of the world.

We therefore wanted to evaluate if, in couples with unexplained subfertility and a poor prognosis for natural conception, EM for 6 months does not harm fertility chances as compared to 6 months IUI-OS. Our hypothesis is that 6 months of EM does not result in decreased live birth rates as compared to the standard practice of IUI-OS in couples with unexplained subfertility and a poor prognosis for natural conception.

Materials and methods

Study design and participants

We performed an open-label, non-inferiority RCT within the setting of the Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynaecology. The study was approved by the Medical Ethics Committee of AMC Amsterdam (METC 2016_133, NL

57383.018.16) and by the boards of all participating hospitals. All participants provided written informed consent before randomization. The study was registered at the Dutch Trial register NL5455 (NTR5599).

All data were systematically recorded using an electronic Clinical Report Form (CRF). These electronic forms were stored in the same web-based data system as the randomization (Castor EDC, Ciwit B.V. Amsterdam, The Netherlands). Data were handled confidentially and, whenever possible, coded. The handling of personal data meets the General Data Protection Regulation (in Dutch: de Algemene Verordening Gegevensbescherming, AVG). The medical record files in each participating centre were used as a source for completion of the CRF. Personal data will be stored for a maximum of 15 years in participating centres.

We included heterosexual couples diagnosed with unexplained subfertility and an unfavourable prognosis for natural conception. Unexplained subfertility was defined as: at least 12 months unprotected intercourse or self-insemination without conception, regular ovulatory cycle, at least one-sided tubal patency (established according to local protocol), total motile sperm count above 3 million.

A prognosis for natural conception was calculated using the prediction model of Hunault (Hunault et al., 2004). Couples could participate if one of the following entry criteria were fulfilled:

- female age between 18 and 38 years with a Hunault score <30%,
- female age between 38 and 43 years and
- female age between 18 and 38 years with an initial favourable prognosis (Hunault score \geq 30%) returning after at least 6 months EM without conception.

Exclusion criteria were previous fertility treatment in the current infertility episode, IUI-OS with sperm bank donation, a medical contra-indication for pregnancy and sexual problems interfering with the chance of a natural conception pregnancy.

For each couple, we collected the following data for the female partner: age, BMI, duration of subfertility, parity and referral status. For the male partner, we collected the results of the first semen analysis.

Randomization and masking

Participants were randomly assigned to either the control or the experimental group with a 1:1 allocation using a web-based data system (Castor EDC) with a permuted-block design, with no stratification. The block sizes (2, 4 and 6) were not disclosed, to ensure concealment. Allocation concealment was ensured, as the data system did not release the randomization code until the couple had been recruited into the trial, which took place after baseline measurements had been entered in the system. Neither the recruiters nor the trial project group could access the randomization sequence. The study was open-label because the nature of the intervention means that masking couples to the assigned intervention was not possible.

Procedures

Couples were informed about the study by the research nurse if they turned out to be eligible after finishing the routine fertility investigations. After informed consent, couples were randomly allocated to EM

(experimental group) or a maximum of six cycles of IUI-OS (control group) both within a time horizon of 6 months.

Couples allocated to EM tried to conceive naturally. After 6 months, they were allowed treatment with IUI or IVF, depending on their preference and local protocols.

The IUI-OS treatment started after randomization until the time horizon of 6 months had passed. IUI-OS was performed with ovarian stimulation, according to local protocol with either oral clomiphene citrate (CC) or s.c. gonadotrophins. In the Netherlands, the costs of IUI-OS are reimbursed by health insurance.

Outcomes

The primary outcome measure was ongoing pregnancy leading to a live birth, conceived within a time horizon of 6 months after randomization. Live birth was defined as the birth of a baby with a heartbeat at 24 or more weeks of gestation.

Secondary outcomes were clinical pregnancy (defined as the presence of a gestational sac seen by transvaginal sonography at 7–9 weeks gestation), ongoing pregnancy (defined as the presence of a heartbeat as seen by transvaginal sonography at 12 weeks gestation), multiple pregnancies (defined as two or more gestational sacs seen by transvaginal sonography at 7–9 weeks gestation), miscarriage (defined as the loss of a pregnancy prior to 16 weeks gestation), ectopic pregnancy (defined as the ectopic nidation of a pregnancy, diagnosed using serum level hCG, sonography or laparoscopy), still birth, time to ongoing pregnancy, pregnancy complications (hypertensive disorders, pre-eclampsia, abnormal placentation, gestational diabetes) and pregnancy outcomes (mean birthweight, mean gestational age, gender, neonatal intensive care unit admission, congenital anomalies) (Duffy et al., 2020).

Conceptions that occurred more than 6 months after randomization are beyond the scope of this study and will be reported separately.

Our hypothesis was that both study arms resulted in comparable pregnancy chances, starting from an accepted medical practice of IUI-OS for these couples. We therefore designed the study as a non-inferiority trial. We considered EM to be inferior when the absolute difference in live birth rate would exceed 7%, using an expected live birth rate of 30% after 6 months of IUI-OS as the benchmark (Bensdorp et al., 2015). To evaluate whether 6 months EM would not result in a decrease of ongoing pregnancy rate of 7%, we needed to randomize 982 couples with a power of 80% and an alpha error of 0.5. Anticipating 10% lost to follow-up we needed to randomize 1091 couples. This sample size calculation was performed with Stata version 14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX, USA: StataCorp LP). The independent Data Safety and Monitoring Committee advised us to plan an interim analysis to rule out a large difference when 500 couples had been randomized and had completed 3 months follow-up.

Statistical analysis

The primary analysis was based on an intention-to-treat (ITT) basis. For live birth, we tested non-inferiority on basis of the absolute difference (RD) with the absolute left boundary margin of 7%. We expressed differences as absolute RD and relative risk (RR) with 90% CI. We constructed Kaplan–Meier curves, estimating the cumulative probability of conception leading to live birth over time and used the

log-rank test and hazard ratio with 95% CI to assess differences. With regard to the remaining secondary outcomes, between-group difference of the proportions was expressed as two-sided 95% CIs. We also performed a per-protocol (PP) analysis.

An unplanned subgroup analysis was performed for the primary outcome on the basis of prognostic group: couples with the woman <38 years old and Hunault score <30%, couples with the woman <38 years returning after 6 months EM without conception, and couples with the woman aged 38–43 years.

This study was prospectively registered with the Dutch Trial register NL5455 (NTR5599) and the full trial protocol can be accessed at www.zorgevaluatienederland.nl/exiui. This study protocol was designed with active input and feedback of experts and patient representatives from the Dutch patient organization Freya (www.freya.nl).

Results

Between October 2016 and September 2020, 360 eligible couples were informed about the RCT. After randomization of 178 couples, the study was halted pre-maturely owing to slow recruitment, lack of funding to extend the trial and study fatigue. Eventually, 92 couples were allocated to EM and 86 couples to IUI-OS (Fig. 1).

Of the 182 couples who declined to participate, 85 couples (47%) declined because they desired to start with IUI or IVF, while 25 still preferred EM. Other motivations not to participate are listed in Fig. 1.

Baseline characteristics were equally distributed between the two groups (Table I). Mean female age was 34 years in both groups. Mean duration of subfertility was 22 months in EM group and 21 months in IUI-OS group.

ITT outcomes are presented in Table II. Couples allocated to EM had lower live births rates than couples allocated to IUI-OS (12/92 (13%) versus 28/86 (33%) RR 0.40, 90% CI 0.24 to 0.67); absolute RD of minus 20% (90% CI: –30% to –9%), hazard rate ratio 0.36 (95% CI 0.18 to 0.70) (Figs 2 and 3).

A *post hoc* logistic regression analysis was performed, correcting for age, BMI, parity, duration of subfertility and total motile sperm count. The difference remained after adjustment (odds ratio 3.46, 95% CI 1.56 to 7.67).

In the PP analyses, five couples were excluded because they turned out to be pregnant at randomization (three in the EM group, two in the IUI-OS group). A further 19 couples in the EM group and 11 couples in the IUI-OS group were excluded because they discontinued the intervention. There is no significant difference in discontinuation between both groups (19/92 (20.6%) versus 11/86 (12.8%)). Four live births in the IUI-OS group were conceived naturally between

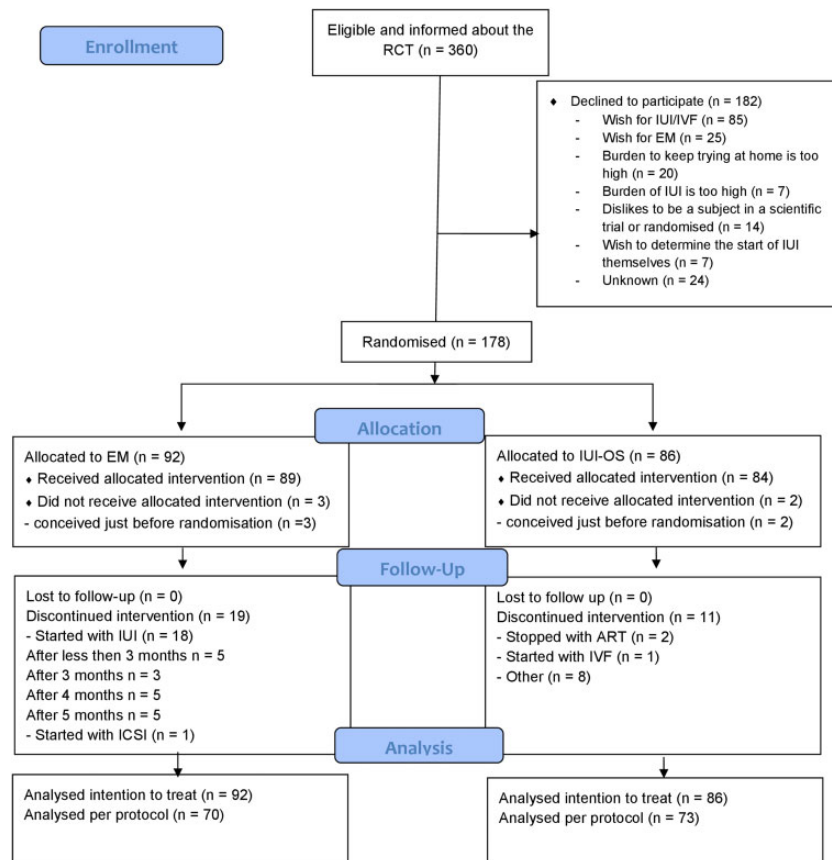


Figure 1. Study flow chart. EM, expectant management; IUI-OS, IUI with ovarian stimulation.

treatment cycles; this can also happen in practice and therefore we did not see it as a discontinuation of the treatment. PP, there were 8/70 (11%) live births in the EM group and 26/73 (36%) in the IUI-OS group (RR 0.32, 90% CI 0.18 to 0.59; RD -24%, 90%

Table I Baseline characteristics of the participating couples.

	Expectant management (n = 92)	IUI-OS (n = 86)
Biometric features		
Female age (years)	33.8 (4.2)	34.4 (4.0)
BMI	24.4 (4.6)	23.2 (4.4)
Fertility history		
Duration of subfertility months (range)	22.0 (16.0–28.8)	21.0 (15.8–30.0)
Primary subfertility	64 (70%)	57 (66%)
Referral status		
General physician	72 (78%)	67 (78%)
Gynaecologist	20 (22%)	19 (22%)
Semen parameters		
Volume (ml)	3.0 (2.0–4.0)	3.0 (1.8–3.8)
Concentration (10^6 /ml)	47.5 (25.0–79.3)	68.0 (28.0–112)
Motility WHO (% A + B)	45.5 (32.8–58.0)	46.0 (31.0–57.0)
TMC (10^6 /ml) pre-wash	51.8 (19.8–109)	53.5 (26.0–135)
Prognosis groups[†]		
Women of 18–38 years with a prognosis <30%	n = 44	n = 48
Women of 18–38 years with an initial favourable prognosis returning after a least six months expectant management	n = 29	n = 21
Women of 38–43 years	n = 19	n = 17

Data are mean (SD), n (%) or median (interquartile range). There were no significant differences between the groups.

IUI-OS, IUI with ovarian stimulation.

[†]Prognosis is chance for natural conception of ongoing pregnancy within a year, calculated at the end of fertility work-up (Hunault et al., 2004). Favourable prognosis is $\geq 30\%$.

CI -36% to -13%), which is in line with inferiority of EM. The hazard ratio for live birth over time was 0.28 (95% CI 0.12 to 0.61) for EM versus IUI-OS (Supplementary Table S1 and Supplementary Fig. S1).

The subgroup analysis on prognosis group showed significantly lower live birth rates in women <38 years of age in the EM group, both in the group with a poor prognosis from the start as well as the group with an initial favourable prognosis. In the women aged 38–43 years, no difference in live birth rate between EM and IUI-OS was seen, while live birth rates were low (RR 0.89, 90% CI 0.26 to 3.05) (Table III).

The IUI-OS cycles were performed according to the local protocol with gonadotrophins or CC. The cycle characteristics can be found in Supplementary Table SII. Of the 28 pregnancies in the IUI-OS group, 6 were conceived naturally before or between the IUI-OS cycles and one woman conceived after IUI without OS.

Table IV depicts pregnancy complications and Table V the neonatal outcomes. There was one congenital anomaly in a child born in the IUI-OS group, a duplex kidney (Q63, classified according to the ICD-10 classification (World Health Organization, 2004)). Supplementary Table SIII depicts neonatal outcomes based on conception.

Discussion

In this RCT in couples with unexplained subfertility and poor natural conception prospects, 6 months of EM is inferior to IUI-OS in terms of live births. The live birth rate following EM was 13% versus 33% after IUI-OS. These results confirm the earlier findings of a similar trial in a poor prognosis group (Farquhar et al., 2018).

Strength of our study is the non-intervention arm. There is a shortage of studies within our field, and in our study, 80% of couples in the EM group completed the 6 months of EM. Our study presents Core outcomes (Duffy et al., 2020) and was set-up as a pragmatic multi-centre trial.

The major weakness of our study is the final number of included couples. We intended to include 1091 couples but since the trial had to be stopped early because of a slow inclusion rate and resulting lack of funding, we only included 178 couples. When recruitment turned out to be too slow while 22 hospitals were open for recruitment, the Dutch Society of OBGYN/(www.nvog.nl) set out a questionnaire

Table II Intention to treat primary and secondary outcomes.

Intention to treat	Expectant management (n = 92)	IUI-OS (n = 86)	RR
Live birth	12 (13%)	28 (33%)	0.40 (90% CI 0.24 to 0.67)
Ongoing pregnancy	12 (13%)	29 (34%)	0.39 (95% CI 0.21 to 0.71)
Clinical pregnancy	17 (19%)	37 (43%)	0.43 (95% CI 0.26 to 0.70)
Miscarriage			
Per randomized women	5 (5.4%)	7 (8.1%)	0.67 (95% CI 0.22 to 2.02)
Multiple pregnancies	2 (2.2%)	0 (0.0%)	–
Ectopic pregnancy	0 (0.0%)	1 (1.2%)	–

IUI-OS, IUI with ovarian stimulation; RR, relative risk.

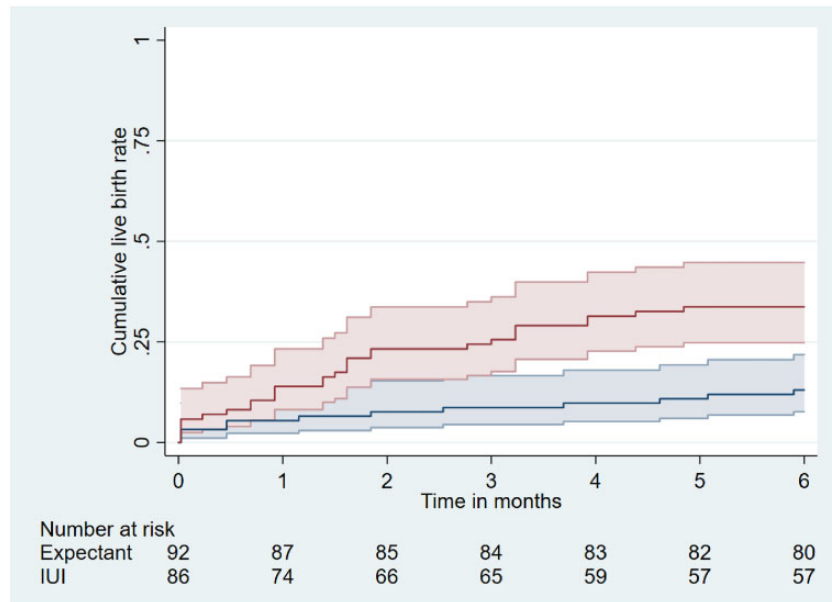


Figure 2. Kaplan–Meier curves of time to last menstrual period leading to a live birth in the expectant management and IUI groups based on intention to treat. Log rank 9.79, *P*-value = 0.002.

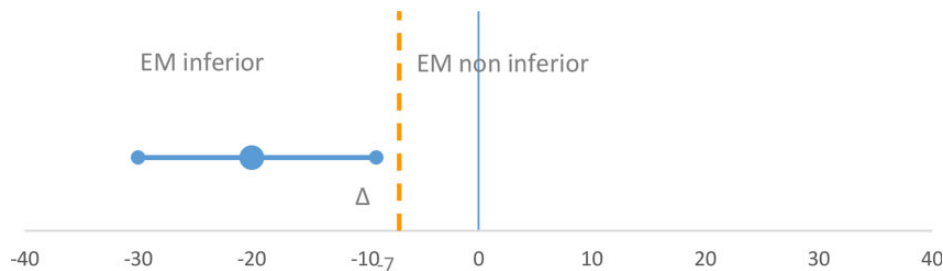


Figure 3. Absolute risk reduction in live birth (%) and 90% CI. EM, expectant management.

about facilitators and barriers for recruitment among healthcare professionals. Results were discussed within the bi-annual meeting of the Dutch SIG ART. Hospitals feared future business economic interests when less IUI cycles will be performed (short term for study patients, long term for all patients with unexplained subfertility and a poor prognosis for natural conception if non-inferiority was established). The subsidizing party (ZonMW and Zorgverzekeraars Nederland) offered the study group a personalized evaluation of our recruitment practise by QUINTET (Bristol Medical School, UK) but no major barriers for recruitment among couples were found. Our interpretation of the slow recruitment is the lack of clinical equipoise experienced by the majority of the participating hospitals, especially after the presentation of the results of the trial from Farquhar *et al.* (2018), which showed a benefit of IUI and also experienced slow recruitment and premature

ending. Despite a recruitment lower than planned, our study allows a clear conclusion to be reached; we found EM clearly to be inferior over IUI-OS.

In our protocol for this pragmatic trial, we had planned to use both the ITT and PP approach to assess non-inferiority, but to present the ITT results first. Both approaches provided similar estimates. In our case, since the number of protocol violations and missing values are considered very low, the ITT analysis may provide a more reliable non-inferiority test compared to the PP analysis excluding non-compliant patients (Matilde Sanchez and Chen, 2006). Though the discontinuation rate was not significantly different, we did find a higher rate in the EM arm (19/92 (20.6%) versus 11/86 (12.8%)). Possibly women allocated to EM were less motivated to follow the study protocol than women receiving active treatment.

Table III Live birth per group with an unfavourable prognosis for natural conception.

	Expectant management (n = 92)	IUI-OS (n = 86)	RR (90% CI)
Women 18–38 years of age with a prognosis <30%	n = 44	n = 48	
Live birth	5 (11%)	17 (35%)	0.32 (0.15 to 0.69)
Women 18–38 years of age with an initial favourable prognosis >30% and returning after 6 months of expectant management	n = 29	n = 21	
Live birth	4 (14%)	8 (38%)	0.36 (0.15 to 0.88)
Women aged 38–43 years	n = 19	n = 17	
Live birth	3 (16%)	3 (18%)	0.89 (0.26 to 3.05)

IUI-OS, IUI with ovarian stimulation; RR, relative risk.

Table IV Pregnancy complications based on intention to treat.

	Expectant management	IUI-OS
Number of ongoing pregnancies	n = 12	n = 29
Termination of pregnancy	0 (0.0%)	1 (3.4%)*
Gestational diabetes	2 (17%)	1 (3.6%)
Hypertension	0 (0.0%)	2 (7.1%)
Pre-eclampsia	1 (8.3%)	0 (0.0%)

*Because of trisomy 18.
IUI-OS, IUI with ovarian stimulation.

With our study, we confirm the results of the TUI trial with 201 participants (Farquhar et al., 2018). We found 13% live births following EM versus 33% following IUI-OS; the TUI trial found 9% live births in the EM group versus 31% in the IUI-OS group.

EM did not reduce twin pregnancies compared to IUI-OS. This is in line with earlier studies where IUI-OS with strict cancellation criteria resulted in low multiple pregnancies rates without lower pregnancy chances (Danhof et al., 2018).

In our sample size calculation, we overestimated live birth chances following 6 months of EM. The live birth numbers were based on the INeS trial (Bensdorp et al., 2015); in this study, the contribution of a natural conception was 4% per cycle, potentially leading to a cumulative percentage of 24% after 6 months, while in our study, the live birth rate was only 13%. Indeed, a study as large as we originally planned was not needed to answer the question.

In a previous study in our network, it was found that in couples with an intermediate prognosis for natural conception (Hunault score 30–40%) IUI-OS was not more effective than EM (Steures et al., 2006), owing to the fact that the natural conception rates were similar to the IUI-OS group.

A prospective cohort study on 800 couples with unexplained subfertility reported that IUI-OS is associated with higher chances of ongoing pregnancy compared to EM, especially in those with poor prognoses of natural conception, i.e. <15% over 6 months or <25% over 1 year (van Eekelen et al., 2019). So, in couples with unexplained

Table V Neonatal outcomes based on intention to treat.

	Expectant management	IUI-OS
Singleton livebirths	n = 10	n = 28
Mean birthweight in grams (SD)	3526 (594)	3693 (401)
Mean gestational age in weeks (SD)	40 (1.40)	40 (1.65)
Premature birth (<37 weeks of gestation)		
Yes	1 (10%)	1 (3.6%)
No	9 (90%)	27 (96%)
Gender		
Female	6 (60%)	9 (32%)
Male	4 (40%)	19 (68%)
NICU admission	0 (0%)	2 (7.1%)
Congenital anomalies	0 (0%)	1 (3.6%) [†]
Multiple livebirths	n = 4	n = 0
Mean birthweight in grams (SD)	2030 (1418)	
Mean gestational age in weeks (SD)	33 (5.7)	
Premature birth (<37 weeks of gestation)		
Yes	2 (50%)	
No	2 (50%)	
Gender		
Female	3 (75%)	
Male	1 (25%)	
NICU admission	2 (50%)	
Congenital anomalies	0 (0%)	

[†]Duplex kidney.
IUI-OS, IUI with ovarian stimulation; NICU, neonatal intensive care unit.

subfertility the Hunault score can be used to differentiate between couples that have favourable chances of conceiving naturally in the next 12 months and those that have poor prognosis.

While numbers in subgroups were low, our *post hoc* exploratory subgroup analyses suggest that IUI-OS may not lead to more live births in unexplained subfertile couples with female age over 38 years. Apparently, IUI does not counteract this natural decline of fertility. The effectiveness of IUI in these women should be studied in future RCTs.

In summary, in couples with unexplained subfertility and poor natural fertility prospects, 6 months of EM is inferior in terms of live births compared to IUI-OS.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

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

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Authors' roles

F.M., M.H.M. and M.v.W. designed the trial, were responsible for the development of the protocol and applied for the grant; F.M. had overall responsibility for the trial. All authors were responsible for implementation of the study and inclusion of the eligible women. J.A.W. was responsible for the overall logistical aspects of the trial and drafted the paper. M.v.W. oversaw the statistical analyses. All authors read and approved the final paper.

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Conflict of interest

E.R.G. receives personal fees from Titus Health care outside the submitted work. M.G. declares unrestricted research and educational grants from Guerbet, Merck and Ferring not related to the presented work, paid to VU medical centre. A.B.H. reports receiving travel and speakers fees from Nordic Pharma and Merck and he is member of the Nordic Pharma ANGEL group and of the Safety Monitoring Board of Womed. C.B.L. reports speakers fee from Inmed and Yingming, and his department receives research grants from Ferring, Merck and Guerbet paid to VU medical centre. B.W.J.M. is supported by a NHMRC Investigator grant (GNT1176437) and reports consultancy for ObsEva and Merck. M.v.W. received a grant from the Netherlands Organisation for Health Research and Development ZonMW

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