

Intrauterine insemination with clomiphene citrate versus expectant management for unexplained infertility: a pragmatic randomised controlled trial

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Abstract

Background

Women with unexplained infertility are often offered intrauterine insemination (IUI) with ovarian stimulation as an alternative to in vitro fertilization (IVF). Yet the evidence for IUI as an effective treatment is lacking. National Institute for Health and Care Excellence (NICE) recommended in 2013 that IUI should not be routinely offered for couples with unexplained infertility.

Methods

We enrolled 201 women with unexplained infertility and an unfavourable prognosis of natural conception in a randomized controlled trial comparing three cycles of IUI with clomiphene citrate ovarian stimulation (IUI-CC) versus three cycles of expectant management (EM). The primary outcome was cumulative live birth rate (CLBR).

Findings

Women allocated to IUI-CC had a higher CLBR than those allocated to EM (31 of 101 [31%] vs. 9 of 100 [9%], $P = 0.0003$; risk ratio (RR), 3.41; 95% confidence interval (CI), 1.71 to 6.79). Of 31 live births in the IUI-CC group, 23 resulted from IUI-CC cycles and eight were conceived without assistance before or between IUI-CC cycles. Of nine live births in the EM group, one resulted from a patient who was pregnant from IUI-CC at study entry and one from off protocol treatment (IVF). There were two sets of twins, both in the IUI-CC group (one from a cancelled cycle for over-response). In a preplanned analysis excluding women who were ineligible (pregnant at study entry, prediction score $\geq 30\%$) and women who conceived off protocol, the CLBR was 22/85 (25.6%) with IUI-CC and 6/88 (6.8%) with EM; RR 3.80, 95% CI, 1.62 to 8.90, $P=0.005$. The number of women who would need to have three cycles of IUI to result in one additional live birth is five (95% CI, 3 to 9).

Interpretation

IUI-CC is a safe and effective treatment for women with unexplained infertility and an unfavourable prognosis for natural conception.

Funding

Auckland Medical Research Foundation, Evelyn Bond Fund of Auckland District Health Board, Mercia Barnes Trust of Royal Australian and New Zealand College of Obstetricians

and Gynaecologists, Maurice and Phyllis Paykel Trust, The Nurture Foundation for Reproductive Research.

Introduction

Intrauterine insemination (IUI) is widely used in the United States, the United Kingdom (UK) and Europe as a low cost, less invasive alternative to in vitro fertilisation (IVF) for couples with unexplained infertility.^{1,2} IUI involves the intrauterine insemination of sperm suspension at the estimated time of ovulation in a natural cycle or following ovarian stimulation.¹

There have been several randomised controlled trials (RCTs) of IUI,³⁻⁹ but only two have considered the question of whether IUI is superior to expectant management (EM), and neither have provided evidence of effectiveness.⁵⁻⁷ One trial of IUI versus EM did not include ovarian stimulation and did not report evidence of benefit after 6 months, with live birth rates of 23% and 17%.⁵ In the other trial, women with intermediate prognosis for natural conception had six cycles of IUI with ovarian stimulation versus EM and the ongoing pregnancy rate was 23% and 27%.⁶

The UK National Institute for Health and Care Excellence (NICE) recommended in 2013 “that intrauterine insemination with or without ovarian stimulation should not be routinely offered for couples with unexplained infertility” and that IVF could be considered after two years of EM.¹⁰ However a recent survey of UK fertility clinicians reported that 96% continued to offer IUI.¹¹

We aimed to compare the effectiveness of three cycles of IUI with clomiphene citrate (IUI-CC) versus three cycles of EM in women with unexplained infertility and an unfavourable prediction score for natural conception (<30%) in the next 12 months.

METHODS

Study design and participants

The Uterine Insemination (TUI) study was a pragmatic, open label, two centre study of women with unexplained infertility and an unfavourable prognosis for natural conception. Women were randomized to three cycles of IUI-CC or three cycles of EM. The New Zealand Ministry of Health Northern B Regional Ethics Committee approved the study protocol (12/NTB/41/AM03), which was prospectively registered on the Australian and New Zealand Clinical Trials Register (ACTRN12612001025820 24/09/2012).

Women attending fertility clinics (Fertility Plus, Auckland District Health Board and Repromed Auckland) in Auckland, New Zealand, were invited to participate. A written patient information sheet was given to all eligible women. All participants provided written informed consent prior to randomisation. We included women aged <42 years, with body mass index <35 kg/m² and unexplained infertility, defined as follows: evidence of ovulation, bilateral patent fallopian tubes as determined by laparoscopy or hysterosalpingography, normal semen analysis (progressive motility ≥32%, concentration ≥15 million/ml) and a prediction score of natural conception leading to live birth in the next year of <30%. We used the validated Hunault prediction model for natural conception, which includes age, length of infertility, any prior pregnancies, source of referral and sperm motility.¹² We included women with mild endometriosis (diagnosed by laparoscopy), polycystic ovarian syndrome according to the Rotterdam criteria (providing ovulation was confirmed with or without ovarian stimulation),¹³ and previous IUI or IVF cycles, but we excluded those requiring donor sperm. All women had screening tests prior to entry in the study: cervical smear <three years, high vaginal swabs, viral testing and immunity against rubella.

Randomisation

We used a computer-generated randomisation sequence in blocks of 4, 6, and 10, without stratification, prepared by an independent statistician. Allocations were concealed in sequentially numbered, sealed, opaque envelopes which were opened by the study coordinator at University of Auckland research department after verification of the inclusion criteria and obtaining written informed consent from each participant. The participating couple and the clinicians were informed of treatment allocation.

Study treatment

Both clinics used the same study protocol. In the IUI-CC group, women received clomiphene citrate (Merck Serono) (50 to 150 mg days two to six) or letrozole (Douglas Pharmaceuticals Ltd) (2.5 to 7.5 mg days two to six) for ovarian stimulation. The choice of ovarian stimulation was made by the clinic. When one to three follicles were present, IUI was performed by injecting the prepared sample of 0.5 ml sperm into the uterus. Estradiol (E2) and luteinising hormone (LH) were measured on day 7. Serial ultrasounds started when $E2 > 400$ pmol/L in the first cycle and if clinically indicated on subsequent cycles. Daily LH tracking started when the leading follicle ≥ 14 mm or when $E2 \geq 400$ pmol/L. When one to three follicles were present, IUI was performed approximately 24 hours after LH surge or 36 hours after a hCG trigger injection. Ultrasound was generally not used in the second or third cycle unless the E2 level was ≥ 2000 pmol/L.

The semen sample was prepared using density gradients of 45% and 90%, and following centrifugation the sample was washed in 3 ml of culture media and resuspended in 0.5ml of culture media. A TomCat catheter (Santesel, Turkey) was used for a single insemination. The prepared sperm sample of 0.5 ml was injected into the uterus. Luteal support was not routinely given. If the progesterone level was < 20 pmol/L seven days after insemination, utrogestan vaginal pessaries 200 mg three times a day were started. Serum β hCG was measured 14 days following the insemination.

Cycles were cancelled if there was no response or if there were > 3 follicles (in which case women were requested to avoid unprotected intercourse). The cancelled cycle was replaced by a further cycle with appropriate dose adjustment.

There were no major protocol changes to the inclusion criteria or the treatment interventions during the study. However, consecutive scheduling of IUI-CC cycles was not always possible because of cancellations, scheduling difficulties and early pregnancy losses. After discussions with the Data Safety Monitoring Committee in early 2014 it was agreed that live births would only be included if three IUI cycles were completed within 6 months (185 days) from the date of randomisation. Exceptions would be made in the case of

miscarriage, when women were allowed recovery time and then time to complete their allocated number of IUI cycles. Natural conceptions were included if they occurred before all three IUI cycles were completed. If an ectopic pregnancy occurred then no further IUI cycles were undertaken.

Couples assigned to EM were followed for three cycles. They were advised to be sexually active around the likely time of ovulation and were provided with a diary to record the first day of each menstrual cycle and dates of sexual activity.

Data collection

We collected the following data for all couples: age, BMI, smoking (ever), ethnicity, previous live births, previous IVF or IUI cycles, duration of infertility, diagnosis of anovulatory polycystic ovary syndrome and mild endometriosis, anti-Mullerian hormone level, sperm count and motility, and prediction score.¹² For couples randomised to the IUI-CC group, additional data were collected regarding the type of stimulation protocol (clomiphene or letrozole), day 12 E2 level, number of follicles >16 mm diameter on day 12, use of ovarian trigger and/or luteal phase support, fresh or frozen sperm, and total motile sperm inseminated.

Pregnancy outcomes and treatment details were collected either from the electronic health record using the National Health Index (NHI) number or from the fertility clinic records. Data were entered into the database at the University of Auckland by the study coordinator. The study clinicians were not formally informed of pregnancy outcomes by the study coordinator, but blinding of study clinicians to the allocation or pregnancy outcomes was not always possible because of their clinical involvement. The study records were kept confidential and secure.

Outcomes

The primary outcome was live birth rate (LBR) after three cycles of treatment and was reported as cumulative live birth rate (CLBR). Secondary outcomes were clinical pregnancy, ectopic pregnancy, miscarriage, multiple pregnancy, ovarian hyperstimulation syndrome,

time to pregnancy leading to a live birth, and birth weight. Live birth, clinical pregnancy and miscarriage were defined using WHO criteria.^{14,15} Women reported pregnancy directly to the study coordinator, while cycle treatment and other clinical outcomes such as live birth were obtained from electronic medical records using the NHI number.

Statistical analysis

We calculated that a sample of 80 women in each group would provide 80% power at a significance level of 0.05 (one-sided test) to detect a difference of 14% in CLBR. We assumed CLBR of 22% for IUI-CC and 8% for EM, based on recent data from one of the participating fertility clinics. The final target was 100 in each group, as the natural conception rate in the IUI-CC group was higher than predicted. We did not stratify by study centre as we did not anticipate demographic or clinical differences between women recruited at the two centres, which are both in the same region.

We performed the following pre-planned analyses: ITT analysis of all randomised women, post-randomisation ITT analysis excluding women who were ineligible (such as prediction score breach ($\geq 30\%$) or pregnant at study entry), and per protocol analysis excluding women who were ineligible and women with protocol violations (defined in the EM group as having any fertility treatment during the three cycles from randomisation and in the IUI-CC group as having an IVF cycle or pregnant between cycles). We also undertook *post hoc* sensitivity analyses; firstly, excluding from the per protocol analysis women who only had CC in the IUI group (strict per protocol), and secondly, examining differing durations of follow up (120 and 185 days from randomisation), in order to assess the possible effect of treatment delays in the IUI-CC group.

For dichotomous variables we calculated risk ratios (RR) with 95% confidence intervals and tested statistical significance using the Chi-squared test. For continuous variables, we used the student's t-test or a Kruskal-Wallis test. We plotted graphically data on the time to pregnancy using a Kaplan-Meier graph. Analyses were performed using IBM SPSS Statistics Version 23. An independent Data Safety Monitoring Committee reviewed the data collection and advised that there were no safety concerns. The statistical analysis was undertaken by two authors.

Role of the funding source

Funding was provided by five charities: Auckland Medical Research Foundation, Evelyn Bond Fund of Auckland District Health Board, Mercia Barnes Trust of Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Maurice and Phyllis Paykel Trust, and The Nurture Foundation for Reproductive Research. The funders did not have any role in planning or conduct of the trial or in the preparation of the manuscript.

Results

We pre-screened 473 women. Of 341 eligible women invited to take part, 140 declined and 201 were randomized, 101 to IUI-CC and 100 to EM (Figure 1) between March 12, 2013 and May 12, 2016. The only significant difference between women agreeing or declining to participate was that those who declined had a shorter duration of infertility (median 24 months versus 44 months, $p=0.03$) and were more likely to be parous (27% versus 12%, $p=0.0009$). There were no missing data for any of the pregnancy, live birth or neonatal outcomes.

Baseline characteristics

There were no significant differences in baseline characteristics between the two groups (Table 1).

Pregnancy outcomes

The IUI-CC group had a higher CLBR than the EM group (31% versus 9%, $P = 0.0003$). In the IUI-CC group (101 women) there were 31 live births, 23 resulting from IUI-CC cycles, three from unrecognised pregnancies at study entry, and five conceived before or between IUI-CC cycles. In the EM group (100 women) there were nine live births, of which two resulted from off protocol treatment (one unrecognised pregnancy at study entry resulting from IUI-CC and another resulting from IVF). In an analysis excluding all protocol violations, the CLBR was 22/85 (25.6%) with IUI-CC and 6/88 (6.8%) with EM ($P=0.005$). This suggests that five women would need to be treated with three IUI-CC cycles to achieve one additional live birth (95% CI 3 to 9) (using ITT data).

There were no significant differences between the groups in rates of pregnancy-related adverse events. In the IUC-CC group there were two sets of twins (one following cancelled cycle for over-response) and four ectopic pregnancies (two from unrecognised pregnancies at study entry, two following IUI-CC cycles) and miscarriages occurred in 6/37 (16%) clinical pregnancies. In the EM group there was one miscarriage (9%) among the 11 clinical pregnancies.

Table 2 presents ITT analysis for all pregnancy outcomes. Table 3 presents ITT, per protocol and sensitivity analyses for CLBR. Time to pregnancy is plotted graphically in a Kaplan-Meier graph in Fig. 2 a and b.

Neonatal outcomes

Mean birth weight for the 33 babies in the IUI group was 3166 g (SD \pm 638), including two sets of twins born at 36 weeks and 38 weeks gestation respectively. Mean birth weight for the nine babies in the EM group was 3470 g (SD \pm 654) ($p=0.21$). In the IUI-CC group one baby was born preterm at 31 weeks gestation following placental abruption and another was born at term with a known tetralogy of fallot; both required specialist care and were healthy at follow up. In the EM group there was one stillbirth at 20 weeks gestation as a result of pregnancy following off-protocol treatment with IUI-CC in the third cycle. All other babies were born at term and considered healthy.

Treatment cycle characteristics

A total of 225 IUI-CC cycles were completed at the two participating clinics (Table 4) and 98% of women (90/92) had at least one cycle. Eighty percent of cycles were completed at one clinic. The live birth rate per cycle was similar between the two clinics (11% and 9%). All IUI-CC cycles with a live birth were commenced within six months of randomisation, except for one woman whose second cycle was delayed due to miscarriage. No cases of ovarian hyperstimulation occurred. With the exception of one participant in cycles two and three, all cycles used fresh sperm. Only seven women received letrozole rather than CC. A trigger was used in 15% (34/225) and luteal support in 2.2% (5/225) of cycles. Cancellation rate was 15% (34/225) over the three cycles; 17 were for over-response, five for under-

response, and four by patient choice. In eight cases no reason was provided.

In the EM group 72 women (72%) returned their diaries and reported on dates of sexual intercourse between day 10 and 18 of the cycle. The mean (\pm SD) frequency of sex was 3.1 (1.3) for cycle 1 (n=72), 3.5 (1.7) for cycle 2 (n=71), and 3.6 (1.5) for cycle 3 (n=67). One or two women in each cycle had no sexual activity recorded.

Discussion

In this RCT we have reported that, in women with unexplained infertility and an unfavourable prognosis for natural conception, three cycles of IUI-CC was associated with a three-fold improved CLBR compared with three cycles of EM. There were two sets of twins, both in the IUI-CC group (6% multiple pregnancy rate).

Although ITT analysis is the recommended approach for reporting clinical trials,^{16,17} there may be concerns that in this study an ITT analysis would overestimate the benefits of IUI-CC because of the increased opportunity for between-cycle pregnancies in the IUI-CC group. Per protocol analysis might therefore appear to be more appropriate. Alternatively, it could be argued that the more reliable outcome is the number of pregnancies leading to live birth using the full dataset (ITT) up to 120 days from randomisation, since the data are complete, data collection was planned, there were no post-randomisation exclusions, and the length of follow up was the same in both groups. Although our findings were robust to each of the analyses, we favour the planned ITT analysis for this pragmatic trial as scheduling consecutive cycles and managing early pregnancy losses are daily reality of fertility clinics. We are also confident that there were no missing data for the primary outcome as we were able to check birth records using the NHI number.

The inclusion of an EM group was a major strength of our study. The CLBR in the EM group was 9% (ITT) after three cycles, which may seem low. However, it is close to the 8% estimate in the power calculation and comparable to the live birth rate (17%) after six months in the EM group in the UK trial of IUI and EM.⁵ Although only 72% of women in the EM group in our study reported on the frequency of sexual activity, these data provide some indication

that women were actively trying to conceive. We also note that only five women from the EM group had other fertility treatments.

We used a simple clomiphene citrate protocol for ovarian stimulation in most cases.⁹ Gonadotrophins are the most commonly used stimulation protocol but have disadvantages including multiple pregnancy rates as high as 22%.⁹ We allowed the clinics to make their own decisions regarding the use of triggering and luteal phase support as there is insufficient evidence for routine use in IUI-CC.^{18,19}

We acknowledge limitations in both study design and conduct. Firstly, five women in the IUI-CC and one in the EM group had unrecognised pregnancies at study entry. This is inevitable unless randomisation is only undertaken on the first few days of the menstrual cycle. Secondly, scheduling the consecutive cycles of IUI proved to be challenging and led to five women conceiving naturally before or between IUI-CC cycles. This is not uncommon in fertility studies^{3,4,5,9} and women may have a 'rest'³ or a 'take a break'.⁴ Failure to complete the full study protocol is also common amongst trials of IUI. In the UK trial of IUI only 20% of women completed six cycles.⁵ Some study designs have attempted to overcome these challenges by giving women 12 months to complete six cycles of IUI and by using ITT analysis including all off-protocol pregnancies.⁸ Thirdly, 8% of women had a higher prediction score than our protocol allowed, in most cases because clinical staff recruiting women overlooked counting early pregnancy loss as a pregnancy. Other breaches included pregnancies in three women who started clomiphene citrate but did not have the insemination. These breaches reflect the challenges of conducting a pragmatic trial in 'real world clinics', and sensitivity analyses excluding these women did not substantially influence our findings.

Multiple pregnancy is considered an adverse event of fertility treatments.¹⁴ The rate in our study was 6%. While this may seem low compared to rates of multiple pregnancy reported following gonadotrophin, where it may be as high as 22%,⁹ it is similar to rates reported in studies of IVF with a single embryo transfer (IVF-SET) where the multiple pregnancy rate is usually no more than 5%.^{8,20,21,22} IUI appears to be more patient-friendly than IVF²³ with a lower burden of treatment, but if the multiple pregnancy rate is shown to be higher with

IUI-CC than with IVF-SET then this may favour IVF.²⁴

Our findings could be used by couples with unexplained infertility in conjunction with their fertility clinicians, when making decisions about treatment with IUI. The prediction calculator is freely available.¹² Our results appear applicable to other settings, as our live birth rate per IUI-CC cycle was 10%, which is similar to other studies.^{2,3,4,9,25} We did not undertake a cost analysis, as EM is not associated with any additional costs unless off-protocol treatment occurs. However, cost effectiveness data from a Dutch RCT of IUI with gonadotrophins versus IVF-SET took neonatal costs into consideration and reported IUI to be the most cost effective strategy.²⁴

Few studies of IUI have considered the question of how IUI improves fertility. We suggest that its effectiveness derives from the combined effect of ovarian stimulation resulting in more than one follicle,^{3,7 8,9,25,26} and the placement of prepared sperm into the uterus close to timing of likely ovulation.²⁷⁻²⁹ It is unlikely that the use of clomiphene for ovarian stimulation is the sole reason that IUI with clomiphene is effective, as clomiphene has not been shown to be superior to unstimulated IUI or EM.⁵ Laboratory techniques for sperm preparation, such as gradient tests, aim to separate motile sperm from seminal plasma and at the same time remove foreign material that has been reported to inhibit the ability of spermatozoa to fertilize.^{28,29} With regard to the role of the intrauterine placement of sperm, studies comparing intracervical and IUI using donor sperm suggest benefit with IUI using cryopreserved sperm, suggesting that intrauterine placement may have an important role.³⁰

Our results offer reliable evidence of a moderate benefit with three cycles of IUI-CC compared to EM. Moreover our findings also compare favourably with outcomes following one cycle of IVF-SET. A RCT comparing three cycles of IVF-SET versus six cycles of IUI with gonadotrophins reported similar CLBRs after 12 months (52% versus 47% by ITT), with lower healthcare costs in the IUI group.²⁴ The authors stated that there was no reason to abandon IUI as a first line treatment for couples with unexplained infertility.

The CLBR of 23% following three cycles of IUI-CC in our study is similar to live birth rates with a single cycle of IVF (fresh transfer only) of 21% for Australia and New Zealand in 2014 and 25% in the United Kingdom in 2013.^{22,31} Live birth rates in the United States are higher (possibly explained by the higher use of double embryo transfer), with reported rates varying from 37% in women under 35 years old to 30% in women aged 35-37.³² Unfortunately, these data are not cumulative as they do not include outcomes from frozen embryo transfers.

The question that this study set out to answer was of effectiveness: that is, whether IUI-CC is associated with better outcomes than EM in women with unexplained infertility and an unfavourable prognosis. We have reported a three-fold improvement in live births. The NICE recommendation that clinics should not offer IUI and instead to consider IVF as first line treatment for unexplained infertility of more than two years duration should be reconsidered.⁹ This recommendation was based on the findings of two RCTs which did not report benefit, but which had different populations, different interventions and higher attrition rates than our study.^{5,7} Few clinics have heeded the NICE guidance and there have been calls for RCTs of IUI compared with an EM.^{8,33} Our study is one such RCT. For couples with unexplained infertility and an unfavourable prediction score, IUI-CC could be offered as a safe and cost-effective first line strategy.

Contributors

Cynthia Farquhar, Emily Liu, Nicola Arroll prepared the protocol, sought funding, applied for the ethics, and recruited patients. Sarah Armstrong and Sarah Lensen recruited patients and with Emily Liu and Nicola Arroll collected and entered data. Julie Brown and Sarah Lensen conducted the statistical analysis. All authors helped prepare the final manuscript.

Declarations of interest

We declare we have no conflicts of interest.

Acknowledgements

We are grateful to the patients who agreed to take part in the study. We are also grateful to the staff of the two fertility clinics in Auckland for their assistance in recruiting and providing treatment within the study protocol. We would also like to thank Dr Emma McGoldrick who assisted with recruitment and Dr Alice Lagas who assisted with recruitment, data collection and data entry. We are also grateful to Mr Andy Vail, University of Manchester for additional statistical advice and Jane Marjoribanks of the University of Auckland for providing assistance with the manuscript preparation.

Funding source

We are grateful to the following New Zealand charities for funding this study: Auckland Medical Research Foundation, Evelyn Bond Fund of Auckland District Health Board, Mercia Barnes Trust of Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Maurice and Phyllis Paykel Trust, and The Nurture Foundation for Reproductive Research. None of the funders had a role in any stage of the conduct of the study or the preparation of the manuscript.

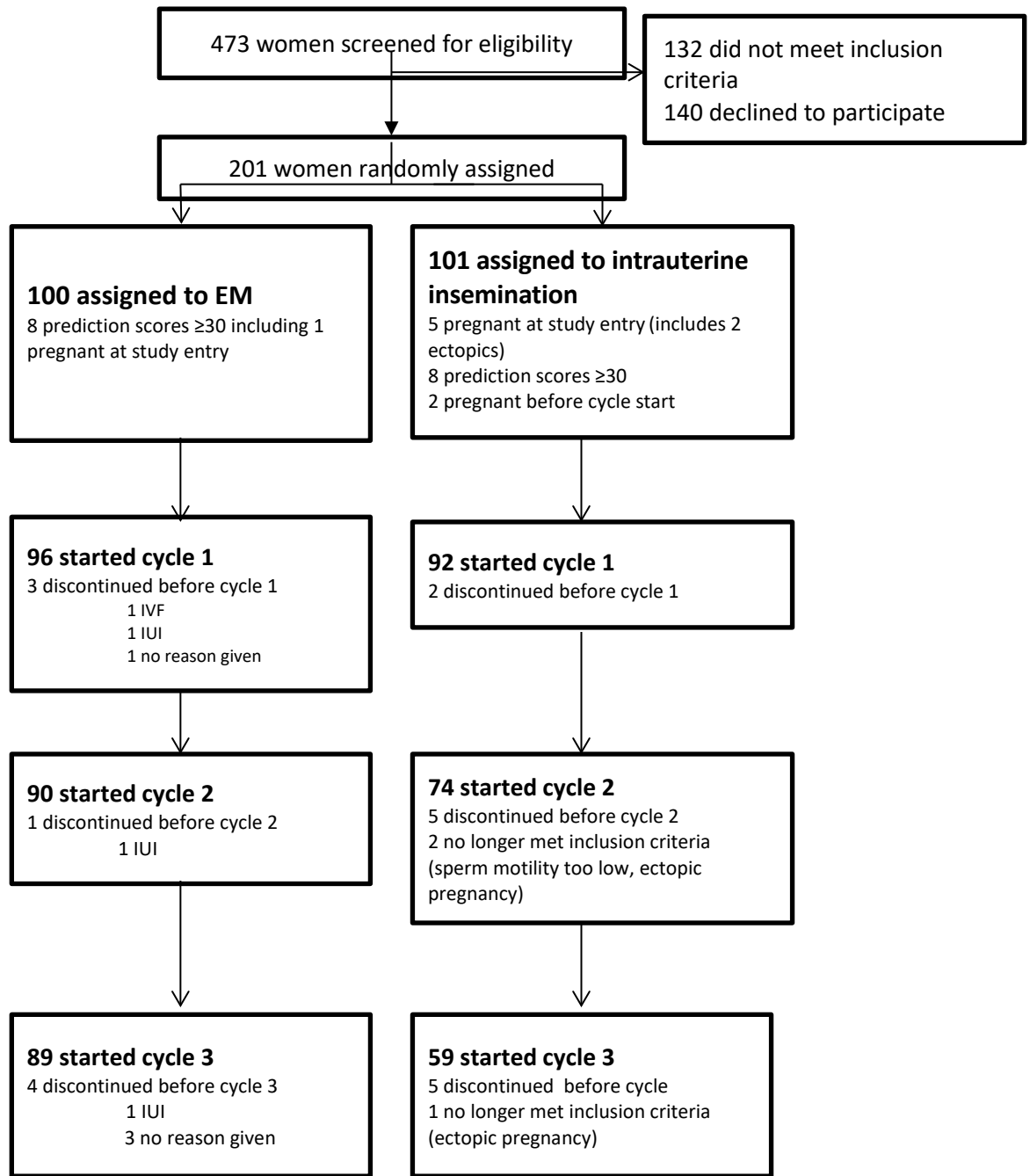
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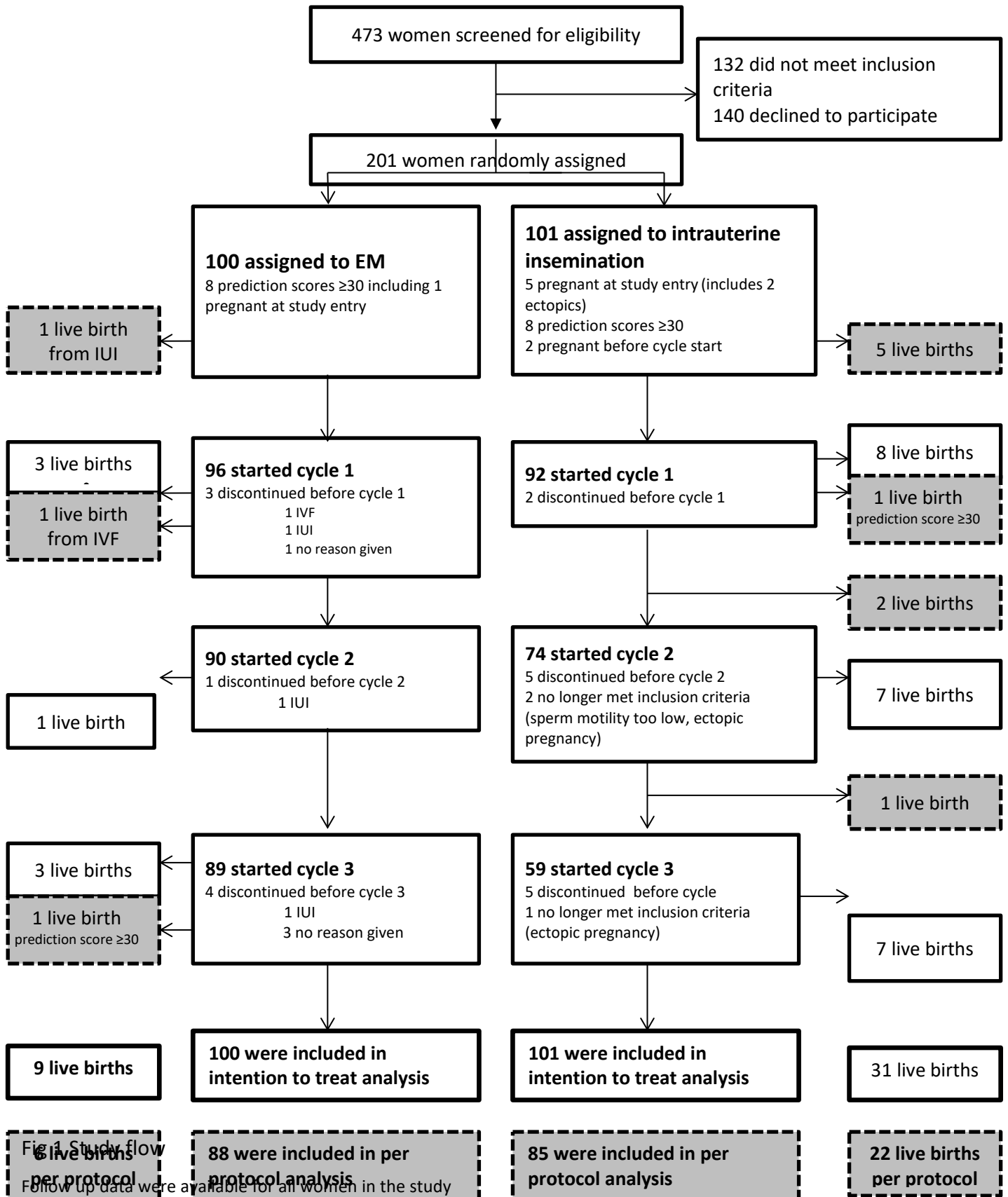


Fig 1 Study flow

Follow up data were available for all women in the study

For the per protocol analysis all data from women who were ineligible (pregnant at study entry, prediction scores ≥ 30) or had off protocol treatments such as IVF or IUI in EM group and natural conceptions in IUI group) were excluded and are in the shaded boxes.

IUI – intrauterine insemination, EM – expectant management, IVF – in vitro fertilisation

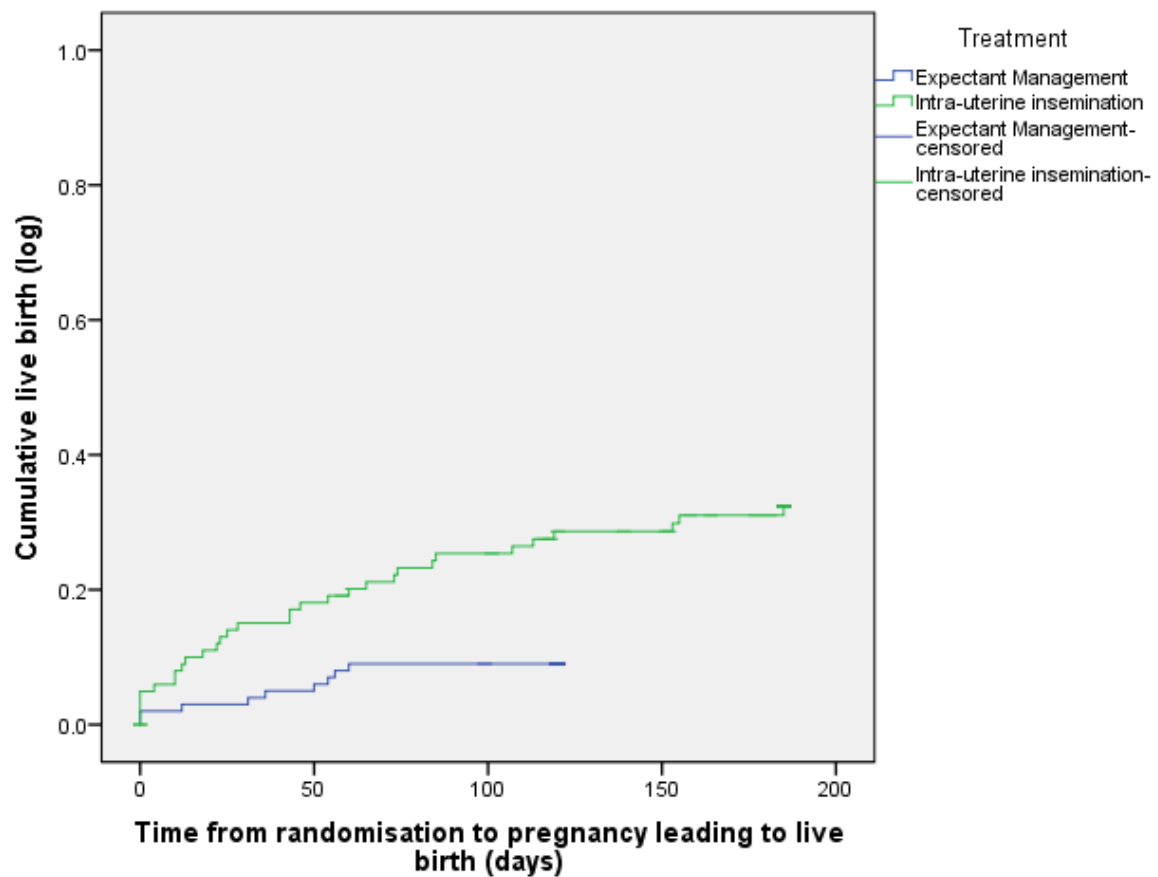


Fig. 2a: Time to pregnancy leading to live birth in groups allocated to IUI-CC and EM. For women with live birth, time to event was defined as the number of days between randomisation and the estimated date of the last menstrual period. Women without live birth were censored at end of their follow up at 185 days for IUI and for EM at the end of three menstrual cycles at 120 days. All data included.

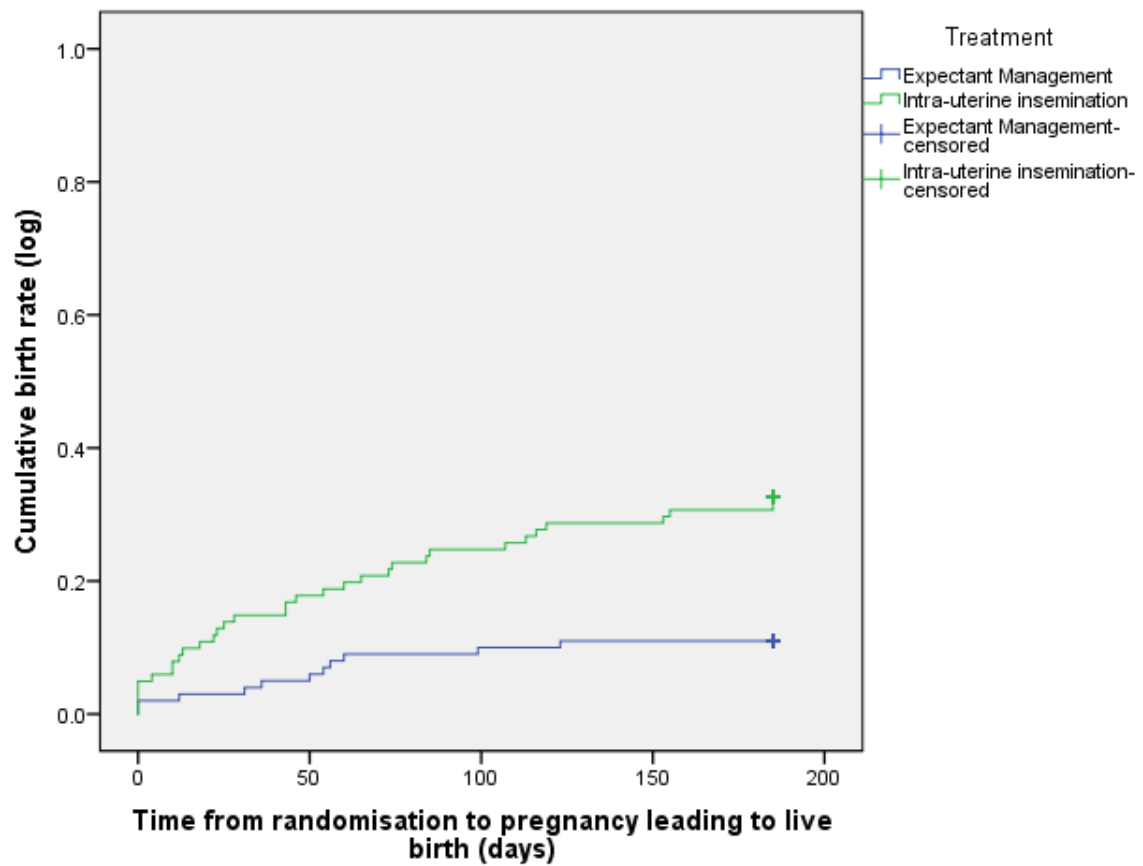


Fig. 2b: Time to pregnancy leading to live birth in groups allocated to IUI-CC and EM. For women with live birth, time to event was defined as the number of days between randomisation and the estimated date of the last menstrual period. Women without live birth were censored at end of their follow up at 185 days for IUI and EM. All data included.

Table 1. Baseline characteristics of participants*		
Characteristic	Intrauterine insemination (n = 101)	Expectant management (n = 100)
Biometric features		
Age - years	34.4±3.5	33.6±3.7
Body mass indices [§]	24.1±4.0	24.0±4.5
Smoking (ever) – no. (%)	18 (17.8%)	19 (19.0%)
Ethnicity - no. (%) [#]		
European	54 (53%)	52 (52%)
Maori	1 (<1%)	3 (3%)
Pacific	2 (2%)	2 (2%)
Asian/Chinese/Indian/Other Asian	38 (38%)	37 (37%)
Other	6 (6%)	6 (6%)
Fertility history		
Duration of infertility - months [⌘]	41.0 (31.0 to 60.0)	46.0 (27.8 to 60.0)
Previous live births - no. (%)	9/101 (9%)	16/100 (16%)
Previous IUI - no. (%)	21/101 (21%)	12/100 (12%)
Previous IVF cycles - no. (%)	5/101 (5%)	4/100 (4%)
Anovulatory polycystic ovarian syndrome - no. (%)	4/101	6/100
Endometriosis (mild) - no. (%)	13/101	7/100
Anti-mullerian hormone pmol/L	19.5±17.6	26.2±24.7
Prediction score % ^x	21.6 ±6.7	23.1±7.1
Semen parameters		
Sperm concentration x 10 ⁶ [⌘]	54.0 (29.0 to 88.0)	64.5 (30.5 to 105.0)
Sperm motility (%)	54.0±15.8	51.9 ± 14.3

*Plus-minus values are means ±SD.

Numbers of women include those who discontinued treatment. There are no missing data apart from AMH levels (6 women in IUI group and 7 women in EM group). Differences between the groups were compared with the use of the Student's t-test for means, the Kruskal-Wallis test for medians and the chi-square test for proportions where appropriate. No significant differences between the groups except for AMH (p = 0.03).

[§] BMI denotes body mass index (weight divided by the square of the height in meters) and IQR interquartile range.

[#] Ethnicity was self-reported

⌘ Median values and numbers in brackets are interquartile range

^x Using the Hunault score based on a model assessing the chance of spontaneous pregnancy in infertile couples with unexplained infertility. Factors in the model are women's age, length of infertility, any prior pregnancy, source of referral and sperm motility. Higher scores indicate a better chance of natural conception.¹²

Table 2. Pregnancy outcomes									
	Expectant management (n = 100)				Intrauterine insemination (n = 101)				
	Cycle 1	Cycle 2	Cycle 3	Total	Cycle 1	Cycle 2	Cycle 3	Total	RR (95%CI)
Live birth	5 ¹	1	3	9	16 ^{2,3}	8 ⁴	7	31	3.41 (1.71, 6.79)*
Clinical pregnancy	6	1	4	11	21	8	8	37	3.33 (1.80, 6.15)
Miscarriage	1	0	0	1	5	0	1	6	5.94 [0.73, 48.46]
Multiple pregnancies	0	0	0	0	0	1	1	2	4.95 (0.24, 101.85)
Stillbirth	0	0	1	1	0	0	0	0	0.33 (0.01, 8.01)
Ectopic	0	0	0	0	2 ⁵	1	1	4	8.91 (0.49, 163.39)

There are no missing data.

*p-values P<0.001

¹One live birth from IUI who was pregnant at study entry and one live birth from IVF in cycle 1

²Includes three unrecognised pregnancies at study entry and two prior to cycle start

³Two natural pregnancies between cycles 1 and 2

⁴One natural pregnancy between cycles 2 and 3

⁵Two ectopic pregnancies at study entry

Table 3: Live births by different intention to treat and per protocol analyses

	Intrauterine insemination			Expectant management			RR (95% CI)
	N	n	%	N	n	%	
Intention to treat analysis	101	31	30.7	100	9	9.0	3.41 (1.71, 6.79)
Intention to treat analysis excluding ineligible women at randomisation [§]	88	26	29.5	92	7	7.6	3.88 (1.78, 8.49)
Per protocol analysis*	85	22	25.8	88	6	6.8	3.80 (1.62, 8.90)
<i>Post-hoc</i> strict per protocol analysis [#]	82	19	23.2	88	6	6.8	3.40 (1.43, 8.09)
<i>Post-hoc</i> intention to treat analysis - 120 days [⌘]	101	25	24.8	100	9	9.0	2.75 (1.35, 5.59)
<i>Post-hoc</i> intention to treat analysis -185 days [§]	101	33	31.7	100	11	11.0	2.97 (1.59, 5.54)

There are no missing data.

All p-values <0.001

[§]Protocol breaches at study entry were unrecognised pregnancies (3 live births and 2 ectopic pregnancies in IUI group, 1 in EM who had IUI) and women with prediction scores ≥30% (8 IUI with two live births – one natural conception and one IUI, 8 EM with two live births - one from IVF and one from IUI who was also pregnant at study entry)

*Excluded 16 women in IUI group: 5 with unrecognised pregnancies at study entry, 5 with natural conception and 8 women with prediction scores ≥30% (includes one natural conception and one pregnant with IUI). Excluded 12 women in the EM group: 8 women with prediction scores ≥30% (includes one pregnancy from IUI at study entry and one pregnant from IVF in cycle 1) and an additional 4 women who received IUI or IVF.

[#]Additionally excluded - three women with live births who had CC only in the IUI group

[⌘]120 days after randomisation - data collection complete.

[§]185 days after randomisation – data collection complete. There were two additional live births in the EM group (one natural conception, one from IVF) and there were two additional live births in the IUI group (one natural conception, one from IUI).

Table 4. Treatment cycle characteristics for women undergoing intrauterine insemination

	Cycle 1 ¹	Cycle 2 ¹	Cycle 3	Total
Total number of motile sperm inseminated x 10 ⁶ ⌘	14.0 (6.0-36.0) (n=90)	18.0 (7.25-34.0) (n=74)	17.0 (9.4-32.0) (n=59)	16.6 (7.0-34.2) (n=223)
Estradiol level –pg/ml ² ⌘	340.3 (196.9-602.5) (n= 88)	429.5 (267.6-652.1) (n = 72)	371.6 (228.4-665.8) (n = 59)	394.4 (223.9-650.5) (n=219)
Number of follicles >16mm ± SD [#]	1.52 ± 0.85 (n=75)	1.59 ± 0.93 (n=44)	1.48 ± 0.88 (n= 44)	1.53 ± 0.91 n = 163
Live birth rate per inseminated cycle [§]	9/90 (10.0%)	7/77 (9.1%)	7/59 (11.9%)	23/230 (10.0%)

¹Two women started IUI cycle 1 but did not have insemination (no motility in one, and patient choice in the other) and in cycle 2 three women took clomiphene citrate only but did not have IUI (two were cancelled cycles for over response)

⌘ Median values and numbers in brackets are interquartile range

[#] Plus-minus values are means ± SD, the difference between the denominators for estradiol or follicles is because they were not measured according to local policy

[§]The live birth rate per cycle was similar between the two clinics (11% and 9%).
Frozen sperm was used in two cycles.