Intrauterine insemination

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ARTICLE

Intrauterine insemination: simultaneous with or 36 h after HCG? A randomized clinical trial

BIOGRAPHY

Odette Rijsdijk began this randomized clinical trial on intrauterine insemination during her specialization in obstetrics and gynaecology at the Maastricht University Medical Centre. She completed her specialization in 2016, and is currently working as a gynaecologist at Regional Spital Emmental in Switzerland.

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KEY MESSAGE

This multicentre randomized controlled trial did not demonstrate that intrauterine insemination carried out at point of HCG-triggering increases pregnancy rates compared with intrauterine insemination carried out around the time of ovulation.

ABSTRACT

Research question: Does intrauterine insemination (IUI) carried out simultaneously with HCG triggering ('simultaneous IUI') increase the ongoing pregnancy rate compared with IUI 32–36 h after HCG triggering ('regular IUI')?

Study design: An open-label randomized clinical trial was conducted in seven Dutch fertility clinics. One hundred and sixty-six couples were randomized to receive simultaneous IUI and 208 couples to receive regular IUI. Treatment was allocated using a computer-based randomization algorithm using sealed opaque envelopes. Data were analysed according to the intention-to-treat principle. Couples with unexplained or mild-to-moderate male factor subfertility were eligible. Exclusion criteria were female age 42 years or older, female body mass index 35 kg/m^2 or over, double-sided tubal pathology or severe male factor subfertility. Mild ovarian stimulation was carried out by subcutaneous FSH self-administration. 'Simultaneous IUI' was carried out at the point of HCG triggering for ovulation. 'Regular IUI' was carried out 32–36 h after HCG triggering.

Results: The cumulative ongoing pregnancy rate after a maximum of four cycles was 26.2% for simultaneous IUI (43 ongoing pregnancies) and 33.7% for regular IUI (70 ongoing pregnancies) (RR 0.78 95% CI 0.57 to 1.07). Ongoing pregnancy rates per cycle in the simultaneous IUI group were 6.8%, 10.5%, 9.5% and 7.4% for the first, second, third and fourth IUI cycle. In the regular IUI group, ongoing pregnancy rates were 8.3%, 16.4%, 13.5% and 9.0% for the first, second, third and fourth IUI cycle.

Conclusions: This multicentre randomized controlled trial did not demonstrate that IUI carried out at the point of HCG triggering increases pregnancy rates compared with IUI carried out around the time of ovulation.

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KEYWORDS

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Subfertility
Timing of insemination

INTRODUCTION

Intrauterine insemination (IUI) is a widely used treatment modality for couples with unexplained subfertility and mild male factor subfertility (*ESHRE Capri Workshop, 2009; Cohlen et al., 2018*). Over 175,000 cycles of IUI using partner semen were reported to the European IVF-Monitoring Consortium in 2013 (*Calhaz-Jorge et al., 2017*). Pregnancy rates per cycle vary between 7 and 12% (*Steures et al., 2007*; *ESHRE Capri Workshop, 2009; Calhaz-Jorge et al., 2017*).

The rationale behind IUI is to increase the gamete density at the site of fertilization by bypassing the cervix (*Cohlen et al., 2018*). It can be carried out with or without mild ovarian stimulation (MOS). In couples with unexplained subfertility, IUI in natural cycles is inferior to IUI with MOS (OR 0.48, 95% CI 0.29 to 0.82) (*Veltman-Verhulst et al., 2016*). In couples with mild male factor subfertility, no significant difference was found in pregnancy rate (OR 1.68, 95% CI 1.00 to 2.82) or live birth rate (OR 1.34, 95% CI 0.77 to 2.33) between IUI with MOS and IUI in a natural cycle (*Cissen et al., 2016*).

Although IUI is a common treatment, timing of IUI is still under debate. The first successful outcome of IUI was reported by *Yovich and Matson (1986)*. Initially, inseminations were carried out over 3 days of the periovulatory period, after ovarian stimulation, beginning the day after triggering ovulation to match vaginal insemination protocols. Current practice in most clinics offering IUI with MOS is to administer HCG for triggering ovulation when the largest follicle has reached a diameter of 16–18 mm, followed by IUI 32–36 h later, i.e. at the expected time of ovulation. Clinical studies to support this 32–36 h interval between HCG and IUI, however, are scarce (*Cantineau et al., 2014*). Studies on pregnancy rates relative to the time interval of a short (24–34 h) and long (36–48 h) interval between HCG administration and IUI did not show significant differences (*Claman et al., 2004; Robb et al., 2004; AboulGheit, 2010; Rahman et al., 2011*).

In non-subfertile couples trying to conceive, highest pregnancy rates were found when couples had intercourse between 1 and 2 days before ovulation and a chance of almost zero after ovulation, which is biologically plausible because spermatozoa should be available in the female reproductive tract before ovulation (*Dunson et al., 1999; 2002*). In a retrospective study (*Järvelä et al., 2010*), pregnancy rates were compared in IUI with MOS cycles when IUI was carried out 24–36 h after HCG (228 cycles) with IUI carried out 3–5 min after HCG (104 cycles). Pregnancy rates were 10.9% and 19.6% ($P = 0.04$), respectively.

On the basis of biological plausibility, and as confirmed by the study by *Järvelä et al. (2010)*, we hypothesized that, in order to achieve best pregnancy chances, the timing of IUI might be better well before ovulation (as triggered by HCG administration), rather than at the expected time of ovulation.

We designed a multicentre randomized controlled trial (RCT) to compare simultaneous IUI (at the point of HCG) with regular IUI (32–36 h after HCG).

MATERIALS AND METHODS

Study design and population

We conducted a multicentre RCT in couples with unexplained or mild-to-moderate male factor subfertility. The trial was registered at Portal Toetsing Online Kenmerk (NL39738.068.12). The study protocol was approved by the local Medical Ethical Committee on 31 October 2012 (reference: METC 12-2-057.7/ivb). The first patient was enrolled 13 February 2013, and the last patient 24 May 2016.

Participants were recruited from hospitals across the Netherlands (two university teaching hospitals, three non-university teaching hospitals and two non-university hospitals). They all underwent basic fertility investigation. This included menstrual cycle analysis, semen analysis and tubal testing (chlamydia antibody titre, hysterosalpingography, laparoscopy and dye test, or a combination of tests). If the Chlamydia antibody titre was negative, this indicated absence of tubal pathology, and further tubal testing was optional. After the basic fertility investigation, couples with unexplained subfertility and an estimated spontaneous pregnancy chance of less than 30% in the following year according to the prognostic model of Hunault (*Van der Steeg et al., 2007*), couples with an estimated spontaneous chance of over 30% without conceiving after at least 6 months of expectant management, and couples with mild-to-moderate male factor subfertility who were eligible for IUI with MOS, were invited to participate in the trial. Couples with anovulatory cycles who did not conceive after 1 year of ovulation induction were classified as unexplained subfertility.

Mild male subfertility was defined as a total motile sperm count (TMSC) of 3–10 million (multiplying volume of the ejaculate in milliliters by sperm concentration and the proportion of A [fast forward progressive] plus B [slowly progressive] motile spermatozoa divided by 100% (*Hamilton et al., 2015*). Moderate male subfertility was defined as a TMSC of 1–3 million as defined by the national guidelines provided by the Dutch Society for Obstetrics and Gynaecology (*Dutch Society for Obstetrics and Gynaecology, 2010*).

Eligibility criteria

Couples with unexplained or mild to moderate male factor subfertility as described above were eligible for inclusion in this RCT. Exclusion criteria were female age 42 years or older, female body mass index 35 kg/m^2 or over, double-sided tubal pathology or severe male factor subfertility (TMSC less than 1 million in repeated semen analyses). Couples who had already started IUI with MOS were not eligible for this study.

The gynaecologist, fertility doctor or fertility nurse identified eligible couples and provided them with verbal and written information about the study. After obtaining written informed consent, and before starting the first IUI with MOS cycle, couples were enrolled into the study.

Randomization procedure

Treatment was allocated using a computer-based randomization algorithm on a 1:1 base for each centre separately. Stratified or block randomization was not used in view of the relatively large study population. Allocation concealment was ensured by using opaque sequentially numbered envelopes, which remained sealed until treatment allocation. The study was not blinded and not placebo-controlled, because pregnancy was the end-point and knowledge, by the couple or the doctor, of the treatment strategy

was not presumed to influence this unambiguous end-point.

Treatment procedures

In both study groups, MOS occurred by subcutaneous administration of FSH (Fostimon®, Gonal-F®, Menopur® or Puregon®), according to local protocol and, if applicable, adapted on the basis of results of previous MOS cycles, starting on cycle day 3–5. The maximum acceptable number of follicles measuring 14 mm or wider was three: in case of more than three follicles over 14 mm, the cycle was cancelled. Couples were randomized for a maximum of four consecutive cycles.

Couples randomized to receive simultaneous IUI underwent IUI the day after the largest follicle had reached 16–18 mm, simultaneously with the administration of HCG subcutaneously (5000 IU Pregnyl® or 6500 IU ml Ovitrelle®). For logistic reasons, simultaneous IUI on the day of the last ultrasound was not possible. Couples randomized to receive regular IUI had HCG administered subcutaneously (5000 IU Pregnyl® or 6500 IU Ovitrelle®) when the largest follicle had reached a diameter of 16–18 mm, followed by IUI 32–36 h later. The side of ovulation was not reported. No luteal phase support was prescribed.

Semen preparation

Fresh semen was produced by the partner by masturbation and collected for insemination within 1 h after production. Semen samples were subjected to a density gradient centrifugation method using PureSperm (Nidacon, Gothenburg, Sweden) according to local protocol of the participating clinic. Semen was evaluated before and after processing. No recommendations on ejaculatory abstinence were made during treatment, and couples were not dissuaded from unprotected intercourse.

During each cycle, all couples were invited to complete a questionnaire about factors potentially influencing pregnancy rate, e.g. weight, smoking and frequency and timing of intercourse during treatment.

Outcome

The primary outcome was the ongoing pregnancy rate after a maximum of four cycles of IUI and MOS. Ongoing pregnancy rate was defined as a pregnancy with fetal cardiac activity visualized on ultrasound at 12 weeks of gestation. Secondary outcomes were ongoing pregnancy rate per cycle, ongoing pregnancy rate per type of subfertility, miscarriage rate (defined as a non-vital intrauterine pregnancy before 12 weeks of pregnancy), multiple pregnancy rate, live birth rate and adverse events.

Statistical analysis

Data were analysed according to the intention-to-treat principle. SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used for all statistical analyses. Relative risks were calculated with 95% CI. $P < 0.05$ was considered to reflect statistical significance. A multivariate logistic regression analysis containing possible confounders was conducted.

Sample size

A difference between ongoing pregnancy rates in the first regular IUI cycle versus the first simultaneous IUI cycle of 10% versus 17.5% (and 21.8% versus 35.7% per treatment strategy of a maximum of four IUI cycles) was considered to be clinically relevant. For our sample size calculation, it was assumed that ongoing pregnancy rate would decrease by 25% per cycle and that study- and treatment drop-out between cycles would be 10–15% combined. It was calculated that 179 couples would be required in each study arm to demonstrate a significant difference in ongoing pregnancy rates, with a two-sided alpha of 5% and a beta of 20%.

RESULTS

Study population

Between February 2013 and May 2016, 374 couples were included in this study. One hundred and sixty-six couples were randomized to receive simultaneous IUI and 208 couples to receive regular IUI. After randomization, two couples, both in the simultaneous IUI group, were excluded from the analysis (one because of starting clomiphene citrate with IUI and one because of previous participation in the study). Six couples were pregnant at randomization (two in the simultaneous and four in the regular IUI group). The selection process is presented in FIGURE 1. Drop-out rates after the first cycle in the simultaneous IUI group varied between 6.2 and 12.4% per cycle (total drop-out rate 21.3% [35 couples]). In the regular IUI group, drop-out rates after the first cycle varied between 8.3 and 14.4% per cycle (total drop-out rate 26.0% [54 couples[). Drop-out rates and reasons for drop-out per cycle per treatment strategy are shown in Supplementary FIGURE 1 and Supplementary FIGURE 2. Baseline characteristics of the two groups are shown in TABLE 1.

Cycle characteristics

A total of 1039 cycles were carried out (481 in the simultaneous IUI group and 558 in the regular IUI group). No important differences were observed in the FSH starting dose (simultaneous group 25–150 IU [median 75 IU]; regular group 25–125 IU [median 75 IU]); total dose of FSH per cycle (simultaneous group 150–2850 IU [median 525 IU]; regular group 75–5100 IU [median 600 IU]); duration of stimulation (median 7–8 days); endometrial thickness (average 8.5 to 8.7 mm) and post-wash TMSC (median 5.6 to 8.1 million) between cycles and between the two treatment strategies.

In the simultaneous IUI group, 68.2% of the cycles had monofollicular growth (328 out of 481 cycles), 28.7% had multifollicular growth (138 of 481 cycles) and, in 3.1%, the number of follicles was unknown (15 of 481 cycles). In the regular IUI group, 68.6% of the cycles were monofollicular (383 of 558 cycles), 28.1% were multifollicular (157 of 558 cycles) and, in 3.2%, the number of follicles was unknown (18 of 558 cycles). The differences were not significant. No cycles produced ovarian hyperstimulation syndrome.

Outcomes

The ongoing pregnancy rate after a maximum of four cycles was 26.2% for simultaneous IUI (43 ongoing pregnancies) and 33.7% for regular IUI (70 ongoing pregnancies) (RR 0.78 95% CI 0.57 to 1.07)) (Supplementary TABLE 1). The cumulative ongoing pregnancy rate per treatment strategy is shown in FIGURE 2.

Live birth rates were comparable between the two groups (Supplementary TABLE 1). One premature intrauterine fetal death was reported in the regular IUI group. Miscarriage rates were 7.3% (12 couples) in the simultaneous IUI group and 7.2% (15 couples) in the regular IUI group. Two (ectopic) pregnancies of unknown location occurred, one in each group.

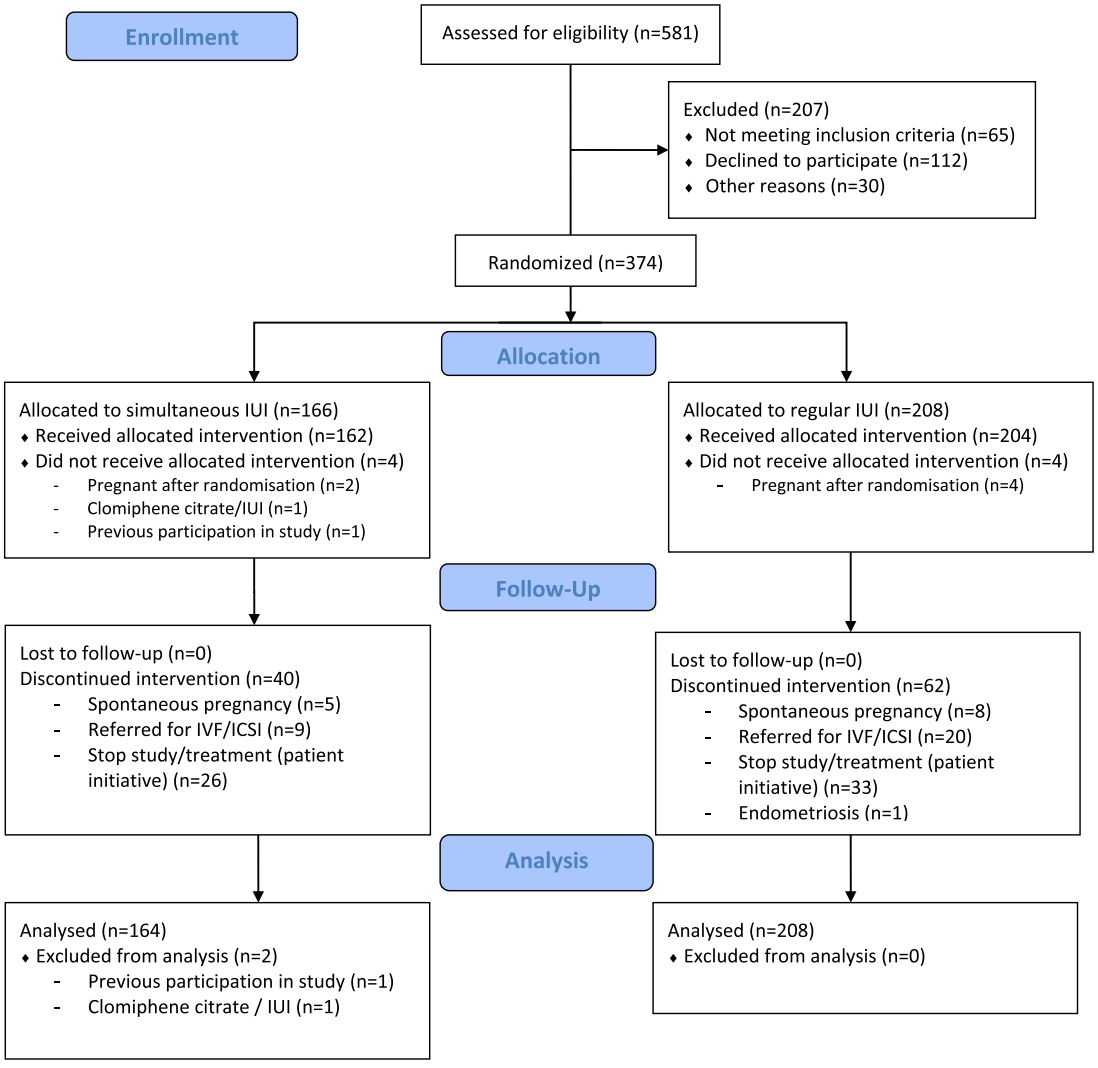

FIGURE 1 Consort 2010 Flow Diagram.

In the simultaneous IUI group, ongoing pregnancy rates in monofollicular and multifollicular cycles were 7.6% (25 out of 328 cycles) and 8.7% (12 out of 138 cycles), respectively; one pregnancy had an unknown number of follicles. In the regular IUI group, ongoing pregnancy rates in monofollicular and multifollicular cycles were 10.2% (39 of 383 cycles) and 12.1% (19 of 157 cycles), respectively.

Overall, four twin pregnancies occurred: one in the simultaneous IUI group (in a cycle with bifollicular growth) and three in the regular IUI group (one in a cycle with monofollicular growth and two in cycles with multifollicular growth).

Ongoing pregnancy rates per cycle in the simultaneous IUI group were 6.8%, 10.5%, 9.5% and 7.4% for the first, second, third and fourth IUI cycle. In the regular IUI group, ongoing pregnancy rates were 8.3%, 16.4%, 13.5% and 9.0% for the first, second, third and fourth IUI cycle (Supplementary **TABLE 2**). The cumulative ongoing pregnancy rate in the unexplained subfertility group was 27.9% (38 of 136 couples) for simultaneous IUI and 32.3% (53 of 164 couples) for regular IUI (RR 0.89 95% CI 0.67 to 1.18).

In the male factor subfertility group, the cumulative ongoing pregnancy rate was 17.9% (five out of 28 couples) for simultaneous IUI and 38.6% (17 out of 44 couples) for regular IUI (RR 0.46; 95% CI 0.19 to 1.11).

A multivariate logistic regression containing predictors known to influence pregnancy rates was conducted, i.e. maternal age, type of subfertility (primary versus secondary), duration of subfertility, mild versus moderate male factor subfertility, bilateral versus unilateral tubal patency and negative versus positive chlamydia antibody titre. Odds ratios for the treatment group were compared with that of a logistic model containing only treatment group as an independent variable. The odds ratios were only slightly different (0.699 and 0.686, respectively, a 2% difference) and both statistically non-significant, which indicates that results were not attributable to baseline differences.

The response rate on the questionnaire on timing of intercourse during treatment was 31.1% (51 of 164 couples) in the simultaneous IUI group and 28.8% (60 of 208 couples) in the regular IUI group. Of all pregnant couples who responded to the questionnaire, 35% (six out of 17 couples) in the simultaneous IUI group and 50% (11 out of 22 couples) in the regular IUI group had intercourse about 36 h after HCG

TABLE I STUDY POPULATION: BASELINE CHARACTERISTICS

Characteristic	*Simultaneous IUI(n = 164)*	*Regular IUI(n = 208)*
Mean age of female partner (years ± SD)[a]	33.3 (3.9)	33.3 (4.0)
Mean age of male partner (years ± SD)[a]	35.9 (5.1)	35.8 (6.0)
BMI (kg/m^2) at fertility work-up	24.3	24.8
Type of subfertility		
Primary	115 (70.1)	137 (65.9)
Secondary	49 (29.9)	71 (34.1)
Duration of subfertility (years ± SD)[a]	2.5 (1.4)	2.3 (1.1)
Median (interquartile range 25–75) TMSC[b] at fertility workup (10^6)	21.1 (7.1-53.7)	26.0 (9.4-80.4)
Tubal patency, *n* (%)		
Chlamydia antibody titre		
Negative	133 (81.1)	176 (84.6)
Positive	23 (14.0)	20 (9.6)
Unknown	8 (4.9)	12 (5.8)
Bilateral open tubes[c]	129 (77.7)	156 (75.0)
Unilateral open tube[c]	17 (10.3)	23 (11.1)
Mean Hunault score (if applicable)[d], (%)	28.3	29.3
Cause of subfertility, *n* (%)		
Unexplained	136 (82.9)	164 (78.8)
Mild male factor[e]	22 (13.4)	40 (19.2)
Moderate male factor[f]	6 (3.7)	4 (1.9)

Values are numbers (percentages) unless stated otherwise

Percentages may not add up to 100 owing to rounding.

[a] At the start of the first intrauterine insemination treatment.

[b] Total motile sperm count (TMSC).

[c] Diagnosed by hysterosalpingography, laparoscopy with dye testing, or both.

[d] Calculated using formula by *Van der Steeg et al. (2007)*.

[e] TMSC 3–10 million.

[f] TMSC 1–3 million.

administration or on the day of HCG administration, respectively.

DISCUSSION

On the basis of evidence of the maximum probability of natural conception relative to ovulation (*Dunson et al., 1999; 2002*), it would be biologically more plausible to inseminate 1 or 2 days before ovulation to better use the biological fertility window and increase pregnancy rates. Our study did not reveal a significant difference in ongoing pregnancy rate between simultaneous IUI (26.2%) and regular IUI (33.7%) (RR 0.78 95% CI 0.57 to 1.07).

An explanation for the difference in biological fertility window between natural conception and conception with IUI and MOS is that the complex process of sperm capacitation for fertilization (*De Jonge, 2017*) is different between the natural and the IUI setting. Another possible explanation for the difference in ongoing pregnancy rates in favour of the regular IUI group is the hypothesis that sperm cells can survive for a longer time after intercourse because of storage in the cervical crypts (*Insler et al., 1980*). After bypassing the cervix in IUI, sperm cells cannot be stored in the cervical crypts and therefore sperm cells in the simultaneous IUI group may not have survived until ovulation. Others, however, hypothesized that, instead of the cervical crypts, the Fallopian tubes are more likely to be the storage site for sperm cells in humans (*Suarez and Pacey, 2006*).

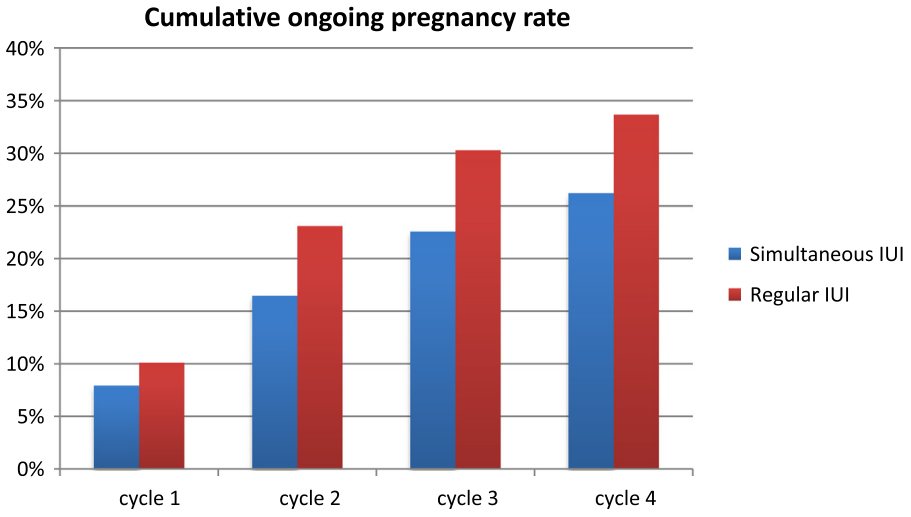

FIGURE 2 Cumulative ongoing pregnancy rate.

This study only included IUI cycles with partner's fresh semen. It might be possible that IUI programmes using frozen semen would benefit more from simultaneous IUI compared with our study population.

A limitation of the study design was that, for logistic reasons, couples who were randomized to receive simultaneous IUI underwent IUI the day after the largest follicle had reached 16–18 mm. This might explain the difference in ongoing pregnancy rates between simultaneous and regular IUI. We know that, in up to 42% of recombinant FSH-stimulated cycles, a spontaneous LH surge was detected and that this might negatively affect pregnancy rates (*Cantineau and Cohlen, 2007*). Because we did not carry out an ultrasound on the day of insemination or measure LH, it is possible that we carried out the simultaneous insemination close to or even after ovulation, explaining the lower pregnancy rate in this group. The purpose of our study was not to find the optimal follicle diameter for triggering ovulation in IUI, but to study the interval between HCG and IUI, which was either nil or 36 h.

A retrospective study (*Järvelä et al., 2010*) reported pregnancy rates (positive urinary pregnancy test) of 10.9% for regular IUI (carried out 24–36 h after HCG) and 19.6% for simultaneous IUI ($P = 0.04$). During our study recruitment, a randomized clinical study was published (*Aydin et al., 2013*), which compared 106 couples after simultaneous IUI with 106 couples after regular IUI (34–36 h after HCG). They found no significant difference in clinical pregnancy rates in the first cycle between simultaneous and regular IUI (12.2 versus 9.4%, respectively (OR 1.35, 95% CI 0.53 to 3.42).

In the mild-to-moderate male factor subfertility group, the chances of ongoing pregnancy were almost one-half in the simultaneous IUI group compared with the regular IUI group (17.9% versus 38.6%; RR 0.46, 95% CI 0.19 to 1.11). It can be hypothesized that, because of the lower sperm concentration, motility, or both, and the expected shorter survival time of these sperm cells in the female genital tract, sperm cells in the simultaneous IUI group did not survive for 36 h, i.e. the expected time of ovulation. The groups, however, were small and this study was not powered to reveal any differences in this subgroup.

The ongoing pregnancy rate in our study varied between 6.8% and 16.4% per cycle, which is comparable to pregnancy rates in previous articles (*Calhaz-Jorge et al., 2017*; *Malchau et al., 2017*).

One twin pregnancy occurred in the simultaneous IUI group and three in the regular IUI group, which is relatively low for IUI with MOS treatment. This can be explained by the large number of monofollicular-stimulated cycles. Multifollicular growth is associated with increased pregnancy rates in stimulated IUI cycles (*van Rumste et al., 2008*); however, our study still showed comparable pregnancy rates with other studies, despite the large amount of monofollicular cycles.

An unwelcome event of our study is that the couples turned out not to be evenly distributed between the two treatment regimens (166 simultaneous IUI and 208 regular IUI). Treatment was allocated using a computer-based randomization algorithm on a 1:1 base and, in view of the relatively large number of participants (2 × 179), we did not consider block randomization necessary (*Lachin, 1988*). This randomization procedure unfortunately led to unequal groups. After the study, we confirmed that, in all centres, the treatment as randomized corresponded correctly with the actual treatment. We calculated that the probability of ending up with these unevenly distributed numbers (or even more extreme) was 2.2%. Baseline characteristics, however, were comparable between the two groups, and we know no bias is introduced because unequal group sizes do not lead to biased estimates of percentages within the groups. After inclusion of all couples, we recalculated the power of our study, which was 81.57%.

Drop-out rates after the first cycle in this RCT were 21.3% in the simultaneous IUI group and 26.0% in the regular IUI group. Previous studies on drop-out rates in IUI showed drop-out rates varying between 13% (*Bensdorp et al., 2016*) and 28% (*Custers et al., 2013*). This study did not report on the side of ovulation in case of unilateral tubal patency. A recent review (*Tan et al., 2019*) showed that couples with proximal unilateral tubal block diagnosed by HSG have similar pregnancy rates after IUI with ovarian stimuation, compared with couples with bilateral tubal patency and unexplained subfertility. Patients with a distal unilateral tubal block had lower chances of pregnancy. In patients with unilateral tubal patency, it is not clear whether the side of the dominant follicle influences pregnancy rates.

It is suggested that double IUI may increase pregnancy rates by delivering more spermatozoa to the site of fertilization and fertilize more oocytes in case of multifollicular cycles; however, a meta-analysis by *Polyzos et al., (2010)* showed no difference in pregnancy rates between single or double IUI in couples with unexplained infertility. Because couples in our trial were not dissuaded to have unprotected intercourse, there is still a chance of spontaneously conceived pregnancies. We can imagine that to increase their pregnancy chances, couples had intercourse at the alternative timing moment, especially since couples were told about the chance of pregnancy at the alternative timing moment. Couples were asked to complete a questionnaire about intercourse during their treatment. Of all the pregnant couples who responded to this questionnaire, 35% in the simultaneous IUI group and 50% in the regular IUI group had intercourse at the alternative time. The response rate to this questionnaire, however, was only 28–30%, which will be biased and may not be representative of the whole study population, so no firm conclusion on the chance of spontaneously conceived pregnancies can be drawn.

In conclusion, although from the results of natural conception in the spontaneous cycle it seemed to be biologically more plausible, this multicentre RCT demonstrated that, with the timing of IUI, simultaneous IUI is not superior to regular IUI. Although the cumulative ongoing pregnancy rate did not differ statistically between the two groups (26.2% in simultaneous IUI versus 33.7% in regular IUI), the observed difference in ongoing pregnancy rate might be clinically relevant; therefore, we advise not to offer simultaneous IUI routinely in stimulated IUI-cycles.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2019.03.208.

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