IVF or IUI as first-line treatment in unexplained subfertility: the conundrum of treatment selection markers

R.I. Tjon-Kon-Fat1,*, P. Tajik1,2, M.H. Zafarmand1,3, A.J. Bensdorp1, P.M.M. Bossuyt2, G.J.E. Oosterhuis4, R. van Golde5, S. Repping1, M.D.A. Lambers6, E. Slappendel7, D. Perquin8, M.J. Pelinck9, J. Gianotten10, J.W.M. Maas11, M.J.C. Eijkemans12, F. van der Veen1, B.W. Mol13,14, and M. van Wely1 on behalf of the INeS study group†

1Department of Obstetrics and Gynaecology, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam, The Netherlands 2Department of Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands 3Department of Public Health, Academic Medical Centre, Amsterdam, The Netherlands 4Department of Obstetrics and Gynaecology, St. Antonius Hospital, Nieuwegein, The Netherlands 5Department of Obstetrics and Gynaecology, University Medical Centre Maastricht, Maastricht, The Netherlands 6Department of Obstetrics and Gynaecology, Albert Schweitzer Hospital, Dordrecht, The Netherlands 7Elisabeth Tweesteden Ziekenhuis, Centrum Voortplantingsgeneeskunde Brabant, Tilburg, The Netherlands 8Department of Obstetrics and Gynaecology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands 9Department of Obstetrics and Gynaecology, Maxima Medical Centre, Veldhoven, The Netherlands 10Department of Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands 11School of Medicine, The Robinson Institute, University of Adelaide, Adelaide, Australia 12The South Australian Health and Medical Research Institute, Adelaide, Australia

*Correspondence address. Department of Obstetrics and Gynaecology, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam, The Netherlands. E-mail: m.vanwely@amc.nl

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STUDY QUESTION: Are there treatment selection markers that could aid in identifying couples, with unexplained or mild male subfertility, who would have better chances of a healthy child with IVF with single embryo transfer (IVF-SET) than with IUI with ovarian stimulation (IUI-OS)?

SUMMARY ANSWER: We did not find any treatment selection markers that were associated with better chances of a healthy child with IVF-SET instead of IUI-OS in couples with unexplained or mild male subfertility.

WHAT IS KNOWN ALREADY: A recent trial, comparing IVF-SET to IUI-OS, found no evidence of a difference between live birth rates and multiple pregnancy rates. It was suggested that IUI-OS should remain the first-line treatment instead of IVF-SET in couples with unexplained or mild male subfertility and female age between 18 and 38 years. The question remains whether there are some couples that may have higher pregnancy chances if treated with IVF-SET instead of IUI.

STUDY DESIGN, SIZE, DURATION: We performed our analyses on data from the INeS trial, where couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception were randomly allocated to IVF-SET, IVF in a modified natural cycle or IUI-OS. In view of the aim of this study, we only used data of the comparison between IVF-SET (201 couples) and IUI-OS (207 couples).

PARTICIPANTS/MATERIALS, SETTING, METHODS: We pre-defined the following baseline characteristics as potential treatment selection markers: female age, ethnicity, smoking status, type of subfertility (primary/secondary), duration of subfertility, BMI, pre-wash total motile count and Hunault prediction score. For each potential treatment selection marker, we explored the association with the chances of a
healthy child after IVF-SET and IUI-OS and tested if there was an interaction with treatment. Given the exploratory nature of our analysis, we used a P-value of 0.1.

**MAIN RESULTS AND THE ROLE OF CHANCE:** None of the markers were associated with higher chances of a healthy child from IVF-SET compared to IUI-OS (P-value for interaction >0.10).

**LIMITATIONS, REASONS FOR CAUTION:** Since this is the first large study that looked at potential treatment selection markers for IVF-SET compared to IUI-OS, we had no data on which to base a power calculation. The sample size was limited, making it difficult to detect any smaller associations.

**WIDER IMPLICATIONS OF THE FINDINGS:** We could not identify couples with unexplained or mild male subfertility who would have had higher chances of a healthy child from immediate IVF-SET than from IUI-OS. As in the original trial IUI-OS had similar effectiveness and was less costly compared to IVF-SET, IUI-OS should remain the preferred first-line treatment in these couples.

**STUDY FUNDING/COMPETING INTEREST(S):** The study was supported by a grant from the Netherlands Organization for Health Research and Development, and a grant from the Netherlands’ association of health care insurers. There are no conflicts of interest.

**TRIAL REGISTRATION NUMBER:** The trial was registered at the Dutch trial registry (NTR939).

**Key words:** treatment selection markers / marker-treatment interaction / IUI / IVF / unexplained subfertility

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**Introduction**

Data generated by randomized controlled trials (RCTs) are seen as the highest form of evidence in clinical research (OCEBM Levels of Evidence Working Group, 2011). By their very design, the conclusions of RCTs are based on the outcomes of all couples that received the allocated intervention, overlooking the possibility that within these couples, treatment might be effective for some, but not for others (Pencina and Peterson, 2016). Awareness of this has opened up a new avenue of research into the field of precision or personalized medicine. In personalized medicine treatment selection markers, i.e. characteristics of couples that are associated with differences in effectiveness or the benefit/harm balance of treatments, are key (Tajik and Bossuyt, 2011).

IUI with ovarian stimulation (IUI-OS) is considered the first-line treatment for couples with unexplained or mild male subfertility before proceeding to more invasive technologies, i.e. IVF (The Practice Committee of the American Society for Reproductive Medicine, 2006). A recent RCT compared IVF with a single embryo transfer (SET) to IUI-OS in couples diagnosed with unexplained or mild male subfertility and a female age between 18 and 38 years and found no evidence of a difference between the treatments in live birth rates and multiple pregnancy rates (Bensdorp et al., 2015). After also taking into account the significantly higher costs for IVF-SET, the inevitable conclusion was that IUI-OS is to be preferred over IVF-SET in these couples (Tjon-Kon-Fat et al., 2015).

Yet, both after IUI-OS and IVF-SET, many couples do not achieve a pregnancy. Therefore, the question remains whether there are some couples who may have had higher pregnancy chances if treated with IVF-SET as the first-line treatment instead of IUI-OS. To date, there is only one small pilot study that looked at the association between female age, duration of subfertility and pre-wash total motile count (TMC) as potential treatment selection markers and pregnancy outcomes after IVF in relation to IUI (Tjon-Kon-Fat et al., 2016). A TMC of <110 million was associated with higher chances of ongoing pregnancy after IVF, compared with IUI-OS. The aim of the current, much larger study was to assess whether there are treatment selection markers that could aid in identifying couples who would have better chances of a healthy child with IVF-SET than with IUI-OS as first-line treatment.

**Materials and Methods**

We performed our analyses on data from the INeS trial (ISRCTN52842271 / NTR939). We randomly allocated couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception, defined as a probability of natural conception within the next 12 months of <30% as calculated with the Hunault prediction model, to IVF-SET, IVF in a modified natural cycle or IUI-OS (Bensdorp et al., 2015). Only couples with a duration of subfertility of >12 months and women between 18 and 38 years were eligible. We only used the data of the comparison IVF-SET to IUI-OS, in view of the aim of this study.

Couples allocated to IVF-SET underwent three cycles of IVF-SET, plus subsequent frozen embryo transfers, with ovarian stimulation and ovarian down regulation according to local IVF regimens. Ovarian stimulation was continued until at least two follicles of at least 18 mm had developed. Follicle aspiration took place 36 h after ovulation induction with hCG. Embryos were scored daily by morphology and embryo transfer took place on Day 3. Couples allocated to IUI-OS were offered six cycles with ovarian stimulation according to the local protocol. If more than three follicles with a diameter of at least 16 mm or more than five follicles with a diameter of 12 mm were present, the cycle was cancelled.

The primary outcome was the birth of a healthy child, resulting from a singleton pregnancy conceived within 12 months after randomization. A healthy child was defined as born at term (gestational age between 37 and 42 weeks), with a birth weight above the fifth percentile (according to the Dutch reference curves), without congenital anomalies, and a normal development up to 6 weeks after birth. All interventions within 12 months after randomization were documented.

**Statistical analysis**

We pre-defined the following baseline characteristics as potential treatment selection markers: female age, ethnicity, smoking status, type of subfertility (primary or secondary), duration of subfertility, BMI, TMC and the Hunault score. We performed a post hoc sample size calculation for each potential treatment selection marker, as this is the first study that looked...
at treatment selection markers in IVF-SET compared to IUI-OS. This sample size required varied between 900 and 19,000 couples.

For each potential marker, we explored the association between the marker and the chance of a healthy child after IVF-SET and IUI-OS and tested if there was a marker by treatment interaction. For continuous markers, we investigated the chances of a healthy child as a function of the marker using a Subpopulation Treatment Effect Pattern Plot (STEPP) (Bonetti and Gelber, 2004; Lazar et al., 2016). For binary markers, we developed logistic regression models and calculated the $P$-value of the marker by treatment interaction. We also performed the same analyses using ongoing pregnancy as main outcome.

Given the exploratory nature of our analysis, we used a more liberal $P$-value for interaction of 0.1 (Selvin, 1996). All analyses were performed based on the intention-to-treat principle. We used R for Windows (Version 3.0.1; R Foundation for Statistical Computing, Austria); STEPP analyses were done by package 'STEPP' and evaluation of the performance of binary markers was done by package 'Treatment Selection' (Janes et al., 2014). SPSS version 22.0 (IBM SPSS Statistics for Windows, 2011) was used for the descriptive analyses.

Results

We studied 408 couples of the INeS trial, of whom 201 were allocated to IVF-SET and 207 to IUI-OS. The baseline characteristics were comparable in the two groups (Table I). There were 104 (52%) couples with a healthy child born in the IVF-SET group and 97 (47%) in the IUI-OS group (RR 1.1, 95% CI: 0.91–1.3). The ongoing and multiple pregnancy rates were 60% and 6% per couple after IVF-SET and 57% and 7% per couple after IUI-OS. In the IVF-SET group, 46% of all included couples achieved an ongoing pregnancy with the allocated treatment strategy, while for 12% the pregnancies were achieved through natural conception and 9% were from additional treatments received within 12 months after randomization. The average time to pregnancy leading to a healthy child was 8.04 months for IVF-SET and 8.39 months for IUI-OS (log-rank test: $P = 0.38$).

The associations between all investigated markers and the chances of a healthy child are shown in Table II. In the couples treated with IVF-SET, primary subfertility was significantly associated with lower chances of having a healthy child. In the couples treated with IUI-OS, a Caucasian ethnicity was significantly associated with higher chances of having a healthy child. CI of the associations in the IVF-SET and IUI-OS groups overlapped. None of the markers were differentially associated with higher chances of a healthy child from IVF-SET compared to IUI-OS ($P$-values for interaction $>0.10$).

There was also no differential association between any of the markers and ongoing pregnancy rates when comparing IVF-SET and IUI-OS ($P$-values for interaction $>0.10$; Supplementary Table S2).

Discussion

We evaluated whether there is a differential effect of potential treatment selection markers on the chances of a healthy child after IVF-SET compared to IUI-OS. Although some markers showed higher chances of a healthy child after IVF-SET compared to IUI-OS, the 95% boundaries of the associations between the investigated markers and each intervention overlapped, indicating no significant difference between IVF and IUI. The treatment interaction tests could not identify any potential treatment selection markers that could indicate better chances of a healthy child with IVF-SET as first-line treatment instead of IUI-OS.

Our analysis was based on data from a RCT and therefore none of the baseline characteristics had affected the allocation of treatment. This gave us the opportunity to study the association between treatment selection markers and IVF-SET or IUI-OS without the risk of selection bias. This analysis also reflects daily clinical practice, as the couples included in the trial were allowed to receive other treatments within the timeframe of the study if they did not achieve an ongoing

<table>
<thead>
<tr>
<th>Table I</th>
<th>Characteristics of INeS trial participants.</th>
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<tbody>
<tr>
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<td>IVF-SET ($n = 201$)</td>
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<tr>
<td>Baseline characteristics</td>
<td></td>
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<tr>
<td>Mean female age, years (SD)</td>
<td>33 (3.39)</td>
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<tr>
<td>Caucasian ethnicity, $n$ (%)</td>
<td>182 (91%)</td>
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<tr>
<td>Smoking, $n$ (%)</td>
<td>45 (23%)</td>
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<tr>
<td>Primary subfertility, $n$ (%)</td>
<td>160 (80%)</td>
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<tr>
<td>Median duration of subfertility, years (IQR)</td>
<td>2.13 (1.73–3.01)</td>
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<tr>
<td>Median BMI, kg/m$^2$ (IQR)</td>
<td>23 (21–26)</td>
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<tr>
<td>Median total motile sperm count, $\times 10^6$ (IQR)</td>
<td>51 (25–100)</td>
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<tr>
<td>Mean Hunault score (SD)</td>
<td>20 (6.56)</td>
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<tr>
<td>Pregnancy outcomes</td>
<td></td>
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<tr>
<td>Healthy child, $n$ (%)</td>
<td>104 (52%)</td>
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<tr>
<td>Ongoing pregnancy, $n$ (%)</td>
<td>121 (60%)</td>
</tr>
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IQR, interquartile range. SET, single embryo transfer. There were missing values in the following variables: duration of subfertility (0.2%), Caucasian ethnicity (2.7%), smoking (1.0%), BMI (4.9%), total motile sperm count (7.1%) and Hunault score (7.8%). There were two couples lost to follow-up in the IVF-SET group and one couple lost to follow-up in the IUI-OS group. One couple in the IVF-SET group with an ongoing pregnancy could not be contacted further.
pregnancy leading to live birth after the allocated treatment. The majority of the couples achieved a pregnancy by the allocated treatment (Bensdorp et al., 2015).

Since this is the first large study that looked at potential treatment selection markers in IVF-SET compared to IUI-OS, we had no data on which to base a power calculation. Based on the data of this study, we calculated the sample size necessary to detect significant results in the chances of a healthy child after IVF-SET compared to IUI-OS for each of the pre-defined markers. These sample sizes varied between 900 and 19 000 couples, indicating the differential effect of biomarkers of pregnancy chances is likely to be small.

It has been suggested that couples with unexplained subfertility would have a shorter time to pregnancy if treated with IVF immediately (Goldman et al., 2014). Yet we did not find a statistically significant difference between time to pregnancy for IVF-SET and IUI-OS (Bensdorp et al., 2015). This could be due to the inclusion criteria, as in our study only women who were between 18 and 38 years were included, while Goldman et al. focused on women 38 years and older.

An explanation for the lack of an association between potential treatment selection markers and a differential effect of IVF-SET and IUI-OS might be the rather strict inclusion criteria of the RCT, i.e. women between 18 and 38 years old and a duration of subfertility of at least 12 months, which ensured similarity of the couples.

In conclusion, we did not identify any potential treatment selection markers indicating better chances of a healthy child with IVF-SET as first-line treatment instead of IUI-OS. IUI rather than IVF should remain the preferred first-line treatment for couples with unexplained or mild male subfertility and a female age between 18 and 38 years.

### Supplementary data

Supplementary data are available at Human Reproduction online.

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### Conflict of interest

None declared.

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