ARTICLE

Long-term follow up of couples initially randomized between immobilization and immediate mobilization subsequent to IUI

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Abstract A previous randomized clinical trial compared immobilization for 15 min with immediate mobilization subsequent to intrauterine insemination (IUI) and showed higher ongoing pregnancy rates in couples immobilizing subsequent to IUI. The current study compared the long-term effectiveness of immobilization subsequent to IUI. All couples (n = 391) included in the trial were followed for 3 years after randomization and pregnancies and treatments were recorded. After the initial trial period, couples in both groups were offered treatment according to local protocol. The primary outcome was an ongoing pregnancy during the 3 years after the initial trial. In this time period, there were 143 ongoing pregnancies in the immobilization group (n = 199 couples) and 112 ongoing pregnancies in the immediate mobilization group (n = 192). The ongoing pregnancy rates were 72% and 58%, respectively (relative risk 1.2, 95% CI 1.1–1.4). The persistent significant difference in ongoing pregnancy rates underpins the importance of immobilization after IUI. There is no valid reason to withhold women from immobilizing for 15 min after IUI.

KEYWORDS: immobilization, intrauterine insemination, long-term follow up

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Introduction

Intrauterine insemination (IUI), with or without ovarian stimulation, is a common used treatment in unexplained subfertility as well as in case of cervical factor, mild male subfertility and mild endometriosis. (Merviel et al., 2010) Various predictive factors for pregnancy after IUI have been assessed and identified (Custers et al., 2007; Merviel et al., 2010). Most predictive factors concern patient characteristics, but differences in technique are also known to influence pregnancy rates (van der Poel et al., 2010). In this respect, the current study group previously showed that 15 min of immobilization subsequent to IUI leads to significantly higher ongoing pregnancy rates than immediate mobilization (RR 1.5, 95% CI 1.1–2.2; Custers et al., 2009).

It remains unclear whether the beneficial effect of immobilization subsequent to IUI remains present after a longer period of follow up. In the fertility clinic, couples do not undergo a single intervention but can continue treatment with IVF after unsuccessful treatment with IUI. From the perspective of proper counselling of patients on their long-term pregnancy chances, it is important to know the long-term effects of IUI with or without immobilization.

This study postulated that, over a longer time period, immobilization subsequent to IUI leads to a shorter time to pregnancy but not to higher pregnancy rates. Therefore, this study assessed the long-term effect of immobilization versus immediate mobilization subsequent to IUI. To do so, a 3-year follow up of all the couples who participated in the original trial was performed.

Materials and methods

Patients

Between September 2005 and October 2007, 391 subfertile couples had been included in a randomized clinical trial performed in seven fertility clinics in the Netherlands (ISRCTN53294431) (Custers et al., 2009). Couples had been eligible for the trial if there was an indication for IUI and the woman was between 18 and 43 years of age. Couples using donor semen could also be included in the trial. No restrictions were made with regard to the use and type of ovarian stimulation during treatment cycles. A basic fertility work up was performed according to the guidelines of the Dutch Society of Obstetrics and Gynaecology. This included a medical history, cycle monitoring, transvaginal ultrasound, semen analysis, postcoital test and assessment of tubal patency.

The woman’s age, duration of subfertility and whether subfertility was primary or secondary were documented. Ovulation was confirmed by basal body temperature, mid-luteal serum progesterone or sonographic monitoring of the cycle. At least one well-timed postcoital test was performed during the basic assessment of fertility. The test was planned according to the basal body temperature curve or findings of ultrasonography. Cervical factor was diagnosed if no progressive spermatozoa were seen in five high-power fields at magnification ×400 and the total motile sperm count was >10 × 10⁶ spermatozoa/ml. Tubal pathology was assessed by a Chlamydia antibody test, a hysterosalpingogram or laparoscopy; in women with a negative Chlamydia antibody test, tubal pathology was considered to be absent. Patients had to have at least one patent tube to be eligible for the study. Ovarian endometriosis was ruled out by transvaginal ultrasound.

Male subfertility was defined as total motile sperm count >10 × 10⁶ spermatozoa/ml and unexplained subfertility as total motile sperm count more than 10 × 10⁶ spermatozoa/ml and exclusion of a cervical factor (NVOG, 2004). The treatment procedures are described in detail in the initial manuscript (Custers et al., 2009). For the current study, a 3-year follow up of the couples that had been included in the initial trial was performed.

Procedures

Couples were randomly allocated before the first insemination to 15 min immobilization after IUI or immediate mobilization after IUI. Depending on allocation, women remained in the supine position for 15 min (timed by an alarm clock) or were mobilized immediately for three treatment cycles in the trial, with a time horizon of 4 months.

After the initial study period, couples of both groups were offered further treatment according to the guidelines of the Dutch Society of Obstetrics and Gynecology (NVOG 2010). Couples with an indication for IUI usually received six, to a maximum of nine, cycles of IUI (Custers et al., 2008). If couples did not conceive after IUI, they could proceed to IVF, usually for a maximum of three cycles. Treatment with IUI was performed according to the protocol described in the initial manuscript. IVF was performed according to local protocol, which usually consisted of a long agonist or short antagonist protocol. After a miscarriage or ectopic pregnancy, IUI or IVF cycles would usually be started again for six and three cycles, respectively. After the initial trial was finished, but before the results were available, four hospitals (232 patients, of whom 171 were not pregnant after the initial trial) used immobilization subsequent to IUI. Three hospitals (159 patients, of whom 132 were not pregnant after the initial trial) asked their patients to mobilize immediately subsequent to IUI.

Follow up

Couples were followed for 3 years after randomization or until an ongoing pregnancy occurred. Data on live birth were collected when possible. Data were obtained from the medical files or, when this information was insufficient, by contacting the general practitioner of the couple.

Primary outcome measure was ongoing pregnancy within 3 years, defined as the presence of fetal cardiac activity by transvaginal sonography at gestational age of 12 weeks. Secondary outcomes were live birth, time to pregnancy and number of treatment cycles. Live birth was defined as the birth of a living neonate from at least 24 weeks onwards. The numbers of IUI and IVF cycles in both groups were recorded and ongoing pregnancy rate per cycle was calculated for both groups.
Statistical analysis

The analysis was performed according to the intention-to-treat principle: i.e. all pregnancies that occurred in the 3 years following randomization were accounted for per randomized group, independent of whether they occurred after natural conception, after IUI (with or without immobilization) or after IVF.

In the initial study, it was assumed that 15 min of immobilization would not perform worse than immediate mobilization. Therefore one-sided statistical tests were also used in the current study. Ongoing pregnancy rates and the corresponding relative risk with 95% confidence interval were calculated in each group. Fisher’s exact test was used to test for significance. Kaplan–Meier curves were plotted to visualize the differences in time to pregnancy between the two groups and log rank test was used to test for differences. A sensitivity analysis was performed by censoring couples at the moment they started IVF, using a log rank test to test for differences in this analysis.

Hazard ratios were calculated to express time to pregnancy for immobilization for 15 min with respect to immediate mobilization. Mann–Whitney U-test was used to compare the number of treatment cycles. Ongoing pregnancy rates per treatment cycle were calculated for IUI cycles during the trial, IUI cycles after the trial and IVF cycles. In all analyses, a P-value < 0.05 was used as to indicate statistical significance. Calculations were performed using PASW statistics version 18 (SPSS, Chicago, IL, USA).

Ethical approval

The institutional review board (IRB) of each included centre approved the initial randomized trial. Written informed consent was then obtained from all patients. The current follow-up study was exempt from IRB approval. The Dutch Medical Research Involving Human Subjects Act states that IRB approval is only required when patients are subjected to an intervention and thus was not mandatory for this observational study using data collected during standard care.

Results

In the initial study, 199 couples had been assigned to immobilization for 15 min after IUI and 192 couples had been assigned to immediate mobilization after IUI. Baseline characteristics at the time of randomization were comparable between both groups (Custers et al., 2009). At randomization, mean woman’s age was 33 years, mean duration of subfertility was 2.7 years and the most frequent indications were unexplained subfertility (48%), cervical subfertility (24%) and male subfertility (11%) with comparable distributions between both groups (Table 1).

At the end of the initial trial, 54 (27%) couples in the immobilization group had an ongoing pregnancy, compared with 34 (18%) couples in the immediate mobilization group, resulting in a relative risk (RR) of 1.5 (95% CI 1.1–2.2). Of these ongoing pregnancies, three did not result in a live birth: one in the immobilization group and two in the immediate mobilization group. These couples were followed again until achieving an ongoing pregnancy leading to live birth.

The remaining 306 couples were followed until they achieved an ongoing pregnancy for a maximum period of 3 years. From these 306 couples, 84 couples (39, 20% in the immobilization group and 45, 23% in the immediate mobilization group) were lost to follow up before the end of the 3-year period: the median follow-up time for these couples was 9 months in the immobilization group versus 16 months in the immediate mobilization group. These couples were included in the analysis until the last moment that it was assured that they were not pregnant.

Figure 1 presents the flow of patients throughout the 3 years of follow up. The overall number of ongoing pregnancies after 3 years was 143 (72%) in the immobilization group and 112 (58%) in the immediate mobilization group (RR 1.2, 95% CI 1.1–1.4, P = 0.003).

Overall after 3 years, treatment-independent ongoing pregnancies occurred in 25 (13%) couples in the immobilization group versus 18 (9%) in the immediate mobilization group (RR 1.3, 95% CI 0.7–2.5). There were 78 (39%) ongoing pregnancies after IUI in the immobilization group and 61 (32%) ongoing pregnancies after IUI in the immediate mobilization group, both in the 4 months of the initial trial and in subsequent IUI cycles (RR 1.2, 95% CI 0.9–1.6). There were 40 (20%) ongoing pregnancies after IVF in the immobilization group and 33 (17%) ongoing pregnancies in the immediate mobilization group (RR 1.7, 95% CI 0.8–1.8). In one pregnancy in the immobilization group, the origin was unknown.

The number of live births were 135 (68%) and 108 (56%) in the immobilization and immediate mobilization groups, respectively (RR 1.2, 95% CI 1.0–1.4, P = 0.022). Eight couples in the immobilization group and four couples in the

### Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th>Immobilization (n = 199)</th>
<th>Immediate mobilization (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman’s age (years)</td>
<td>33.9 ± 3.8</td>
</tr>
<tr>
<td>Duration of subfertility</td>
<td>2.7 ± 1.4</td>
</tr>
<tr>
<td>Primary subfertility</td>
<td></td>
</tr>
<tr>
<td>Cause of subfertility</td>
<td></td>
</tr>
<tr>
<td>Cervical factor</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Male factor</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Unexplained</td>
<td>101 (51)</td>
</tr>
<tr>
<td>Anovulation</td>
<td>5 (3)</td>
</tr>
<tr>
<td>One-sided tubal pathology</td>
<td>11 (6)</td>
</tr>
<tr>
<td>More than one diagnosis</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Use of donor semen</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Use of ovarian stimulation</td>
<td>118 (59)</td>
</tr>
<tr>
<td>Clomiphene citrate</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Recombinant FSH</td>
<td>91 (46)</td>
</tr>
<tr>
<td>Gonadotrophin-releasing hormone</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Prognosis on natural conception within 1 year</td>
<td>27</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Adapted from Custers et al. (2009).

*Total motile sperm count <10 x 10⁶ spermatozoa/ml.*
immediate mobilization group were lost to follow up after at least 12 weeks of pregnancy.

Time to ongoing pregnancy was 15 months (95% CI 13–17) in the immobilization group versus 19 months (95% CI 17–22) in the immediate mobilization group ($P = 0.001$; Figure 2). Sensitivity analysis, performed by censoring couples at the start of IVF, showed a mean time to ongoing pregnancy of 18 months (95% CI 15–20) versus 23 months (95% CI 20–25, $P = 0.015$). The hazard ratio expressing time to pregnancy for a period of 3 years was 1.5 (95% CI 1.2–1.9).

The total numbers of IUI and IVF treatment cycles performed since randomization were comparable in both groups (Table 2). In the immobilization group, 864 IUI cycles leading to insemination took place in 3 years compared with 875 IUI cycles leading to insemination in the immediate mobilization group. Ongoing pregnancy rates per cycle during the trial were 11% (47 ongoing pregnancies/442 cycles) and 6% (29 ongoing pregnancies/453 cycles) for the immobilization and the immediate mobilization groups, respectively. In IUI cycles performed after the trial period, ongoing pregnancy rates per cycle were 7% (29 ongoing pregnancies/422 cycles) and 8% (34 ongoing pregnancies/422 cycles) for the immobilization and the immediate mobilization groups, respectively.

With respect to IVF, 166 cycles were started in the immobilization group, compared with 165 in the immediate mobilization group. Ongoing pregnancy rates per started IVF cycle were 24% (39 ongoing pregnancies) and 20% (33 ongoing pregnancies) for the immobilization and the immediate mobilization groups, respectively.

**Discussion**

This study compared the long-term effect of three cycles of IUI with 15 min of immobilization to three cycles of IUI with immediate mobilization. The ongoing pregnancy rate after 3 years was significantly higher in the immobilization group.

![Figure 1](https://example.com/figure1.jpg)  
**Figure 1** Flowchart of treatment and pregnancy outcome.
Also, time to pregnancy was significantly shorter in the immobilization group. The strength of this study is that it followed a treatment protocol with intention-to-treat analysis over a long period, in which couples were able to complete six cycles of IUI with ovarian stimulation followed by three cycles of IVF, if necessary. Therefore, this study reflects daily practice and the results should be applicable to all couples with an indication for IUI treatment.

In the literature, long-term ongoing pregnancy rates of subfertile couples range from 50% to 73% (Brandes et al., 2010; Custers et al., 2012; Donckers et al., 2011; Pinborg et al., 2009). The current study found 3-year ongoing pregnancy rates of 72% and 58% respectively, which corresponds well to the previously reported rates. The women only underwent laparoscopy in case of suspected tubal pathology and, therefore, the presence of endometriosis was not investigated in all of them. In theory, misclassification of these couples as unexplained subfertility could have taken place. Previous studies have confirmed that medical history and Chlamydia antibody testing are well able to select couples at risk for tubal pathology and the theoretical misclassification of couples with tubal pathology to unexplained subfertility is therefore not likely (Coppus et al., 2007a,b).

A limitation of this study is that a considerable proportion of couples was not followed for 3 years. However, these couples were followed 9 and 16 months in the immobilization versus immediate mobilization groups, respectively. Follow up in the immediate mobilization group was longer without reaching a higher pregnancy rate, which is another indication of a real difference in pregnancy rates. Moreover, lost-to-follow-up rates were similar between the groups. Furthermore, the Kaplan–Meier analysis, which accounted for this incomplete follow up, also showed a significant difference in pregnancy rates.

Although equal treatment protocols were applied after the initial trial, a difference in pregnancy rates between the groups remained over time. Therefore, immobilization subsequent to IUI not only shortens time to pregnancy as postulated but also increases pregnancy rates in the long run. Several factors in the execution of IUI, such as timing of insemination and number of follicles obtained, are assumed to influence pregnancy chances (Merviel et al., 2010). Nevertheless, it is unlikely that these differ between both groups as the initial study was a randomized clinical trial and baseline characteristics were comparable. Furthermore, stratification took place per clinic, making a fair distribution of couples per local protocol regarding immobilization after the trial. This study was not able to gain individual information about whether or not women were immobilized subsequent to the IUI cycles that took place after the initial study period. Therefore, this study can only draw conclusions on the cycles within the initial study.

Although this study cannot present a clear biological rationale for the data, the significant difference in ongoing pregnancy rates persists in the long run and underpins the importance of immobilization after IUI. Unless new well-designed and adequately powered trials challenge these findings, there is no valid reason to withhold women from immobilizing for 15 min after IUI.

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Coppus, S.F., Opmeer, B.C., Logan, S., van der Veen, F., Bhattacharya, S., Mol, B.W., 2007a. The predictive value of


Declaration: The authors report no financial or commercial conflicts of interest.

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