

# Intrauterine insemination or intracervical insemination with cryopreserved donor sperm in the natural cycle: a cohort study

P.A.L. Kop<sup>1</sup>, M. van Wely<sup>1</sup>, B.W. Mol<sup>2</sup>, A.A. de Melker<sup>1</sup>, P.M.W. Janssens<sup>3,4</sup>, B. Arends<sup>5</sup>, M.H.J.M. Curfs<sup>6</sup>, M. Kortman<sup>7</sup>, A. Nap<sup>3,4</sup>, E. Rijnders<sup>8</sup>, J.P.W.R. Roovers<sup>1</sup>, H. Ruis<sup>9</sup>, A.H.M. Simons<sup>10</sup>, S. Repping<sup>1</sup>, F. van der Veen<sup>1</sup>, and M.H. Mochtar<sup>1,\*</sup>

<sup>1</sup>Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands <sup>2</sup>The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia, Australia <sup>3</sup>Department of Clinical Chemistry and Haematology/Semenbank, Rijnstate Hospital, Arnhem, The Netherlands <sup>4</sup>Department of Obstetrics and Gynaecology, Rijnstate Hospital, Arnhem, The Netherlands <sup>5</sup>MCK Fertility Centre, Leiden, The Netherlands <sup>6</sup>Isala Fertility Centre, Zwolle, The Netherlands <sup>7</sup>Department of Obstetrics and Gynaecology, University Medical Centre Utrecht, Utrecht, The Netherlands <sup>8</sup>Department of Obstetrics and Gynaecology, Reinier de Graafgroep, Voorburg, The Netherlands <sup>9</sup>Stichting Geertgen, Elsendorp, The Netherlands <sup>10</sup>Department of Obstetrics and Gynaecology, University Medical Centre Groningen, Groningen, The Netherlands

\*Correspondence address. E-mail: m.h.mochtar@amc.uva.nl

Submitted on May 23, 2014; resubmitted on December 19, 2014; accepted on January 5, 2015

**STUDY QUESTION:** Does intrauterine insemination in the natural cycle lead to better pregnancy rates than intracervical insemination (ICI) in the natural cycle in women undergoing artificial insemination with cryopreserved donor sperm.

**SUMMARY ANSWER:** In a large cohort of women undergoing artificial insemination with cryopreserved donor sperm, there was no substantial beneficial effect of IUI in the natural cycle over ICI in the natural cycle.

**WHAT IS KNOWN ALREADY:** At present, there are no studies comparing IUI in the natural cycle versus ICI in the natural cycle in women undergoing artificial insemination with cryopreserved donor sperm.

**STUDY DESIGN, SIZE, DURATION:** We performed a retrospective cohort study among all eight sperm banks in the Netherlands. We included all women who underwent artificial insemination with cryopreserved donor sperm in the natural cycle between January 2009 and December 2010. We compared time to ongoing pregnancy in the first six cycles of IUI and ICI, after which controlled ovarian stimulation was commenced. Ongoing pregnancy rates (OPRs) over time were compared using life tables. A Cox proportional hazard model was used to compare the chances of reaching an ongoing pregnancy after IUI or ICI adjusted for female age and indication.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** We included 1843 women; 1163 women underwent 4269 cycles of IUI and 680 women underwent 2345 cycles of ICI with cryopreserved donor sperm.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Baseline characteristics were equally distributed (mean age 34.0 years for the IUI group versus 33.8 years for the ICI group), while in the IUI group, there were more lesbian women than in the ICI group (40.6% for IUI compared with 31.8% for ICI). Cumulative OPRs up to six treatment cycles were 40.5% for IUI and 37.9% for ICI. This corresponds with a hazard rate ratio of 1.02 [95% confidence interval (CI) 0.84–1.23] after controlling for female age and indication. Increasing female age was associated with a lower OPR, in both the IUI and ICI groups with a hazard ratio for ongoing pregnancy of 0.94 per year (95% CI 0.93–0.97).

**LIMITATIONS, REASONS FOR CAUTION:** This study is prone to selection bias due to its retrospective nature. As potential confounders such as parity and duration of subfertility were not registered, the effect of these potential confounders could not be evaluated.

**WIDER IMPLICATIONS OF THE FINDINGS:** In women inseminated with cryopreserved donor sperm in the natural cycle, we found no substantial benefit of IUI over ICI. A randomized controlled trial with economic analysis alongside, it is needed to allow a more definitive conclusion on the cost-effectiveness of insemination with cryopreserved donor sperm.

**STUDY FUNDING/COMPETING INTEREST(S):** No funding was used and no conflicts of interest are declared.

**Key words:** donor sperm / cryopreservation / intrauterine insemination / intracervical insemination / natural cycle

## Introduction

Artificial insemination with donor sperm (AID) may be performed for medical reasons or to assist lesbian couples or single women to achieve pregnancy. Medical reasons include obstructive and non-obstructive azoospermia, severely impaired semen quality in couples who do not want to undergo or were not successful with ICSI, severe rhesus isoimmunization, prevention of vertical transmission of a genetic defect or prevention of transmission of human immunodeficiency virus (HIV) (NICE, 2013).

Although fresh sperm leads to higher pregnancy rates, cryopreserved donor sperm is inseminated to prevent transmission of sexually transmitted diseases such as HIV and Hepatitis B and C (ASRM, 2012).

AID can be done via the intrauterine (IUI) or the intracervical route (ICI), with or without ovarian stimulation. The guidelines of the UK-based National Institute for Health and care Excellence (NICE) recommends IUI (NICE, 2013). The recommendation to perform IUI relies upon a Cochrane review in which IUI gives higher ongoing pregnancy rates (OPRs) per cycle compared with ICI (Besselink *et al.*, 2009). The NICE guideline does not recognize that this review includes only studies in which ovarian stimulation was performed. To reduce multiple pregnancies and their attendant risks, NICE considers it reasonable to try six cycles of unstimulated donor insemination initially in regularly ovulating women, since these women are not infertile. However, they also acknowledge that there is no evidence from randomized controlled trials (RCTs) to support this recommendation.

In the absence of proof of superiority of IUI over ICI in the natural cycle, it should be realized that IUI is more expensive than ICI, due to the sperm processing.

Considering that IUI in the natural cycle is recommended over ICI in the natural cycle in the first six cycles, without any evidence that in the natural IUI generates higher pregnancy rates compared with ICI, and in view of the higher costs generated by processing the sperm for IUI, the aim of this retrospective study was to assess whether IUI does achieve higher OPRs compared with ICI in the natural cycle.

## Materials and Methods

### Patients

We performed a retrospective cohort study among Dutch women who underwent AID between January 2009 and December 2010. Data were collected from all eight sperm banks in the Netherlands: Center for Reproductive Medicine Amsterdam (Academical Medical Center), Isala Fertility Centre Zwolle, MCK Fertility Centre Leiderdorp, Reinier de Graafgroep Voorburg, Rijnstate Hospital Arnhem, Stichting Geertgen Elsendorp, University Medical Center Groningen, University Medical Center Utrecht.

Indications for AID were azoospermia, severely impaired semen quality or failed TESE-ICSI. Also, couples who were at risk of vertical transmission of a genetic defect and lesbian couples or single women were admitted to the AID programs.

We studied up to six treatment cycles of IUI or ICI with cryopreserved donor sperm in the natural cycle in these women.

Four centres performed IUI as a routine, two centres performed ICI, while two centres performed both IUI and ICI: these centres switched during the period under study from ICI to IUI because they experienced low success rates after ICI. For this retrospective cohort, we only included therapy-naïve women who started the initial treatment strategy and did not switch to another AID method.

In the ICI cycles, women were inseminated once or twice per cycle according to local protocol. One straw was thawed at room temperature and insemination took place without processing of the sperm. For insemination, sperm was deposited near the cervical canal.

### Data analysis

The primary outcome was ongoing pregnancy, defined as the presence of fetal cardiac activity at transvaginal ultrasonography at a gestational age beyond 12 weeks.

We compared OPRs over time using life table analysis. On the basis of the cumulative pregnancy rates, a curve was constructed showing the time to pregnancy over multiple cycles. A number of women who started were given per cycle. The univariable and multivariable Cox regression analysis was performed for variables possibly affecting the OPR. Variables considered in the analysis were female age and indication for AID. The linearity of the association between age and ongoing pregnancy was evaluated with spline functions. Results were expressed as hazard rate (HR) with corresponding 95% intervals. Data analysis was carried out using the STATA version 11.

## Results

The eight clinics had considerable practice variation. In all clinics, ovulation was detected by LH testing in urine; in two clinics, ovulation was induced by human chorionic gonadotrophin if a dominant follicle was present at ultrasonography (Pregnyl, Organon, Oss, The Netherlands). In the case of IUI, various methods of sperm processing were used. Five sperm banks froze the unprocessed sperm and performed processing after thawing and one sperm bank performed processing before freezing. One clinic performed two inseminations per cycle for ICI. All baseline characteristics of the clinics are summarized in Table I.

We studied 1843 women of whom 1163 underwent 4269 cycles of IUI (3.7 cycles per woman) and 680 women underwent 2345 cycles of ICI (3.4 cycles per woman). Baseline characteristics of the women are summarized in Table II. The average age was 34.0 in the IUI group and 33.8 in the ICI group ( $P$ -value 0.55). In the IUI group, there were more lesbian women than in the ICI group: 41.0% for IUI compared with 31.8% for ICI, respectively ( $P < 0.001$ ). In 10% of the IUI group, the indication for AID was unknown compared with none in the ICI group ( $P < 0.001$ ).

There were 361 ongoing pregnancies in the IUI group resulting in an OPR of 40.5% after six treatment cycles. In the ICI group, there were 177 ongoing pregnancies that resulted in an OPR of 37.9% after six

**Table I** Baseline characteristics of practice variation between clinics.

Clinic	1	2	3	4	5	6	7	8
Insemination technique	ICI	ICI	IUI	ICI IUI	ICI IUI	IUI	IUI	IUI
Ovulation detection	LH tests	LH test	HCG or LH test	LH test	LH test	HCG or LH test	LH test	LH test
Number of inseminations per cycle	2	1	1	1	1	1	1	1
Sperm processing <sup>a</sup>			Before freezing	After freezing	After freezing	After freezing	After freezing	After freezing

LH tests were performed in urine.

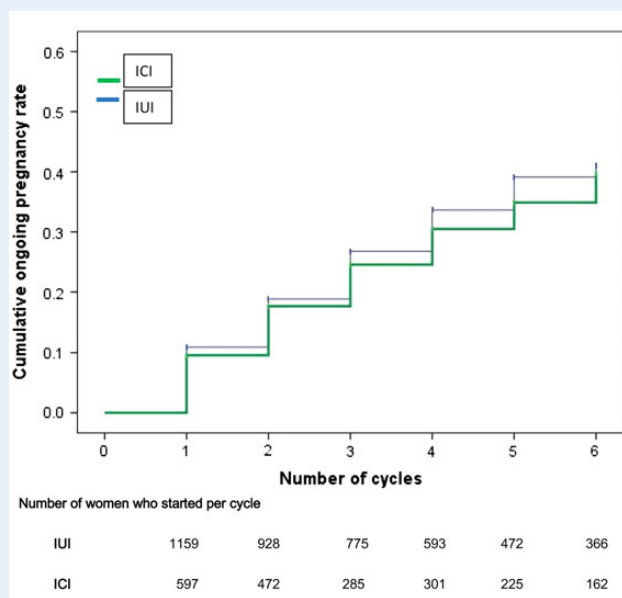
<sup>a</sup>Sperm processing was only performed in the case of IUI.**Table II** Baseline characteristics of women undergoing AID.

	IUI (n = 1163)	ICI (n = 680)	P-value
Age years (mean ± SD)	34.0 ± 4.3	33.8 ± 4.5	0.55
Indication for AID n (%)			<0.001
Heterosexual couples	295 (25.4)	249 (36.6)	
Lesbian couples	477 (41.0)	216 (31.8)	
Single women	273 (23.5)	215 (31.6)	
Unknown	118 (10.0)	0	<0.001

**Table III** Results of the Cox regression analysis after adjusting for factors influencing ongoing pregnancy outcome from Cycle 1 to 6.

	HR <sub>adj</sub>	95% CI	P-value
IUI versus ICI	1.02	0.84–1.23	0.85
Age	0.94	0.93–0.96	<0.001
Indication for AID <sup>a</sup>			
Lesbian couples	1.0		
Heterosexual couples	1.2	0.98–1.48	0.08
Single women	0.83	0.66–1.04	0.12

There was no interaction between indication and female age.

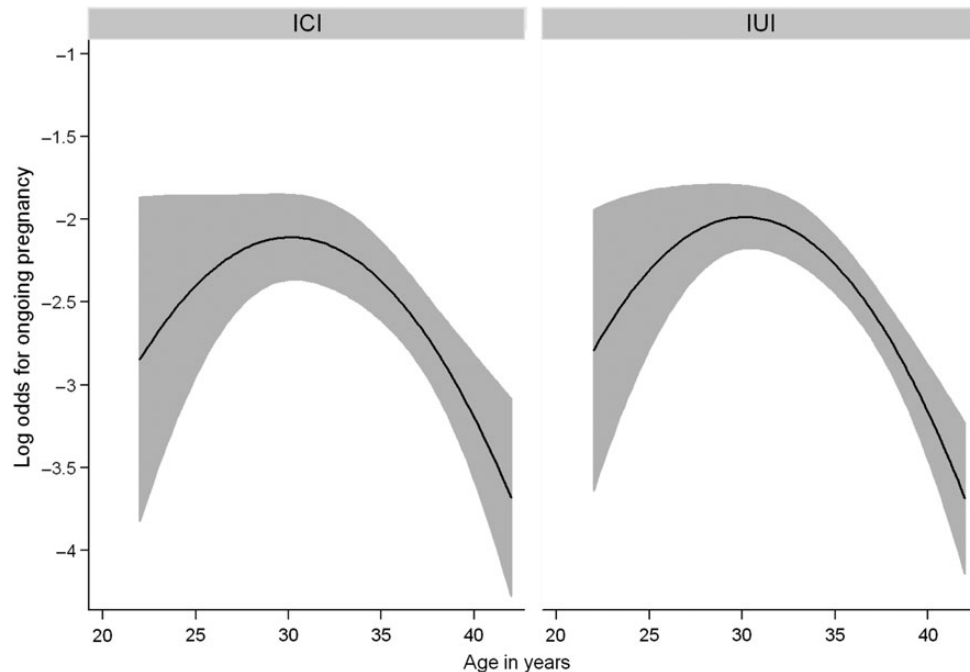
<sup>a</sup>Analysis done with and without imputation for missing indication values.**Figure 1** Kaplan–Meier: cumulative OPR's from first to sixth cycle and number at risk for ongoing pregnancy per cycle.

treatment cycles [uncontrolled hazard ratio (HR) 1.2 (95% confidence interval (CI) 0.95–1.40)]. The number of women who started a next cycle decreased per cycle (Fig. 1). Dropout rates were 11% for IUI and

15% for ICI after five cycles ( $P = 0.013$ ). Note in Fig. 1, the first cycle includes 1159 out of 1163 women in the IUI group and 597 out of 680 women in the ICI group. Although the study included all women who underwent artificial insemination with cryopreserved donor sperm between January 2009 and December 2010, some women started their first cycles in 2008 but did not become pregnant. For this analysis, these cycles were excluded because they were prone to bias since women who became pregnant in their first cycles in 2008 were not included. The outcome did not differ to that found when these women were included in the cohort. Therefore, these women were not excluded from our overall analysis in order to have a complete overview of all women who underwent AID in the Netherlands in the period under study.

After controlling for female age and indication, the HR for IUI versus ICI was 1.02 (95% CI 0.84–1.23). Increasing female age was associated with a lower OPR, in both the IUI and ICI groups [HR for ongoing pregnancy (HR) 0.94; 95% CI 0.93–0.96] (Table III). A spline showed that pregnancy rates increased up to the age of 32, and thereafter there was a general decline both in IUI and ICI cycles (Fig. 2). There was no interaction between the applied insemination technique and age. With lesbian couples as a reference for the indication for AID, OPR did not significantly differ for heterosexual couples (HR 1.2; 95% CI 0.98–1.48) and single women (HR 0.83; 95% CI 0.66–1.04). There was no interaction between female age and indication.

One clinic performed two inseminations per ICI treatment. Excluding this clinic from the analysis in a sensitivity analysis resulted in an HR for IUI versus ICI of 0.89 (95% CI 0.73–1.10).



**Figure 2** Spline: age in relation to OPR. Results are expressed as HR with corresponding 95% intervals. The HR is the black line, and the CI is the grey area around the line.

## Discussion

In this multicentre nationwide cohort study in women undergoing AID in the natural cycle, we found no statistically significant differences between the first six treatment cycles of IUI and ICI in terms of OPR.

An increasing female age from 32 years onward was the only factor influencing OPR negatively for both treatments. Other factors, such as applied insemination technique and indication for AID, had no effect on the OPR.

This cohort is unique since it is the largest cohort study on this topic and compares IUI and ICI in the natural cycle. Furthermore, it describes heterosexual, lesbian couples and single women, while all previous studies were limited to heterosexual couples and single women (Bessink et al., 2009).

One of the limitations of this retrospective cohort is that there was considerable practice variation in semen processing, single or double insemination and timing of insemination between the participating centres. For ICI, sperm processing was never used. For IUI, five sperm banks froze the donor sperm and performed processing after thawing and one sperm bank performed processing before freezing. Therefore, it was not feasible to evaluate the confounding or modifying effect of semen processing on the ongoing pregnancy chances following IUI and ICI. The only evidence that semen processing does not affect pregnancy chances comes from a study that combined retrospective data from 209 women and prospective data from 39 women (Wolf et al., 2001).

In the case of ICI, one clinic performed two inseminations per cycle. Excluding this clinic from the analysis did not result in evidence of a difference between IUI and ICI.

Also the timing of insemination was performed in different ways; some clinics used urine LH tests and some ovulation induction by human

chorionic gonadotrophin (Pregnyl). Guidelines do not report on timing of insemination in the case of AID. Because of these variations, it is impossible to subscribe any effect of IUI or ICI on OPR on the insemination technique only.

A second limitation is that data on the medical history including previous pregnancies and duration of subfertility were not obtained. These factors may influence pregnancy rates (van der Steeg et al., 2008). Nevertheless, the main prognostic factor to predict conception, e.g. age, is incorporated in the analysis. From a theoretical point of view, we do not expect that duration of infertility and previous obstetric history results will add any additional information, since most women who opt for AID are not subfertile at all. Evidence of whether medical history does influence pregnancy outcome in this population is lacking.

Thirdly, in heterosexual couples, it is known that partners of azoospermic men conceive more quickly with AID than partners of men with spermatozoa in their ejaculates, suggesting that in the latter, unknown female factors also contribute to the subfertility of the couples (NICE, 2013). In this cohort, we did not differentiate between the indications for AID in heterosexual couples, because the data were not available. This could have resulted in lower OPRs in heterosexual women.

Finally, the number of women who started inseminations dropped after the first cycle, which makes calculation of OPRs less reliable. OPRs dropped after the first cycle, but cycles up to the sixth cycle still gave ongoing pregnancies.

Several findings in our study warrant further discussion. First, in our cohort, the cumulative OPRs were lower compared than expected for a normal fertile population. This may be explained by a study that compared the use of fresh sperm with cryopreserved sperm and found that

pregnancy rates after 3 months were 48% for fresh sperm versus 22% for cryopreserved sperm (Subak *et al.*, 1992). We assume that the lower OPR in this cohort is due to the use of cryopreserved donor sperm.

Second, after every cycle, there were non-pregnant women who stopped treatment before the six cycles were completed. Dropout rates were higher in the ICI group. Fear of failure is a well-known and important factor in fertility treatment from the point of view of the patient, but also from the perspective of the doctor, and this may have led to the number of dropouts (Campana *et al.*, 1996; Olivius *et al.*, 2004). Reasons for discontinuing inseminations are numerous; for a couple with repeated failed attempts, continuing AID may become a frustrating experience; from the clinician's perspective, repeating AID cycles can be time-consuming and it may seem easier to offer alternative options than to motivate patients who have lost confidence. In view of this, we have to realize that women applying for AID are not proven to be subfertile. Furthermore, our data show that continuation of treatment after several failed attempts may be rewarding. Appropriate counselling should help the couples to understand the principle of the treatment without ovarian stimulation and their pregnancy chances.

Current guidelines recommend IUI in the natural cycle, since women who start with AID are not subfertile and multiple pregnancy rates should be prevented, but this advice is based upon inferences drawn from the studies applying IUI and ICI with ovarian stimulation (NICE, 2013). Our study provides for the first time data questioning the use of IUI and at the same time underpinning the recommendation to inseminate in the natural cycle and thus not to add ovarian stimulation.

The costs for IUI have been estimated to be four times higher than ICI, mostly because of the additional sperm preparation required. In the Netherlands, costs for ICI are estimated to be 150 Euros per cycle versus 650 Euros per cycle for IUI (NZU, 2011). Assuming pregnancy rates of 20.1 and 22.4% for ICI and IUI after three cycles, the costs per ongoing pregnancy will be 1768 Euros over three ICI cycles, versus 7012.5 Euros per three IUI cycles. In the absence of a significant difference, ICI should therefore be the preferred treatment. Even if IUI would be 2.5% more effective, this would implicate a cost of 6841.5 Euros to establish one additional ongoing pregnancy, while even at a 5% increase (corresponding with the upper level of our 95% CI), these costs would be 6678.6 Euros. Obviously, it is more efficient to invest in additional cycles of ICI, even if the ICI cost 300 Euros.

In conclusion, this retrospective cohort study showed no substantial benefit of IUI in the natural cycle above ICI in the natural cycle for insemination with cryopreserved donor sperm. An RCT with an economic analysis alongside it is highly recommended to provide definitive evidence on the most cost-effective insemination technique.

## Acknowledgements

We thank Jock de Rooij for helping with the collection of the data in Fertibase.

## Authors' roles

P.A.L.K. contributed to the design of the study, the acquisition of the data and the analysis of the data. She also drafted the manuscript. M.W. contributed to the analysis and interpretation of the data and revised the manuscript critically. B.W.M. and F.V. contributed to the design of the study, interpretation of the data and to the revisions of the manuscript. A.A.M., B.A., M.H.J.M.C., M.K., A.N., E.R., H.R. and A.H.M.S. contributed to the acquisition of the data and revised the manuscript. P.M.W.J. and J.P.W.R.R. contributed to the revision of the manuscript. S.R. contributed to the acquisition of the data, the interpretation of the data and revised the manuscript. M.H.M. contributed to the design of the study, participated in interpretation of the data and revised the manuscript critically.

## Funding

No external funding was either sought or obtained for this study.

## Conflict of interest

None declared.

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