ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Longer time interval between semen processing and intrauterine insemination does not affect pregnancy outcome

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Objective: To study whether the pregnancy outcome of intrauterine insemination (IUI) is affected by a longer time interval between semen processing and insemination.
Design: Retrospective cohort.
Setting: Teaching hospital.
Patient(s): Couples with subfertility and an indication for IUI over a 10-year period.
Intervention (s): Insemination performed the day after but within 24 hours of semen collection and processing (delayed insemination) compared with insemination performed immediately after sperm collection and processing (immediate insemination).
Main Outcome Measure(s): Ongoing pregnancy rate, defined as a pregnancy confirmed by ultrasound at 10 to 12 weeks of gestation.
Result(s): In total, 1,136 cycles were analyzed. In 77 of 547 couples (14%) an ongoing pregnancy occurred after delayed insemination, and in 77 of 589 couples (13%) an ongoing pregnancy occurred after immediate insemination. Both groups had similar baseline characteristics. After adjustment for confounders, there was no difference in the ongoing pregnancy rate between delayed as compared with immediate insemination (odds ratio 0.89; 95% confidence interval, 0.63–1.25).
Conclusion(s): There is no negative effect on pregnancy rate when IUI of processed sperm is delayed until the next day. This approach allows additional flexibility for couples when the male partner is not available on the day of ovulation, and it allows for a spread of workload in the laboratory. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, pregnancy, semen processing, time interval

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In many clinics intrauterine insemination (IUI) is used as the first-line treatment for unexplained subfertility, cervical subfertility, and mild to moderate male subfertility. With this treatment the partner's sperm is prepared and inseminated directly into the uterus at the time of ovulation (1). There are several clinical factors that influence the pregnancy rates after IUI such as type of ovarian stimulation, woman's age, type and duration of infertility, sperm count, and quality and number of preovulatory follicles (2). Timing in the insemination process is important because oocytes and spermatozoa have a limited life span, so IUI with processed sperm is performed closely to the time of ovulation (3).

For therapeutic recovery of sperm, spermatozoa are separated from seminal plasma and processed before insemination. For successful IUI outcomes, two phases in the preparation of sperm appear to be important: the time between semen collection and semen processing, and the time between semen processing and insemination. The time interval between semen production, separation of spermatozoa from seminal fluid, and processing spermatozoa for therapeutic use needs to be short because the prostaglandins, leucocytes, bacteria, and dead spermatozoa present in the ejaculate produce

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oxygen radicals that may harm motile spermatozoa (4). The processed semen should result in a small volume of fluid with a high concentration of capacitated, morphologically normal, and motile spermatozoa without debris and dead spermatozoa, which is then inseminated.

In accordance with the recommendations of the World Health Organization (5), patients are advised that semen specimens should be delivered to the laboratory within 1 hour of collection and should be protected from extremes of temperature. There are no guidelines specifying the time between the end of sperm preparation and IUI, and little is known about the optimal time interval between semen processing and insemination or the effect on pregnancy rates.

To our knowledge only two studies have addressed this question. One study showed that IUI procedures performed <60 minutes after sperm wash resulted in higher pregnancy rates than did IUI performed >60 minutes after sperm wash ($P=.01$) in IUI cycles and ovarian stimulation with human menopausal gonadotropins (6). Another study showed an optimal clinical pregnancy rate when insemination took place between 40 and 80 minutes after sperm preparation (7).

In our clinic, as in many others, laboratory staffing is reduced on the weekends, which limits the use of the laboratory facilities to process sperm. For this reason, semen from men whose partners' ovulation is on a Saturday is collected and processed on Fridays and is subsequently stored and inseminated the next day, within 24 hours.

In this study we analyzed the influence of a longer time interval between semen processing and IUI on pregnancy outcomes in a large cohort of patients. We analyzed the pregnancy rates in patients who were inseminated on Saturday—the day after semen preparation but within 24 hours after semen processing. As controls, we used the patients who were inseminated on Fridays within 1 hour after semen processing.

MATERIALS AND METHODS

Patients

This study was conducted at the fertility department of OLVG-Oost in Amsterdam, the Netherlands. All IUI cycles from November 2005 until April 2015 in which insemination was performed on either a Friday or a Saturday were retrospectively evaluated. All couples underwent a basic fertility workup consisting of semen analysis, a postcoital test, a gynecologic examination, an ultrasound scan, and a tubal patency test. Eligible couples were identified, and the files retrieved by recording prospectively all semen samples that were processed for IUI in the laboratory on Fridays from November 2005 until April 2015. As some couples had more than one treatment cycle in this cohort, and to avoid bias through duplicate evaluation of several couples, only the last treatment of these couples on either a Friday or a Saturday was used.

The baseline clinical characteristics and cycle-specific information were collected from our general hospital database and the database of the fertility department and laboratory of OLVG. We recorded general patient information such as male and female age, gravidity and parity, subfertility diagnosis, type and duration of subfertility, and IUI outcome as well as IUI specific information such as medication used for ovarian stimulation and the total motile sperm count (TMSC) before and after processing.

Our primary outcome was the ongoing pregnancy rates confirmed by ultrasound of the patients who had been inseminated within 1 hour of sperm preparation (Friday: "immediate insemination") or the next day (Saturday: "delayed insemination") within 24 hours of processing the sperm. The institutional review board approved the study protocol (WO15.111).

Ovarian Stimulation, IUI, and Confirmation of Pregnancy

Subfertility was classified according to three possible diagnoses: [1] unexplained subfertility and a prognosis for natural conception <30% in the next year according to the model of Hunault (8); [2] mild male subfertility (defined according to WHO criteria, most frequently reported as TMSC 5–10 million and total motility of 30% (5); or [3] cervical factor subfertility.

Cervical factor subfertility or mild male subfertility were treated with IUI in a natural cycle. In men with mild male subfertility, the sperm quality was deemed suitable for IUI treatment if the postwash TMSC was at least 3 million. This was assessed during the fertility workup, before the onset of IUI treatment. Patients with unexplained subfertility were treated with controlled ovarian hyperstimulation, which could consist of recombinant follicle-stimulating hormone (FSH) or clomiphene citrate.

In all patients—both natural cycles and ovarian-stimulated cycles—ultrasound monitoring was performed to determine the time for induction of ovulation. Ovulation was induced with human or recombinant chorionic gonadotropin when the follicle size reached ≥16 mm. Processed sperm, concentrated in a small volume of 0.3 mL, was inseminated 40 hours after induction of ovulation. An ongoing pregnancy was confirmed by transvaginal ultrasound at a gestational age of 10 to 12 weeks.

Semen Collection, Analysis, and Processing

Semen specimens were collected by masturbation into a sterile plastic jar, either at home or at our clinic. The specimens collected at home were delivered to the laboratory within 1 hour after collection, and these patients had been advised to protect the specimens from extremes of temperatures (<20°C or >37°C) during transport. Couples were asked to abstain from intercourse for 2 to 3 days before insemination but not more than 5 days. The men whose tests were positive for antisperm antibodies (SpermMar IgG test >40%) were asked to ejaculate directly into 8 mL of FertiCult Flushing medium (FertiPro N.V.). The specimens were processed within 15 minutes of liquefaction or delivery.

The processing of sperm consists of separating the sperm in the ejaculate from the prostaglandin-rich