Meer flexibiliteit voor patiëntkoppels bij IUI behandeling

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Als een spontane zwangerschap niet (meer) vanzelfsprekend is en er toch een kinderwens is, dan is IUI een van de behandelmethodes om alsnog een zwangerschap tot stand te laten komen. Het sperma van de man wordt opgewerkt tot een superconcentraat en het zaad wordt vlak voor ovulatie hoog in de baarmoeder gebracht. Deze behandeling is vraagt nogal wat van het koppel en de logistiek die hiermee gemoeid is.

Allereerst wordt de behandelafspraak zo ingepland dat er sprake is van een bijna ovulatie, en daarbij moest de man vlak voor behandeling sperma produceren dat direct werd opgewerkt voor terugplaatsing. Dit laatste geeft ook regelmatig stress bij de man, hetgeen de kwaliteit van het sperma niet ten goed komt. Het produceren op commando gaat ook niet altijd goed, waardoor er soms weer een cyclus van de vrouw voorbij gaat zonder kans op bevruchting. Daarbij geeft het een logistiek gehannes, op een moment waarbij de partners het liefst wat dichter bij elkaar zijn.

Eén van de oorzaken van deze stresssituatie voor het moment van inseminatie was dat er geen informatie was over hoe lang sperma bewaard kan worden zonder negatieve gevolgen voor de zwangerschapskans. In nauwe samenwerking tussen klinische chemie, gynaecologie en fertiliteitspoli is onderzocht of bewerkt sperma bewaard kan worden en toch nog steeds geschikt blijft voor terugplaatsing. Dit bleek mogelijk te zijn. Sperma, mits opgewerkt, kan worden bewaard en tot 24 uur later worden geïnsemineerd waarbij de kans op zwangerschap gelijk blijft.

In de praktijk betekent dit resultaat dat op het moment dat de inseminatieafspraak is vastgelegd op basis van het ovulatiemoment van de vrouw, de partner een ruim tijdvenster van 24 uur heeft om sperma te produceren. Deze “vrijheid” is niet alleen patiëntvriendelijk maar de praktijk laat zien dat dit ruimer tijdvenster letterlijk “druk van de ketel” bij de man haalt. De mannelijke partner kiest zelf het moment in plaats van te moeten presteren onder tijdsdruk.

Een bijkomend groot voordeel is dat deze werkwijze het mogelijk maakt om 7 dagen per week continuïteit van zorg te bieden. Tot op heden zijn er nogal wat ziekenhuizen die in het weekend geen IUI behandelingen doen omdat er geen mogelijkheden zijn voor semenopwerking in het weekend, wat in enkele gevallen weer ten koste gaat van een cyclus van een vrouw.

Zowel in het OLVG als in de MC Groep is er al jarenlang 7 dagen per week continuïteit van behandeling door deze werkwijze en wordt er bijvoorbeeld op zaterdagen sperma opgewerkt dat op de zondag kan worden geïnsemineerd omdat dan de timing voor de vrouwelijke partner optimaal is.

De studie waaraan in totaal 10 jaar is gewerkt en waarbij 1136 behandelkoppels zijn onderzocht is in het najaar van 2017 gepubliceerd in het toonaangevende internationale tijdschrift *Fertility & Sterility*. Deze werkwijze is voor alle ziekenhuizen mogelijk en praktisch toepasbaar, waarmee de IUI behandelingen in Nederland een stuk patiëntvriendelijker kunnen worden.

Met deze inzending voor de publieksprijs willen wij dan ook alle ziekenhuizen oproepen om deze patiëntvriendelijke behandelwijze over te nemen.

<u>Publicatie</u>

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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

prostatic secretions and seminal fluid, then concentrating the sperm in a small volume of culture medium that enhances capacitation and the acrosome reaction. Determination of motility and concentration (before and after preparation) was performed with CellVision 1020-102 disposable counting chambers (CellVision). Semen preparation was performed by density gradient centrifugation followed by washing with flushing medium: after liquefaction, the ejaculate was divided into two equal parts, placed on 2-mL aliquots of SilSelect-Plus Lower Layer density gradient (FertiPro N.V.), and centrifuged at 375 × *g* for 16 minutes. The pellet was washed twice (centrifuged at 375 × *g* for 10 minutes) with FertiCult Flushing medium (FertiPro N.V.). After the last washing step, the pellet was resuspended in 0.3–0.5 mL flushing medium for insemination. This sample was then stored at room temperature. For each semen preparation, the TMSC results ($\times 10^6$) were registered before and after preparation.

Insemination took place within 1 hour after preparation or the next day, but maximally 24 hours after preparation, with a soft IUI catheter or sometimes with a firm embryo-transfer catheter (TDT set; CCD International) if the soft catheter did not reach the uterine cavity. If the samples were inseminated the next day after preparation, the tubes were manually resuspended before insemination.

Data Collection and Analysis

This study is a noninferiority study. We assumed that the pregnancy rates would be comparable between the two groups and considered a difference of >5% clinically relevant. We used SPSS 22 (IBM, Inc.) for all statistical analyses. All continuous data were expressed as mean with standard deviation (SD) or median with interquartile range (IQR 25% to 75%). Categorical variables were shown as number and percentages. The differences between the two groups were tested with an independent sample *t*-test (continuous data) or chi-square contingency test (categorical data). $P<.05$ was considered statistically significant.

Multivariate logistic regression analysis was used to assess the relation between delayed IUI of processed sperm and pregnancy outcomes. In addition, we calculated the pregnancy rate and odds ratios per subgroup.

RESULTS

Patients

Between November 2005 and April 2015, 2,154 IUI cycles fulfilled the inclusion criteria for our cohort. Because some couples had multiple treatments in this cohort, we excluded 1,010 duplicate cycles to avoid bias from evaluating these couples twice. Duplicate cycles were evenly distributed between immediate and delayed insemination (see Fig. 1).

After exclusions, our cohort consisted of 1,144 cycles for evaluation. In addition, data from eight couples were excluded; in five couples the data were missing on whether the pregnancy outcome was positive or negative. One couple had a natural pregnancy just before the IUI, and two couples were inseminated on a different day than planned. After exclusion of these eight couples our final cohort consisted of 1,136 couples (Fig. 1).

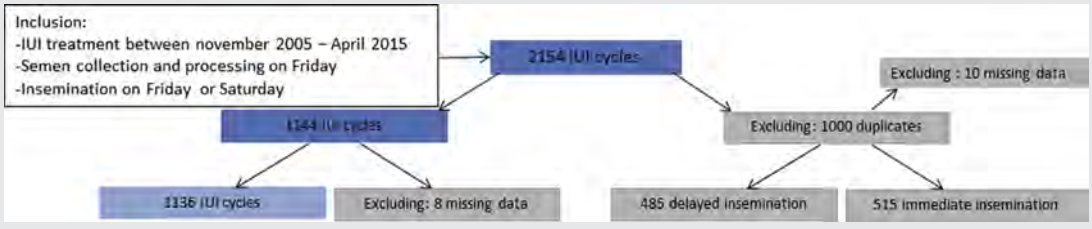
Table 1 shows all the baseline characteristics. The baseline characteristics of the patients with delayed insemination were similar to those with immediate insemination ($P>.05$). Of the 1,136 patients, 547 of 1,136 (48%) had Saturday ovulation with delayed insemination, and 589 of 1,136 (52%) were inseminated within 1 hour of processing the sperm. The indications for IUI were a male factor subfertility in 13%, cervical factor subfertility in 15%, and unexplained subfertility in 72%. Of these, 42% of the women were secondary subfertile, and 58% of women were primary subfertile. We provided clomiphene citrate for ovarian hyperstimulation to 4.0% of the women, and recombinant FSH to 79%; 17% were inseminated in a natural cycle. Patients who received one or more previous IUI cycles were evenly distributed between both groups.

The mean female age was 35.4 (3.8 ± SD) years, and was comparable between all subgroups. The mean male age was 38.6 (5.8 ± SD) years at time of insemination. The postwash TMSC determined in the semen analysis was 14.5 (15) millions of motile spermatozoa.

Pregnancy Outcome

Table 2 lists the outcome of the study. The two groups were similar according to the pregnancy rate, with 77 of 589 couples (13%; 95% CI, 10.4–15.8%) pregnant after immediate insemination and 77 of 547 (14%; 95% CI, 11.2–17.0%) of the couples pregnant after delayed insemination ($P=.62$).

FIGURE 1



Comparison of immediate and delayed insemination: study flowchart inclusions.

Jansen. Extended interval for semen processing and IUI. Fertil Steril 2017.

TABLE 1

Clinical characteristics and *P* values for intrauterine insemination after immediate or delayed insemination.

Characteristic	Total (n = 1,136)	Immediate (n = 589)	Delayed (n = 547)	*P* value
No. of previous treatment cycles				.92
First cycle	534 (47)	288 (49)	256 (47)	
1 previous cycle	330 (29)	170 (29)	160 (30)	
2 previous cycles	169 (15)	85 (15)	84 (16)	
3 previous cycles	61 (5.4)	32 (5.5)	29 (5.3)	
4 previous cycles	21 (1.9)	8 (1.4)	12 (2.2)	
5 previous cycles	9 (0.8)	4 (0.7)	5 (0.9)	
6 previous cycles	3 (0.3)	2 (0.3)	1 (0.2)	
IUI indication				.36
Unexplained/other	817 (72)	425 (72)	393 (72)	
Male subfertility	151 (13)	71 (12)	79 (14)	
Cervical factor	168 (15)	93 (16)	75 (14)	
Prior pregnancy				.53
Primary	661 (58)	348 (59)	313 (57)	
Secondary	475 (42)	241 (41)	234 (43)	
Stimulation				.49
FSH	898 (79)	464 (79)	434 (79)	
Clomid	45 (4.0)	21 (3.4)	25 (4.6)	
No stimulation	192 (17)	104 (18)	88 (16)	
Miscarriage	48 (4.1)	26 (4.4)	22 (4.1)	.75
	Total	**Friday**	**Saturday**	
Female age (y), mean (±SD)	35.4 (3.8)	35.4 (3.9)	35.4 (3.6)	.98
IUI indication				
Unexplained/other	35.5 (3.6)	35.5 (3.8)	35.5 (3.4)	
Male subfertility	34.1 (4.2)	33.7 (4.5)	34.5 (3.9)	
Cervical factor	35.8 (3.8)	35.9 (3.6)	35.6 (3.9)	
Prior pregnancy				
Primary	34.8 (3.8)	34.8 (3.9)	34.8 (3.7)	
Secondary	36.2 (3.6)	36.2 (3.8)	36.1 (3.4)	
Stimulation				
FSH	34.8 (4.3)	34.9 (4.4)	34.7 (4.2)	
Clomid	35.5 (3.6)	35.5 (3.8)	35.6 (3.4)	
None	34.6 (3.7)	34.9 (3.9)	34.4 (3.5)	
Male age (y), mean (±SD)	38.6 (5.8)	38.6 (6.0)	38.6 (5.7)	.88
TMSC after processing, mean (±SD)	14.5 (15)	14.9 (15)	14.0 (14)	.29

Note: Values are number (%) unless noted otherwise. FSH = follicle-stimulating hormone; IUI = intrauterine insemination; SD = standard deviation; TMSD = total motile sperm count.

Jansen. Extended interval for semen processing and IUI. Fertil Steril 2017.

This corresponds to an odds ratio, delayed insemination compared with immediate insemination, of 0.92 (95% CI, 0.65–1.29). After adjustment for female age, male age, type of subfertility, indication of IUI, type of stimulation, and total motile count, there was no difference in ongoing pregnancy rate after immediate or delayed insemination, odds ratio 0.89 (95% CI, 0.63–1.25). Table 3 shows all baseline pregnancy rates and odds ratios per subgroup ($P>.05$ for all).

DISCUSSION

This is the first study to report on the impact on ongoing pregnancy of a long time interval between processed sperm and intrauterine insemination in a large cohort of patients. This study demonstrates that there is no negative impact if IUI of sperm is delayed until the next day in terms of ongoing pregnancy rate.

Our findings are different from the only two studies that reported on the effect of time between sperm processing and pregnancy outcome in IUI. Yavas and Selub (6) observed more pregnancies if the time between processing of sperm and insemination was below 60 minutes.

Fauque et al. (7) observed that most pregnancies occurred 40 to 80 minutes after insemination and observed a steady decline in pregnancy rate beyond 80 minutes to below 5% if the interval between the end of processing sperm to insemination was 180 minutes. They hypothesised that a decrease of performance of processed sperm could be expected due to harmful effects of in vitro conditions on sperm such as increased DNA fragmentation, as has been shown in long incubation compared with short incubation of testicular sperm from men with obstructive azoospermia (9) or to an excessive spontaneous acrosome reaction which appeared to be culture-time dependant in another study (10). Our findings do not underpin this hypothesis.

There are differences between our study and these two studies (6, 7). First these studies were small and did not have a control group. Second, in these studies 82% of the samples were stored at a temperature of 37°C whereas in our study semen was stored at room temperature. These storage

TABLE 2

Pregnancy outcome after immediate or delayed insemination.

Outcome	Immediate insemination n/N (%)	Delayed insemination n/N (%)	Odds ratio	Adjusted odds ratio
Pregnancy	77/589 (13)	77/547 (14)	0.92 (0.65–1.29), *P*= .62	0.89 (0.63–1.25), *P*= .51

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conditions might have had a negative effect on the prepared sperm quality, especially if stored for a longer period. According to the World Health Organization (5), sperm incubation conditions must be limited to a threshold value of temperature at 37°C. But the storage conditions such as temperature could become deleterious for spermatozoa, leading to DNA damage. Aboulmaouahib et al. (11) suggested sperm motility could be improved by incubating prepared sperm samples at room temperature compared with incubation at 35°C.

Finally, our control group was treated according to the same protocol as the patients who were inseminated the next day. In the other studies, clinical protocols, patient characteristics, and laboratory protocols may have been different because they were treated in different centers which could have influenced the results.

A strength of our study is the pseudo randomization. Patients could not choose whether they had their ovulation on Friday or Saturday, so the two groups had comparable clinical characteristics. Still, we cannot exclude confounders and biased allocation such as a difference in follicle size for the timing of ovulation, or the influence of patients' or doctors' preferences for the day of insemination on the outcome; nor did we analyze whether there was a difference in length of subfertility between the two groups. However, all couples were at least 1 year subfertile and had a low prognosis for natural conception in accordance with the prognostic model of Hunault et al. (8).

A possible weakness of our study might be that it is uncertain whether couples with delayed insemination had intercourse on Friday, and it is possible that in couples where IUI was performed on Saturday, a pregnancy occurred naturally because they had intercourse on Friday. In general the couples were advised to abstain from intercourse for at least 2 days before IUI to improve their sperm quality. However, when semen is processed on the day before insemination, it is possible that more couples had intercourse the evening before insemination compared with those inseminated on the day of semen processing. Although this may have caused a difference, ovarian stimulation and timed intercourse for unexplained subfertility have not been shown to result in more ongoing pregnancies compared with expectant management or IUI (1, 12). We thus do not believe that this influenced the study outcome.

We did perform a subanalysis on the influence of natural cycle IUI and stimulation with clomiphene citrate or recombinant FSH on the outcome, and this showed no differences between these groups on pregnancy outcome. However, the majority of our patients received recombinant FSH; the subgroups for clomiphene citrate ovarian stimulation and natural cycle IUI were very small and thus inconclusive for a meaningful statistical analysis.

In conclusion, our results show that there is no negative effect on ongoing pregnancy rates when IUI of processed

TABLE 3

Pregnancy rates in all subgroups with *P* value, OR, and 95% CI.

		Insemination			
Parameter	**Total n = 154 (%)**	**Immediate n = 77 (%)**	**Delayed n = 77 (%)**	**OR (95% CI)**	***P* value**
IUI indication					
Unexplained/other	114 (74)	58 (75)	56 (71)	1.15 (0.56–2.35)	.71
Male subfertility	15 (9.7)	5 (6.5)	10 (13)	0.47 (1.15–1.43)	.18
Cervical factor	25 (17)	14 (18)	11 (16)	1.33 (0.56–3.16)	.51
Prior pregnancy					
Primary	92 (60)	46 (60)	46 (60)	Ref	Ref
Secondary	62 (40)	31 (40)	31 (40)	1.0 (0.53–1.90)	1.0
Stimulation					
No stimulation	28 (18)	11 (14)	17 (22)	Ref	Ref
FSH	117 (76)	62 (81)	55 (71)	0.57 (0.23–1.33)	.19
CC	8 (3.2)	3 (3.9)	5 (6.5)	1.08 (0.21–5.45)	.93
Age (y), mean (±SD)					
Female	35.03 (3.8)	35.34 (4.0)	34.71 (3.7)		.31
Male	37.83 (6.3)	38.58 (6.7)	37.08 (5.8)		.12
TMSC, mean (±SD)	15.76 (15.3)	17.73 (15.5)	13.79 (14.79)		.11

Note: CC = clomiphene citrate; CI = confidence interval; FSH = follicle-stimulating hormone; IUI = intrauterine insemination; OR = odds ratio; Ref = reference value; SD = standard deviation; TMSD = total motile sperm count.

Jansen. Extended interval for semen processing and IUI. Fertil Steril 2017.

sperm is delayed until the next day. This approach allows for flexibility in the timing of insemination for couples and for the laboratory processing.

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