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How to Perform the Best Intrauterine Insemination? A Review

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Abstract

Intrauterine insemination is a treatment used in couples with mild/moderate male factor, when female partner has at least one tube patent. Numerous studies have attempted to determine for many years which parameters are limiting to ensure pregnancy with this technique of assisted reproduction. This review focuses on prognostic factors for a successful outcome, as semen quality, female etiology, synchronization with ovulation, assessment of follicle rupture, number of inseminations per cycle and influence of uterine contractions. We conclude with this review that intrauterine insemination is a less invasive and expensive option than others [IVF], with acceptable results when adequately indicated. We conclude with this review that intrauterine insemination can be performed when patient is less than 40 years old and there are at least 5 million of motile sperm to be inseminated. The abstinence interval of 3 days prior to produce the sperm sample is the optimal period and either one or two inseminations are valid, ideally performed in the frame time between 12 and 38 hours after ovulation induction. Also, follicle rupture and uterine contractions observed by ultrasound scan following intrauterine inseminations are favorable prognostic factors.

Keywords: Intrauterine insemination; Male factor; Double versus single; Timing; Follicle rupture; Uterine contractions

Abbreviations

ART: Assisted Reproductive Technology; IUI: Intrauterine Insemination; IVF: In-vitro Fertilization; ICSI: Intra-Cytoplasmic Sperm Injection; TMSC: Total Motile Sperm Count; ROS: Reactive Oxygen Species; PCOS: Polycystic Ovarian Syndrome; BMI: Body Mass Index; WHO: World Health Organization; RCT: Randomize Clinical Trial; US: Ultrasound Scan

Introduction

The use of Assisted Reproductive Technology [ART] is a highly successful methodology for the treatment of infertility. Intrauterine Insemination [IUI] is considered the simplest and least invasive procedure with reasonable live birth rates and not needing expensive infrastructure [1]. Inseminations have been done in domestic and farm animals since the 1900's while human artificial inseminations began in the 1940's [2]. Human intrauterine inseminations were first reported by Cohen in 1962 [3].

In 2014, data were reported on IUI-H and IUI-D cycles performed in Europe along 2010. With regard to IUI-H, 176 512 cycles [+13 669] were reported by 23 countries—the main contributors being France, Italy and Spain. Among the countries reporting deliveries, the mean delivery rate per cycle was 8.9%, with a 9.3% of twin deliveries and a 0.5% of triplet deliveries. For IUI-D, 38 124 cycles were reported [+8889] by 20 countries, the main contributors being Denmark, France, Spain and the United Kingdom. The delivery rate per cycle was 13.8%, with multiple delivery rates of 7.9% for twins and 0.2% for triplets [4].

Over the years, there have been numerous studies focused on improving pregnancy rates when an intrauterine insemination is performed. However, published results are highly controversial and many questions remain unanswered: Which are the optimal semen parameters for IUI? How the female age and etiology affect the results of IUI? Which is the best strategy to synchronize ovulation and IUI? How crucial is to detect follicle rupture? Is it better to perform a single or a double intrauterine insemination? Which is the actual role of uterine contractions during IUI? The objective of this review is to attempt to clarify these questions in order to establish the optimal parameters to perform an intrauterine insemination.

In this review we do not compare different drug treatments to achieve ovarian stimulation, considering mild stimulation with gonadotropins as the gold standard [over clomiphene citrate stimulation] [5]. Regarding luteal support, progesterone administration is considered the gold standard.

Influence of Semen Quality

Intrauterine insemination is a simple and non-invasive technique widely indicated in assisted reproduction for treating infertility in couples with male factor subfertility or unexplained infertility. Studies try to elucidate which standard semen parameters impact more on pregnancy rates for couples undergoing IUI, and it seems that sperm motility is the most predictive [6-8]. It must be remembered that Total Motile Sperm Count [TMSC] inseminated has been cited as the most predictive index of conception after IUI cycles [9-11]. A minimalTMSC of 1 million for insemination was initially reported to be a requirement for pregnancy after insemination [12], but the systematic review of the literature by Ombelet et al. in 2014 indeed confirms that the native sperm TMSC which shows the best correlation with IUI success is in the range of 5-10 million [6,13-16]. According to a previous study, sperm concentration above 10 million is not related to further improvement in conception rates [12], while other investigators have reported the best pregnancy rates when more than 10 million motile spermatozoa are inseminated [9,17].

Many authors have described how standard semen parameters and/or ejaculatory abstinence impact on the success of these treatments [12,18-22]. Although there is no consensus in the literature to establish

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the recommended period of ejaculatory abstinence in order to achieve the optimal semen quality, Jurema et al. suggested that an abstinence interval around 3 days or less is associated with higher pregnancy rates following Intrauterine Insemination [IUI]. Other authors also suggest an ejaculatory abstinence period of ≤2 days before IUI, despite a lower total motile sperm count is inseminated [12]. It has been described that increasing ejaculatory abstinence generally increases sperm count but decreases motility, meanwhile sperm morphology seems to be independent of abstinence period [18,19,21].

We could expect that the longer the abstinence interval is, the higher the sperm count and TMSC are. However, a long period of abstinence may be related to a higher exposure of spermatozoa to Reactive Oxygen Species [ROS] and, consequently, to a higher sperm DNA damage. ROS causes defective sperm function in some cases as a result of lipid peroxidation of the polyunsaturated fatty acids in the head and mid-piece of the spermatozoon. This deleterious effect affects motility, capacitation, acrosome reaction and decondensation of sperm head [23-25]. As low sperm DNA damage is considered an important factor in order to achieve a healthy pregnancy, different strategies have been used to reduce it, including the intake of certain antioxidants compounds or reducing the recommended sexual abstinence period, as well as using especial techniques for sperm selection [26-29].

Levitas et al. suggest modifying the recommendations for abstinence duration according to patient condition. In patients with male factor infertility, the recommendation is to collect the sample after just 1 day of sexual abstinence, meanwhile normozoospermic patients should be advised not to exceed 10 days, according to the initial sperm quality analysis [30]. However, the percentage of sperm cells with immature chromatin is statistically significantly increased with 1 day of abstinence, probably because immature sperm produced after recurrent ejaculation accumulates higher levels of sperm containing fragmented DNA [31]. In this respect, novel sperm selection methods have recently been developed, and are focused on the isolation of mature and non-apoptotic spermatozoa with high DNA integrity [1,32].

Finally, it has been shown that sperm morphology is not a good cut-off value to predict IUI outcome. Any semen analysis with significant teratozoospermia [normal forms less than 4%] treated with IUI have the same options of success as long as TMS count is over 1 million [1].

Female Factors: Age and Infertility Etiology

Infertility is a matter of two, and in proposing a treatment, both partners should be taken into account.

Having at least one permeable fallopian tube is a requisite to perform IUI. The other female factors that influences pregnancy rate are: woman's age, infertility etiology, type of cycle [natural versus stimulated and number of pre-ovulatory follicles] and length of infertility.

Age is of paramount importance in the success rate of IUI: chances of achieving a live birth are negatively correlated with advancing maternal age [33]. The age-related decline in female fecundity has been well documented, particularly in women undergoing IUI with donor spermatozoa [34,35]. Up to 38 years, intrauterine inseminations are a valid approach. Between 38 and 40 years, careful evaluation of ovarian reserve, presence of endometriosis or tubal factor should be done prior to advise IUI over IVF.

In women 40 years old and older, treatment beginning with immediate IVF would be the most successful strategy [36-38]. Female etiologies are usually classified in ovulatory disorders [PCOS, unexplained ovulatory disorder, etc.], endometriosis and unexplained infertility [or normal female factor with male factor]: IUI performed for anovulation has a better prognosis [39], and endometriosis stage III or IV the worst [40].

IUI in natural cycles have roughly half the pregnancy rate of stimulated cycles [either with clomiphene or gonatropins] [41,42], especially when 2 pre-ovulatory follicles are developed. Ideally, to limit multiple pregnancy risk maximizing pregnancy rate, 2 pre-ovulatory follicles have to be developed with stimulation. Three follicles, especially in older women, are acceptable [15], while most centers cancel the procedure if more than 3 mature follicles are observed.

Another success factor for post-IUI pregnancy is the length of infertility. Nuojua-Huttunen et al. reported significantly different pregnancy rates according to whether the length of infertility was below or above 6 years [14.2% vs. 6.1%]. IUI should not be recommended to patients with a long-standing duration of infertility [43].

Regarding obesity, there are controverted results, but most studies conclude that with increasing doses of FSH to achieve bi-follicular development, there are similar outcomes with any BMI [44-46]. Smoking has not shown correlation to pregnancy rate in IUI [44].

Synchronizing Intrauterine Insemination with Ovulation

Oocytes have a fertilization window of 12-16 hours, while spermatozoa are able to fertilize the oocyte and survive in the female reproductive tract for around 3 days since the moment of ejaculation [47,48]. However, this only happens in natural conception, in which the spermatozoa go through the cervix in vivo. In the case of IUI, the sperm cells are processed and the seminal plasma is washed away, selecting the motile cells to be injected directly into the uterus. In such case, spermatozoa can only be observed in the abdominal cavity for a few hours, after going through and abandoning the oviduct [49,50]. Therefore, the time frame to achieve a correct fertilization during IUI is brief and, consequently, insemination must be performed at an optimal time for the success of the treatment and the achievement of a clinical pregnancy [51-54].

Physicians have at their disposal different methods to determine the moment of ovulation and synchronize it with IUI. Two strategies are the most widely employed: [a] the detection of the LH surge previous to spontaneous ovulation in the context of a natural cycle; or [b] the induction of ovulation by administering HCG [Human Chorionic Gonadotropin] in the context of an stimulated cycle [55].

Regarding the first strategy, one of the most precise techniques to predict spontaneous ovulation is analyzing the levels of LH in urine or blood [55]. According to WHO, ovulation in natural cycles takes place 24-56 hours after the onset of the LH surge, with a mean time of 32 hours [56]. The advantages of using this method are the convenience of doing urine tests at home, the lower costs associated and its non-invasiveness [57]. However, it also has drawbacks, such as the possibility of obtaining false-negative results. Besides, the LH surge may be under the detection limit of the urine kit employed for the analysis, or be too short to be detected [58,59].

In the second strategy, serial ultrasound scans are performed to monitor follicle growth. Once the dominant follicle reaches a conventionally accepted diameter of 16-18 mm [depending on the

physician or centre], HCG is administered and ovulation is expected in 34-38 hours [60].

Some authors believe that detecting the LH surge may improve the results of the IUI procedure. Since there are HCG receptors present at the uterus, the administration of HCG to induce ovulation could theoretically interfere with endometrial receptivity [61]. Other authors believe that the endogenous LH surge induces a more natural response of the uterus and improves its receptivity in comparison to using HCG to trigger ovulation. Besides, as mentioned before, if HCG is administered prematurely, the follicle may not have time to mature [62]. Furthermore, the use of a natural cycle involves a reduction of medication costs and the prevalence of multiple pregnancies is lower in comparison to stimulated cycles [63,64]. However gonadotropins stimulated cycles have higher pregnancy rates compared with natural cycles [65].

Another crucial aspect debated by different authors is the optimum time interval between the administration of HCG and the IUI in natural cycles. In the majority of published studies, IUI is performed 32-36 hours following HCG administration [66] and it is widely accepted that doing IUI 32-38 hours after HCG injection provides the best results [52]. This time interval is based on ultrasonographic and hormonal studies that have proved the occurrence of follicle rupture at day +2 after HCG administration in 68% of cases in natural cycles [67] and in 81% in stimulated cycles [68]. However, different physiological studies suggest that fertilization is also possible when IUI is performed 24 hours after HCG administration [48,52,56,59,60,69-71]. A few studies have compared different intervals between HCG and IUI, finding no differences in terms of clinical pregnancy: 24 versus 36 hours [72-74] and 24 versus 48 hours [75]. These results suggest that physicians may have a greater flexibility to program IUI after HCG and avoid cancellations because of unavoidable delays.

A very recent meta-analysis has included multiple studies in order to compare the different strategies and treatments previously commented to synchronize ovulation and IUI. These authors have not found any difference when comparing live birth and pregnancy rates between natural cycles detecting the LH rise and stimulated cycles with HCG induction. In the same way, there is no evidence of differences between using urinary and recombinant HCG to induce ovulation in stimulated cycles, between a short and a longer interval between HCG and IUI [32-34 versus 38-40 hours], or between the use of HCG versus a GnRH agonist to induce ovulation [55]. Therefore, choices of treatment should be based on hospital facilities, work routines, staff, costs and drop-out rates. Using urinary HCG or recombinant HCG should be based on patient preferences and costs since pregnancy rates are not significantly altered. Similarly, distinct time intervals between HCG and IUI do not suppose any difference in pregnancy rates, so physicians may be flexible when programming IUI.

Follicle Rupture and Intrauterine Insemination

Follicle rupture is evidenced by the presence of free fluid in Douglas pouch and visible corpus luteum or absence of follicle using ultrasound scanning [76]. This event is conventionally interpreted as a sign of ovulation, but there are few published studies relating follicle rupture detection with the success of intrauterine insemination. A group of researchers found that clinical pregnancy was significantly higher when follicle rupture was detected just after the IUI procedure, in comparison to those cases in which follicle rupture was not detected [77]. Subsequent studies confirmed this finding [76,78]. In one of these studies, the authors only found a higher pregnancy rate in association with follicle rupture when analyzing cases of non-male factor etiology, but not when comparing cases with a male factor etiology. This can be explained by the fact that, in presence of a fertile semen [non-male factor etiology], the only limiting factor is oocyte availability and its limited survival.

Therefore, physicians may use the ultrasound detection of follicle rupture after performing IUI as an additional tool to predict the success of the cycle [78].

Single versus Double Intrauterine Insemination

Since the first intrauterine inseminations were performed, some clinicians choose a double insemination per IUI cycle to improve the chances of success [79], while others prefer to perform a single one, because the pregnancy rates in double inseminations does not seem to be higher [80]. Literature contains studies defending both insemination procedures: double and single IUI and no consensus have been established to date [81,82].

Osuna et al. published a systematic review comparing the effect of double vs single IUI in women with different causes of infertility [81]. This article showed a trend in favour of double IUI. However, the infertility causes infertility of the clinical trials selected were different and these are strongly correlated with live birth and clinical pregnancy rates in IUI cycles. Therefore, the results of this review might be deficient.

A meta-analysis comparing single versus double intrauterine inseminations was published in 2010, in women with unexplained infertility [83]. In this, 6 RCT were included and clinical pregnancy rate did not show significant differences between both groups, although double IUI may provide more spermatozoa and fertilize more oocytes sequentially.

In 2013, other meta-analysis comparing single versus double IUI was published, but in couples with male factor infertility [82]. In this case, double IUI is initially suggested to provide a higher number of inseminated motile spermatozoa, and this number is associated with clinical pregnancy rate, especially in couples with male factor problems. In this meta-analysis, 5 randomized clinical trials were considered from the 2904 reports reviewed. The authors only considered RCTs comparing one versus two IUI when clinical pregnancy or live birth rate data were available. Furthermore, as previous studies showed that no clear benefits are obtained when a second IUI is performed more than 48 h after HCG administration, RCTs were considered only when the second IUI was performed before than 48 h after HCG induction [82].

The first of these RCTs was published by Ragni et al. in 1999, where single IUI was performed 34 h or 36 h after HCG administration whereas in double IUI in group A, in group B the first IUI was performed 12 h after induction and the second was performed 34 h after induction and in group C, IUIs were performed at 34 and 60 hours. The pregnancy rate was higher when a double IUI was performed at 12 and 34 hours, perhaps because while the first IUI provides enough sperm for the first ovulation, the second IUI provides additional sperm to fertilize the subsequently ovulated oocyte, improving the probabilities of success [84].

In 2003 Albrozi et al. published other RCT, where IUI were performed 12 h and 34 h after HCG administration in double IUI

cycles, and 12 h after HCG administration in single IUI cycles. Although the pregnancy rate was higher using double IUI, results were not statistically significant and they concluded that no significant differences occur between double and single IUI [85].

In 2006, two RCTs were published. In one of them, double IUI was performed 12 h and 36 h after HCG induction and single IUI 36h after induction, where no statistical significance were found [86]. In the other, in double inseminations the first IUI was performed 18 to 24 hours after HCG administration whereas the second takes place 36 to 48 hours after HCG, while single IUI was performed 34 h after induction with HCG. In this case, double IUI increased the pregnancy rate significantly [86].

The last RCT referenced by the meta-analysis of Zavos et al. was published in 2010. In this study, double IUI were performed 18 and 24 hours after HCG administration, while single IUI was performed 36 hours after induction. This study also showed no significant differences between both groups [87].

Given this controversy, Zavos et al. concluded in their meta-analysis, after analyzing these 5 RCT, no significant differences were found between the two groups, although there was a trend towards double IUI cycles. They suggest the need for a new well-designed and powered RCT for male factor infertility, to confirm this fact, due to the low number of RCTs included in this meta-analysis and to the limitations they present [82].

Importantly, most of the studies analyzed homologous IUI, however, some studies compared one versus two donor inseminations. The first articles are in favor of double insemination [88], including those where frozen-thawed donor sperm was used [89,90], while current studies are against double IUI, showing similar clinical pregnancy rates in both groups and proving no double IUI cycles are needed when donor sperm is used [91,92].

In conclusion, single intrauterine insemination is acceptable to couples when semen quality is adequate, for example when donor sperm is used or in case of unexplained infertility. On the one hand, there are no significant differences with double IUI for these couples, and on the other hand, the cost of double insemination is higher. However, couples with male factor infertility could benefit when double IUI is used, because it seems to be a trend of better pregnancy rate, but this is not statistically significant for the moment and more RCT are needed to prove it.

Uterine Contractility

Uterine contractions of the non-pregnant uterus has far less publications compared with contractility during pregnancy, but it is well-known that it has an important role in human reproduction [93]. In 1966, Hendriks described myometrial contractions in the nongravid uterus. First results were obtained from painful and invasive transducers inside uterine cavity [94] and it has dissuaded extensive research [95,96]. Since ultrasonography began to be used, it has been possible to investigate uterine contractions without interfering with pregnancy outcome. In order to diminish the subjectivity of the analysis of ultrasonographic records, Fanchin developed a specific software [IôTEC 3.1.2] for three-dimensional ultrasound recordings that is the most effective approach to identify uterine contractions [93].

The hormonal origin of uterine activity was demonstrated with estrogen administration to women without ovarian function. Uterine contractions favour sperm transportation, in part stimulated by prostaglandines present in seminal plasma. The higher number of contractions during the follicular phase facilitate sperm movement to fallopian tubes and the relaxation period after ovulation assist embryo implantation due to progesterone production by the corpus luteum [93].

Birnholz published in 1984 a study including 32 examinations using ultrasound scanning. He visualized endometrial movements for 30 seconds and classified them using a subjective score: None for 0 stripping movements, occasional for 1 and frequent for 2. He observed movements in 19 of 26 women. They did not associate endometrial movements with visible myo-metrial contractions. Patients with frequent movements seemed to have more endometrial fluid and it occurred more frequently when they have had intercourse close to ultrasound exploration [94].

Naturally, uterine contractions are less frequent after ovulation. The overall mean frequency decreases from 4.4 per minute in the follicular phase to 3.5 contractions/min the HCG day [four days later], and 1.5 per minute on day 7 after HCG administration [93].

Two opposite uterine contractility patterns have been described to occur during the follicular phase. In the early follicular phase, there are contractions in every myometrium layer, most times felt be the patient and occasionally painful. Movements are mostly from fundus to cervix with 2-3 contractions every minute, a high mean amplitude [60 mmHg] and a mean resting tone of 40 mmHg [similar to the minimal contractions of labor] [96]. When using macroalbumin aggregates labeled with ^{99}Tc, the group of Leyendecker found in women with endometriosis more extensive retrograde transport towards fundus and tubes when placing these aggregates in the vaginal fornix in comparison with healthy controls [97]. By contrary, in late follicular phase women do not feel the uterine activity. Investigators described more uterine contractions at or near ovulation involving only subendometrial layers of the myometrium similar to wavelike contractions with a peak frequency of 4-5 uterine contractions per minute. When using hysterosalpingo-scintigraphy technique with ^{99}Tc, Kunz described a retrograde transport towards the fallopian tubes only if a follicle of 16 mm or more was present in the ovary and the retrograde transport of macroalbumin aggregates previously placed in the vagina fornix ocurred exclusively towards the tube with the major follicle [96,98].

After observing 5 minutes of uterine contractions by ultrasound, Fanchin et al found an overall number of 4.3 contractions just before the embryo transfer in IVF stimulated cycles. Most contractions [55%] were retrograde from cervix to fundus, 28% were anterograde towards the cervix, 11% were antagonic and the rest [6%] were non-propagated [95].

It was thought that seminal fluid can induce endometrial movements and it is possible to speculate that inherent endometrial hypo-activity and a diminished sperm transport may contribute to human infertility [94]. In mammals, uterine contractions help to favor embryo implantation in natural and IUI cycles [95]. As uterine contractions remain until the moment of fertilization, contractions at IUI may not affect clinical pregnancy rate. A previous study showed that a group of patients with moderate and difficult mock insemination [even using tenaculum] do not differ significantly [$p<0,001$] to a group with an easy mock insemination [99]. Furthermore, Brown et al published that

uterus stimulation during IUI has been shown to improve the results of an IUI cycle [100].

There seems to be unanimity regarding a neutral or positive effect of uterine contractility in IUI cycles. In the same way that in IUI, Woollcott & Stanger described a better IVF outcome when uterine contractility is present during embryo transfer [95], but talking about IVF, the majority are on the contrary. Fanchin published that a gentle mock embryo transfer does not induce significant changes in the number of uterine contractions even with different types of catheter [100]. High-frequency uterine contractions diminish pregnancy and implantation rates and it is better when plasma progesterone concentration on the embryo transfer day is higher [95]. It is also advisable in an IVF cycle to administer progesterone 2 days before embryo transfer instead of starting it the transfer day, this way there are less uterine contractions [2.8 vs. 4.1 contractions/min] and better clinical pregnancy rate [42% vs. 29%]. Hence, in IVF it will be better to transfer blastocysts instead of cleavage embryos in women with high uterine contractions frequency [more than 4 per minute].

In 2001, Brown et al. published a better pregnancy rate after vaginal administration of 400 micrograms of misoprostol at the time of IUI [93]. De Ziegler, in an X-ray based procedure, mimicked the IUI protocols depositing 0.5 mL of iodine-based contrast medium in the middle of the uterine cavity of infertile women and found that about 60% of women promptly emptied the uterine content towards both fallopian tubes. However, about 40% of women did the opposite, and most women with proven endometriosis belonged to this group. Hence, this could be an explanation for the poor success of IUI in women with endometriosis. Findings about retrograde uterine contractility reinforce the Sampson retrograde menstruation theory [96].

Due to the consensus that endometrial contractions occur because of an increase in estradiol levels just before ovulation, a group of investigators used terbutaline [a betamimetic with utero-relaxant properties] to revert the uterus to a retrograde contractile pattern in five of seven of their IVF diskinetic patients. However, none of the studies were held in real IUI conditions, therefore lacking the stimulating influence of prostaglandins present in semen [96].

With a large number of cycles [979 IUI cycles], Blasco et al. published an association between uterine contractility and the success of human IUI cycles. They postulated a new predictive model to correlate the follicle rupture and the number of uterine contractions with the outcome of human IUI. A ruptured follicle and a higher number of uterine contractions per minute observed by ultrasound scan the day of IUI both correlate positively with clinical pregnancy rate [O.R. 2.13, 95% C.I. [1.34-3.41] P value = 0.002] and live birth rate [O.R. 1.67.95% C.I.[1.02-2.74] P value = 0.041] [78].

Conclusions

IUI is a valid approach to solve infertility in couples in which the patient has at least one patent tube, she is less than 40 years old and there are at least 5 million of motile sperm to be inseminated. In women older than 40, with endometriosis, or with a suspected diminished ovarian reserve, a more aggressive but more effective technique as IVF should be considered as first line treatment.

To maximize success rate with low multiple pregnancy rates, gonadotrophin ovarian stimulation to reach bi-follicular development is preferred over multi-follicular development or a natural cycle. Ovulation induction can be achieved either administering HCG or using the spontaneous LH surge, being the first strategy more popular in order to plan clinic workload.

An abstinence interval of approximately 3 days prior to produce the sperm sample is the optimal period for IUI. Either one or two inseminations are valid, ideally performed in the frame time between 12 and 38 hours after ovulation induction. Follicle rupture and uterine contractions observed by ultrasound scan following intrauterine inseminations are favorable prognostic factors.

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