Evaluation of intrauterine insemination practices: a 1-year prospective study in seven French assisted reproduction technology centers

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Objective: To determine the best practices of intrauterine insemination with the partner’s fresh sperm.

Design: Prospective multicenter observational study.

Setting: Assisted reproduction technology (ART) centers.

Patient(s): Seven hundred and seven patients entering the program, regardless of age or cause of infertility.

Intervention(s): Intrauterine insemination by standard procedures.

Main Outcome Measure(s): Effect of patient characteristics (duration of infertility, indications, age, parity, body mass index, semen parameters) as well as IUI parameters on delivery rates per couple or per attempt.

Result(s): The overall live birth rate was 11.4% per cycle, varying from 8.4% to 17.6% between centers. The main differences in practice that had a statistically significant impact on the delivery rate were the use of gonadotropin-releasing hormone (GnRH) antagonists (15.2% with versus 9.4% without) and the number of mature recruited follicles (9.4% for one versus 15.2% for two).

Conclusion(s): Our results indicate that the use of GnRH antagonists has a positive effect on the delivery rate, especially in the multifollicular stimulations that are required when women are older than 27 years. (Fertil Steril® 2016;105:1589–93. ©2016 by American Society for Reproductive Medicine.)

Key Words: Delivery, GnRH antagonist, IUI, ovarian stimulation

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Intrauterine insemination (IUI) is one of the first lines of infertility treatments and assisted reproductive technologies (ART). According to the French registry, the mean delivery rate (DR) per insemination is 10.7%, with wide variations from one center to another (4.4% to 19%) (1). Such variations have been reported in other registries (2, 3). One possible explanation could be the heterogeneity of the treated population. The results may vary as a function of infertility causes, women's age, duration of infertility, or number of motile spermatozoa (4–6). Another explanation could be differences in the IUI procedures, including the protocol of ovarian stimulation, the use (or not) of gonadotropin-releasing hormone (GnRH) antagonists, the time required
for sperm preparation, the number of inseminations per cycle (one or two), or the luteal phase support. It has been reported that ovarian stimulation with follicle-stimulating hormone (FSH) as well as the number of recruited follicles are associated with an increased pregnancy rate (5,7–9).

The benefit of addition of GnRH antagonists to prevent the premature luteinizing hormone (LH) surge is still debated. Some studies have reported an increase in the ongoing pregnancy rate whereas others have reported no effect. It is therefore difficult to reach a conclusion by meta-analysis (10, 11). The number of inseminations per cycle (one or two) has also been reported to influence the pregnancy rate (12), as has the use of luteal support (13) and the delay between sperm preparation and insemination (14). Our study aim to identify the best practices in IUI through a prospective multicenter study that compared the results from ART centers following their normal practices in performing IUI.

MATERIALS AND METHODS

Patients

A total of 707 couples treated in IUI programs from September 1, 2012, to August 31, 2013, were included in the study. The distribution of the number of couples and IUI attempts among the ART centers is reported in Table 1. All couples underwent an extensive infertility evaluation before IUI treatment that examined couple factors (duration of infertility, indications), female characteristics (age, parity, body mass index [BMI]), and male characteristics (age, semen parameters). Exclusion criteria were the use of donor or cryopreserved sperm or female age over 43 years.

All IUI attempts were performed after ovarian stimulation using gonadotropins (human menopausal gonadotropin, recombinant FSH, extracted FSH) with or without a GnRH antagonist according to the protocol of each center. Stimulation monitoring used ultrasound (measurement of the number and size of follicles and of endometrial thickness) and estradiol measurement to determine the timing of ovulation triggering. Ovulation was induced by spontaneous LH surge, extracted human chorionic gonadotropin (hCG), or recombinant hCG.

The primary outcome measures were DR per couple and per cycle, according to predictive factors. The secondary outcome measure was the cost of a live birth obtained by IUI.

Semen Preparation

The semen sample for insemination was analyzed for conventional semen parameters (volume, sperm count, and motility). It was prepared using discontinuous density gradient centrifugation.

Data Collection

Data were recorded anonymously by each center in a common database.

Statistical Analysis

Results were given as the mean ± standard deviation or as the percentage. Qualitative data were compared using the chi-square test, and quantitative data were compared using Student’s t test. P < .05 was considered statistically significant. The data were analyzed with Stat-View software (SAS Institute).

The database was declared to the Comité Consultatif sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé of the French Ministry of Research. According to the French law, patients are informed that their clinical data are registered in a database and can be used for clinical research unless they declare their opposition.

RESULTS

Demographic Data

We included 707 couples who underwent 1,827 IUI cycles. The mean number of IUI cycles per couple was 2.6 ± 1.3. The mean age for women was 33.0 ± 4.8 years (range: 19–43 years) and for men was 35.4 ± 6.0 years (range: 20–62 years), with a statistically significant difference between women and men (P < .001). The average BMI for women was 22.7 ± 4.1 kg/m² (range: 15.6–40.2 kg/m²). Concerning obstetric history, 481 couples had primary infertility (68.5%), and 221 couples had secondary infertility (31.5%); for 7 couples, the history was unknown. The cause of infertility was ovulation disorder (16%), endometriosis (3%), multiple female causes (19%), sperm abnormalities (12%), male and female causes (11%), and unexplained infertility (39%).

The DR was 29.3% per couple and 11.6% per attempt. The multiple DR was 15% (twins only). Also of note, two high-order multiple pregnancies (0.9% of clinical pregnancies: one triplet and one quadruplet) necessitated selective reduction. Figure 1 shows that the DR per couple and per attempt varied in a statistically significant way from one center to another (P < .01).

Couples’ Parameters Influencing the Delivery Rate per Couple

The woman’s age influenced the results, with a decline in DR with older ages. Women younger than 27 years had a DR of 19 (25%) of 77; in women older than 39 years, the DR was 7 (12%) of 59 (P < .01). The DR also statistically significantly decreased when the woman’s BMI was lower than 19 kg/m² (17 of 85, 20%; P < .05), but we found no effect for excess weight (≥ 30 kg/m²).
The duration of infertility (9–151 months) and its causes did not influence the DR. However, it was noteworthy that no delivery was obtained in the 14 couples who had a history of ectopic pregnancy. The DR per couple was statistically significantly reduced when the number of progressive motile spermatozoa recovered after semen preparation was <1 × 10⁶ (4/31, 13%; \(P < .05\)). When the number exceeded 1 million, it had no influence on DR.

**Parameters of Attempts Influencing the delivery Rate per Attempt**

The DR statistically significantly increased with the number of mature follicles \(\geq 15\) mm \((P < .0001)\) (Fig. 2). The use of a GnRH antagonist was associated with a higher DR: 9% (115/1,214) without versus 15% (94 of 613) with an antagonist \((P < .001)\). However, as shown in Figure 3, GnRH antagonist use appeared to be of benefit solely when at least two mature follicles were obtained: for two follicles 8% without a GnRH antagonist versus 17% with \((P < .001)\). The DR was statistically significantly lower when ovulation was triggered by spontaneous LH peak (6%) rather than by extracted hCG (MSD Paris) (12%) or by recombinant hCG (Ovitrelle; Merck Serono) (12%) \((P < .05)\). The optimal interval between ovulation triggering and insemination appeared to be 36 hours, giving a DR of 15% compared with 10% when insemination was performed sooner or later, respectively \((P < .01)\). Duration of delay between sperm preparation and insemination, the volume inseminated, and the temperature of sperm conservation had no influence on the DR. Endometrial thickness and luteal phase supplementation (none or vaginal progesterone) did not influence the DR in either antagonist or nonantagonist cycles.

**Cost of Intrauterine Insemination**

Evaluation of the cost of one IUI attempt (including ovarian stimulation and monitoring, laboratory work, and clinical procedures according to the French tariff system) showed that the use of a GnRH antagonist increased the cost from €500 to €700. However, because the efficiency of the GnRH antagonist cycles was higher, the cost of one delivery was lower (€5,280 vs. €4,565).

**DISCUSSION**

Our study has found wide differences in the birth rates among seven ART centers, and analysis of the database revealed that they were mainly due to differences in ovarian stimulation (number of recruited follicles and use of GnRH antagonists). We found a DR of 9% after monofollicular and 16% after bifollicular stimulation. This is in agreement with the results of other studies \((5, 15, 16)\). However, the risk of multiple pregnancy increases with the number of follicles, mainly when three or more follicles are recruited \((9)\). Because the DR is greatly influenced by the woman’s age and the risk of multiple pregnancy decreases with age, the optimum number of mature follicles must be adjusted as a function...
of age [5]. We observed no multiple pregnancies in patients older than 39 years, even when three follicles were recruited. Conversely, the multiple pregnancy rate was as high as 38% in patients aged younger than 27 with two mature follicles, which clearly pleads for monofollicular stimulation in very young patients.

In our study, the use of GnRH antagonists was associated with a higher DR, but only after multifollicular stimulations. However, because these results come from a nonrandomized study, they must be interpreted with caution. Although a recent meta-analysis drew clear conclusions about the beneficial value of GnRH antagonists in controlled ovarian stimulation for IUI [11], their use is still debated as their benefit seems dependent on the number of mature follicles. In a randomised, controlled trial, Gómez-Palomares et al. [17] also found evidence that the clinical pregnancy rate was higher in the antagonist group only if more than one follicle ≥18 mm was present on the day of hCG triggering. Bakas et al. [18] reported an enhancement of pregnancy rate with a mean number of 2.1 ± 1.1 follicles. Lambalk et al. [19] found no benefit in GnRH antagonists, but the number of mature follicles was only 1.3 ± 0.6. This can be explained by a higher risk of premature LH surge when two or more follicles are recruited, inducing a desynchronization between ovulation and insemination [19]. This argument was confirmed by Luo et al. [11]; eight randomized, controlled trials reporting premature luteinization events found that the use of a GnRH antagonist decreased this risk by 78% (odds ratio 0.22; 95% confidence interval, 0.16–0.30; \( P < .00001 \)). Desynchronization between ovulation and insemination could also explain the poor results obtained when ovulation was triggered by a spontaneous LH peak compared with an hCG-induced one, as has been observed by ourselves and others [16].

We found no effect of infertility duration, in agreement with Merviel et al. [5] but unlike Nuojua-Huttunen et al. [4]. It should be noted that in the latter study, the investigators compared couples with over versus under 6 years of infertility duration whereas in our study only a few patients exceeded 6 years (49 of 707).

Concerning female BMI, we found no effect of excess weight (BMI >30 kg/m²), in agreement with Souter et al. [20] and Dodson et al. [21], whereas Soria et al. [22] found an increase in pregnancy rate when BMI was higher than 25. However, in overweight women, Aydin et al. [23] reported a lower success rate and Veleva et al. [24] an increase in the risk of miscarriage. These discrepancies could be due to the degree of obesity in the studied populations. Conversely, low BMI (<19 kg/m²) was associated with a lower DR, which is in agreement with the study of Veleva et al. [24] that reports a higher miscarriage rate after IVF in overweight women.

With regard to sperm parameters and sperm preparation and conditioning, the only influential parameter appeared to be the number of progressive motile spermatozoa recovered after semen preparation with a threshold of 1 \( \times 10^6 \), corresponding to that reported by other investigators [6, 25, 26] although the threshold varied greatly (from 0.8 to 5 million) according to the studies; for a review, see Ombelet et al. [27]. Unlike Fauque et al. [14], we found no effect with a delay between sperm preparation and insemination, but the delay was quite short in our study, which perhaps accounts for the lack of effect. One weakness of our study is that it did not evaluate the effect of sperm morphology on IUI success. This was a voluntary omission because the use of different morphology classifications in the various centers made any comparison impossible [28].

Finally, we found no effect of luteal phase support, regardless of the ovarian stimulation protocol used (with or without GnRH antagonists). The literature on this topic is conflicting, as some investigators have found an increase in live births with progesterone supply but others have not [13].

In optimal IUI practice, bifollicular stimulation associated with the use of GnRH antagonists allows high DRs. However, the number of follicles recruited must be adjusted to the woman’s age to limit the risk of multiple pregnancies, as shown by the absence of multiple pregnancies in women older than 38 years even with three recruited follicles, and by the high multiple pregnancy rate (38%) in patients younger than 28 years with two mature follicles.

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REFERENCES


