

# Ovarian stimulation in infertile women treated with the use of intrauterine insemination: a cohort study from China

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**Objective:** To study the effectiveness of different ovarian stimulation protocols compared with natural cycle treatment in an intrauterine insemination (IUI) program.

**Design:** Retrospective cohort study.

**Setting:** Large reproductive medicine center.

**Patient(s):** Couples with unexplained or mild male-factor infertility.

**Intervention(s):** Couples were treated with the use of natural-cycle IUI, or IUI after ovarian stimulation with the use of clomiphene citrate (CC), letrozole, or gonadotropins.

**Main Outcome Measure(s):** Live birth, multiple pregnancy rates, and cumulative live birth rates after three IUI cycles.

**Result(s):** We performed 14,519 IUI cycles in 8,583 couples. Compared with natural-cycle IUI (6.2%), live birth rates were significantly higher in IUI cycles stimulated with the use of CC (8.9%), letrozole (9.4%) and gonadotropins (9.5%). The multiple pregnancy rate resulting from natural cycles was 0.7%, compared with 4.6% in CC cycles, 1.3% in letrozole cycles, and 4.2% in gonadotropin cycles. Cumulative live birth rates after three IUI cycles were 18.4% after natural-cycle IUI, and 25.7%, 26.2%, and 23.7% with the use of CC, letrozole, and gonadotropins, respectively.

**Conclusion(s):** In an IUI program for unexplained or mild male-factor infertility, ovarian stimulation with letrozole may significantly increase live birth rates while controlling multiple pregnancy rates. (Fertil Steril® 2018;109:872–8. ©2018 by American Society for Reproductive Medicine.)

**Key Words:** Intrauterine insemination, ovarian stimulation, unexplained infertility, mild male factor, letrozole

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In many countries, intrauterine insemination (IUI) is the treatment of first choice for couples with unexplained or mild male-factor infertility because it is thought to improve the pregnancy chances while being simple, easy to manage, and relatively low cost (1, 2). Although IUI can be applied in the natural cycle, it is often combined with ovarian

stimulation with the aim to establish multiple follicle growth. Multiple follicle growth is thought to increase the chances of pregnancy, but bears at the same time the risk of multiple pregnancy (3). Multiple pregnancy is associated with an increased risk of perinatal complications, including preeclampsia, hemorrhage, and spontaneous preterm birth, as well as

the risks associated with the birth of multiple children (4).

It is therefore controversial whether ovarian stimulation should be applied in women with unexplained or mild male-factor infertility treated in an IUI program. Some investigators have advocated in favor of ovarian stimulation, whereas others argue that IUI without ovarian stimulation should be the treatment of first choice (5, 6). In addition, there is no consensus on the optimal protocol for ovarian stimulation in an IUI program (7, 8).

To study the effectiveness and safety of different ovarian stimulation protocols used in IUI programs, we compared the live birth and multiple

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pregnancy rates of natural and stimulated IUI cycles in a large reproductive medicine center in Beijing, China.

## MATERIALS AND METHODS

### Patients

We performed a retrospective study in the Center of Reproductive Medicine of Peking University Third Hospital. The clinical data were retrieved from our clinical database. The study was approved by the local Ethics Committee.

We studied women undergoing IUI with or without ovarian stimulation. Couples had to have childwish for  $\geq 1$  year, had at least one patent fallopian tube (as established with the use of hysterosalpingography or laparoscopy), and had to have an ovulatory cycle. Couples were excluded if they had bilateral tubal pathology, irregular cycles, polycystic ovarian syndrome, or other endocrine disorders. We distinguished couples with mild male-factor infertility, defined as sperm concentration  $>5$  million and  $<20$  million per milliliter or progressive motility sperm  $\geq 10\%$ , and couples with unexplained infertility, in whom semen analyses and the rest of the fertility work-up were normal.

### Ovarian Stimulation Protocols and Management in IUI Program

In addition to natural cycles without ovarian stimulation, there were three types of ovarian stimulation protocols used in the study:

1. Clomiphene citrate (CC) at 50–100 mg/d starting from day 3 of the menstrual cycle for 5 days.
2. Letrozole at 2.5–5 mg/d starting from day 3 of the menstrual cycle for 5 days.
3. HMG or urofollitropin (Zhuhai Livzon) at 75 IU/d starting from day 3 for a various duration depending on the ovarian response.

Follicle growth was monitored with the use of transvaginal ultrasound by gynecologists in the reproductive medicine center. In both natural and stimulated cycles, we monitored follicle development from day 8 to day 10 of the cycle, and then repeated every 2 or 3 days based on the follicle sizes. Couples were advised to cancel a cycle if four or more dominant follicles were present. We performed ovulation triggering with the use of intramuscular injection of 5,000–10,000 IU urinary hCG (Zhuhai Livzon) when at least one mature follicle was assessed to  $\geq 18$  mm. Insemination was performed 36–40 hours after hCG injection.

### Semen Preparation and Insemination

On the day of insemination, semen was collected at the laboratory after 3–7 days of abstinence and prepared with density-gradient centrifugation after liquefaction. The volume of washed semen sample used for insemination was 0.5 mL. After evaluation of count and motility of spermatozoa, the insemination procedure was performed by a gynecologist in a room adjacent to the laboratory. After insemination, women had bedrest for 30 minutes.

### Luteal Phase Support

Luteal phase support was applied in all patients, commencing on the 2nd day after insemination. It consisted of 200 mg/d progesterone soft capsules (Asen) or 20 mg/d dydrogesterone (Duphaston; Abbott) for 14 days. A serum hCG assay was performed on the 16th day after insemination to assess whether pregnancy occurred. If the result was positive, ultrasound examination was performed after 16–19 days.

### Outcomes

A clinical pregnancy was defined after sonographic evidence of an intrauterine gestational sac was observed. A live birth was defined as the birth of an infant after 28 weeks gestation with postnatal evidence of life. Multiple pregnancy was defined as more than one intrauterine gestational sac observed.

### Statistical Analysis

We reported continuous variables as mean  $\pm$  SD and dichotomous variables as percentages. We compared clinical pregnancy, multiple pregnancy, and live birth rates for IUI cycles stimulated with the use of CC, letrozole, and gonadotropins and for IUI cycles without ovarian stimulation. First, we calculated unadjusted relative risks (RRs) and 95% confidence intervals (CIs), with the use of IUI in the natural cycle as the reference. We then performed a log binomial regression model for multivariate analysis in which we controlled for female age, duration of infertility, cycle number, primary infertility (as dichotomous variables), and sperm count after washing. A generalized estimating equation with exchangeable working correlation structure and robust variance estimation was used to account for clustering (multiple cycles within the same couple). Estimates were RR of live birth in each of the three ovarian stimulation groups compared with the natural group, along with 95% CI. Next, we performed an analysis limited to the first cycle only and compared fertility outcome stratified for follicle numbers. Finally, to assess the impact of multiple IUI cycles with one stimulation protocol, we calculated the cumulative live birth rates over three cycles. A log binomial regression model was used to estimate the RR of cumulative live birth rates by adjusting for female age, duration, primary infertility, and sperm count after washing. A chi-square test was used to compare qualitative data between groups. Analysis of variance was used to compare means between groups. A *P* value of  $<.05$  was considered to indicate statistical significance. Statistical analysis was performed in SPSS 19.0 software (IBM).

## RESULTS

From April 2011 to December 2015, data from 14,519 IUI cycles from 8,583 couples were included in this study. Among these cycles, 6,746 were performed during natural cycles, 3,205 in CC-stimulated cycles, 1,989 in letrozole-stimulated cycles, and 2,579 in gonadotropin-stimulated cycles. Baseline characteristics per couple, including female age, duration of infertility, and proportion of the first cycle were significantly different between the groups. Women undergoing natural-cycle IUI were slightly older (32.4 vs. 31.6 years),

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