Intrauterine Insemination Treatment Strategy for Women over 35 Years Old: Based on a Large Sample Multi-center Retrospective Analysis

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INTRODUCTION

As we all known, maternal age and ovarian reserve are two of the most important prognosis factors for fertility. In 1980, the study of Menken et al.[1] showed the female fertility declined after 32 years old, especially after 37 years old. The numbers of infertile couples are increasing worldwide, because of the delayed child-bearing. With two-child policy implemented in China, more and more infertility women with advanced ages seek for assist reproductive technology (ART) to achieve pregnancy and get their babies. However, ART choices for infertility women with advanced ages are still controversial.

Although in vitro fertilization and embryo transfer (IVF-ET) have been widely used to treat infertility women with a relatively higher pregnancy rate, intrauterine insemination (IUI) remains a prevalent procedure as a low-cost and less invasive therapeutic approach for infertile couples.[2-4] The clinical pregnancy rates (CPRs) of IUI ranged between 10% and 20% per cycle,[5,6] and large population-based data from the European Society of Human Reproduction and Embryology showed the delivery rate per cycle was about 9%.[7,8] However, the management strategy for women with advanced age (older than 35 years, especially than 38 years) still confused clinicians. This study aimed to investigate the suitable management for women over 35 years old by analyzing success rate of IUI between different ages based on multicenter data from four reproductive medical centers in China.

METHODS

Study design

A retrospective study design and a data collection protocol, which was approved by the Ethics Committee of Peking University Third Hospital, were used to collect information of infertility couples undergoing IUI cycles in four reproductive medical centers (Reproductive Medical Centers of Peking University Third Hospital, Haidian Maternal and Child Health Hospital, Beijing Obstetrics and Gynecology Hospital, and Tianjin Fifth Central Hospital) between January 1, 2013 and December 31, 2013. Inclusion criteria were as follows: Infertility couples underwent IUI treatment. The indications of IUI were as follows: Unexplained infertility; endometriosis with healthy fallopian tubes; ovulation disorders including polycystic ovarian syndrome, idiopathic ovulation disorder or diminished ovarian reserve; mild-to-moderate oligo/asthenospermia; and mixed infertility. The patients were unilateral tubal patency at least, without any endocrine disorders or abnormal uterus cavity, such as hyperprolactinemia, endometrial polyps, uterus septum or adhesion, or submucous uterine myoma.

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The recorded parameters were as follows: indications, number of attempts, female characteristics including age, duration of infertility, body mass index (BMI), basal follicle stimulating hormone (FSH) level, tubal patency, antral follicle count (AFC), ovulation induction (OI) and OI regimens, and male characteristics, such as semen parameters after processing on the IUI day. Technical aspects of IUI, such as cycle regimen (natural cycle or OI cycle, or the OI protocol), endometrial thickness on IUI day, ovulation triggering (human chorionic gonadotropin [hCG]) or not, and luteal phase support protocol, were involved.

Ultrasound-monitor ovulation in natural or ovulation induction cycle

If the patient had regular menstrual cycles or normal ovulation, we started the ultrasound monitor ovulation on days 8–10 until ovulation in natural cycles. If the patients had ovulation disorders, or failed in natural cycles several times, we would start stimulated cycle on days 3–5 of the cycle and choose appropriate stimulating protocols accordingly, such as clomiphene citrate (CC), letrozole (LE), human menopausal gonadotropin (hMG), CC + hMG, or LE + hMG. The interval for ultrasound monitoring was once for 2–3 days depending on the ovarian response, and changed to once a day when the dominant follicle reached 15 mm, until the follicle ruptured.

When at least one mature follicle was assessed to have ranged in diameter between 18 mm and 20 mm, we performed ovulation triggering via intramuscular injection of urinary hCG (5000–10,000 U of hCG) or subcutaneous injection of recombinant hCG (250 μg of ovitrelle) in stimulated cycles or in some natural cycles. With the help of ultrasound monitoring, urine/serum luteinizing hormone test and hCG administration, insemination was performed within 24 h before and/or after ovulation. When more than three mature follicles were observed, the cycle should be canceled.

Semen processing and intrauterine insemination

After 2–7 days of abstinence and 2 h before insemination, semen was collected at the laboratory. After liquefaction, semen was examined according to the World Health Organization guidelines and processed using the swim-up method. Insemination was carried out using an intrauterine catheter.

Luteal phase support and pregnancy outcomes

Luteal phase support protocol was progesterone (100 mg/capsule, ASEN Pharmaceutical, China) or dydrogesterone (10 mg/pill, Abbott Laboratories, USA), started 3 days after ovulation and continuously taking to 6–12 gestational weeks. A serum or urine hCG assay was performed 16 days after IUI. Clinical pregnancy was defined as a fetal heartbeat on an ultrasound performed 30–40 days after IUI. The pregnancy outcomes were obtained by telephone follow-up.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or percentage. The statistical analysis was performed using the Statistical Package for Social Sciences (version 13.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using Chi-square test. The multiple regression analysis was performed to reveal prognosis factors. The main outcomes were CPR and live birth rate (LBR). A $P < 0.05$ was considered statistically significant.

RESULTS

During the study, there were 3990 eligible cycles in four reproductive centers, including 2600 cycles (65.16%) in Reproductive Medical Center of Peking University Third Hospital, 840 cycles (21.05%) in Haidian Maternal and Child Health Hospital, 297 cycles (7.44%) in Beijing Obstetrics and Gynecology Hospital, and 253 cycles (6.34%) in Tianjin Fifth Central Hospital. The CPR was 12.66% (505/3990), and the LBR was 8.29% (330/3982). Eight patients were lost to follow-up without the pregnancy outcomes (the dropout rate was 0.20%).

The basic characteristics of involved women were as follows: The mean age was 31.5 ± 3.7 years (range 21–48 years), the mean infertility time was 3.4 ± 2.2 years (range 0.5–18.0 years), mean BMI was 22.5 ± 3.4 kg/m^2 (range 15.6–35.3 kg/m^2), basal FSH was 6.9 ± 2.3 mU/ml (range 0.4–27.3 mU/ml), and the mean AFC was 14.7 ± 9.0 (range 1.0–70.0).

Since the maternal age is one of the most important factors for the CPR and LBR, and the aim of this study was analyzing the success rate of IUI between different ages, we did stratified analysis according to the different female ages [Figure 1]. The CPR and LBR were decreased with the increasing of maternal age and significantly decreased in those aged 38 years and older.

Besides maternal age, there were other factors might affect the outcomes of IUI, including primary or secondary infertlity, duration of infertility, BMI, basal FSH, AFC, and attempts of IUI. The multiple regression analysis showed that the predictive factors for CPR and LBR were maternal age (odds ratio [OR]: −0.214, 95% confidence interval [CI]: 0.616–0.931, P = 0.001 for CPR; OR: −0.214, 95%
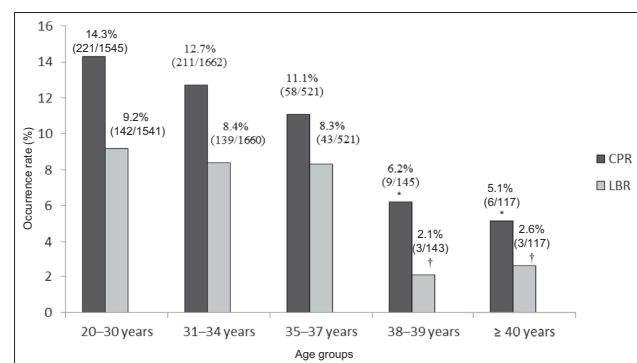

Figure 1: The different CPR and LBR among women with different ages. *$P < 0.05$ for CPR, compared with age groups of 20–30 years, 31–34 years, and 35–37 years; †$P < 0.05$ for LBR, compared with age groups of 20–30 years, 31–34 years, and 35–37 years. CPR: Clinical pregnancy rate; LBR: Live birth rate.

CI: 1.074–1.624, *P* = 0.013 for LBR) and AFC (*OR*: 0.001, 95% *CI*: 0.998–1.003 *P* = 0.005 for CPR; *OR*: 0.001, 95% *CI*: 0.997–1.002, *P* = 0.008 for LBR). Moreover, when we analyzed women aged under and over 35 years old (*n* = 3207 and 783, respectively), the predictive factor for CPR and LBR was AFC only (<35 years old: *OR*: 0.040, 95% *CI*: 1.354–1.963, *P* < 0.001 for CPR and *OR*: 0.589, 95% *CI*: 1.142–1.020, *P* = 0.002 for LBR; ≥35 years old: *OR*: 0.934, 95% *CI*: 0.546–1.406, *P* < 0.001 for CPR and *OR*: 2.014, 95% *CI*: 0.485–1.517, *P* < 0.001for LBR).

DISCUSSION

This study was a large multicenter comprehensive analysis to reveal the outcomes of IUI for women with different ages, especially over 35 years old. This study included 3990 IUI cycles of 4 ART centers, the overall CPR and LBR were 12.66% and 8.29%, respectively similar to the published data.[7,9]

As all we known, the maternal age and ovarian reserve are two of the most important prognosis factors for fertility.[9-11] This study showed a decreased CPR and LBR with increasing age (over 35 years old), and when the woman aged 38 years and above, the CRP and LBR dropped significantly. The multiple regression analysis also indicated age and AFC as the predictive factors for IUI outcomes. However when we analyzed women under or over 35 years old separately, age was not an impact factor any more, the AFC, representing for ovarian reserve, was the most important impact factor. Depending on our data, we suggested for the women under 35 years old with proper indications; IUI was a low-cost and less invasive therapeutic strategy, but those aged 35 years and above, should be suggested more aggressively IVF-ET than those under 35 years, especially for those with decreased ovarian reserve. Depending on the data of our center, women accepting IVF-ET/intracytoplasmic sperm injection diagnosed poor responder following Bologna criteria,[9] the CPR was 19.1% and LBR was 11.8% (unpublished data). Hence, we suggested for patients over 35 years old, especially older than 38 years, IVF-ET should be the first choice even they had indication for IUI. Moreover, for those aged between 35 and 37 years, IUI could be a choice with proper indications. Although in our study, the attempts of IUI was not the predict factor for IUI outcomes, we still suggested that those patients should consider 3–6 attempts of IUI and take no more than 1 year. The data from Dinelli *et al.*[9] analyzed 2019 cycles IUI, and showed the similar results, they found that pregnancy rate decreased after 30 years old and significantly decreased after 40 years old. They suggested patients aged 36–38 years to consider up to four attempts of IUI and take within no more than 1 year. For women aged 39–40 years, only secondary infertlity women with good ovarian reserve should accept two to three attempts of IUI. No IUI attempt should be proposed in women older than 40 years. In this study, the times of attempts were not the predict factor for IUI, so we did not suggest any IUI attempt for those aged 38 years and older, especially with for those with decreased overian reserve.

In conclusion, the success rate of IUI decreased with increasing maternal age. We suggested IUI should be provided for patients under 35 years old with normal ovarian reserve. For those aged 40 years and older, no IUI attempt should be proposed.

Conflicts of interest
There are no conflicts of interest.

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