Outcome Analysis of In Vitro Fertilization-Embryo Transfer Treatment in Women Aged 40 and Above: Postprint

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Abstract

Objective To investigate the treatment outcomes of in vitro fertilization-embryo transfer (IVF/ICSI-ET) in women over 40 years of age. Methods A retrospective analysis was conducted on the clinical data of 1050 initiated cycles of non-donor oocyte IVF/ICSI-ET in women aged 40 years at the Reproductive Medicine Center of Nanfang Hospital, Southern Medical University from January 2007 to December 2015. The women were divided into groups based on age: 40-year-old group (n=393), 41-year-old group (n=266), 42-year-old group (n=158), 43-year-old group (n=107), 44-year-old group (n=64), and 45 years (45-51 years) group (n=62). The clinical characteristics and assisted reproductive outcomes were compared and analyzed among the groups. Pregnancy outcomes were compared among different ovarian stimulation protocols and different numbers of transferred embryos. Results There were 1032 oocyte retrieval cycles and 750 transfer cycles. Clinical pregnancy was achieved in 113 cycles, with a clinical pregnancy rate of 17.7%. Among these, 64 cycles resulted in live births, with a live birth rate of 8.5%. The clinical pregnancy rates for each group were 23.4%, 21.0%, 13.1%, 9.2%, 5.6%, and 0%, respectively. The embryo implantation rates were 11.2%, 10.2%, 6.3%, 5.1%, 2.3%, and 0%, respectively. The early spontaneous abortion rates for each group were 31.0%, 35.9%, 42.9%, 42.9%, and 100%, respectively. The live birth rates were 11.9%, 11.8%, 2.8%, and 3.9%, respectively. The clinical pregnancy rates for the long protocol, short protocol, antagonist protocol, and ovulation induction protocol were 23.6%, 10.2%, 13.3%, and 2.3%, respectively. Among the 750 transfer cycles, the clinical pregnancy rate was 3.8% when one embryo was transferred, 12.6% when two embryos were transferred, and 23.0% when three embryos were transferred. Conclusion The clinical pregnancy rate decreased significantly year by year in patients older than 40 years, and the probability of achieving live birth was extremely low for women aged 44 years. For women aged 40 years, even without other obvious causes of

infertility, assisted reproductive technology treatment should be implemented after informed consent. For women aged 44 years, seeking donor oocytes is a better option.

Full Text

Preamble

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Abstract

Objective: To investigate the clinical outcomes of in vitro fertilization or intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) in women aged over 40 years.

Methods: We retrospectively analyzed 1050 non-donor IVF/ICSI-ET cycles performed from January 2007 to December 2015 in women aged 40 years or above, including 393 women at 40 years of age, 266 at 41 years, 158 at 42 years, 107 at 43 years, 64 at 44 years, and 65 at 45-51 years. The clinical characteristics and outcomes of the women in different age groups were compared and analyzed. The pregnancy outcomes of different ovarian stimulation protocols and different numbers of embryos transferred were also compared.

Results: Oocyte retrieval was achieved in 1032 treatment cycles. Of the 750 embryo transfer cycles, the clinical pregnancy rate was 17.7% (113/750), and the live birth rate was 8.5% (64/750). The clinical pregnancy rates in the six age groups were 23.4%, 21.0%, 13.1%, 9.2%, 5.6% and 0%, and the implantation rates were 11.2%, 10.2%, 6.3%, 5.1%, 2.3% and 0%, respectively. The early spontaneous abortion rates were 31.0%, 35.9%, 42.9%, 42.9% and 100%, respectively, and the live birth rates were 11.9%, 11.8%, 2.8% and 3.9%. The clinical pregnancy rates for the long protocol, short protocol, GnRHa antagonist protocol, and ovulation induction protocol were 23.6%, 10.2%, 13.3%, and 2.3%, respectively. In the 750 transfer cycles, the clinical pregnancy rate was 3.8% with single embryo transfer, 12.6% with double embryo transfer, and 23.0% with triple embryo transfer.

Conclusion: In women aged 40 years or above, the clinical pregnancy rate decreased significantly with age, and the live birth rate was extremely low in women aged beyond 44 years. Assisted reproductive technique is recommended

for women aged 40 years and above even when no identifiable causes of sterility are present. For women aged above 44 years, oocyte donation may be a better option.

Keywords: in vitro fertilization; intracytoplasmic sperm injection-embryo transfer; assisted reproductive techniques; elderly women of child bearing age

Introduction

With the development of modern society, women are increasingly postponing childbearing, leading to a growing number of older women seeking assisted reproductive treatment. Following the implementation of China' s universal two-child policy, many women over 40 years of age who meet the fertility policy requirements have shown strong desire for childbearing and are actively seeking assisted reproductive treatment. However, female fertility potential declines significantly with advancing age, posing a major clinical challenge in helping older women achieve pregnancy. Currently, there are only a few domestic studies with small sample sizes reporting treatment outcomes of assisted reproductive technology in women over 40 years old, showing that clinical pregnancy rates gradually decrease while miscarriage rates increase with age, resulting in declining live birth rates [1-3]. The demand for assisted reproductive technology among older women is increasing, yet satisfactory treatment outcomes remain elusive, and there is ongoing controversy regarding the upper age limit for assisted reproductive treatment in this population [4].

This study retrospectively analyzed the clinical characteristics and treatment outcomes of 1050 cycles in infertile women aged 40 years and above who underwent non-donor in vitro fertilization-embryo transfer (IVF-ET) or intracytoplasmic sperm injection-embryo transfer (ICSI-ET) in our center from January 2007 to December 2015. We aimed to investigate the treatment efficacy and clinical value of IVF/ICSI-ET in older women to provide better evidence for clinical decision-making in assisted reproductive treatment for this population.

1.1 Study Subjects and Grouping

We collected clinical data from 1050 initiated cycles in 717 women aged 40 years and above who underwent non-donor IVF/ICSI-ET treatment at the Reproductive Medicine Center of Nanfang Hospital, Southern Medical University between January 2007 and December 2015. The age range was 40-51 years, with a mean age of 41.5 years. The duration of infertility ranged from 1 to 22 years, with an average of 7.1 years. Among them, 153 patients (21.3%, 153/717) were diagnosed with primary infertility, and 564 patients (78.7%, 564/717) with secondary infertility. The 1050 initiated cycles were divided into six age groups: 40-year-old group (n=393), 41-year-old group (n=266), 42-year-old group (n=158), 43-year-old group (n=107), 44-year-old group (n=64), and 45-year-old group

(n=62). The 45-year-old group had a mean age of 46.2 years. Causes of infertility included pelvic tubal factors, endometriosis, ovulation disorders, diminished ovarian reserve, advanced maternal age, uterine factors, and male factors.

1.2 Methods

Based on patients' ovarian reserve function and underlying conditions, controlled ovarian stimulation protocols were employed, including the long protocol, short protocol, super-long protocol, antagonist protocol, and ovulation induction protocol. The decision to perform IVF or ICSI was made according to gamete quality and fertilization outcomes in previous IVF/ICSI cycles. One to three embryos with the highest morphological scores were selected for transfer 72 hours after oocyte retrieval. Starting on the day of oocyte retrieval, routine luteal support was provided with intramuscular progesterone, oral dydrogesterone (Duphaston), and estradiol valerate (Progynova). Serum -human chorionic gonadotropin (-hCG) was measured 12 days after embryo transfer, and transvaginal ultrasound was performed 4 weeks after transfer. The presence of a gestational sac was defined as clinical pregnancy, and the presence of two or more gestational sacs was defined as multiple pregnancy. Pregnancy termination before 12 weeks was defined as early spontaneous abortion. At 12 weeks of gestation, B-ultrasound examination showing at least one normally developing fetus was defined as ongoing pregnancy [5]. Pregnancy termination between 12 and 28 weeks due to various causes was defined as late pregnancy loss.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 20.0 software. Measurement data were expressed as mean ± standard deviation, and count data as percentages. Comparisons of multiple groups of measurement data were performed using one-way ANOVA or non-parametric tests. Comparisons of rates were performed using the ^{2} test. $P<0.05$ was considered statistically significant.

Results

2.1 Patient General Conditions and Clinical Characteristics

A total of 717 patients with 1050 initiated cycles were included. Among these, 19 cycles were canceled due to poor ovarian response to gonadotropin (Gn) (1.8%), 19 cycles had no oocytes retrieved (1.8%), 76 cycles were canceled due to fertilization failure or lack of transferable embryos (7.2%), and 186 cycles were canceled for other reasons (17.7%). A total of 750 transfer cycles were performed, with a transfer cancellation rate of 28.6% (300/1050). The general conditions of patients in different age groups are shown in Table 1 . There were no statistically significant differences in basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), or estradiol (E2) levels among the groups. However, basal antral follicle count (AFC) decreased gradually with age, showing a statistically significant difference ($P<0.001$). Body mass index (BMI) and

transfer cancellation rate also showed statistically significant differences among groups (P=0.001).

2.2 Comparison of Ovarian Stimulation and Embryo Parameters Across Age Groups

The average total Gn consumption in each age group was greater than 3500 IU, showing an increasing trend with age, although the average Gn consumption in both the 44-year-old and 45-year-old groups was lower than in the 43-year-old group, with no statistically significant difference among groups (P=0.328). There were no statistically significant differences in Gn stimulation duration, LH level on hCG administration day, or progesterone level on hCG administration day across age groups. The 40-year-old group had the highest average E2 level on hCG administration day, while the 44-year-old group had the lowest, with a statistically significant difference among groups (P=0.007). With increasing age, the number of retrieved oocytes, fertilization rate, normal fertilization rate, and number of transferable embryos all decreased. However, the 42-year-old group had higher average oocyte retrieval, and the 45-year-old group had a higher normal fertilization rate and more transferable embryos than the 44-year-old group. All these parameters showed statistically significant differences among groups (all P<0.05). The ovarian stimulation and embryo parameters of patients in different age groups are shown in Table 2 .

2.3 Comparison of Pregnancy Outcomes Across Age Groups

Among the 1032 oocyte retrieval cycles, 750 cycles underwent fresh embryo transfer (72.7%). Clinical pregnancy was achieved in 133 cycles, with a clinical pregnancy rate of 17.7% (133/750). Live birth was achieved in 64 cycles, with a live birth rate of 8.5% (64/750). In the 44-year-old group, only 2 transfer cycles achieved clinical pregnancy, but both resulted in early spontaneous abortion. In the 45-year-old group, none of the 42 transfer cycles achieved clinical pregnancy. With increasing age, clinical pregnancy rate, ongoing pregnancy rate, live birth rate, and embryo implantation rate all decreased gradually, showing statistically significant differences among age groups (P<0.01). Early spontaneous abortion rate and late pregnancy loss rate increased with age, but the differences were not statistically significant (P>0.05). There were no statistically significant differences in multiple pregnancy rate or premature birth rate among groups (P>0.05). The pregnancy outcomes of patients in different age groups are shown in Table 3 .

2.4 Comparison of Pregnancy Outcomes Across Different Ovarian Stimulation Protocols

Based on individual patient conditions, the following controlled ovarian stimulation protocols were used: long protocol, short protocol, super-long protocol, antagonist protocol, and ovulation induction protocol. The proportions of these protocols in fresh embryo transfer cycles were: long protocol 48.5%

(364/750), short protocol 7.9% (59/750), antagonist protocol 37.1% (278/750), super-long protocol 0.6% (5/750), and ovulation induction protocol 5.9% (44/750). The overall clinical pregnancy rates for each protocol were 23.7%, 10.2%, 13.3%, 60.0%, and 2.3%, respectively, with statistically significant differences (P<0.001). The overall live birth rates were 55.8%, 50.0%, 29.7%, 66.7%, and 0, respectively, with statistically significant differences (P=0.038). When comparing clinical pregnancy rates of different protocols within each age group, statistically significant differences were found in the 40-year-old and 41-year-old groups (both P<0.05), but not in the other age groups (all P>0.05). Comparison of clinical pregnancy and live birth rates between the long protocol and antagonist protocol showed statistically significant differences in overall rates (both P<0.05). Within the 40-year-old group, the difference in clinical pregnancy rate between the two protocols was statistically significant (P=0.008), but no significant differences were found in other age groups (all P>0.05). The pregnancy outcomes of different ovarian stimulation protocols are shown in Table 4 .

2.5 Pregnancy Outcomes with Different Numbers of Transferred Embryos

In the 750 transfer cycles, the number of embryos transferred depended on the number of available embryos. In 106 cycles with single embryo transfer, 4 cycles achieved clinical pregnancy, resulting in a clinical pregnancy rate of 3.8% (4/106). In 182 cycles with double embryo transfer, 23 cycles achieved clinical pregnancy, resulting in a rate of 12.6% (23/182). In 461 cycles with triple embryo transfer, 106 cycles achieved clinical pregnancy, resulting in a rate of 23.0% (106/461). The differences among groups were statistically significant (P<0.001). The clinical pregnancy rates within each age group stratified by number of embryos transferred are shown in Table 5 . In all age groups, transferring 3 embryos achieved higher clinical pregnancy rates compared to transferring 1 or 2 embryos.

Discussion

The 2013 annual summary report on assisted reproductive technology in the United States published by the Centers for Disease Control and Prevention (CDC) showed that among patients undergoing autologous IVF/ICSI treatment, clinical pregnancy rates were 25% at age 40, 21% at age 41, 16% at age 42, 12% at age 43, 8% at age 44, and 4% at age >44, while the corresponding live birth rates were 17%, 13%, 9%, 6%, 3%, and 1%, respectively [6]. The conclusions of our study are similar to these data, indicating that clinical pregnancy rates decrease significantly year by year with age, and the probability of achieving live birth is extremely low at age >44.

Numerous studies have demonstrated that age-related diminished ovarian reserve, ovarian aging, and declining oocyte quality are the main factors affecting pregnancy in older women [7-8]. Elevated basal FSH levels and reduced basal

AFC are considered direct evidence of diminished ovarian reserve [9-10]. In this study, the mean basal AFC decreased progressively with age, but there were no statistically significant differences in mean basal FSH, mean Gn consumption, or Gn stimulation duration among groups. This may be because clinicians selectively accepted patients whose ovarian reserve had not yet significantly declined for IVF/ICSI treatment to meet the fertility demands of older infertile women aged 40, and increasing Gn dosage could not improve ovarian response. In the 40-44 age groups, the mean number of transferable embryos decreased gradually with age, while the decline in clinical pregnancy rate and live birth rate was more pronounced. Additionally, mean fertilization rate, mean normal fertilization rate, and embryo implantation rate showed downward trends with age, while early spontaneous abortion rate increased with age, reaching 100% in the 44-year-old group. These data indicate that when there are no significant differences in average ovarian reserve function among age groups, the decline in oocyte quality has a more important impact on pregnancy outcomes than oocyte quantity [11-12].

Many studies have proven that oocyte quality declines with age, leading to decreased embryo quality. The increased incidence of aneuploidy during oocyte meiosis is considered the primary reason [13]. Some studies have shown that during meiosis I (MI), abnormal centromere structure and function leading to abnormal sister centromere alignment and spindle connection may contribute to increased aneuploidy in oocytes [14]. Other studies suggest that mitochondrial dysfunction is also an important cause of declining oocyte quality, as mitochondrial dysfunction in oocytes may lead to related epigenetic changes, and energy transfer 障碍 caused by mitochondrial dysfunction in granulosa cells may also affect oocyte quality [15-17].

The low pregnancy rate, low live birth rate, and high miscarriage rate associated with assisted reproductive technology in women aged 40 not only consume patients' time, energy, and financial resources but also pose a major challenge for clinicians. Currently, no study has reported whether an optimal ovarian stimulation protocol exists for older women, and the advantages and disadvantages of various stimulation protocols remain controversial. In this study, the super-long protocol achieved a pregnancy rate of 60%, but the small sample size limits its statistical significance and requires further research with expanded sample size. The long protocol and antagonist protocol are currently the more commonly used stimulation protocols. In our study, the long protocol achieved higher clinical pregnancy rates compared to the antagonist protocol, but no significant differences were found between the two protocols in patients aged 41. The antagonist protocol has been applied for a relatively short time in China, and as this is a retrospective study, the data may contain certain biases that need to be confirmed by randomized controlled trials. A meta-analysis demonstrated that for poor ovarian responders, there was no statistically significant difference in clinical pregnancy rates between antagonist and agonist protocols [18]. Recent studies suggest that luteal phase oocyte retrieval can accumulate more oocytes in a shorter time, thereby helping to form more transferable embryos and po-

tentially improving pregnancy outcomes in patients with diminished ovarian reserve [19-21]. Although some studies have shown that luteal phase oocyte retrieval does not significantly differ from follicular phase retrieval in terms of euploid blastocyst formation rate in poor ovarian responders [22], and luteal phase retrieval does not increase the risk of abnormal delivery, the long-term effects of luteal phase retrieval remain unclear and its safety is still controversial [23]. Whether pretreatment with DHEA before stimulation or combined use of growth hormone and luteinizing hormone during stimulation can improve clinical pregnancy rates in patients with diminished ovarian reserve also remains controversial [24-26].

Some studies have shown that for poor ovarian responders, the live birth rate of non-elective single embryo transfer is significantly lower than that of transferring 2 or more embryos, with the former group also having significantly lower ovarian reserve [27]. Our study also found that among patients, those with single embryo transfer had significantly lower clinical pregnancy rates than those with double or triple embryo transfer, suggesting that transferring 2 or 3 embryos helps improve per-cycle clinical pregnancy rates and shortens the time to pregnancy for older patients. Some scholars previously believed that embryo selection technology could solve the problem of high miscarriage rates caused by embryo aneuploidy [28], but recent studies suggest that preimplantation genetic screening (PGS) and Time-Lapse closed embryo culture systems cannot effectively improve pregnancy outcomes [29]. Donor oocyte-assisted reproductive technology remains the most effective approach for addressing infertility in older women [6].

Current advanced IVF technology cannot improve the problems of oocyte aging and declining embryo quality in older women, nor can it reduce miscarriage rates or increase live birth rates. Therefore, older women should be informed of various risks associated with childbearing, and women should be broadly educated about childbearing at optimal ages. Women who cannot conceive at the optimal reproductive age due to various reasons may consider oocyte, ovarian, and embryo cryopreservation in the future.

In summary, in women over 40 years of age, embryo implantation rate, clinical pregnancy rate, and live birth rate decrease year by year with advancing age, while spontaneous abortion rate increases annually, and various pregnancy-related complications also rise significantly. Therefore, we believe that female age should be an indication for assisted reproductive treatment in older women. Women aged 40 years, even without other obvious causes of infertility, should undergo IVF treatment promptly to help achieve pregnancy, but they should be fully informed of the risks of low pregnancy rate, low live birth rate, high miscarriage rate, and various pregnancy complications, and should be advised to accumulate more embryos before transfer. Under current technical conditions, for women aged >44 years, whether IVF treatment using autologous oocytes should still be performed requires fully informed consent about the disadvantages, and seeking donor oocytes may be a better option. With social development and de-

layed childbearing age, the demand for assisted reproductive treatment among older women will continue to increase, and further research is needed on how to improve treatment outcomes. In the future, oocyte, ovarian, and embryo cryopreservation may become effective methods for fertility preservation in women who cannot conceive at the optimal reproductive age.

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Tables

Note: Figure translations are in progress. See original paper for figures.