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Original Research

Reproductive Outcomes of *in Vitro* Fertilization and Embryo Transfer in Women with Unexplained Repeated Implantation Failure are Significantly Improved with Intravenous Immunoglobulins

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Abstract

Background: The aim of this study was to investigate the effects of intravenous immunoglobulins (IVIg) in the immunotherapy of *in vitro* fertilization and embryo transfer (IVF-ET) patients and to provide insights into the treatment strategy for implantation failure. **Methods**: A retrospective observational study of 245 patients with unexplained repeated implantation failure in our hospital from 2016 to 2021 was conducted. Among these patients, 124 were administered IVIg according to their preferences during the preparation of implantation, while the others were not given IVIg as a control group. The basic characteristics of the patients in the two groups did not show any significant differences. Biochemical pregnancy rate, clinical pregnancy rate, and live birth rate were compared in the two groups, and also in the IVIg group and the control group, by age (<40 years old and ≥40 years old). **Results**: The biochemical pregnancy rate, clinical pregnancy rate, and live birth rate in the IVIg group were significantly higher ($p < 0.05$) than in the control group. However, it was found that there were no significant differences in the reproductive outcomes between the IVIg group and the control group for patients older than 40 years. While for the patients less than 40 years old, the biochemical pregnancy rate, clinical pregnancy rate, and live birth rate of the IVIg group were all higher than those of the control group ($p < 0.05$). **Conclusions**: The results of this study suggest that IVIg treatment had a better reproductive outcome for IVF-ET patients with unexplained repeated implantation failure, particularly for patients under age 40.

Keywords: intravenous immunoglobulins; *in vitro* fertilization and embryo transfer; immunotherapy; repeated implantation failure; live birth rate

1. Introduction

Among women of reproductive age all over the world, some experience the suffering of not being able to conceive or miscarriage. In China, recurrent pregnancy loss (RPL) is defined as three or more fetal losses before 28 weeks of gestation [1]. It might be due to immune abnormality, while the exact pathological mechanism is still unknown [2]. The application of intravenous immunoglobulins (IVIg) in patients with unexplained recurrent pregnancy loss has been reported in many cases [2–16]. Some possible mechanisms of the effects of IVIg in RPL are as follows: (1) Inhibition of natural killer (NK) cell activity: Studies have shown that giving high doses of IVIg in early pregnancy can reduce the damage to embryos by inhibiting the activity of maternal peripheral blood NK cells and improve pregnancy outcomes [2–5]; (2) Regulating the balance of Th1/Th2 subsets: IVIg can regulate the ratio of Th1 cells (pro-inflammatory cells)/Th2 cells (anti-inflammatory cells), restore the immune balance, and reduce the attack on embryos [6–10]; (3) Anti-inflammatory effect: IVIg may reduce the risk of embryo damage by inhibiting inflammatory cell activity and reducing inflammatory cytokine production [10,11]; (4) Regulating maternal immune tolerance: IVIg may affect the number and the function of regulatory T cells (Tregs), thereby enhancing maternal immune tolerance to embryos [12]; (5) Inhibition of antiphospholipid antibodies: Antiphospholipid antibodies are frequently found in patients with systemic lupus erythematosus (SLE). Persistent positive antiphospholipid antibodies with manifestations of intravascular thrombosis and/or pregnancy disorders are known as antiphospholipid syndrome (APS). The IVIg antibody spectrum contains specific antibodies that can neutralize antiphospholipid antibodies and reduce damage to embryos [13].

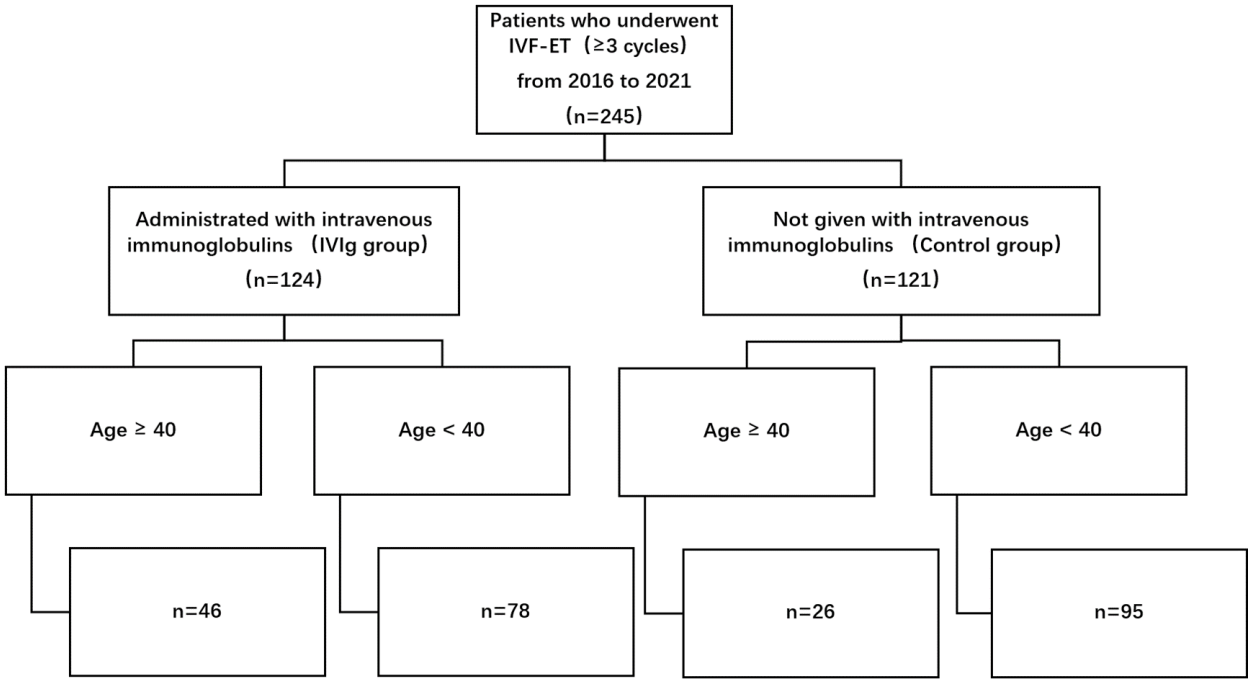

Fig. 1. Schematic diagram for the inclusion criteria of the study. IVF, *in vitro* fertilization; ET, embryo transfer; IVIg, intravenous immunoglobulins.

Clinically, patients with a strong desire to have a healthy baby, whether with primary infertility or not, will choose to undergo *in vitro* fertilization and embryo transfer (IVF-ET) if their economic conditions permit it. The implantation techniques are mature. However, repeated implantation failure (RIF) is still one of the biggest obstacles to improving the success of pregnancy. There is no consensus definition of RIF at present. It is frequently used to describe cases where a patient has experienced three or more failed implantation attempts following IVF-ET [14]. Alternatively, this condition can be diagnosed when 10 or more embryos with normal morphology fail to lead to a successful pregnancy [15–17].

There is no effective treatment yet to solve the problem because implantation and maintenance of pregnancy require a complex and delicate immunological equilibrium [18]. Inflammation during implantation, temporary immune senescence during the 2nd and 3rd trimesters, and the subsequent inflammation for the preparation of parturition are integral parts of normal gestation. Any imbalances or untimely and excessive inflammation can lead to implantation failure, spontaneous abortion, preterm labor, and intrauterine growth restriction [18].

In view of the high cost of transplantation and to avoid wasting embryos, multiple detailed screening is conducted before transplantation to exclude all possible causes of pregnancy failure, such as autoimmune diseases, uterine malformations, chromosomal abnormalities, endometrial damage, and so on. However, there is still a subset of patients who fail to have a successful outcome. It is difficult to figure out any clear reason and no other effective interventions. Based on the immunological regulatory effects of intravenous immunoglobulins in patients with recurrent pregnancy loss (RPL) and anti-phospholipid syndrome (APS) [2,9–17], the patients with three or more implantation failures following *in vitro* fertilization and embryo transfer (IVF-ET) while having no other clear factors that contribute to infertility in our hospital were given IVIg treatment besides a conventional *in vitro* fertilization and embryo transfer according to their own preferences after full communication with the patients. This study compared the reproductive outcomes of the patients with or without IVIg treatment, to explore whether IVIg has a positive impact on the pregnancy rate and the live birth rate of women who have received IVF more than three times with unknown causes and to provide evidence to optimize the immunotherapy strategy to improve the IVF-ET success rate.

2. Materials and Methods

2.1 Study Population

This study was a retrospective observational study. The trial was carried out at the Department of Obstetrics and Gynecology, the Sixth Medical Center of People's Liberation Army (PLA) General Hospital, Beijing, China. It was performed in adherence to Helsinki Declaration which is a guideline for clinical trials [19]. The study protocol was approved by the ethics committee of the Sixth Medical Center of People's Liberation Army General Hospital. The study was supported by the Innovation Cultivating Foundation of the Sixth Medical Center of People's Liberation Army Gen-

Table 1. Comparisons of baseline features of the two groups.

	Control	IVIg	*p*-value
	n = 121	n = 124	
Age (years) (mean ± SD)	36.60 ± 4.02	37.32 ± 5.10	0.216
Basic FSH (mIU/mL)	7.9 (6.40, 9.89)	7.85 (6.57, 10.05)	0.990[a]
Primary infertility rate	45.5% (55/121)	49.2% (61/124)	0.558
Infertile duration (years)	3 (2, 6)	3 (2, 5)	0.633[a]
BMI (kg/m^2)	22.60 (20.89, 24.50)	22.39 (20.55, 24.80)	0.684[a]
Endometrial thickness (mm) (mean ± SD)	9.00 ± 2.09	8.71 ± 1.94	0.272
IVF number (cycles)	3 (3, 4)	3 (3, 4)	0.675[a]

IVIg, intravenous immunoglobulins; SD, standard deviation; BMI, body mass index; FSH, follicle stimulating hormone; IVF, *in vitro* fertilization.

Numerical data were analyzed for normal distribution by the Shapiro-Wilk test. Continuous data that satisfied the normal distribution were tested by independent sample *t*-test, numerical variables were expressed in mean ± standard deviation; Mann Whitney test was used for continuous data that did not comply with the normal distribution, and the statistics were indicated with quartiles. $p < 0.05$ was set as the threshold for significance. [a] The *p*-value that has a lowercase letter a as a superscript shows that the data was analyzed by the Mann-Whitney test.

eral Hospital (No: CXPY201927). The patient included in this study had three or more implantation failures following *in vitro* fertilization and embryo transfer (IVF-ET) from June 2016 to June 2021, normal morphology of endometrium, and normal results of the routine physical examination such as blood, platelet, and serum syphilis test. Patients were excluded if they (1) had a history of endocrine disease, immune system disease, blood disease, thrombotic disease, and other systems diseases; (2) were diagnosed with any organic disease of the uterus; (3) had karyotype abnormality. A total of 245 patients with a history of RPL who underwent IVF-ET ($\geq$3 cycles) were divided into four groups based on whether or not they received IVIg administration and their age ($\geq$40 or $<$40) (Fig. 1). The reason to divide the patients by the age of 40 is that the reserve capacity of the ovarian follicle or oocyte pool is declined dramatically around the age of 40, both in quantity and quality [20]. All patients have favorable economic statuses and no smoking history. All participants did not undergo Preimplantation Genetic Diagnosis (PGD) testing.

2.2 Intervention

A total of 245 patients underwent *in vitro* fertilization and embryo transfer treatment at the Center for Assisted Reproduction in our hospital. The ovulation induction cycles were conducted according to each patient's individual conditions. Following the maturation of the follicles, the eggs were retrieved via transvaginal puncture, and high-quality day 3 embryos were selected for vitrification.

The endometrium preparation scheme for the artificial cycle was used as follows: oral estradiol valerate tablets (J20130009, DELPHARM Lille S.A.S., Boulogne-Billancourt, France) 4 mg–6 mg were given daily from the 3rd to the 5th day of menstruation. On the 14th to 16th days of menstruation, the endometrium was transformed and estradiol valerate tablets (4 mg to 6 mg) were given and dydroxyprogesterone tablets (HJ20170221, Abbott Biologicals B.V., Olst, Netherlands) (20–40 mg) were taken orally every day. Progesterone was added for supplementary luteal support according to the specific situation of the patient. Two D3 embryos were thawed and transferred 3 days after oral administration of dydrogesterone tablets.

In the preparation process for endometrial thawing and transplantation in patients from the IVIg group, a dose of 0.4 g/kg of human immunoglobulin (pH4) for intravenous injection (S19993042, Chengdu Rongsheng Pharmaceuticals Co., Ltd, Chengdu, Sichuan, China) was administered once on the day of ovulation or the following day after endometrial transformation. Patients in our study were given the choice to use IVIg based on their own preferences.

2.3 Measurement

Age, basic follicle stimulating hormone (FSH) levels, infertility history, endometrial thickness, and IVF attempts were recorded and analyzed for all participants. Primary infertility was defined as patients who had not been pregnant prior to IVF treatment. Pregnancy was assessed about 10 days after frozen embryo transfer (FET) by measuring human chorionic gonadotropin (hCG) levels in peripheral blood. Results with hCG levels above 30 mIU/mL were considered positive and indicative of biochemical pregnancy. Patients who received positive hCG results were monitored for clinical pregnancy rate and live birth rate. Clinical pregnancy was confirmed via ultrasound showing normal development of an intrauterine gestational sac.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Numerical data were analyzed for normal distribution by the Shapiro-

Table 2. Comparisons of baseline features of the groups with the patients under the age of 40.

	Control	IVIg	*p*-value
	n = 95	n = 78	
Age (years)	37.00 (33.00, 38.00)	35.00 (31.75, 38.00)	0.133[a]
Basic FSH (mIU/mL)	7.40 (6.12, 9.77)	7.72 (6.18, 9.72)	0.987[a]
Primary infertility rate	45.3% (43/95)	51.3% (40/78)	0.430
Infertile duration (years)	3 (2, 6)	3 (2, 5)	0.690[a]
BMI (kg/m^2)	22.58 (20.54, 24.60)	21.98 (20.20, 24.22)	0.295[a]
Endometrial thickness (mm)	9.00 (7.80, 10.30)	8.70 (7.40, 10.02)	0.350[a]
IVF number (cycles)	3 (3, 4)	3 (3.5, 4)	0.453[a]

IVIg, intravenous immunoglobulins; BMI, body mass index; FSH, follicle stimulating hormone; IVF, *in vitro* fertilization.

Numerical data were analyzed for normal distribution by the Shapiro-Wilk test. Continuous data that satisfied the normal distribution were tested by independent sample *t*-test, numerical variables were expressed in mean ± standard deviation; Mann Whitney test was used for continuous data that did not comply with the normal distribution, and the statistics were indicated with quartiles. $p < 0.05$ was set as the threshold for significance. [a] The *p*-value that has a lowercase letter a as a superscript shows that the data was analyzed by the Mann-Whitney test.

Table 3. Comparisons of baseline features of the groups with the patients over 40 years old.

	Control	IVIg	*p*-value
	n = 26	n = 46	
Age (years)	41.00 (40.00, 42.00)	41.50 (41.00, 44.00)	0.131[a]
Basic FSH (mIU/mL)	9.39 (8.07, 11.97)	8.44 (7.07, 11.40)	0.193[a]
Primary infertility rate	46.2% (12/26)	45.7% (21/46)	0.967
Infertile duration (years)	3 (2, 8)	3.5 (2, 6.25)	0.623[a]
BMI (kg/m^2)	23.06 (21.17, 24.52)	22.84 (21.35, 25.10)	0.734[a]
Endometrial thickness (mm)	8.40 (6.50, 9.65)	8.40 (6.90, 9.60)	0.907[a]
IVF number (cycles)	3 (3, 4)	3 (3, 6)	0.891[a]

IVIg, intravenous immunoglobulins; BMI, body mass index; FSH, follicle stimulating hormone; IVF, *in vitro* fertilization.

Numerical data were analyzed for normal distribution by the Shapiro-Wilk test. Continuous data that satisfied the normal distribution were tested by independent sample *t*-test, numerical variables were expressed in mean ± standard deviation; Mann Whitney test was used for continuous data that did not comply with the normal distribution, and the statistics were indicated with quartiles. $p < 0.05$ was set as the threshold for significance. [a] The *p*-value that has a lowercase letter a as a superscript shows that the data was analyzed by the Mann-Whitney test.

Wilk test. Continuous data that satisfied the normal distribution were tested by independent sample *t*-test, numerical variables were expressed as mean ± standard deviation; Mann Whitney test was used for continuous data that did not comply with the normal distribution, and the statistics were indicated with quartiles; categorical variable data were tested by chi-square test. $p < 0.05$ was set as the threshold for significance.

3. Results

3.1 Patient Characteristics and Baseline Laboratory Results of the Study Population

Patient characteristics and baseline laboratory results are listed in Table 1. The ages, basal FSH levels, primary infertility rates, years of infertility, body mass index (BMI), endometrial thickness (on the day of endometrial transformation in the artificial cycle), and the numbers of previous IVF transplantation cycles of the two groups had no statistically significant differences ($p > 0.05$).

The infertile duration, BMI, endometrial thickness, and the number of previous IVF cycles of the control group and the IVIg group had no statistically significant differences ($p > 0.05$) in the patients under 40 years and over 40 years old, respectively, shown in Tables 2,3.

3.2 Pregnancy Outcomes

The control group (n = 121) had a biochemical pregnancy rate of 40.5% (49/121), with a clinical pregnancy rate of 31.4% (38/121). Of the patients in the control group, six cases of spontaneous abortion, one late abortion discovered

Table 4. Pregnancy success rates.

Groups	Number of patients	Biochemical pregnancy rate	Clinical pregnancy rate	Live birth rate
Control	121	40.5% (49/121)	31.4% (38/121)	24.8% (30/121)
IVIg	124	54.8% (68/124)	44.4% (55/124)	37.9% (47/124)
p-value		0.025*	0.037*	0.027*

IVIg, intravenous immunoglobulins; *p*-value, compared the patients between the control group and the IVIg group by chi-square test; * statistical significance. $p < 0.05$ was set as the threshold for significance.

Table 5. Pregnancy success rates in patients under the age of 40.

Groups	Number of patients	Biochemical pregnancy rate	Clinical pregnancy rate	Live birth rate
Control	95	46.3% (44/95)	35.8% (34/95)	27.4% (26/95)
IVIg	78	66.7% (52/78)	52.6% (41/78)	43.6% (34/78)
p-value		0.007**	0.027*	0.026*

IVIg, intravenous immunoglobulins; *p*-value, compared between the patients under the age of 40 in the control group and the patients under the age of 40 in the IVIg group by chi-square test; * statistical significance. $p < 0.05$ was set as the threshold for significance. ** particular statistical significance. $p < 0.01$ was set as the threshold for particular significance.

Table 6. Pregnancy success rates in patients over 40 years old.

Groups	Number of patients	Biochemical pregnancy rate	Clinical pregnancy rate	Live birth rate
Control	26	19.2% (5/26)	15.4% (4/26)	15.4% (4/26)
IVIg	46	34.8% (16/46)	30.4% (14/46)	28.3 % (13/46)
p-value		0.163	0.157	0.217

IVIg, intravenous immunoglobulins; *p*-value, compared the patients over 40 years old in the control group and the patients over 40 years old in the IVIg group by chi-square test. $p < 0.05$ was set as the threshold for significance.

during follow-up, and one case of artificial abortion after 24 weeks of pregnancy due to fetal chromosome "47, XXY" were found. The remaining patients in the control group delivered live-born infants, resulting in a live birth rate of 24.8% (30/121) (Table 4).

Within the IVIg group (n = 124), FET was initiated following IVIg treatment. Notably, the biochemical pregnancy rate was 54.8% (68/124), while the clinical pregnancy rate was 44.4% (55/124). During follow-up, one case of late abortion was discovered in addition to seven spontaneous abortions. In the end, 47 of the 124 participants in the IVIg group delivered live-born infants, resulting in a live birth rate of 37.9% (Table 4).

When comparing the reproductive outcomes of the two groups (Table 4), statistically significant differences were observed in the biochemical pregnancy rates, clinical pregnancy rates, and live birth rates (all $p < 0.05$).

Further analysis was conducted by screening patients under the age of 40 in both groups. The results revealed that the biochemical pregnancy rates of the IVIg group's under-40 patients were even significantly higher than those of the control group's under-40 patients ($p < 0.01$). Additionally, the clinical pregnancy rates and live birth rates of the IVIg group's under-40 patients were higher than their control group counterparts ($p < 0.05$). Data were shown in Table 5.

While no statistically significant differences were observed in the biochemical pregnancy rates, clinical pregnancy rates, and live birth rates of patients aged over 40 in the control group and IVIg group ($p > 0.05$), as shown in Table 6.

4. Discussion

In recent years, *in vitro* fertilization and embryo transfer (IVF-ET) technology has advanced considerably. However, the live birth rate of IVF-ET continues to remain low at 25.6%, with a clinical pregnancy rate of around 50% for women under 35 years of age [21]. Despite the progress in IVF-ET technology, the success rate of reproductive outcomes is still unsatisfactory, and approximately 10% of couples experience repeated implantation failure (RIF) [22]. After implantation, the immune system has the challenging task of not only protecting the mother's body from invading microorganisms but also avoiding the immune rejection of intrauterine embryo grafts. Multiple maternal immune mechanisms can lead to the failure of embryo implantation [23].

Among the various treatment methods available to improve the outcome of IVF, IVIg is a potential therapy for IVF failure and recurrent pregnancy loss due to its anti-inflammatory and immunological regulatory effects [2–17]. IVIg is a compound of multiple antibodies, over 95% of

which is immunoglobulin G. It is isolated and purified from tens of thousands of healthy human plasma donors. The immunoglobulin G in IVIg is structurally intact and has excellent biocompatibility, making it safe and efficient for clinical application. Additionally, the Fab segment of IVIg can bind to pathogens and induce macrophages to clear them, thereby enhancing the body's anti-infection ability [24]. The Fc segment of IVIg is capable of binding to Fc receptors on immune cells, regulating their activity [25]. It can also bind excessive complements, mitigating the cascade reactions caused by an excess of complements and reducing tissue and cell damage due to complement deposition [26]. The exogenous input of IgG can stimulate the body to produce more regulatory T cells. The regulatory T cells play a crucial role in enhancing immune regulatory abilities and maintaining immune homeostasis [27,28]. Immunoglobulin G can also accelerate the clearance of inflammatory factors and anti-autoantibodies, thereby contributing to the maintenance of immune homeostasis [29–32].

Clinical practice has demonstrated that IVIg is effective in treating both primary and secondary immunodeficiency and autoimmune diseases [33]. Additionally, they have also been utilized to treat recurrent spontaneous abortion [3,4,6,7]. IVIg treatment can regulate the TH1/TH2 ratio and improve pregnancy outcomes [6–10]. Some experts suggest that the causes of recurrent abortion and embryo implantation failure share common immunological factors [34]. Moreover, some studies have emphasized the ability of IVIg to regulate abnormal immune reactions related to human leukocyte antigens [5]. In a randomized controlled trial, the intravenous application of human immunoglobulin effectively improved the pregnancy rate and live birth rate of patients who had previously experienced embryo transfer failure and exhibited NK and natural killer T (NKT) cell expansion in their blood circulation [35]. IVIg treatment has also been found to increase Treg numbers, Foxp3, and cytokine levels such as IL-10 and TGF-β mRNA expression [35].

In this study, patients with repeated implantation failure (RIF) and other detectable causes of infertility ruled out, were given IVIg. Taking into account that the half-life of human immunoglobulin is 16–20 days, the administration of IVIg was administrated after ovulation or endometrial transformation to ensure sufficient dosage and duration during embryo implantation. Results showed that patients who underwent IVF transplantation and received human immunoglobulin treatment had higher rates of biochemical pregnancy and live birth compared to the control group. These findings suggest that some patients may have certain immune dysfunctions that IVIg can address.

It has been reported that in the PubMed, EMBASE, and CNKI databases, there are 10 studies on the application of human immunoglobulin in IVF-ET [36]. In the six studies of them, the implantation rate of patients treated with IVF-ET using human immunoglobulin is 34.3% (394/1147), while the implantation rate of patients treated with placebo is 13.7% (68/495). The pregnancy rates in the total 10 studies using human immunoglobulin and placebo were 60.2% (503/835) and 34.3% (637/1620), respectively. In 9 of those studies, the live birth rate of human immunoglobulin and placebo was 49.8% (406/816) and 31.6% (506/1599), respectively. These studies suggest that the use of human immunoglobulin can enhance the pregnancy and live birth rates of IVF failure patients, which aligns with our study's findings. Our results indicate that the reproductive outcomes of patients receiving IVIg were superior to those in the control group.

We further divided the IVIg group and the control group into subgroups according to the age of 40 with subgroups of age less than 40 and age greater than or equal to 40, because, beyond this age, there is a significant decline in the ovarian follicle or oocyte pool, not only in quantity but also in quality [20]. The results in our study showed that the IVIg group of women under the age of 40 had significantly higher rates of biochemical pregnancy, clinical pregnancy, and live birth compared to the control group. The IVIg group of age under 40 also demonstrated a remarkable increase in the biochemical pregnancy rate compared to the control group. However, for women over the age of 40, there was no statistically significant difference between the IVIg group and the control group, potentially due to the sufficient sample size. Nevertheless, IVIg may still have therapeutic effects on women over the age of 40, but there could be undetectable inflammatory or autoimmune symptoms or other illnesses that may contribute to pregnancy failure. Other interventions combined with IVIg therapy may be necessary to address these issues. It is also possible that the challenge of achieving successful pregnancy or experiencing spontaneous abortion in some of these patients may be due to insufficient blocking effects and immunoregulatory functions of human immunoglobulin before pregnancy.

In future studies, it may be necessary to figure out the sufficient amount of the IVIg dose and other factors that would affect the reproductive outcomes. Further research in this area may help to optimize the application of human immunoglobulin as a treatment for infertility. Prospective studies are also needed to further investigate the mechanism of the key role of IVIg on patients with repeated implantation failures.

Overall, the study suggests that intravenous immunoglobulin may be a beneficial treatment for patients with repeated IVF transplantation failure, especially for those under the age of 40. However, as a retrospective study, there are limitations and the results should be interpreted with caution. Prospective research with larger sample sizes and biomarker investigation is needed to better understand the mechanism of IVIg and its specific effects on IVF transplantation failure patients and other recurrent pregnancy loss. In sum, the study provides important in-

sights and highlights the potential of immunotherapy in improving reproductive outcomes for these patients.

5. Conclusions

Our research has demonstrated that IVIg treatment can enhance the reproductive outcomes of IVF-ET patients presenting with unexplained recurrent failure in implantation, especially those aged under 40. This approach is safe and convenient, providing those who have undergone several unsuccessful IVF cycles with a viable therapeutic option, once other possible underlying reasons for pregnancy failure have been ruled out.

Abbreviations

IVIg, intravenous immunoglobulins; IVF, *in vitro* fertilization; ET, embryo transfer; FET, Frozen embryo transfer; RPL, recurrent pregnancy loss; RIF, repeated implantation failures; SD, Standard Deviation; BMI, body mass index; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MS and YZ designed the research study. MS, YZ, HL and HH performed the research. WZ, SY, ZR participated in acquisition and analysis of the data. MS, YZ, DY and WS analyzed and interpreted the data. MS, YZ, DY and WS wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was approved by the ethics committee of the Sixth Medical Center of People's Liberation Army (PLA) General Hospital, Beijing, China. The ethics code of this research is 2022-149. The ethics committee agreed to exempt the informed consent of the subjects because the study was retrospective observational.

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Conflict of Interest

The authors declare no conflict of interest. The author Yujuan Zhou is employed by China National Biotec Group Company Limited. The author Hong Liang is employed by Chengdu Rongsheng Pharmaceuticals Co., Ltd. The author Ding Yu is employed by Beijing Tiantan Biological Products Co., Ltd and Chengdu Rongsheng Pharmaceuticals Co., Ltd. These companies did not participate in the preparation and publication of the article.

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