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Comparison of Pregnancy Outcomes in Thyroid Antibody-Positive Women with Different Fertilization Methods

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Abstract: *Objective* To compare the pregnancy outcomes of thyroid antibody (ATA) positive women treated by different fertilization methods during in vitro fertilization-embryo transfer. Methods A total of 204 female patients with normal thyroid function and positive ATA in the reproductive Medicine Center of the First Hospital of Shanxi Medical University from January 2020 to January 2022 were selected. According to different fertilization methods, they were divided into IVF group and ICSI group, including 115 IVF cycles and 89 ICSI cycles. The general data, clinical indicators after ovulation induction, fertilization, embryo status, and pregnancy outcome of the two groups were compared. *Results* There were no significant differences in age, BMI, bE_2, FSH, FT_3, FT_4, AFC, Gn dosage, Gn stimulation time, E_2 on HCG day, P on HCG day, intrauterine thickness on HCG day, number of retrieved oocytes and average number of embryos transferred between the two groups ($P>0.05$). The fertilization rate of the ICSI group was higher than that of IVF group within the group, while the high-quality embryo rate was significantly lower than that of the IVF group, with statistical significance ($P<0.05$). There were significant differences in sperm motility and sperm density between the two groups ($P<0.05$), and there was no significant difference between sperm volume and normal morphology rate ($P>0.05$). There were no significant differences in embryo implantation rate, biochemical pregnancy rate, clinical pregnancy rate, early abortion rate and live birth rate between the two groups ($P>0.05$). Logistic regression analysis showed that the method of assisted pregnancy and semen quality were not independent factors affecting high-quality embryo ($P>0.05$). In IVF group, TGAb was negatively correlated with fertilization rate ($r=-0.202$, $P<0.05$); and in ICSI group, TPOAb was negatively correlated with high quality embryo rate ($r=-0.349$, $P<0.05$). *Conclusion* Thyroid autoimmunity (TAI) in infertile women undergoing assisted reproductive technology (ART), the semen quality should be considered as the priority criteria for ATA. ICSI should not be recommended as routine fertilization.

Keywords: Thyroid Antibodies, Thyroid Autoimmunity, Different Fertilization Methods, Pregnancy Outcomes

1. Introduction

Infertility is defined as the absence of pregnancy in women of childbearing age who have had normal sexual intercourse without contraception for one year or more. The main causes of infertility are pelvic tubal factors, uterine factors, immune factors, and unexplained factors, among which immune causes account for 10% of infertility [1]. Among the immune factors, thyroid autoimmunity (TAI) is the most common autoimmune state and is the primary cause of thyroid dysfunction. TAI is defined as simple positive thyroid autoantibodies without elevated thyroid-stimulating hormone (TSH) and free Thyroxine (fT4), also known as an autoantibody-positive state with normal thyroid function [2], has a prevalence of up to 25% [3] and is more common in

women aged 18-45 years. Antithyroid antibody (ATA) mainly includes thyroglobulin antibody (TPOAb) or thyroid peroxidase antibody (TgAb) [4], and the incidence of those who are positive for both is about 10% in the population [5]. Thyroid autoimmunity increases the risk of infertility and miscarriage [5], leading to reproductive failure and poor pregnancy outcomes even in the presence of normal thyroid function [6].

Assisted reproductive technology (ART) brings hope to families with infertility and also responds to the national call for a "three-child policy". Assisted reproductive technology has been carried out for more than 30 years, from the classical in vitro fertilization-embryo transfer (IVF-ET) to intracytoplasmic sperm injection (ICSI), pre-implantation genetic diagnosis (PIGD), and the development of a new method of fertilization and embryo transfer (IVF-ET). ICSI, Preimplantation genetic diagnosis (PGD), and embryonic stem cell technology. With the gradual improvement of ICSI techniques, the live birth rate has greatly increased from 26% in the 1990s to about 40% today [7], and this increasing trend has been observed even in non-male factor-induced infertility [8]. ICSI can be a powerful alternative to IVF failure, effectively improving fertilization rates and reducing the incidence of complete infertility [9]. In a 2018 meta-analysis [10], researchers noted that ICSI does not have to go through the natural mechanism of fertilization and can be the preferred method of pregnancy assistance for TAI patients. Another new proposal likewise recommends ICSI as the preferred method for the treatment of women with TAI [11]. Therefore, the choice of fertilization method is of greater interest, and in addition, whether pregnancy outcomes differ between people with different levels of TSH within the normal range of IVF or ICSI assisted conception has not been reported in studies. Therefore, in this paper, we retrospectively analyzed the clinical data of women with normal thyroid function and positive autoantibodies who underwent IVF/ICSI at our center from January 2020 to January 2022, to investigate the effect of different fertilization methods on the pregnancy outcome of TAI patients.

2. Subjects and Methods

2.1. Study Population

Retrospective analysis of 204 patients with normal thyroid function and positive ATA who underwent IVF-ET/ICSI-ET to assist pregnancy at our center from January 2020 to January 2022, including 115 treatment cycles in the IVF group and 89 treatment cycles in the ICSI group. The IVF and ICSI groups were divided into two subgroups with TSH ≤ 2.5uIU/mL and TSH > 2.5uIU/mL, respectively, according to the Chinese expert consensus on the diagnosis and management of subclinical hypothyroidism in infertile women [2] and the guidelines on the diagnosis and management of thyroid disorders in pregnancy and postpartum [12] using TSH as the boundary.

Inclusion criteria: normal thyroid function (TSH: 0.27-4.2uIU/mL, FT4: 10-23pmol/L, FT3: 3.1-6.8pmol/L); cycles with IVF or ICSI; normal semen of male partner; all without eugenol intervention treatment. Exclusion criteria: severe endometriosis, adenomyosis, or hydrosalpinx; abnormal development of reproductive organs; severe endocrine diseases; patients with combined cardiovascular diseases, malignant tumors, or mental disorders; chromosomal abnormalities in one of the male and female partners.

2.2. Protocol

All patients were treated with either the agonist long protocol or the antagonist protocol.

The use of the long protocol is initiated with exogenous gonadotropins for ovulation from mid-luteal phase after 14-21 days of GnRH-a and the pituitary gland reaches the criteria for descending regulation (serum LH and FSH < 5 IU/L and E2 < 25 pg/ml). When the diameter of 2-3 dominant follicles reached 18 mm and the average E2 per mature follicle was 200-300 pg/ml, HCG 6000-1000 IU or GnRH agonist was injected, and eggs were retrieved by transvaginal puncture under ultrasound guidance 36-38 hours later. In antagonist protocol Gn was started on the 2nd or 3rd day of menstruation and GnRH-ant was given when the dominant follicle (≥12-14mm) or LH level (>10IU or up to 2 times the baseline level) or E2 level (>500pg/ml) and the dosing were adjusted according to the follicle size until the day of HCG injection. Ovulation was routinely induced with HCG 6000-10000 IU or GnRH agonist trigger and eggs were retrieved 36-38 hours later.

Depending on the parameters of semen properties, sperm concentration, and viability, different semen processing methods are selected, such as standard washing method, sperm upstream method, or density gradient centrifugation to obtain fertilization fluid. IVF procedures are as follows. The oocyte corona cumulus complex (OCCC), which has been cultured for about 4-6 hours, is transferred into the in vitro fertilization fluid, and the spermatozoa are cultured for 16-20 hours to remove the oocyte corona Radiata granulosa cells, and then transferred into the embryo growth culture fluid via the oocyte. ICSI procedures are as follows. 2 hours after the collection of oocytes, the oocyte corona, and the oocyte corona, the above operation was repeated by injecting sperm into the oocyte plasma using a microinjection needle. After injection, oocytes were washed with a fertilization culture medium and transferred to the fertilization culture medium for incubation.

On the first day, fertilization was observed. embryos with double protoplasts and the presence of two polar bodies in the periplasmic gap were considered normally fertilized, while eggs with single protoplasts, three or more multiple protoplasts, or no protoplasts were judged to be abnormally fertilized or unfertilized. On the second and third days, embryo development was observed and scored according to the uniformity of the ovoid spheres, fragmentation, and nuclei. grade 1: embryos developed at a normal rate, with uniform or approximately uniform ovoid spheres, uniform cytoplasm, no vacuoles, and no more than 5% fragmentation; grade 2:

embryos developed at a normal rate, with uniform or approximately uniform ovoid spheres, uniform or approximately uniform number, uniform cytoplasm, no vacuoles, and 5%-10% fragmentation Grade 1 and 2 are collectively referred to as high-quality embryos; grades 1, 2 and 3 are collectively referred to as transferable/freezable embryos. The embryos were selected. Two to three embryos with high scores were selected for fresh transfer and the rest were frozen for preservation. After embryo transfer, oral progesterone capsules combined with dydrogesterone were given for luteal support until 8-10 weeks of gestation when the drug was discontinued. For patients with a positive pregnancy test, an ultrasound examination was performed 2-3 weeks later to confirm the number of gestational sacs and embryos.

2.3. Statistical Analyses

SPSS 25.0 statistical software was used for statistical analysis. Count data were statistically described by the Pearson $\chi 2$ test using rates. The measurement data all conformed to a normal distribution, and the T-test was used for those with homogeneous variance by F-test, and the corrected t-test was used for those with non-homogeneous variance, which was expressed as " $\bar{x}\pm S$". The correlation factors were analyzed by multiple Logistic regression. Speaman correlation was used to analyze the correlation between ATA and assisted pregnancy outcomes. Differences were considered statistically significant at $P<0.05$.

3. Results

A total of 115 IVF cycles and 89 ICSI cycles were collected. They were divided into two subgroups according to different TSH levels: TSH≤2.5uIU/mL and TSH>2.5uIU/mL. The results of baseline indexes comparing between groups are shown in Table 1. Among them, there were no statistical differences in age, BMI, bE2, FSH, FT3, FT4, and AFC between groups (P>0.05). There were no statistical differences in Gn dosage, Gn stimulation time, HCG day E2, HCG day P, and HCG day endometrial thickness between the two groups (P>0.05) in Table 2.

There was no statistically significant difference between the two groups in terms of the number of eggs obtained and the average number of embryos transferred (P>0.05). Regardless of the TSH level, the fertilization rate was higher in the ICSI group than in the IVF group, while the rate of superior embryos was significantly lower than in the IVF group, with statistically significant differences (P<0.05) in Table 3. Comparison between patients with TSH ≤2.5uIU/mL and TSH >2.5uIU/mL revealed no significant differences in embryo implantation rate, biochemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, and live birth rate between the IVF and ICSI groups (P>0.05) in Table 4. There were statistical differences in sperm motility and sperm density between the two groups of male patients (P<0.05), but there was no significant difference in sperm volume and sperm normal morphology rate (P>0.05) in Table 5. Logistic regression analysis of the impact of various indicators on the high-quality embryo rate in Table 6. Factors with statistical differences (IVF assisted pregnancy, sperm density, and sperm motility) were used as independent variables, and the high-quality embryo rate was used as the dependent variable. Multi-factor Logistic regression analysis was performed, and it was found that the method of assisted pregnancy and semen quality were not independent factors affecting high-quality embryo (P>0.05). The results of correlation analysis of TPOAb, TGAb and fertilization rate, high-quality embryo rate are shown in Table 7. There was a negative correlation between TGAb and fertilization rate in IVF group, and a negative correlation between TPOAb and high quality embryo rate in ICSI group.

Table 1. *Comparison of general data between the two groups.*

Characteristics	n	Age (years)	BMI (kg/m^2)	bE$_2$ (pg/ml)	bFSH (mIU/ml)	FT$_3$ (pmol/L)	FT$_4$ (pmol/L)	AFC
TSH≤2.5uIU/mL								
IVF	58	30.91±4.55	22.23±2.12	42.57±16.58	7.65±1.81	4.80±0.60	16.16±2.86	13.53±3.92
ICSI	52	30.87±3.67	22.24±2.14	44.84±15.21	7.22±2.35	4.74±0.51	15.14±2.28	14.27±3.59
t		0.062	0.033	0.749	1.080	0.503	2.039	1.021
P		0.951	0.974	0.455	0.283	0.616	0.064	0.309
TSH>2.5uIU/mL								
IVF	57	31.11±3.89	22.16±1.99	46.81±28.99	7.46±1.86	4.96±0.68	15.40±2.53	14.82±4.56
ICSI	37	29.03±2.24	21.50±2.11	42.98±17.63	7.62±2.17	4.81±0.46	16.65±2.06	14.68±5.03
t		3.278	1.529	0.722	0.391	1.326	2.511	0.149
P		<0.001	0.130	0.472	0.697	0.188	0.054	0.882
Total	115	31.01±4.22	22.20±2.05	44.67±23.57	7.55±1.83	4.88±0.64	15.78±2.72	14.17±4.28
	89	30.10±3.27	21.94±2.14	44.07±16.19	7.38±2.27	4.77±0.49	15.77±2.30	14.44±4.23
t		1.730	0.881	0.206	0.577	1.391	0.350	0.440
P		0.085	0.380	0.837	0.565	0.181	0.972	0.660

Table 2. *Comparison of clinical indicators after ovulation induction treatment between the two groups.*

Characteristics	n	Gn dosage (IU)	Gn stimulation time (d)	E2 on HCG day (pg/ml)	P on HCG day (ng/ml)	the intrauterine thickness on HCG day (mm)
TSH≤2.5uIU/mL						
IVF	58	2683.17±845.27	10.79±2.94	1413.10±769.70	0.76±0.42	11.21±2.35
ICSI	52	2462.02±919.61	10.25±3.09	1584.97±946.18	0.64±0.32	12.70±2.32

Characteristics	n	Gn dosage (IU)	Gn stimulation time (d)	E2 on HCG day (pg/ml)	P on HCG day (ng/ml)	the intrauterine thickness on HCG day （mm）
t		1.314	0.884	1.012	1.554	3.316
P		0.192	0.379	0.314	0.123	0.065
TSH>2.5uIU/mL						
IVF	57	2845.61±1093.44	11.79±3.98	1474.90±896.06	0.92±1.54	11.05±7.26
ICSI	37	2523.65±791.60	11.54±3.32	1422.66±713.85	0.77±0.37	15.30±7.26
t		1.546	0.316	0.299	0.594	1.688
P		0.126	0.753	0.766	0.552	0.095
Total	115	2763.69±975.30	11.27±3.52	1443.07±829.64	0.84±1.12	11.13±2.31
	89	2487.64±864.52	10.79±3.24	1517.49±856.61	0.70±0.34	12.38±2.49
t		2.105	1.008	0.605	1.157	3.677
P		0.136	0.315	0.546	0.249	0.080

Table 3. *Comparison of fertilization and embryo status between the two groups.*

Characteristics	n	number of retrieved oocytes	the fertilization rate (%)	high-quality embryo rate (%)	the average number of embryos transferred
TSH≤2.5uIU/mL					
IVF	58	13.03±6.84	78.44 (593/756)	63.98 (238/372)	1.98±0.30
ICSI	52	16.60±9.82	82.04 (708/863)	30.60 (142/464)	2.04±0.19
t/χ2		2.225	25.184	92.760	1.153
P		0.058	<0.001	<0.001	0.251
TSH>2.5uIU/mL					
IVF	57	14.25±7.26	75.74 (615/812)	63.66 (261/410)	2.02±0.35
ICSI	37	15.30±7.26	82.51 (467/566)	21.59 (76/352)	2.08±0.28
t/χ2		0.945	37.851	135.881	0.945
P		0.347	<0.001	<0.001	0.347
Total	115	13.63±7.05	77.04 (1208/1568)	63.81 (499/782)	2.00±0.32
	89	16.06±8.82	82.22 (1175/1429)	26.70 (218/816)	2.06±0.28
t/χ2		2.118	75.310	223.132	1.391
P		0.136	<0.001	<0.001	0.166

Table 4. *Comparison of pregnancy outcomes between the two groups.*

Characteristics	n	embryo implantation rate (%)	biochemical pregnancy rate (%)	clinical pregnancy rate (%)	early abortion rate (%)	live birth rate (%)
TSH≤2.5uIU/mL						
IVF	58	32.17 (37/115)	6.67 (2/30)	26.09 (30/115)	13.33 (4/30)	80.00 (24/30)
ICSI	52	24.34 (28/106)	14.29 (3/21)	18.26 (21/106)	9.52 (2/21)	85.71 (18/21)
χ2		1.737	0.811	2.041	0.173	0.278
P		0.188	0.368	0.153	0.678	0.598
TSH>2.5uIU/mL						
IVF	57	20.87 (24/115)	23.81 (5/21)	18.26 (21/115)	9.52 (2/21)	66.67 (14/21)
ICSI	37	24.00 (18/75)	5.88 (1/17)	22.67 (17/75)	5.88 (1/17)	76.47 (13/17)
χ2		0.258	0.243	0.096	0.171	0.439
P		0.611	0.622	0.757	0.679	0.508
Total	115	26.52 (61/230)	13.73 (7/51)	22.17 (51/230)	11.76 (6/51)	70.59 (36/51)
	89	25.31 (46/181)	10.53 (4/38)	20.99 (38/181)	7.89 (3/38)	81.58 (31/38)
χ2		0.065	0.206	0.083	0.359	1.414
P		0.800	0.650	0.773	0.549	0.234

comparison between the two groups, P > 0.05

Table 5. *Comparison of sperm related parameters between the two groups of male patients.*

Characteristics	n	sperm volume (/ml)	sperm density (×10^5/ml)	sperm motility (%)	normal sperm morphology rate (%)
IVF	115	3.82±1.84	69.88±29.05	64.19±24.78	5.82±3.01
ICSI	89	3.96±1.75	50.23±19.17	32.07±9.57	6.50±3.98
t		-0.524	5.803	12.728	-1.356
P		0.601	<0.001	<0.001	0.177

Table 6. *The impact of multiple logistic regression analysis on the high-quality embryo rate.*

Influencing factors	*B*	*SE*	*Waldχ2*	*OR*	*95%CI*	*P*
sperm density	0.009	0.006	2.218	1.009	(0.997,1.020)	0.136
sperm motility	0.007	0.007	0.883	1.007	(0.993,1.022)	0.347
IVF	-0.294	0.379	0.601	0.746	(0.355,1.566)	0.438

Table 7. *Correlation analysis of TPOAb, TGAb and Fertilization Rate, Excellent Embryo Rate.*

Characteristics	fertilization rate	high-quality embryo rate
IVF		
TPOAb		
r	0.102	0.142
P	0.331	0.176
TGAb		
r	-0.202	-0.144
P	0.049*	0.169
ICSI		
TPOAb		
r	-0.131	-0.349
P	0.467	0.047*
TGAb		
r	-0.129	-0.264
P	0.474	0.138

P>0.05 for comparison between two groups. *: correlation is significant at 0.05 level (two-tailed).

4. Discussion

The thyroid gland is the largest endocrine gland in the body and secretes thyroid hormones for regulating growth, development, and metabolism. 2021 European Thyroid Association (ETA) published guidelines for thyroid disorders during assisted reproductive technology, stating that thyroid insufficiency can lead to menstrual disorders and reduced fertility in women, and even if the thyroid function is normal, it can still affect women in the presence of thyroid autoantibodies pregnancy [13], whereas the use of ART can achieve the fertility requirements of women with TAI.

Thyroid autoimmunity in normal thyroid function is also associated with infertility, with a prevalence 4-5 times higher in women than in men. ATA is not only present in women with TAI but is also frequently detected in the serum of patients without significant thyroid dysfunction [14]. The presence of thyroglobulin antibodies (TGA) and thyroid peroxidase antibodies (TPOAb), which are currently measured clinically, initiates the immune system to attack the thyroid tissue, producing symptoms of hyper- or hypothyroidism, which may lead to infertility if it occurs in women of childbearing age, and is also associated with poor outcomes at all times after pregnancy. Monteleone et al [15] verified that thyroid autoantibodies in the follicular fluid can cross the blood-follicular barrier and destroy mature oocytes [16]. Antibody-mediated changes in cytotoxicity, hormone, and metabolite levels cause damage to mature oocytes [17], reducing their quality and affecting early embryonic development [18]. In addition, ATA may alter the conformational arrangement of zona pellucida cells on the egg surface and reduce the fertilization potential of oocytes [19].

Currently, IVF or ICSI combined with embryo transfer is becoming increasingly sophisticated for the treatment of female infertility or male infertility and has brought benefits to many infertile couples. ICSI is now an important tool for the treatment of male infertility with increased fertilization rates [20]. ICSI allows the direct use of better-matured oocytes, reducing physical barriers to fertilization and reducing fertilization failure [22]. However, complete fertilization failure also occurs in ICSI cycles, accounting for 1-5%, and is usually attributed to sperm factors [21]. A large RCT study in 2021 [23], which included male patients with normal sperm count and viability randomized to conventional IVF or ICSI in infertile women, found that ICSI increased fertilization rates and failed to improve live birth rates compared to IVF. ICSI technique has a higher fertilization rate and relatively less risk of total fertilization failure and is recommended for use in complex treatment cycles [20].

It has been demonstrated in previous topics that there is no significant difference in clinical pregnancy rate, miscarriage rate, or live birth rate after IVF-ET in thyroid antibody-positive women undergoing IVF for pregnancy, regardless of whether the TSH level is above or below 2.5uIU/mL. In this context, whether the use of IVF or ICSI would make a difference in pregnancy outcomes in women with TAI deserves more attention.

To find the appropriate fertilization modality among women with TAI, 204 patients were included in this study, including 115 IVF cycles and 89 ICSI cycles. In the subgroup, a stratified analysis of TSH levels within the normal range revealed that regardless of the level of TSH values, there was no significant difference in embryo implantation rate, biochemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, and live birth rate in patients receiving IVF group compared to ICSI group (P>0.05). Consistent with the findings of Song et al [24]. The fertilization rate was higher in the ICSI group compared to patients in the IVF group, while the rate of euthyroid embryos was significantly lower (P<0.05). the fertilization rate in ICSI was higher than in IVF, which is consistent with its fertilization mechanism [9]. In addition, this study confirmed that TGAb had a significant negative effect on fertilization rate during IVF cycles. Previous studies have shown that ICSI, as an invasive procedure, may cause damage to oocytes and affect embryo quality. It is considered that the presence of TPOAb may lead to a decrease in embryogenesis rate. The choice of fertilization method and pregnancy outcome is not affected by the level of TSH, which is divided within the normal range of TSH at 2.5uIU/mL.

The 2014 prospective study [25] showed that TPOAb titers were significantly higher in women who miscarried than those who delivered after treatment with IUI and IVF, whereas there was no significant association between TPOAb titers and pregnancy outcome in women treated with ICSI. This may be related to the fact that the ICSI technique overcomes the effect of thyroid autoantibodies in follicular fluid on the zona pellucida and suggests that we should consider the effect of the two different fertilization modalities, IVF and ICSI, on pregnancy outcome when conducting our study [26]. Poppe et al [10] meta-analysis showed that women with TAI treated with ICSI had a similar risk of early pregnancy miscarriage as normal women, suggesting that in ICSI in which TAI is not a risk factor for miscarriage, thus proposing ICSI as the

recommended ART technique for patients with TAI. women with TAI are more likely to conceive after ICSI during ART-assisted conception compared to IVF, pointing out that ATA affects sperm-oocyte binding and abnormal fertilized egg formation [15]. A previous study found that zona pellucida cells and granulosa cells express thyroid-like antigens on their surface, with which thyroid antibodies cross-react [27]. In contrast, ICSI involves the microscopic injection of sperm into the oocyte and does not require interaction between sperm and zona pellucida [19], so it can be a preferred method for women with TAI. However, this study pointed out that the high-quality embryo rate of ICSI decreased, in which TPOAb played a major negative role. Therefore, there is no conclusion on the method of assisted pregnancy for TAI women, and the main reference standard is still the classification of ATA.

ICSI is beyond the natural physiological mechanisms of fertilization, invasive, more complex from a technical point of view, and expensive, and its safety for the offspring is still controversial and therefore has not been widely performed in infertile women. In a population-based data analysis, a higher incidence of any birth defects was found after ICSI-assisted conception [28]. Davies et al [29] similarly confirmed this. However, other researchers have pointed out that it is more far-fetched to attribute the higher genetic risk in newborns with ART-assisted conception to ICSI [30]. Therefore, continuous developmental follow-up of the newborn is essential [31].

5. Conclusion

In women with TAI, the use of ICSI for fertilization improves fertilization rates but fails to improve pregnancy outcomes and is not recommended as a routine method of fertility assistance. ATA type can be used as reference standards to further select multicenter and large sample population and future prospective studies should be conducted to analyze whether different fertilization modalities have an impact on pregnancy outcomes in women with TAI by selecting a multicenter, large sample of the population. The high rate of high-quality blastocyst formation in ICSI cycles [32] suggests that blastocyst transfer is feasible in women with TAI to improve pregnancy outcomes, but further confirmation is needed.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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