Husband/Wife Joint AB Blood Group is Associated With Clinical Outcomes of IVF/ICSI Treatment in Chinese Women

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Research

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Abstract

Background: A number of publications have been studied the relation between blood group and female infertility including ovarian reserve, recurrent miscarriage and live birth, there is a lack of literature investigating joint wife/husband ABO blood type in large cohort. The aim of this study was to investigate the association between couple combinations for ABO blood groups and ART outcomes in patients undergoing IVF/ICSI.

Methods: This retrospective cohort study included 30,717 couples underwent IVF cycles between 2010 and 2019. Clinical outcomes of IVF treatment was the primary outcome. History of spontaneous miscarriage, embryo quality, and birth sex, weights, defects rate were also studied. Multivariable logistic regression was used to examine the association. Odds ratios (OR) with 95% confidence intervals (CI) for each outcome were estimated.

Results: There was no difference in the baseline demographics between the blood type groups. There was a statistically significantly positive association between the combination of female blood type AB and male blood type AB with biochemical pregnancy, clinical pregnancy, and live birth rate (OR 1.36; 95% CI, 1.05-1.78; P 0.02 and OR 1.31; 95% CI, 1.03-1.68; P 0.031 and OR 1.28; 95% CI, 1.01-1.63; P 0.041 respectively). No statistically significant difference was observed between joint wife/husband ABO blood types and high-quality embryo rate, early abortion rate, birth sex, birth weights and birth defects rate.

Conclusions: Our findings suggest that husband/wife mating AB blood type may increase the success rate of IVF/ICSI cycles.

Introduction

ABO blood group antigen is a complex molecule expressed on the surface of human red blood cells and some other cell types and various tissues, they play major role in transfusion medicine, meanwhile, an increasing evidence suggested ABO blood group is related to the development of many human diseases. A number of publications have been studied the relation between blood group and female infertility including ovarian reserve, recurrent miscarriage and live birth.

As early as 1960, some authors proposed that ABO blood incompatibility may be associated with infertility.^(1, 2) In 1967 Schwimmer et al. suggested that ABO blood group incompatibility was one of the possible immunologic causes of infertility, they found that compared with couples with organic causes of infertility, couples with primary and secondary unexplained infertility possessed of higher incidence of ABO incompatibility.⁽³⁾ However, the association between ABO blood groups and infertility has been a point of controversy, while some studies support the absence of any relationship between blood groups and infertility in different populations.⁽⁴⁾ The correlation of blood groups to ovarian reserve was investigated by multiple studies. Nejat et al showed that blood type O was associated with diminished ovarian reserve and that the A blood group antigen appears to be protective of ovarian reserve.⁽⁵⁾ On the contrary, Lin et al⁽⁶⁾ showed that Chinese women with blood type O had less diminished ovarian reserve than women with blood types B and AB, who had more diminished ovarian reserve while blood type A was not associated with ovarian reserve. Other studies could not confirm this and show no correlation of blood groups to ovarian reserve response during IVF treatment.⁽⁷⁻¹⁰⁾ Recently, a systematic review and meta-analysis was conducted and suggested ABO blood groups not associated with ovarian reserve, Ovarian hyperstimulation syndrome (OHSS) and outcomes of ART.⁽¹¹⁾

Two retrospective studies on infertile women undergoing IVF that live birth relates to ABO blood type came to conflicting conclusions.^(12, 13) There were also studies suggest ABO blood type has impact on female infertility by related with incidence of ovarian hyperstimulation syndrome and endometriosis, which are important influence factors of pregnancy. A predominance of blood group A was shown in patients with endometriosis by studying 231 women with endometriosis and 166 infertile women without endometriosis.⁽¹⁴⁾ One case-control study on 121 patients in Caucasians supposed a positive association between A blood group and early-onset ovarian hyperstimulation syndrome.⁽¹⁵⁾

Despite the aforementioned findings, there is a lack of literature investigating joint wife/husband ABO blood type in large cohort, we set out to explore whether ABO blood type is associated with clinical outcomes of IVF treatment, history of spontaneous miscarriage, embryo quality parameters, and birth sex, weights, defects rate in Chinese infertile couples.

Materials And Methods

Study Population

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. Patients undergoing cycles of IVF/ICSI at the Reproductive Medical Center, First Affiliated Hospital of Zhengzhou University, between January 2010 and December 2019 were included in this study. 30,717 infertility couples with ABO blood groups and Rhesus factor testing, with the wife's age between 25–35 years old. Potential confounders may cause spontaneous abortion or affect ART outcomes were excluded in this study. The complete information of age, body mass index (BMI), ABO and Rh blood type, duration of subfertility, Primary subfertility, ART outcomes and birth information of each couple were collected from the Clinical Reproductive Medicine Management System/Electronic Medical Record Cohort Database of the Reproductive Medical Center of the First Affiliated Hospital of Zhengzhou University.

Clinical and Laboratory Protocols

A blood type and screen is obtained in all patients as part of the initial infertility workup at hospital's laboratory. Controlled ovarian stimulation (COS), hCG trigger, oocyte retrieval, embryo culture, and ET performed based on established protocols.⁽¹⁶⁾

In fresh ET, Patients with fresh embryo transfer were treated with gonadotropin releasing hormone (GnRH) agonists to achieve suppression of ovulation and prevent a premature LH surge.⁽¹⁷⁾ When the patient achieved the criteria for pituitary suppression, Gonadotropin (Gonal-F, Merck, Germany; Puregon, Organon, Netherlands; Urofollitropin, Livzon, China) was used to initiate ovarian stimulation with the dose range of 75–300 IU based on the ovarian response (75–150 IU for normal or high ovarian response; 150–300 IU for reduced ovarian response). Exact dose of gonadotropin was adjusted based on age, body mass index (BMI, kg/m²), antral follicle count (AFC), and AMH level of individual patient. hCG (Livzon) was injected the oocyte maturation trigger and was administered when at least three follicles had reached 18 mm and the lead follicle was ≥ 20 mm. Oocytes were collected by transvaginal ultrasound-guided puncture at 37 h after hCG injection. Progesterone in oil was used for luteal support at a dose of 60 mg per day after oocyte pick-up.

Based on the condition of semen and the couples' reproductive history, fertilization was carried out with short-time insemination or ICSI insemination.⁽¹⁸⁾ The embryo morphology in the cleavage stage was observed and graded according to the Peter's standards⁽¹⁹⁾ on day 3. Day 5 blastocyst-stage embryos were graded according to the Gardner standard.⁽²⁰⁾ The condition and the willingness of patient were comprehensively considered to decide whether to perform fresh ET or FET.

Based on the regularity of the menstrual cycle, Frozen ET cycles were divided into natural cycles and artificial cycles. For natural cycles, patients were allocated to undergo ultrasonic evaluation starting from day 8–9 of the menstrual cycle. When the diameter of the dominant follicle was 16–20 mm, blood sample test for progesterone and LH levels was conducted to monitor ovulation. Thawing and transferring were performed 3 days for cleavage-stage embryos or 5 days for blastocyst-stage embryos after ovulation. Intramuscular (im) progesterone (40 mg) starting on the day of ovulation and oral dydrogesterone (20 mg) starting on the embryo transfer day were used for luteal support. For artificial cycles, patients began oral estradiol [2mg, Progynova; Bayer, Leverkusen, Germany] twice a day on cycle day 3. This dose was adjusted based on the endometrial thickness every 4 days. After 12–14 days, an ultrasound was performed and a serum progesterone level was determined. If no leading follicle was present, progesterone (60 mg im) and oral dydrogesterone [10mg [this dose was changed to 20mg 2 days later]] would be added to the regimen.

The serum hCG biochemical pregnancy tests were performed 14 days and 18 days after the embryo transfer. For patients with hCG was more than 50 IU/L, transvaginal ultrasound was performed 35 days after embryo transfer.

Study Variables

Baseline demographics recorded for each patient included age (years), BMI (kg/m²), infertility diagnosis, ABO blood type, and rhesus factor type. The primary outcome in this study was clinical outcomes of IVF treatment. Biochemical pregnancy was defined as an increase in the serum β -hCG concentration at 14 days after embryo transfer. Clinical pregnancy was defined as one or multiple gestational sac(s) and cardiac activity seen via ultrasound 35 days after embryo transfer. Live birth was defined as any birth event in which at least one baby is born alive. Early spontaneous miscarriage, which was defined as a pregnancy loss before 14 weeks of gestation following clinical pregnancy. Recurrent spontaneous abortion (RSA) was defined as the occurrence of at least two spontaneous losses before fetal viability.

Statistical Analysis

Association analysis were performed using custom R scripts. Results for continuous data are given as mean $\pm$ standard deviation (SD). Results for categorical variables are given as number of cases (n) with percentage of occurrence (%). The proportions of the different blood types were compared by the chi-squared test. ANOVA was used for parametric data between blood type groups. Previous spontaneous abortion, embryo quality parameters, ART outcomes, birth sex, weight (log₂ transformed) and defects were compared by blood type groups using Multivariable logistic regression models while adjusting for potential confounders. ORs with 95% CIs were estimated from the model. Three models were used to test spontaneous abortion association: (1) a dosage model, which treated as recurrent miscarriage marked 1 and as 0; (2) a dominant model, which treated 0 as absent and more than 1 abortion as present; and (3) a continuous model to study the number of spontaneous abortion. $P < 0.05$ was considered to be statistically significant.

Results

From the initial pool 39,477 cycles, 39,154 cycles have complete ABO and Rh blood type information with the female age > 25 years and < 35 years. We excluded potential confounders may cause spontaneous abortion or affect ART outcomes: chromosome abnormality(n = 976), congenital disease (n = 258), cervical incompetence (n = 345), uterine malformation (n = 1031), hypomenorrhea (n = 25), endometriosis or ovarian surgery history (n = 581), POI / oocyte maturation disorder (36), uterine fibroids (n = 216), endometrial lesions (n = 2), trophoblastic disease (n = 15), cervical cancer (n = 2), Male: azoospermia (n = 1981), necrozoospermia (n = 16), severe oligoasthenospermia (n = 2953). A total of 30,717 cycles met the inclusion criteria.

The distribution of these patients based on blood type was as follows: 8846 (28.80%) females with blood type A; 3257 (10.60%) females with blood type AB; 9712 (31.62%) females with blood type B; and 8902(28.98%) females with blood type O. For Rh blood type, 98 (0.032%) females with blood type Rh-; 30,619 (99.68%) females with blood type Rh+; This distribution of blood types is similar to the males': 8624 (28.08%) males with blood type A; 3257 (10.76%) males with blood type AB; 9771 (31.81%) males with blood type B; and 9016(29.35%) males with blood type O. For Rh blood type, 120 (0.039%) females with blood type Rh-; 330597 (99.61%) females with blood type Rh+. As shown in Fig. 1 and Supplemental Table 1, there was no difference in the distribution of blood type between infertile females and males.

Demographic and clinical characteristics of study population are shown in Table 1 and Supplemental Table 1. The women's average age was 30.0 ± 2.83 years. There was no difference in the age, BMI, duration of subfertility, primary subfertility by blood type in both female and male groups.

Given the small sample size of patients having Rh negative in population, especially when it was split into the four ABO blood groups, we do not include rhesus factor for downstream association test.

Table 1

Overall demographics and patients characteristics of female group stratified by blood type (n = 30,717)

Characteristics	All	A(n = 8846)	B(n = 9712)	AB(n = 3257)	O(n = 8902)	P value
Age	30.06 ± 2.83	30.09 ± 2.84	30.06 ± 2.85	29.98 ± 2.82	30.05 ± 2.81	0.236
BMI	22.83 ± 3.22	22.82 ± 3.20	22.83 ± 3.19	22.91 ± 3.36	22.82 ± 3.20	0.554
Duration of subfertility (m)	48.22 ± 33.58	48.47 ± 33.31	48.36 ± 34.09	47.68 ± 32.06	48.03 ± 33.83	0.613
Primary subfertility	44.93% (13801/30717)	45.16% (3995/8846)	45.53% (4422/9712)	45.26% (1474/3257)	43.92% (3910/8902)	0.145
Note: Data presented as mean ± SD or n (%).						

History of Spontaneous Miscarriage Association Analysis

We investigated the potential interaction between ABO blood group of husband/wife mating and the history of spontaneous miscarriage by three models as described before. There was a statistically significantly higher

percentage of combination of female blood type AB and male blood type O in couples with at least one spontaneous miscarriage history (odds ratio [OR] 1.03; 95% confidence interval [CI], 1-1.05; P = 0.0234) than for the rest. However, no statistically significant difference was observed in Dosage and Continuous models (OR 1.01; 95% CI, 1-1.01; P 0.243 and OR 1.03; 95% CI, 1-1.06; P 0.08 respectively), as shown in Table 2.

Table 2

Multivariate logistic regression analyzes between history of spontaneous miscarriage and parental blood types combinations.

Female Blood Type	Male Blood Type	Dosage model		Dominant model		Continuous model	
		OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
AB	B	1.00 (0.99–1.01)	0.874	0.99(0.97–1.01)	0.433	0.99(0.96–1.02)	0.384
AB	A	1.00 (0.99–1.01)	0.753	0.99(0.97–1.01)	0.348	1.00(0.97–1.03)	0.843
AB	O	1.01(1.00-1.01)	0.243	1.03(1.00-1.05)	0.023	1.03(1.00-1.06)	0.080
AB	AB	0.99(0.98–1.01)	0.304	0.99(0.96–1.02)	0.426	0.98(0.94–1.02)	0.323
B	B	1.00 (0.99-1.00)	0.521	1.00 (0.99–1.01)	0.871	0.99(0.97–1.01)	0.438
B	A	1.00(0.99–1.01)	0.966	1.01(0.99–1.02)	0.262	1.01(0.99–1.03)	0.213
B	O	1.00 (1.00-1.01)	0.443	0.99(0.98–1.01)	0.214	0.99(0.98–1.01)	0.566
B	AB	1.00 (0.99–1.01)	0.963	1.00 (0.98–1.03)	0.646	1.00 (0.98–1.03)	0.802
A	B	1.00 (1.00-1.01)	0.465	1.01(0.99–1.02)	0.433	1.02(1.00-1.04)	0.113
A	A	1.00 (0.99-1.00)	0.467	0.99(0.98–1.01)	0.355	0.99(0.97–1.01)	0.166
A	O	1.00 (0.99-1.00)	0.525	1.00 (0.98–1.01)	0.561	0.99(0.97–1.01)	0.388
A	AB	1.00 (1.00-1.01)	0.373	1.01(0.99–1.03)	0.308	1.01(0.98–1.04)	0.370
O	B	1.00 (0.99–1.01)	0.993	1.00 (0.99–1.01)	0.910	1.00 (0.98–1.02)	0.816
O	A	1.00 (1.00-1.01)	0.321	1.00 (0.99–1.02)	0.676	1.00 (0.98–1.02)	0.806
O	O	1.00 (0.99-1.00)	0.356	1.00 (0.99–1.02)	0.731	1.00 (0.98–1.02)	0.767
O	AB	1.00 (0.99–1.01)	0.885	0.99(0.97–1.01)	0.348	0.99(0.96–1.02)	0.635

Embryo Quality parameters Association Analysis

We also assessed the association between husband/wife blood types combinations and embryo quality parameters, including fertilization rate, cleavage rate and high-quality embryo rate, by adjusting the number of transfer embryos. The combination of female blood type B and male blood type A has a negative association with fertilization rate (OR 0.98; 95% CI, 0.97-1; *P* 0.01), while the combination of female blood type O and male blood type A has a slightly negative association with cleavage rate (OR 1; 95% CI, 0.99-1; *P* 0.027). As evident in Table 3,

no statistically significant difference was observed between ABO blood group of husband/wife mating blood types and High-Quality Embryo Rate.

Table 3

Female Blood Type	Male Blood Type	Dosage model		Dominant model		Continuous model	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
AB	B	1.00 (0.99–1.01)	0.874	0.99(0.97–1.01)	0.433	0.99(0.96–1.02)	0.384
AB	A	1.00 (0.99–1.01)	0.753	0.99(0.97–1.01)	0.348	1.00(0.97–1.03)	0.843
AB	O	1.01(1.00-1.01)	0.243	1.03(1.00-1.05)	0.023	1.03(1.00-1.06)	0.080
AB	AB	0.99(0.98–1.01)	0.304	0.99(0.96–1.02)	0.426	0.98(0.94–1.02)	0.323
B	B	1.00 (0.99-1.00)	0.521	1.00 (0.99–1.01)	0.871	0.99(0.97–1.01)	0.438
B	A	1.00(0.99–1.01)	0.966	1.01(0.99–1.02)	0.262	1.01(0.99–1.03)	0.213
B	O	1.00 (1.00-1.01)	0.443	0.99(0.98–1.01)	0.214	0.99(0.98–1.01)	0.566
B	AB	1.00 (0.99–1.01)	0.963	1.00 (0.98–1.03)	0.646	1.00 (0.98–1.03)	0.802
A	B	1.00 (1.00-1.01)	0.465	1.01(0.99–1.02)	0.433	1.02(1.00-1.04)	0.113
A	A	1.00 (0.99-1.00)	0.467	0.99(0.98–1.01)	0.355	0.99(0.97–1.01)	0.166
A	O	1.00 (0.99-1.00)	0.525	1.00 (0.98–1.01)	0.561	0.99(0.97–1.01)	0.388
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O	A	1.00 (1.00-1.01)	0.321	1.00 (0.99–1.02)	0.676	1.00 (0.98–1.02)	0.806
O	O	1.00 (0.99-1.00)	0.356	1.00 (0.99–1.02)	0.731	1.00 (0.98–1.02)	0.767
O	AB	1.00 (0.99–1.01)	0.885	0.99(0.97–1.01)	0.348	0.99(0.96–1.02)	0.635
Multivariate logistic regression analyzes between embryo quality parameters and couple blood types combinations by adjusting for controlled ovarian hyperstimulation protocols.							

Table 3

Multivariate logistic regression analyzes between embryo quality parameters and parental blood types combinations by adjusting for controlled ovarian hyperstimulation protocols.

Female Blood Type	Male Blood Type	Fertilization Rate		Cleavage Rate		High Quality Embryo Rate	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	Pvalue
B	A	0.98(0.97-1.00)	0.010	1.00(1.00-1.01)	0.251	0.99(0.97-1.01)	0.354
B	O	1.01(0.99-1.02)	0.245	1.00 (1.00-1.00)	0.942	1.02(1.00-1.04)	0.110
B	B	1.01(0.99-1.02)	0.315	1.00 (1.00-1.00)	0.783	0.99(0.97-1.01)	0.442
B	AB	1.01(0.98-1.03)	0.563	1.00 (0.99-1.00)	0.254	1.00 (0.97-1.03)	0.843
AB	A	1.00 (0.98-1.02)	0.813	1.00 (1.00-1.01)	0.343	0.99(0.96-1.02)	0.564
AB	O	1.00 (0.98-1.03)	0.854	1.00 (0.99-1.00)	0.386	1.01(0.98-1.04)	0.520
AB	B	1.00 (0.98-1.02)	0.847	1.00 (0.99-1.01)	0.818	1.01(0.98-1.04)	0.529
AB	AB	1.01(0.97-1.04)	0.701	1.00 (0.99-1.01)	0.832	0.98(0.94-1.02)	0.313
A	A	1.01(0.99-1.02)	0.278	1.00 (1.00-1.01)	0.654	1.01(0.99-1.03)	0.510
A	O	1.00 (0.99-1.02)	0.839	1.00 (0.99-1.00)	0.464	0.98(0.96-1.00)	0.061
A	B	0.99(0.98-1.01)	0.282	1.00 (1.00-1.00)	0.992	1.01(0.99-1.03)	0.308
A	AB	1.00 (0.97-1.02)	0.782	1.00 (1.00-1.01)	0.658	1.00 (0.97-1.03)	0.816
O	A	1.01(1.00-1.03)	0.089	1.00 (0.99-1.00)	0.027	1.01(0.99-1.03)	0.497
O	O	0.99(0.97-1.00)	0.127	1.00 (1.00-1.01)	0.171	1.00 (0.98-1.02)	0.860
O	B	1.00 (0.99-1.02)	0.840	1.00 (1.00-1.00)	0.680	0.99(0.98-1.01)	0.508
O	AB	0.99(0.97-1.02)	0.565	1.00 (1.00-1.01)	0.559	1.00 (0.98-1.03)	0.808

ART Outcomes Association Analysis

We have further compared the outcomes of treatment to blood groups, including Biochemical and clinical Pregnancy, early abortion rate, live birth rate. As shown in Table 4, there was a statistically significantly positive association between the combination of female blood type AB and male blood type AB with biochemical pregnancy, clinical pregnancy, and live birth rate (OR 1.36; 95% CI, 1.05–1.78; P 0.02 and OR 1.31; 95% CI, 1.03–1.68; P 0.031 and OR 1.28; 95% CI, 1.01–1.63; P 0.041 respectively). No statistically significant difference was observed between couple combinations for ABO blood groups and early abortion rate.

Table 4

Female Blood Type	Male Blood Type	Fertilization Rate		Cleavage Rate		High Quality Embryo Rate	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	Pvalue
B	A	0.98(0.97-1.00)	0.010	1.00(1.00-1.01)	0.251	0.99(0.97-1.01)	0.354
B	O	1.01(0.99-1.02)	0.245	1.00 (1.00-1.00)	0.942	1.02(1.00-1.04)	0.110
B	B	1.01(0.99-1.02)	0.315	1.00 (1.00-1.00)	0.783	0.99(0.97-1.01)	0.442
B	AB	1.01(0.98-1.03)	0.563	1.00 (0.99-1.00)	0.254	1.00 (0.97-1.03)	0.843
AB	A	1.00 (0.98-1.02)	0.813	1.00 (1.00-1.01)	0.343	0.99(0.96-1.02)	0.564
AB	O	1.00 (0.98-1.03)	0.854	1.00 (0.99-1.00)	0.386	1.01(0.98-1.04)	0.520
AB	B	1.00 (0.98-1.02)	0.847	1.00 (0.99-1.01)	0.818	1.01(0.98-1.04)	0.529
AB	AB	1.01(0.97-1.04)	0.701	1.00 (0.99-1.01)	0.832	0.98(0.94-1.02)	0.313
A	A	1.01(0.99-1.02)	0.278	1.00 (1.00-1.01)	0.654	1.01(0.99-1.03)	0.510
A	O	1.00 (0.99-1.02)	0.839	1.00 (0.99-1.00)	0.464	0.98(0.96-1.00)	0.061
A	B	0.99(0.98-1.01)	0.282	1.00 (1.00-1.00)	0.992	1.01(0.99-1.03)	0.308
A	AB	1.00 (0.97-1.02)	0.782	1.00 (1.00-1.01)	0.658	1.00 (0.97-1.03)	0.816
O	A	1.01(1.00-1.03)	0.089	1.00 (0.99-1.00)	0.027	1.01(0.99-1.03)	0.497
O	O	0.99(0.97-1.00)	0.127	1.00 (1.00-1.01)	0.171	1.00 (0.98-1.02)	0.860
O	B	1.00 (0.99-1.02)	0.840	1.00 (1.00-1.00)	0.680	0.99(0.98-1.01)	0.508

Multivariate logistic regression analyses between ART outcomes and couple blood types combinations with adjusting for number of transfer embryo(s).

Female Blood Type	Male Blood Type	Fertilization Rate		Cleavage Rate		High Quality Embryo Rate	
		OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
O	AB	0.99(0.97–1.02)	0.565	1.00 (1.00–1.01)	0.559	1.00 (0.98–1.03)	0.808
Multivariate logistic regression analyses between ART outcomes and couple blood types combinations with adjusting for number of transfer embryo(s).							

Table 4

Multivariate logistic regression analyses between ART outcomes and parental blood types combinations with adjusting for number of transfer embryo(s).

Female Blood Type	Male Blood Type	Biochemical Pregnancy		Clinical pregnancy		Early Abortion Rate		Live Birth Rate	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
AB	B	1.04(0.88–1.23)	0.614	0.93(0.79–1.09)	0.374	0.87(0.69–1.10)	0.255	0.91(0.78–1.06)	0.234
AB	A	0.92(0.78–1.10)	0.361	0.98(0.83–1.16)	0.824	1.08(0.87–1.35)	0.479	0.96(0.82–1.13)	0.646
AB	O	0.90(0.76–1.07)	0.239	0.97(0.83–1.14)	0.742	1.04(0.83–1.30)	0.708	1.02(0.87–1.20)	0.769
AB	AB	1.36(1.05–1.78)	0.020	1.31(1.03–1.68)	0.031	1.01(0.71–1.42)	0.975	1.28(1.01–1.63)	0.041
B	B	0.99(0.89–1.10)	0.841	0.98(0.88–1.09)	0.749	1.19(0.94–1.50)	0.155	0.99(0.90–1.10)	0.920
B	A	0.97(0.86–1.09)	0.585	1.00(0.90–1.11)	0.972	0.83(0.66–1.05)	0.119	0.99(0.89–1.10)	0.809
B	O	1.06(0.95–1.19)	0.305	1.05(0.94–1.17)	0.383	0.96(0.76–1.21)	0.738	1.07(0.96–1.19)	0.222
B	AB	0.97(0.82–1.14)	0.678	0.94(0.80–1.10)	0.458	1.17(0.81–1.65)	0.395	0.90(0.77–1.05)	0.196
A	B	0.99(0.88–1.11)	0.861	1.03(0.93–1.15)	0.572	1.01(0.71–1.42)	0.959	1.01(0.91–1.13)	0.802
A	A	1.05(0.93–1.18)	0.435	0.99(0.88–1.10)	0.806	1.13(0.81–1.56)	0.477	1.03(0.93–1.15)	0.556
A	O	0.97(0.86–1.08)	0.550	0.96(0.86–1.08)	0.515	0.82(0.58–1.16)	0.275	0.92(0.83–1.03)	0.137
A	AB	1.00(0.84–1.19)	0.981	1.04(0.88–1.23)	0.623	1.15(0.68–1.86)	0.593	1.09(0.92–1.28)	0.315
O	B	1.00(0.90–1.12)	0.962	1.02(0.92–1.14)	0.690	0.97(0.76–1.23)	0.781	1.04(0.93–1.15)	0.500
O	A	1.03(0.91–1.15)	0.680	1.02(0.92–1.15)	0.675	1.04(0.83–1.31)	0.714	1.00(0.89–1.11)	0.971
O	O	1.02(0.91–1.14)	0.739	1.00(0.89–1.11)	0.966	1.08(0.86–1.37)	0.490	1.00(0.9–1.120)	0.980
O	AB	0.90(0.77–1.07)	0.242	0.91(0.77–1.07)	0.240	0.78(0.53–1.13)	0.201	0.92(0.79–1.08)	0.303

Birth Sex, Weights, Defects Rate Association Analysis

Finally, multivariate logistic regression analysis was performed to determine the relationship between blood type and birth sex, birth weights and birth defects rate after adjusting for the number of live births. As shown in Table 5, no blood type was statistically significantly associated with birth sex, birth weights and birth defects rate.

Table 5

Female Blood Type	Male Blood Type	Biochemical Pregnancy		Clinical pregnancy		Early Abortion Rate		Live Birth Rate	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
AB	B	1.04(0.88–1.23)	0.614	0.93(0.79–1.09)	0.374	0.87(0.69–1.10)	0.255	0.91(0.78–1.06)	0.234
AB	A	0.92(0.78–1.10)	0.361	0.98(0.83–1.16)	0.824	1.08(0.87–1.35)	0.479	0.96(0.82–1.13)	0.646
AB	O	0.90(0.76–1.07)	0.239	0.97(0.83–1.14)	0.742	1.04(0.83–1.30)	0.708	1.02(0.87–1.20)	0.769
AB	AB	1.36(1.05–1.78)	0.020	1.31(1.03–1.68)	0.031	1.01(0.71–1.42)	0.975	1.28(1.01–1.63)	0.041
B	B	0.99(0.89–1.10)	0.841	0.98(0.88–1.09)	0.749	1.19(0.94–1.50)	0.155	0.99(0.90–1.10)	0.920
B	A	0.97(0.86–1.09)	0.585	1.00(0.90–1.11)	0.972	0.83(0.66–1.05)	0.119	0.99(0.89–1.10)	0.809
B	O	1.06(0.95–1.19)	0.305	1.05(0.94–1.17)	0.383	0.96(0.76–1.21)	0.738	1.07(0.96–1.19)	0.222
B	AB	0.97(0.82–1.14)	0.678	0.94(0.80–1.10)	0.458	1.17(0.81–1.65)	0.395	0.90(0.77–1.05)	0.196
A	B	0.99(0.88–1.11)	0.861	1.03(0.93–1.15)	0.572	1.01(0.71–1.42)	0.959	1.01(0.91–1.13)	0.802
A	A	1.05(0.93–1.18)	0.435	0.99(0.88–1.10)	0.806	1.13(0.81–1.56)	0.477	1.03(0.93–1.15)	0.556
A	O	0.97(0.86–1.08)	0.550	0.96(0.86–1.08)	0.515	0.82(0.58–1.16)	0.275	0.92(0.83–1.03)	0.137
A	AB	1.00(0.84–1.19)	0.981	1.04(0.88–1.23)	0.623	1.15(0.68–1.86)	0.593	1.09(0.92–1.28)	0.315
O	B	1.00(0.90–1.12)	0.962	1.02(0.92–1.14)	0.690	0.97(0.76–1.23)	0.781	1.04(0.93–1.15)	0.500
O	A	1.03(0.91–1.15)	0.680	1.02(0.92–1.15)	0.675	1.04(0.83–1.31)	0.714	1.00(0.89–1.11)	0.971
O	O	1.02(0.91–1.14)	0.739	1.00(0.89–1.11)	0.966	1.08(0.86–1.37)	0.490	1.00(0.9–1.120)	0.980
O	AB	0.90(0.77–1.07)	0.242	0.91(0.77–1.07)	0.240	0.78(0.53–1.13)	0.201	0.92(0.79–1.08)	0.303
Multivariate logistic regression analyzes between birth sex, birth weights and birth defects and couple blood types combinations in single live born cycles.									

Discussion

To our known, our study represents the largest retrospective cohort study evaluating the association between wife/husband ABO blood group pairs and ART outcomes published so far, the result suggests there was a

statistically significantly positive association between the combination of female blood type AB and male blood type AB with biochemical pregnancy, clinical pregnancy, and live birth rate. No statistically significant difference was observed between couple combinations for ABO blood groups and High-quality embryo rate, early abortion rate, birth sex, birth weights and birth defects rate.

As early as 1943, Levine had identified ABO incompatibility as a cause of early abortions and stillbirths. By analyzing the relation of husband/wife joint ABO blood group on 79 couples suffering from recurrent abortion in India, Malekasgar AM et al shows an excess of joint "A/B" blood groups in couples with RSA.⁽²¹⁾ However, this study presented the difference simply by the percentage of blood types not P value of statistical analysis. By screening the ABO blood groups aborted fetuses and their parents in 124 early spontaneous abortions, Bandyopadhyay AR found a significantly higher ($P < 0.05$) frequency of ABO incompatibility in couple with miscarriage when compared with newborns and their parents from the same area.⁽²²⁾ This conclusion indicates that the ABO incompatibility between the husband and wife may be a risk factor for early spontaneous abortions. However, we observed lacked statistical power to detect relevant associations of blood groups either to history of spontaneous abortions before ART treatment, nor to early spontaneous abortions following IVF-ET.

Awartani K et al⁽¹⁰⁾ compared clinical parameters of 566 IVF treatment cycles with different ABO blood type and found no significant association between blood type and pregnancy rate. This result is agreed by another retrospective study which evaluated the effect of non-O blood type on clinical pregnancy of 497 women, and found no statistically significant association between them. As regarding live birth, two retrospective studies on infertile women undergoing IVF came to different conclusions. One study in a cohort of 626 infertile women suggested that woman with blood type B had significantly higher likelihood of live birth following IVF-ET.⁽¹²⁾ However, Pereira N et al observed no relation of blood groups to live-birth rate by assessing 2,329 patients undergoing fresh IVF with day 5 single embryo transfer.⁽¹³⁾ In our study population, couples who have joint "AB/AB" blood types had significantly higher likelihood of biochemical pregnancy, clinical pregnancy, and live birth. Using the ABO incompatibility effect infertility hypothesize is easy to explain our finding considering same blood type were completely compatible and no antibodies was activated to attack each other.

We found no association between ABO blood type and birth weight at delivery, which result in the same conclusion with Pereira N.⁽¹³⁾ In 1975 Allan TM reported the birth sex ratio of male to female babies is related with ABO blood group of babies and mothers by study 53,679 mother-baby combinations, for AB mothers to have higher sex ratio babies while A babies have lower sex ratio,⁽²⁴⁾ the authors suggested these differences may cause by interaction of the ABO genes and some unknown sex-determining genes with estrogen and progesterone. No correlation was found between blood type and birth sex in our cohort.

As mentioned before, the current evidence available is not sufficient to confirm that the blood type ABO is related to some aspects of female fertility. The underlying mechanisms of ABO blood type incompatibility may play some role in abortion are uncovered. Some authors hypothesized that ABO blood type may result in infertility because the presence of incompatible antibodies of spermatozoa in the serum or in the secretions of the wife's genital tract. Genetic is another possible mechanism, given the candidate *NR5A1* and *TGFBR1* genes impacting oocyte quality or early implantation are proximity to the 9q34 locus of the ABO gene.⁽²⁵⁾ The other possible mechanism of ABO-related infertility was its effect on thrombosis, some studies suggested the formation of blood vessels at the maternal fetal interface may lead to the failure of implantation or placenta, further influent the clinical outcomes of IVF,⁽²⁶⁾ the relationship between non-O blood type and venous thromboembolism was observed by previous

studies,⁽²⁷⁾ but the data remains controversial.⁽²⁸⁾ In consideration of maternal-fetal differences in ABO membrane protein structure, studying on couple combinations for ABO blood groups was not sufficient to address the underlying mechanisms. With the limitation of lack of newborn's blood type, it is notable that our results of no association between blood type and birth ratio do not exclude other possibilities. Thus, further prospective studies are needed to prove our results.

Conclusion

In conclusion, the current large sample size retrospective cohort study demonstrated the statistically significantly positive association between the combination of female blood type AB and male blood type AB with biochemical pregnancy, clinical pregnancy, and live birth rate. Couples who have joint "AB/AB" blood types had significantly higher likelihood of the success rate of IVF/ICSI cycles.

Abbreviations

ART: Assisted reproductive technology; ICSI: Intracytoplasmic sperm injection; IVF: In vitro fertilization; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; COS: Controlled ovarian stimulation; AFC: Antral follicular count; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; OHSS: Ovarian hyperstimulation syndrome; ET: embryo transfer; FET: Frozen thawed embryo transfer; hCG: Human chorionic gonadotropin; RSA: Recurrent spontaneous abortion

Declarations

Competing interests

Authors have declared that no competing interests exist.

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Authors' contributions

XB, YPS designed the study; XB, Feifei Zhao and Hao Shi analyzed the data; XB, Zhiqin Bu and Yuling Liang wrote the manuscript; YPS revised the manuscript. All authors contributed to the article and approved the submitted version.

Ethics approval and consent to participate

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University.

Consent for publication

Not applicable.

Availability of data and material

All data supporting the conclusion of this article are included.

Competing interests

The authors declare that they have no competing interests.

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Figures

Distribution of Female ABO Blood Type
%(n=30717)

Distribution of Male ABO Blood Type
%(n=30717)

Figure 1

Distribution of ABO blood type in infertile females and males.

Supplementary Files

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