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Impact of Antiphospholipid Antibodies on Intracytoplasmic Sperm Injection Outcome

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ABSTRACT

Introduction and Aim: The effect of antiphospholipid syndrome on pregnancy is extensively discussed but the debate is still ongoing. This debate increased when the association was examined after assisted reproductive techniques for infertility. The current work aimed to evaluate the influence of Antiphospholipid antibodies in patient undergo first cycle of intracytoplasmic sperm injection.

Subjects and Methods: The study comprised 130 of infertile females, who were scheduled for the first ICSI cycle. Before protocol selection, basal hormonal assay was performed and included FSH, LH, E2, prolactin and AMH. Plasma concentration of anti-phospholipids (APAs) was measured. Then, females were categorized into groups according to APAs (positive and negative groups). After ICSI, the clinical pregnancy was confirmed by presence the gestational sac or sac with positive pulsation. Ongoing pregnancy was recognized if the pregnancy continued after 12 weeks of the gestation and clinical miscarriage if pregnancy terminated before 12 weeks of gestation.

Results: All females were in their reproductive age (18- 40 years). Their fertility duration ranged between 1 and 7 years, and it was of primary type among 96 women. The long agonist protocol was used for 72 women and the antagonist protocol done for 58 women. The Antiphospholipid antibodies were positive among 27 females (20.8%), and there was no significant difference between APL positive and negative groups regarding pregnancy results (either chemical, clinical, incidence of abortion or ongoing pregnancy after 12 weeks) for all females. However, in women with positive clinical pregnancy, the rate of abortion was significantly increased in patients with APL- positive than negative females (66.7% vs 26.7%).

Conclusion: The presence of APA was associated with higher significant abortion rate after the first cycle of ICSI. Thus, screening for APA in women with infertility scheduled for assisted reproduction is recommended.

Keywords: Antiphospholipid; Autoantibodies; Infertility; Intracytoplasmic Sperm Injection; Abortion.

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INTRODUCTION

Antiphospholipid antibodies (APAs), a group of antibodies that attached to negatively charged phospholipid they have clinical significance because of their association of thromboembolic event [1]. The potential benefits of anticoagulant therapy for women undergoing intracytoplasmic sperm injection (ICSI) is based on several observation. Firstly, phospholipid function is adhesive molecules during the formation of syncytiotrophoblast [2]. It has been proposed that antiphospholipid antibodies (APAs) may have some relationship with infertility and ICSI outcome [3]. Secondly, the attachment of Antiphospholipid antibodies (APAs) to surface phospholipids on trophoblast may result in direct cellular injury and indirect damage of intravascular thrombosis [4].

The presence of Antiphospholipid antibodies (APAs) in women who experienced recurrent pregnancy loss (RPL) unexplained infertility allow the diagnosis of RPL [5]. The prevalence of Antiphospholipid antibodies (APAs) was higher in infertile women than fertile, and presence of APAs appear to be associated with intracytoplasmic sperm injection ICSI failure [3]. APAs positively were associated statistically significant lower pregnancy rate and higher abortion rate after ICSI [6]. Study done in Korean women by **Zhong *et al.*** [7] decided that the prevalence of Antiphospholipid antibodies (APAs) is low in infertile women undergoing to intracytoplasmic sperm injection ICSI cycles and presence of Antiphospholipid antibodies (APAs) appear to neither decrease ICSI success nor abortion rate.

Immunological testing for women undergoing ICSI was recommended especially for women with increase antibodies such as endometriosis and unexplained infertility [8]. It has been proposed that APS may have some relationships with infertility and ICSI outcomes **(3).** More recently, **Hong *et al.*** [6], found that the presence of APA neither decrease ICSI success nor abortion rate in women undergoing to ICSI cycle.

THE AIM OF THE WORK

The aim of this work was to evaluate the influence of (Anti-phospholipid antibodies) in patient undergo first (intracytoplasmic sperm injection) ICSI Cycle.

SUBJECTS AND METHODS

A prospective observational study had been conducted at the international Islamic Center of The Popular Studies and Research. It comprised 130 of infertile females, selected from the outpatient clinic, and scheduled for the first ICSI cycle. They were recruited from March 2020 to September 2020. The study protocol was submitted for approval by the Institutional Review Board (IRB), Damietta Faculty of Medicine, Al-Azhar University (New Damietta). Additionally, each female signed an informed consent for participation in the study. The confidentially and personal privacy were respected in all levels of the study. The inclusion criteria for the current work were female age between 25 and 40 years, with body mass index (BMI) below 30kg/m^2 and infertility was due to female factor (unexplained, ovarian, tubal, or multiple). On the other extreme, the exclusion criteria were male factor infertility (e.g., azoospermia), obesity (BMI > 30kg/m^2), uterine anomalies, intrauterine adhesions, thyroid dysfunction, immunological diseases (e.g., rheumatoid arthritis and systemic lupus erythematous), and other endocrine diseases (e.g., hyperprolactinemia and diabetes mellitus). Before protocol selection and ovarian stimulation for ICSI, basal hormonal assay (follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen (E2), and prolactin (PRL)) on the second day of the cycle, had been performed. In addition, anti-Mullerian (AMH) was assessed for all patients. Plasma concentration of anti-phospholipids (APAs) was measured for by the enzyme-linked immunosorbent assay method. Then, females were categorized into groups according to positivity and negativity of APAs results (Negative <10 unit, Borderline 10-19 unit, Positive 20-80 unit, and highly positive >80 unit).

All were submitted to ovarian stimulation for ICSI by using recombinant or urinary FSH (150-225 IU/day). Two types of pituitary suppression protocols were used (the luteal long agonist protocol, and flexible antagonist protocol. After more than three follicles had reached a diameter of >18 mm, 500 IU of human chorionic gonadotropin (hCG) was injected. The oocyte was retrieved 35 hours after the injection of hCG. Two distinct pro-nuclei and a second polar body were visible. The quality of the embryos was evaluated by morphological criteria based on fragmentation degree and regularity of blastomeres on the third day after fertilization [9]. Embryo transfer was performed day three after oocyte collection. The luteal phase was supported easily by daily progesterone injection or vaginal progesterone gel. The clinical pregnancy was confirmed by presence the gestational sac or sac with positive pulsation. Ongoing pregnancy was recognized if the pregnancy continued after12 weeks of the gestation and clinical miscarriage if pregnancy terminated before 12 weeks of gestation.

Statistical analysis and data interpretation: Data were fed to the computer and analysed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Chi square test was used to compare between two or more groups for qualitative variables. However, if more than 25% of cells have a count less than 5 in a 2 x 2 tables, Fisher Exact test was used. In addition, Student *t*-test was used to compare 2 quantitative parametric groups, and Mann-Whitney "U" test was used to compare 2 non-parametric independent groups.

RESULTS

In the current research, female age ranged between 18 and 40 years, the mean age was 29.34±5.3 years. The mean BMI was 25.78±3.32 (range 19.47-29.76 kg/m^2). The indications for seeding first ICSI cycle were unexplained infertility, tubal factor, ovarian factors, poor responders and multifactorial. The duration of infertility ranged between 1 and 7 years. The infertility was primary among the majority of patients (96 patients). The regimen used in induction protocol was mainly the long agonist (72 patients), while the antagonist protocol was assigned for 58 females. The suppression type was Deca 0.1 among 73 cases (57.7%) and cetrotide among 57 females (42.3%). The laboratory parameters at inclusion were detailed in table (1). The Antiphospholipid antibodies were positive among 27 females (20.8%) and negative among 103 cases (79.2%). There was no significant difference between APL positive and negative groups regarding pregnancy results (either chemical, clinical, incidence of abortion or ongoing pregnancy after 12 weeks) (Table 2). In addition, there was no significant differences between APL negative and APL positive groups regarding patient age,

BMI, duration of infertility, used protocol or laboratory data at inclusion or initial outcome (Table 3). In cases with positive clinical pregnancy, the rate of abortion was significantly increased in patients with APL- positive than negative females (66.7% vs 26.7%) (Table 4).

Table (1): Patient demographics, indications for ICSII, infertility data and laboratory values at inclusion

Items		Mean ±SD	Median (min-max)
Age (years)		29.34±5.3	30 (18-40)
BMI (kg/m²)		25.78±3.32	26.55 (19.47 – 29.76)
Indications for ICSI (n,%)	Tubal factors	53(40.8%)	
	Ovarian factors	27 (20.8%)	
	Unexplained infertility	33 (25.4%)	
	Multifactorial	7 (5.4%)	
	Poor responders	10 (7.7%)	
Infertility duration (years)		3.14±1.23	3 (1-7)
Infertility type (n,%)	***Primary / secondary***	96(73.8%) / 34 (26.2%)	
Regimen (n,%)	***Long agonist/ antagonist***	58 (66.7%) / 45 (33.3%)	
Type of suppression	***Deca 0.1 / Cetrotide***	73 (57.7%) / 57 (42.3%)	
FSH (IU/ml)		6.01 ± 2.51	5.7 (0.5-21.5)
LH (IU/ml)		4.16 ± 2.47	3.6 (0.1-15.5)
PRL (ng/ml)		17.11 ± 10.15	14.51 (0.11-67.11)
AMH (ng/ml)		2.19 ± 2.59	0.83 (0.09-9.1)
E2 (ng/ml)		0.047 ± 0.021	0.044 (0.01-0.14)

Table (2): Pregnancy results with positive and negative (APL)

	APL -ve (N=103)	APL +ve cases (N=27)	Test	p
Chemical pregnancy	40 (38.8%)	9 (33.3%)	0.27	0.60
Clinical pregnancy	32 (31.1%)	5 (18.5%)	1.65	0.19
Abortion	8 (7.8%)	2 (7.4%)	0.004	0.95
Ongoing pregnancy >12 weeks	24 (23.3%)	3 (11.1%)	1.93	0.16

Table (3): Patient characteristics according to positive state of antiphospholipid antibodies

		APL –ve (n=103)	APL+ve (n=27)	Test	p
Age (years)		28.96 ± 5.31	27.21 ± 4.57	1.244	0.267
BMI (Kg/m²)		25.74 ± 3.39	26.12 ± 2.86	0.278	0.775
Duration of infertility (years)		3.06 ± 1.20	3.86 ± 1.35	1.656	0.102
Used protocol	Long agonist	58(56.3%)	14 (51.9%)	0.17	0.67
	Antagonist	45(43.7%)	13 (48.1%)		
Laboratory	FSH (IU/ml)	5.9 (4.8-7.3)	5 (4.22-6.55)	2.453	0.293
	LH (IU/ml)	3.6 (2.6- 5)	3.4 (3.2-4.65)	1.208	0.547
	PRL (ng/ml)	14.31 (10.46-21.26)	17.26 (11.61-23.41)	1.120	0.571
	AMH (ng/ml)	0.95 (0.63-4.35)	0.81 (0.65-1.24)	1.285	0.526
	E2 (ng/ml)	0.043 (0.033-0.055)	0.046 (0.036-0.062)	1.107	0.575
	TSH (IU/ml)	2.1 (1.5-3)	2.5 (1.9-3.3)	5.845	0.054
	E2 at trigger (ng/ml)	2.92 (2 -3.54)	2.67 (2.02-3.43)	0.802	0.670
Initial outcome	Number of retrieved oocytes	9(7-11)	10(8-11)	1.315	0.142
	Number of available Embryos	3(1-5)	2(1-5)	1.546	0.108
	Number of available embryos	1(1-3)	1(1-3)	0.617	0.208

Table (4): Analysis of abortion according to positive state of antiphospholipid antibodies in patients with positive clinical pregnancy

	APL-ve with positive clinical pregnancy (N=15)		APL +ve with positive clinical pregnancy (N=3)		Test	P value
Abortion	4	26.7%	2	66.7%	***5.147***	***0.002****

DISCUSSION

The association of anti-phospholipid antibodies with infertility is debated. Infertile women are commonly screened for APA [10]. However, no sufficient studies explored the association between APA and pregnancy outcome after in-vitro fertilization. Thus, we tried to explore the situation. Results showed that, APA was positive among 20.8% of studied females which higher than reported incidence in literature (0 to 17%) [6, 11, 12]. Miscarriage was significantly increased among those with positive APA than females with negative APA. Otherwise, no significant differences were observed between APA positive and negative groups regarding patient demographics,

indications, laboratory investigations or other variables. In line with the results of the current work, a Korean study revealed that abortion rate was significantly higher in APA-positive than APA-negative group (62.5% vs. 20.0%) after IVF, although pregnancy rate was similar between APA-positive and APA-negative group [11]. **Zhong *et al.*** [7] also demonstrated a significantly lower pregnancy rates in positive than negative (31.3% vs. 48.6%) and higher pregnancy loss (32.0% vs. 15.1%) after IVF.

The higher rate of abortion could be explained by the increased attachment of APA to the trophoblasts, with direct cellular damage effects and inhibition of conversion from cytotrophoblast to syncytiotrophoblast. In addition, the formation of microthrombi may lead to indirect trophoblastic damage. APA was also associated with pregnancy associated medical diseases like hypertension and preeclampsia [13-15].

Deeb *et al.* [12] from Syria reported a very low incidence of APA in females submitted to IVF (<1.0%), with no association between APA and any of patient demographics or IVF outcome. However, **Hong *et al.*** [6] reported a prevalence rate of 14.8% positive APA among infertile females. But they did not report any effects on the ICSI cycles outcome. The very low percentages of positive APA in Deeb et al. (12) study may explain absent association between IVF outcome and presence of APA. The different inclusion criteria could explain the contradiction with the study of **Hong *et al.*** [6], as they included females with different autoimmune antibodies other than APA (the sole one in the current work). **Simopoulou *et al.*** [16] conducted a systematic review to explore the role of autoantibodies on ART outcome. They confirmed the presence of positive association between miscarriage and the presence of autoantibodies. However, the effect on pregnancy outcome differ according to the type of antibodies. **Del Porto *et al.*** [10] carefully selected records of 151 out of 2000 women. The selected women had idiopathic infertility and treated by ICSI. The APS was diagnosed in 25.0% of women, irrespective of the higher laboratory features suggestive of APS (higher APA among 37.5%). They concluded that, women with idiopathic infertility show a high prevalence of APA, suggesting that this APA can affect conception. Thus, measuring APA can represent a valid method to recognize women at higher risk for potential pregnancy-related complications and unfavorable outcome from those undergoing ART. In such situations, an accurate diagnosis and an adequate therapy are associated with a better outcome.

A major limitation of the current work is the small sample size in APA-positive group, irrespective of sample size justification before the study. Thus, more women would be required in the future studies to assess the real association between positive APA and pregnancy outcome after ICSI.

Conclusion: The present study concluded that the presence of APA demonstrated statistically significant difference between positive and negative groups who underwent first ICSI cycle regarding pregnancy rate and abortion rate.

Declaration of Financial and Non-Financial Relationships and Activities of Interest: None

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