Serum anti-endometrial antibodies as a biomarker for implantation rate in patients with endometriosis who had recurrent implantation failure and prepared for Intracytoplasmic Sperm Injection

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Abstract

Background: Endometriosis is a common disease that affects 10% of reproductive-age women, which extrapolates to approximately 190 million women worldwide.

Objectives: we aimed to assess the prognostic value of serum anti-endometrial antibodies estimation in connection to the implantation rate in endometriosis patients with recurrent implantation failure who underwent intracytoplasmic sperm injection cycles (ICSI).

Patients and Methods: A prospective cohort study examined infertile patients with endometriosis who underwent ICSI cycles after recurrent implantation failure at assisted reproduction units, Obstetrics and Gynecology departments, South Valley University, and Cairo University. All patients were evaluated and serum anti-endometrial antibodies were measured, followed by an ICSI procedure, and the implantation rate was recorded

Results: 32 patients were included; 24 (75%) had primary infertility, and 8 (25%) had secondary infertility. Antiendometrial antibodies were positive in 21 (65.62%) patients, with a significant negative correlation between anti-endometrial antibodies and implantation rate in patients with recurrent implantation failure (P= 0.010).

Conclusion: Serum anti-endometrial antibodies exhibited a negative association with implantation rate and oocyte quality, suggesting a potential use as a biomarker in endometriosis patients with recurrent implantation failure undergoing ICSI cycles.

Keywords: Autoantibodies; Assisted reproduction; *In vitro* fertilization

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Introduction

Endometriosis is a disease that affects 10% of women during the age of reproduction, which represents about 190 million women around the world (**Sarria-Santamera et al., 2020**). Autoimmune disease is well-related to infertility in females (**Geva et al., 1997);** Autoantibodies to certain endometrial and ovarian tissues as well as other organ-specific and non-organ-specific antibodies have been observed in the sera and cervical mucus of infertile patients. The presence of anti-endometrial antibodies (AEA) is strongly related to endometriosis. **(Choudhury and Knapp 2001).**

The AEA may affect female fertility by various mechanisms, anti-endometrial antibodies have been detected in patients with ovulatory dysfunction (**Palacio et al.,2006)** as well as in patients with decreased endometrial receptivity and recurrent implantation failure (**Van Voorhis and Stovall1997).** AEA has a wide range of endometrial antigens with molecular weights (MWs) of 15–170 kDa. However, the nature of most of these cognate antigens is unclear **(Gajbhiye et al., 2008**). The study aimed to determine the predictive value of serum AEA in patients with recurrent implantation failure and endometriosis who undergoing intracytoplasmic sperm injection (ICSI) cycles and to correlate these antibodies with oocyte quality.

Patients and methods

The study included infertile patients (with endometriosis) who underwent ICSI cycles after recurrent implantation failure at the assisted reproduction units, Obstetrics and Gynecology departments, South Valley University, and Cairo University, From December 2020 to June 2023.

Inclusion criteria; infertile women with endometriosis who passed through ICSI cycles after recurrent implantation failure, Age: 18-35 years, body mass index (BMI): ≤ 30, primary or secondary infertility, duration of infertility less than 10 years and husband's semen examination within the World Health Organization (2010) reference range **(Cooper et al., 2010).**

Exclusion criteria; other gynecological problems e.g. fibroid, uterine polyp, hydrosalpinx, congenital structural abnormalities of the reproductive tract, pelvic tuberculosis, ovarian tumor, polycystic ovary syndrome, hyperprolactinemia, adrenal disease, thyroid disease or other endocrine disease and abnormal male factor.

Methodology: The following steps were done for all patients included in this study

1. History and clinical examination.
2. Ovarian reserve testing (serum antimullerian hormone, basal serum follicular stimulating hormone, Cancer Antigen-125, and basal antral follicle count by Ultrasound)
3. Uterine cavity examination by transvaginal 3-dimensional ultrasound (Samsung, Korea) and evaluation of endometriosis (shape, size, unilateral or bilateral, unilocular or bilocular, and if it is associated with adenomyosis)
4. Perform laparoscopy (Karl Storz, Germany) for confirmation of endometriosis and staging of endometriosis using the revised American Society for Reproductive Medicine classification for endometriosis, The American Society for Reproductive Medicine (ASRM) classifies endometriosis into four stages of disease progression based on the number of lesions and the depth of implantation. Stage 1 is the least severe and includes mainly superficial lesions; whereas, stage 4 is the most severe with many deep lesions **(Johnson et al., 2017).**
5. Measurement of AEA (IgG and IgA) in the serum of women with endometriosis one month before ICSI using qualitative human Endometrium Antibody, EMAb ELISA Kit (SinoGeneclone Biotech-Hang Zhou, China), Catalogue Number: SG-14202. Test results interpretation was as follows: Human endometrial antibody (EMAb) valence was calculated by

comparing the samples to the control, we calculated optical density (OD) as 0.1 if it is negative (＜0.1), OD sample/OD negative ≥2.1: Positive in contrast, and OD sample/OD negative < 2.1: Negative.

6. ICSI procedure and oocyte assessment: Recombinant FSH (Gonal F pen) was the gonadotrophin stimulation drug used, individualization of stimulation dose and slight modifications were done according to ovarian response. A long GnRH agonist protocol was used (decapeptyle 0.1mg by subcutaneous injection daily started at the mid-luteal phase of the cycle before the ICSI cycle till gonadotrophins stimulation drug started then decapeptyle dose was reduced to half and continued to HCG triggering day. A baseline assessment of AFC by transvaginal scans was performed by an experienced gynecologist using a 7.5 MHz vaginal probe (Samsung, Korea). Ovarian response monitoring to stimulation drugs till the time of ovum pick-up and the number and quality of oocytes obtained were recorded and analyzed at the end of the study. When 3-4 follicles acquired >18 mm, triggering of ovulation was done using human chorionic gonadotrophins (ovitrelle 250 IU 2 ampoules subcutaneously 36 hours before pick-up of oocytes. after oocyte retrieval, the ICSI procedure was done for all cases. Only 1-2 embryos were transferred to each mother on day 3 or day 5 according to embryo quality and the remaining good-quality embryos were frozen for subsequent transfer. The pregnancy test was done 14 days post-embryo transfer **(Yao and Schust, 2005).**

The oocyte quality was determined morphologically according to **(Wang and Sun, 2007**) by light and polarized light microscopy for evaluation of the peculiarities of the oocyte cumulus-corona-complex (OCCC) structure, oocyte cytoplasm, dimension of the perivitelline space, zona pellucida, polar body, and meiotic spindle on a collective basis**.**

Embryo assessment and grading at (day 3) according to **Veeck's (1986)** morphological grading system that depends on the morphological appearance of the embryo, cleavage state, cell symmetry, and fragmentation: Grade I: 8 cells, blastomeres of equal size; Grade II: 8 cells, blastomeres of equal size, and <20% cytoplasmic fragmentation; Grade III: Eight cells with uneven blastomeres size and no cytoplasmic fragmentation; Grade IV: Four or eight cells with >20% cytoplasmic fragmentation; Grade V: blastomeres (of any size) with major or complete fragmentation.

Ethical consideration: This study was approved by the Institutional Review Board (IRB). Ethical approval code: SVU-MED-OBG024-2-20-12-106.

Statistical analysis

Data were analyzed using the IBM SPSS software package version 25, and qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of the data, and quantitative data were described using mean, standard deviation, and median. The p-value was set at $p < 0.05$.

Unpaired t-tests were conducted to compare the means between the groups. Chi-square tests were used to explore associations among categorical variables. Pearson's correlation was used to examine the associations between variables. Odds ratio (OR) confidence intervals were calculated to assess the likelihood of outcomes. Logistic regression analysis was used to identify the dominant factors affecting pregnancy, including age, BMI, period of infertility, type of infertility, oocyte quality, embryo quality, and AEA.

Receiver operating characteristic (ROC curve) used to evaluate the AEA diagnostic performance with sensitivity, specificity, area under the curve, and positive and negative predictive values

Results

In this study, we included 36 women who had gone through 82 cycles. Patients were

infertile (with endometriosis) and underwent ICSI cycles after recurrent implantation failure; four patients were excluded from our analysis as they didn't respond to stimulation drugs. The study involved 32 patients admitted to assisted reproduction units of obstetrics and gynecology departments, six admitted to South Valley University, and 26 admitted to Cairo Universities.

The mean (±SD) age of the included patients was 32.35 ± 5.04 years. The mean (±SD) BMI was 28.2 ± 4.81 kg/m^2, 24 (75%) patients had primary infertility, and 8 (25%) patients had secondary infertility. The mean (±SD) period of infertility was 7.44 ± 3.65 years **(Table 1).**

Table 1. Demographic data

Parameter		**Value**
Included patients N (%)		32 (100%)
Age (years) (Mean ±SD)		32.35 ± 5.04
BMI (Mean ±SD)		28.2 ± 4.81
Type of infertility N (%)	1ry	24 (75%)
	2ry	8 (25%)
Period of infertility (years) (Mean ±SD)		7.44 ± 3.65

Of the patients, 21 (65.62%) had positive AEA results 11 (34.38%) had negative results, 8 patients had stage 1 endometriosis,12 patients had stage 2 endometriosis,8 patients had stage 3 endometriosis, and 4 patients had stage 4 endometriosis **(Table 2).** Of the patients, 30 (93.75%) had successful oocyte retrieval. The mean number of oocytes retrieved was 5.11 ± 4.74. There were 17 (56.67%) patients with poor oocyte quality, 12 (40%) patients with fair oocyte quality, 1 (3.33%) patient with good oocyte quality, and 26 (81.25%) patients with successful embryo transfers. The mean number of embryos collected was 2.87 ± 2.66. There were 11 (42.31%) patients with grade (A) embryo quality, 10 (38.46%) patients with grade (B) embryo quality, and 5 (19.23%) patients with grade (C) embryo quality. There were 10 (38.46%) patients with a fresh cycle and 16 (61.54%) patients with a frozen cycle. There were 5 (19.23%) patients who had a positive pregnancy test, while 21 (80.76%) patients had a negative pregnancy test (**Table 2**).

Table 2: Clinical characteristics of the included patients

Parameters		N (%)
Total number of included patients		32 (100%)
Number of oocytes retrieved	(Mean ±SD)	5.11 ± 4.74
Success of oocytes retrieved from patients		30 (93.75%)
Success of oocyte fertilization		26 (81.25%)
Success of embryos transferred to patients		26 (81.25%)
Number of embryos collected	(Mean ±SD)	4.88 ± 3.78
Stage of endometriosis	1	8 (25%)
	2	12 (37.5%)
	3	8 (25%)
	4	4 (12.5%)
AEA	Negative	11 (34.38%)
	Positive	21 (65.62%)
Oocyte quality	Poor	17 (56.67%)
	Fair	12 (40%)

	Good	1(3.33%)
Embryo quality	Grade A	11 (42.31%)
	Grade B	10 (38.46%)
	Grade C	5 (19.23%)
Fresh/frozen cycle	Fresh	10 (38.46%)
	Frozen	16 (61.54%)
Pregnancy test	Positive	5 (19.23%)
	Negative	21 (80.76%)

There was a significant negative correlation between AEA and implantation rate in patients with recurrent implantation failure, and there was a significant negative correlation between AEA and oocyte quality **(Table 3).**

Table 3. Pearson Correlation between AEA, pregnancy test, and oocyte quality

		Pregnancy test	Oocyte quality
AEA	r	-0.274	-0.462
	P	0.010	0.002

Compared to the secondary infertility group, the mean age of primary infertility cases (29.2 ±2.9 years) was significantly younger than that of secondary infertility cases (32.4 ±3.2 years) (p = 0.0179). The number of embryos collected was significantly lower in the primary infertility group (3.7 ±1.3) compared to the secondary infertility group (5.9 ±1.4) (p = 0.0005), **(Table 4)**.

Table 4. Primary and secondary infertility concerning demographic data, stage of endometriosis, AEA, oocyte retrieved, and embryo collected

Type of infertility		Primary infertility	Secondary Infertility	P-Value
Number (%)		24(75%)	8(25%)	-
Age (Years)		29.2±2.9	32.4±3.2	0.0179*[t]
BMI (Kg/m^2)		28.3±2.8	29.6±2.7	0.2518[t]
Period of infertility		7.5±1.6	7.3±1.2	0.7114[t]
Stage of endometriosis	Stage 1	5 (20.83%)	3 (37.5%)	0.34578[x]
	Stage 2	9 (37.5%)	3 (37.5%)	0.99[x]
	Stage 3	7 (29.17%)	1 (12.5%)	0.34578[x]
	Stage 4	5 (20.83%)	1 (12.5%)	0.60099[x]
AEA	positive	15 (62.5%)	6 (75%)	0.51915[x]
	negative	9 (37.5%)	2 (25%)	0.51915[x]
Oocyte	retrieved	4.2±1.3	5.7±2.1	0.0668[t]
Embryo	collected	3.7±1.3	5.9±1.4	0.0005*[t]

*: Significant; [t]: unpaired t-Test; [x]: Chi square test

AEA was positive in 21 (65.62%) of patients, and 11(34.38%) tested negative. The mean age of positive AEA cases (33.1±3.6 years) was significantly older than that of negative AEA cases (28.8±2.2 years) (p= 0.00023). The positive AEA group showed a substantial decrease in retrieved oocytes (3.2±1.2 vs. 7.1±1.4, p < 0.0001) and embryos collected (4.3 ±1.1 vs. 5.9±1.5, p = 0.00393). The positive AEA cases also had a lower positive pregnancy rate (4.76%) compared to the negative AEA cases (36.36%, p = 0.01936). **(Table 5).**

Table 5. AEA concerning patient's age, BMI, number of oocytes retrieved, embryo collected, and pregnancy rate

AEA		Positive (N = 21)	Negative (N = 11)	P-Value
N (%)		21 (65.62%)	11 (34.38%)	-
Age (Years)		33.1±3.6	28.8±2.2	0.00023*[t]
BMI (Kg/m^2)		26.6±3.2	30.7±2.2	0.00019*[t]
Period of infertility (Years)		8.2±2.3	6.8±3.5	0.24028[t]
Oocyte retrieved		3.2±1.2	7.1±1.4	<0.0001*[t]
Embryo collected		4.3±1.1	5.9±1.5	0.00393*[t]
Pregnancy rate	positive	1 (4.76%)	4 (36.36%)	0.01936*[x]
	negative	16 (76.19%)	5 (45.45%)	0.08209[x]

*: Significant; [t]: unpaired t-Test; [x]: Chi square test

Logistic regression analysis revealed that the possible predictive factors for a decreased probability of pregnancy were poor oocyte quality, poor embryo quality, and positive AEA (**Table. 6).**

Table 6. Logistic regression analysis for factors predicting pregnancy

Variables		(Total No = 26)				Regression analysis			
		Positive pregnancy test (N=5)		Negative Pregnancy test (N=21)		P-value	OR	95%CI	
		No.	%	No.	%			LL	UL
Age (years)	Mean± SD	30.21± 4.26		28.52± 3.17		0.967	0.998	0.900	1.106
	Median (IQR)	27 (18-34)		28 (20-35)					
BMI (Kg/m^2)	Mean± SD	26.47± 3.29		29.51± 2.7		0.558	1.170	0.754	1.441
	Median (IQR)	22.5 (20-29)		23.45 (18-30)					
Type of infertility	Primary	2	11.1%	16	88.9%	0.723	2.673	1.255	3.774
	Secondary	3	37.5%	5	62.5%				
Infertility duration (years)	Mean± SD	6.33± 2.01		5.92± 2.96		0.674	0.910	0.553	2.132
	Median (IQR)	5 (2-9)		4 (1.5-10)					
Oocyte quality	Poor	1	6.3%	15	93.7%	0.033*	0.329	0.150	1.185
	Fair	3	33.3%	6	66.7%				
	Good	1	100%	0	0.0%				
Embryo quality	Grade A	4	36.4%	7	63.6%	0.041*	0.682	0.356	1.305
	Grade B	1	10%	9	90%				
	Grade C	0	0.0%	5	100%				
Anti-endometrial antibodies	Positive	1	5.9%	16	94.1%	0.010*	0.552	0.230	0.853
	Negative	4	44.4%	5	55.6%				

*: significant; t: unpaired t-test, X: Chi-square test, OR: Odds ratio, CI: Confidence interval LL: lower limit, UL: Upper limit

The ROC curve analysis of positive AEA and its effect on pregnancy rate revealed that the Area Under the Curve (AUC) was determined to be 0.23 with a standard error of 0.116. Sensitivity and specificity were recorded at 20% and 25.93%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were observed at 4.76% and 63.64% respectively, while the accuracy of

the analysis was measured at 25%. The associated p-value was calculated to be 0.58, indicating the statistical borderline significance of the observed results. (**Table.7** and **Fig.1**).

Table 7. The ROC curve analysis of the association between AEA positivity and pregnancy rate

AUC	Std. Error	Sensitivity	Specificity	PPV	NPV	Accuracy	P. Value
0.23	0.116	20%	25.93%	4.76%	63.64%	25%	0.58

*: significant

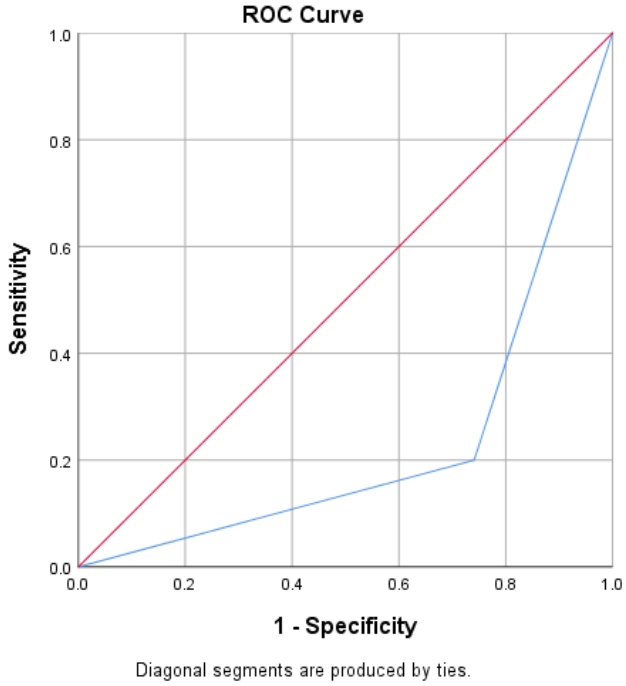

Fig.1. ROC curve analysis of AEA positivity association with pregnancy rate

Discussion

The main aim of this study was to assess the predictive value of serum anti-endometrial antibodies in the prediction of implantation rate in patients with endometriosis with recurrent implantation failure who performed ICSI cycles.

This cohort study was conducted on 32 infertile patients (with endometriosis) undergoing ICSI cycles.

The mean age of included patients was 32.35 ± 5.04 years, the mean BMI was 28.2 ± 4.81 Kg/m^2, there were 24 (75%) patients had primary infertility, and 8 (25%) patients had secondary infertility. The mean period of infertility was 7.44 ± 3.65 years.

Our findings were consistent with those of **Wafa et al., (2019)** who studied 40 patients with endometriosis, and revealed that the mean age was 32.7±3.5 years and the mean BMI was 24.3 ±3.5 Kg/m^2. The majority (70%) of women have primary infertility with a mean period of infertility being 5.17 years.

The current study revealed that 8 (25%) patients had stage 1 endometriosis, 12 (37.5%) patients had stage 2 endometriosis, 8 (25%) patients had stage 3 endometriosis, and 4 (12.5%) patients had stage 4 endometriosis.

Shebl et al. (2017) showed that among 114 endometriosis patients, 34.8% had stage 1, 13.2% had stage 2, 23.2% had stage 3, and 10.8% had stage 4 endometriosis. There were 15 (13.1%) patients who had previous IVF cycles. Whereas **Shahrokh et al. (2009),** who studied 80 cases, found that 60% of the enrolled cases had stage 3 and 4 endometriosis and 40% of cases had stage 1 and 2 endometriosis.

In this study, 11 (34.38%) patients had negative AEA, while 21 (65.62%) patients were positive for AEA.

Fernandez-Shaw et al. (1993) showed that the presence of AEA is strongly related to endometriosis. Moreover, **Ozhan et al. (2014),** in a case-controlled study involving 80 cases, found that the serum levels of AEA had a significant difference between the endometriosis group (60 cases) and the control group (20 cases) ($P<0.01$) among endometriosis and control groups and can be used as a biomarker for endometriosis. **Gajbhiye et al. (2008)** showed that 60% of IgG or IgM AEA was present in endometriosis patients, **Mathur et al. (1990)** found that IgG antibodies were present in 78% of women with endometriosis and 22% of healthy controls, and **Odukoya et al. (1995)** found that there was a correlation between IgG and endometriosis. IgG antibodies were present in 56% of women with endometriosis and 5% of healthy controls. Another study reported the presence of IgG and IgM in 33% and 27% of patients, respectively **(Long et al., 2013).**

The current study showed that 30 patients (93.8%) underwent successful oocyte retrieval. The mean number of oocytes retrieved was 5.11 ± 4.74, there were 17 (56.7%) patients had poor oocyte quality, 12 (40%) patients had fair oocyte quality, and 1 (3.3%) patients had good oocyte quality, there were 26 (81.25%) oocytes fertilized.

However, **Wafa et al. (2019)** found that the mean number of ova retrieved was 6.2 ±3.6, with a fertilization rate of 64.8% in affected patients. However, **Kasapoglu et al. (2018)** recognized that the median number of ova retrieved was 10.5 (2–29), with a fertilization rate of 71 (0–100%) in the affected patients. **Boucret et al. (2020)** reported that the mean number of ova retrieved was 7.0 ± 4.3.

In the current study, there was low oocyte quality among endometriosis patients, suggesting the negative effect of endometriosis on oocyte quality. This is in agreement with the findings of a systematic review by **Sanchez et al. (2017),** who showed that endometriosis negatively affects ovum quality. In addition, **Borges et al. (2015)** showed that patients with endometriosis have significantly poorer oocyte quality compared to healthy controls.

In the current study, 26 (81.2%) patients had a successful embryo transfer. The mean number of embryos collected was 2.87 ± 2.66. Of the 26 patients, 11(42.3%) had grade A embryos, 10(38.4%) had grade B embryos, and 5 (19.2%) had grade C embryos. Ten (38.5%) patients had a fresh cycle and 16 (61.5%) patients had a frozen cycle.

However, **Wafa et al. (2019),** who studied 40 patients with endometriosis, showed that 69.5% of patients had successful embryo transfer, and the mean number of embryos transferred was 2.24 ± 1.07. In addition, **Borges et al. (2015)** showed that the mean number of embryos was 6.1 ± 4.43, transferred embryos was 2.2 ± 0.9, and implantation rate was 28.1 ± 38.9 among endometriosis patients. Moreover, **Boucret et al. (2020)** showed that women with endometriosis had a low number of oocytes, and therefore, a low number of embryos.

In the current study, 5 (15.6%) patients had a positive pregnancy test result, while 21 (65.6%) patients had a negative pregnancy test result. Similar to the current study, **Muteshi et al. (2018)** showed that the pregnancy test results were positive in 142 (26.7%) patients with endometriosis. However, higher pregnancy rates were reported by **Borges et al. (2015),** who reported a pregnancy rate of 36.9% among patients with endometriosis. Additionally, **Wafa et al. (2019)** reported a pregnancy rate of 19 (47.5%) among 40 patients with endometriosis. The difference in pregnancy rates may be due to the infertility type and

grade of endometriosis.

There was a poor outcome in implantation rate after IVF in patients with endometriosis; this is due to poor oocyte quality, resulting in lower fertilization rates and endometrial dysfunction that leads to failed implantation **(Wafa et al., 2019).**

We found a significant negative correlation between AEA pregnancy test results and oocyte quality. However, there was no significant correlation between AEA and embryo quality. This finding was supported by **Sarapik et al. (2010),** who showed that AEA was related to poor implantation outcomes.

The literature revealed that serum AEA was high in endometriosis patients **(Mathur et al., 1990; Fernandez-Shaw et al., 1993; Odukoya et al., 1995; Gajbhiye et al., 2008; Long et al., 2013; Ozhan et al., 2014)** and affected ICSI cycle outcomes **(Randall et al., 2009; Sarapik et al., 2010).** Few studies assessed the prognostic accuracy of serum anti-endometrial antibodies in the detection of implantation rates for patients with endometriosis undergoing ICSI cycles.

The current study has some limitations, such as a low number of cases and a relatively short follow-up period. Further comparative studies with longer follow-ups are needed to confirm our results.

Conclusion

Serum anti-endometrial antibodies are negatively correlated with oocyte quality and implantation rate. The AEA may possibly serve as a biomarker for implantation rate in endometriosis patients with recurrent implantation failure undergoing ICSI cycles.

Conflict of interest

The authors of this study have no conflict of interest related to this publication.

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