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Value of Serum Anti-Endometrial Antibodies in Prediction of Implantation Rate in Patient with Endometriosis Undergoing Intracytoplasmic Sperm Injection Cycles

Mostafa M khodry[2], Abdelrahman A Elsaid[2], Abd El-Naser Abd El-Gaber Ali[2], Mohammed Zain[2], Radwa M.Fahmy[1]

[1]Obstetrics & Gynecology, Department Faculty of Medicine-Cairo University

[2]Obstetrics & Gynecology, Department Faculty of Medicine-South Valley University

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*Corresponding Author

Mostafa M khodry, Obstetrics & Gynecology, Department Faculty of Medicine-South Valley University, Tel.: 00201007088098, E-mail: khodrymesh@yahoo.com

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Abstract

Background: Endometriosis is a common disease that occurs in 6 to 10% of reproductive-age women. Approximately 25% to 50% of infertile women have endometriosis, and 30% to 50% of women with endometriosis are infertile.

Aim and objectives: The aims of this study were to assess the predictive value of serum anti-endometrial antibodies in prediction of implantation rate in patient with endometriosis who undergoing intracytoplasmic sperm injection cycles. Subjects and methods: The cohort study had been conducted at the assisted reproduction units, Obstetrics and Gynecology departments, South Valley University and Cairo University. Result: Mean age of included patients was 30.85 ± 4.04. Mean BMI was 26.1 ± 3.81. 27 patients had 1ry infertility. While 7 patients had 2ry infertility. Mean period of infertility was 6.22 ± 2.75. Significant negative correlation between Anti-endometrial Ab and implantation rate and Oocyte quality. Conclusion: In conclusion; the current study suggested that serum anti-endometrial antibodies can be used as a biomarker to detect implantation rate for patient with endometriosis undergoing intracytoplasmic sperm injection cycles. Serum anti-endometrial antibodies was negatively correlated with outcome (pregnancy test and Oocyte quality). Patients with endometriosis have positive serum anti-endometrial antibodies, have low oocyte quality and pregnancy rate.

Keywords: Serum Anti-Endometrial Antibodies; Endometriosis; Intracytoplasmic Sperm Injection Cycles

Introduction

Endometriosis is considered a debilitating gynecological pathology with a high prevalence among young women. The incidence of the disease varies between 6–10% [1]. Endometriosis is characterized by the migration of endometrial--like cells in ectopic places outside the uterus. The clinical manifestations consist of chronic pelvic pain, dysmenorrhea, and infertility, the latter being reported in 30–50% of cases, while 20–25% of patients remain asymptomatic [2].

Humoral autoimmune activation is well known phenomenon in female infertility [3]. Autoantibodies to fertility specific endometrial and ovarian tissue as well as other organ specific and non-organ specific antibodies have been detected in the sera and cervical mucus of infertile patients. The presence of anti-endometrial antibodies (AEA) is mainly associated with endometriosis [4]. Anti-endometrial antibodies may hamper female fertility by diverse mechanisms, as the presence of AEA has been demonstrated in patients with ovulatory disorders [5] as well as in patients with decreased endometrial receptivity and recurrent implantation failure [6]. AEA recognize a wide range of endometrial antigens with molecular weights (MWs) of 15–170kD [7]. However, the nature of most of these cognate antigens is unclear.

Aim of Work

Primary outcome: The aims of this study is to asses the predictive value of serum anti_endometrial antibodies in prediction of implantation rate in patient with endometriosis who undergoing intracytoplasmic sperm injection cycles.

Secondary outcome: to find correlation between serum anti-endometrial antibodies and egg quality retrieved .

Patients and Methods

This study included infertile patients (with endometriosis) who undergone ICSI cycles at the assisted reproduction units, Obstetrics and Gynacology departments , South Valley University and Cairo University.

Full history, clinical examination, US findings, laparscopy-,and investigations were recorded.

Clear verbal counseling and written consent were obtained from all participants in the research according to the committee of Medical Ethics of Faculty of Medicine, South Valley University.

Inclusion criteria; infertile patients (with endometriosis) who passed through ICSI cycles, Age: 18-35 years, Body mass index (BMI): ≤ 30, primary or secondary infertility, duration of infertility less than 10 years, results of semen examination of patients' husbands within the World Health Organization (WHO) reference range.

Exclusion criteria; gynecological problem e.g. fibroid, uterine polyp, hydrosalpinx will be excluded,Male factor: Abnormal sperm morphology;(globozoospermia and pin- point sperm), congenital structural abnormalities of the reproductive tract, pelvic tuberculosis, ovarian tumour, polycystic ovary syndrome, hyperprolactinaemia, adrenal disease, thyroid disease or other endocrine disease.

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

1. Detailed history and clinical examination.

2. Ovarian reserve testing (serum AMH , basal serum FSH, CA_125 and basal AFC by US)

3. Uterine cavity examination (by trasvaginal 3-dimentional ultrasound or office hysteroscopy)

4. Evaluation of male factor (husbnad semen analysis)

5. Transvaginal ultrasound for evaluation of endometriosis (shape , size , unilateral or bilateral , unilocular or bilocular and if it is associated with adenomyosis)

6. Perform laparscopy for confirmation of endometriosis and staging of endometriosis using revised ASM classification for endometriosis

7. Measurement of serum anti_endometrial antibodies:

Take blood samples from patients to measure anti-endometrial antibody concentrations in the serum of women with endometriosis prior to ICSI procedures using human Endometrium Antibody, EMAb ELISA Kit .

This assay employs the qualitative enzyme immunoassay technique. The microtiter plate provided in this kit has been pre--coated with antigen. Samples are pipetted into the wells with

anti-human immunoglobulin conjugated Horseradish Peroxidase (HRP). Any antibodies specific for the antigen present will bind to the pre-coated antigen. Following a wash to remove any unbound reagent, a substrate solution is added to the wells and color develops in proportion to the amount of human endometrium antibody (EMAb) bound in the initial step. The color development is stopped and the intensity of the color is measured.

Sample Collection And Storage - Serum Use a serum separator tube (SST) and allow samples to clot for two hours at room temperature or overnight at 4°C before centrifugation for 15 minutes at 1000 ×g. Remove serum and assay immediately or aliquot and store samples at -20°C or -80°C. Avoid repeated freeze-thaw cycles.

Sample Preparation - Serum samples require a 101-fold dilution into Sample Diluent before test. The suggested 101-fold dilution can be achieved by adding 2µl sample to 200µl of Sample Diluent.

Assay Procedure - Bring all reagents and samples to room temperature before use. Centrifuge the sample again after thawing before the assay. It is recommended that all samples and controls be assayed in duplicate.

1. Prepare all reagents, and samples as directed in the previous sections.

2. Refer to the Assay Layout Sheet to determine the number of wells to be used and put any remaining wells and the desiccant back into the pouch and seal the ziploc, store unused wells at 4°C.

3. Set a Blank well with 100µl of Sample Diluent.

4. Add 100µl of Negative Control, Positive Control or diluted Sample per well. Samples and controls must be assayed in duplicate. Cover with the adhesive strip provided. Incubate for 30 minutes at 37°C.

5. Aspirate each well and wash, repeating the process four times for a total of five washes. Wash by filling each well with Wash Buffer (300µl) using a squirt bottle, multi-channel pipette, manifold dispenser, or autowasher, and let it stand for 2 minutes, complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining Wash Buffer by aspirating ordecanting. Invert the plate and blot it against clean paper towels.

6. Add 100µl of HRP-conjugate to each well (not to Blank!). Cover the microtiter plate with the adhesive strip. Incubate for 30 minutes at 37°C.

7. Repeat the aspiration/wash process for five times as in step 5.

8. Add 50µl of Substrate A and 50µl Substrate B to each well. Incubate for 10 minutes at 37°C. Protect from light. 9. Add 50µl of Stop Solution to each well, gently tap the plate to ensure thorough mixing.

10. Take blank well as zero, determine the optical density of each well within 10 minutes, using a microplate reader set to 450 nm.

Ethical Consideration

Clear verbal counseling and written consent were obtained from all participants in the research according to the committee of Medical Ethics of Faculty of Medicine, South Valley University.

Ethical Approval Code: SVU-MED-OBG024-1-20-12-107.

Statistical Analysis: The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric by using the Statistical Program for Social Sciences (SPSS Inc., Version 21.0, Chicago, IL, USA).

Results

We included 36 patients in this study. Patients were infertile (with endometriosis) and undergo ICSI cycles,2 patients were cancelled from our analysis as they didn't respond to stimulation drugs . Our analysis included only 34 patients.

7 patients were admitted to assisted reproduction units,Obstetrics and Gynacology departments , South Valley University. While 27 patients were admitted to assisted reproduction units,Obstetrics and Gynacology departments, Cairo University.

As regard demographic data the Mean age of included patients was 30.85 ± 4.04. Mean BMI was 26.1 ± 3.81. 27 pa-

tients had 1ry infertility. While 7 patients had 2ry infertility. Mean period of infertility was 6.22 ± 2.75. Table 1.

8 patients had stage 1 endometriosis. 12 patients had stage 2 endometriosis. 8 patients had stage 3 endometriosis. 6 patients had stage 4 endometriosis. 9 patients had previous IVF cycle. Table 2 and Figure 1

16 patients had negative Antiendometrial antibodies. While 18 patients had positive Antiendometrial antibodies. Table 3 and Figure 2

Table 4, Figure 3 showed that 33 patients had successful oocytes retrieval. Mean number of oocytes retrieved was 8.29 ± 5.74. 18 patients had poor oocyte quality. 13 patients had fair oocyte quality. 2 patients had good oocyte quality.

Table 5 showed 29 patients had successful embryos transferred. Mean number of embryos collected was 4.88 ± 3.78. 18 patients had grade a embryo quality. 11 patients had grade B embryo quality. 18 patients had fresh cycle. 11 patients had frozen cycle

Table 6 showed that 7 patients had positive pregnancy test. While 22 patients had negative pregnancy test.

Table 7 showed significant negative correlation between Antiendometrial Ab and implantation rate and Oocyte quality.

Table 8 showed significant negative correlation between Antiendometrial Ab and Oocyte quality.

Table 1: Demographic Data

Parameter		Value
Included patients (N and %)		34 (100%)
Age (years) (Mean ±SD)		30.85 ± 4.04
BMI (Mean ±SD)		26.1 ± 3.81
Type of infertility (N and %)	1ry	27 (79.4%)
	2ry	7 (20.6%)
Period of infertility (years) (Mean ±SD)		6.22 ± 2.75

Table 2: Stages of endometriosis and history of previous IVF

Parameter		**Value**
Stage of endometriosis (N and %)	**1**	**8 (23.5%)**
	2	**12 (35.3%)**
	3	**8 (23.5%)**
	4	**6 (17.6%)**
Previous IVF cycle (N and %)		**9 (26.5%)**

Table 3: Anti-Endometrial antibodies

Parameter		**Value**
Antiendometrial antibodies(N and %)	**Negative**	**16 (47.05%)**
	Positive	**18 (52.9%)**

Table 4: Oocytes retrieval

Parameter		Value
Number of oocytes retrieved (Mean ±SD)		8.29 ± 5.74
Success of oocytes retrieved from patients (N and %)		33 (97.05%)
oocyte quality (N and %)	Poor	18 (54.54%)
	Fair	13 (39.39%)
	good	2 (6.06%)

Table 5: Embryo transfer

Parameter		Value
Success of embryos trasfered to patients (N and %)		29 (85.3%)
Number of embryos collected (Mean ±SD)		4.88 ± 3.78
Embryo quality (N and %)	Grade A	18 (62.06%)
	Grade B	11 (37.9%)
Fresh/frozen cycle (N and %)	Fresh	18 (62.06%)
	Frozen	11 (37.9%)

Table 6: Pregnancy test

Parameter		Value
Pregnancy test (N and %)	Positive	7 (24.1%)
	Negative	22 (75.86%)

Table 7: Correlation between Antiendometrial Ab and Pregnancy test

		Anti-endometrial Ab
Pregnancy test	r	-.384-
	P	0.040

Table 8: Correlation between Antiendometrial Ab and oocyte quality and embryo quality.

		Anti-endometrial Ab
Oocyte quality	r	-.582--
	P	0.001
Embryo quality	r	-0.240
	P	0.209

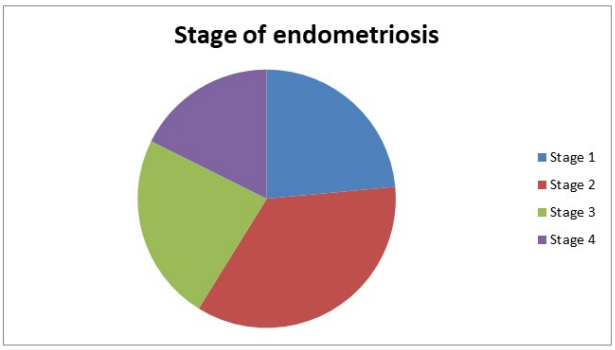

Figure 1: Stage of Endometriosis

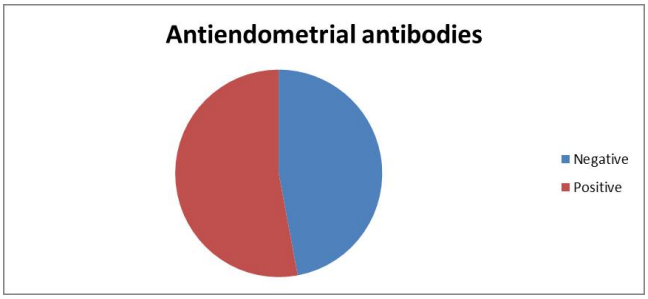

Figure 2: Antiendometrial Antibodie

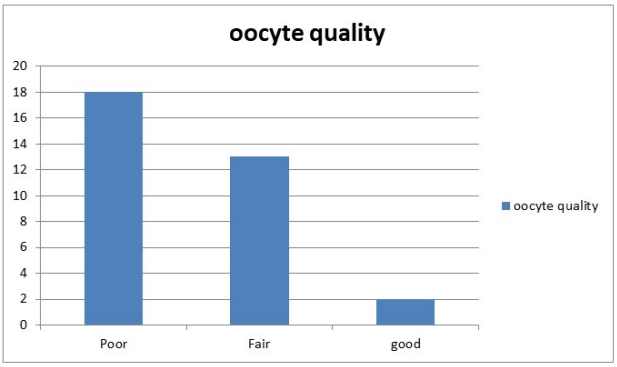

Figure 3: Oocyte quality

Discussion

Endometriosis is considered a debilitating gynecological pathology with a high prevalence among young women. The incidence of the disease varies between 6–10% [1]. Endometriosis is characterized by the migration of endometrial--like cells in ectopic places outside the uterus. The clinical manifestations thereof consist of chronic pelvic pain, dysmenorrhea, and infertility, the latter being reported in 30–50% of cases, while 20–25% of patients remain asymptomatic [2].

Chronic inflammation and hormonal dependance are the main underlying pathophysiologic mechanisms that drive endometriosis, and the association of these two key biological features make the natural history of this disease distinct [8].

The process of implantation represents a critical step involving the interaction between the embryo and uterine epithelium [9]. During implantation two immunologically and genetically distinct tissues are challenged into achieving successful communication. In the current bibliography, several autoimmune factors have been associated with implantation failure outcomes [9, 10]. In order to investigate reproductive failure, certain studies focused on associations between the autoimmune system and the IVF/ICSI outcome highlighting the role of autoantibodies during treatment [9]. Furthermore, recently

it has been suggested that autoimmune diseases, such as systematic lupus, erythematosus, and anti-phospholipid syndrome, play a crucial role in infertility and its management. This relationship is established either through a direct association between autoimmune disorders, compromising an otherwise good fertility status, or autoimmune disorders adding another level of complexity to an existing poor fertility status [8].

Sarapik et al., suggested that serum anti-endometrial antibodies in infertile women was a potential risk factor for implantation failure, but this was not fully established. The role of autoantibodies in IVF has been debated for almost three decades and still global literature lacks the clinical evidence in order to delineate their role in infertility and standardize respective management [11].

The main aim of this study was to assess the predictive value of serum anti-endometrial antibodies in prediction of implantation rate in patient with endometriosis who undergoing intracytoplasmic sperm injection cycles.

This cohort study was conducted on 34 infertile patients (with endometriosis) undergoing ICSI cycles at the assisted reproduction units, Obstetrics and Gynecology departments, South Valley University and Cairo University.

The main results of this study were as follows:

Regarding demographic data, the current study showed that the mean age of the studied patients was 30.85 ± 4.04. Mean BMI was 26.1 ± 3.81. The majority of patients 27/34 had 1ry infertility, while 7/34 had 2ry infertility. Mean period of infertility was 6.22 ± 2.75.

Comparable with the current study Wafa et al., enrolled 40 patients with endometriosis, and revealed that the mean age was 32.7±3.5 years and mean BMI was 24.3±3.5. The majority (70%) of women have primary infertility with mean period of infertility was 5 .17 years [12].

Also, Shahrokh et al., enrolled 80 patients with endometriosis, and revealed that the mean age was 33.0 ± 5.1years and mean BMI was 25.1 ± 4.5. The mean period of infertility was 8.3 ± 5.2 years [13].

Regarding Ultrasound and semen analysis results, it was revealed that the mean Anti-Mullerian Hormone (AMH) was 2.05 ± 2.02. Mean basal AFC was 11.82 ± 5.84.

Comparable with the current study Wafa et al., showed that the mean AMH was 2.9±1.4 and the mean AFC was 11.1±5.1, among patients with endometriosis [12].

Also, Kasapoglu et al., showed that that the median AMH was 2.10 (0.01–10.10) among 72 patients with endometriosis, furthermore this study showed that there was significant reduction in AMH level in endometriosis patients compared to matched controls (p=0.007) [14].

As well, Boucret et al., showed that Patients in the endometriosis patients had a significantly lower ovarian reserve, with a significantly lower mean serum AMH level (2.7 ± 2.3 ng/mL vs 3.9 ± 3.9 ng/mL, p = 0.0002) and a significantly lower mean AFC (16 ± 10 vs 20 ± 11 p < 0.0001) compared to control group [15].

In agreement with Botha et al., who revealed that a total of 65.8% of the semen analysis were reported normal according to the Tygerberg strict criteria and 34.2% were reported sub-fertile. Of the total, 11.96% of the patients studied had a severe defect (azoospermia, double, and triple defects) [16].

Regarding stages of endometriosis and history of previous IVF, the current study showed that 8 (23.5%) patients had stage 1 endometriosis. 12 (35.3%) patients had stage 2 endometriosis. 8 (23.5%) patients had stage 3 endometriosis. 6 (17.6%) patients had stage 4 endometriosis. 9 (26.5%) patients had previous IVF cycle.

The American Society for Reproductive Medicine (ASRM) classifies endometriosis into four stages of disease progression which is based on the quantity 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 [17].

Among 114 endometriosis patients with 129 cycles, there were 34.8% have stage I, 13.2% have stage II, 23.2% have stage III and 10.8% have stage IV endometriosis. 15 (13.1%) patients had previous IVF cycle [18].

While, Shahrokh et al., revealed that 60% of the studied cases have stage III / VI endometriosis and 40% of cases have stage I / II endometriosis [13].

As regard Anti Endometrial antibodies, 16 (47.05%) patients had negative Antiendometrial antibodies. While 18 (52.9%) patients had positive Antiendometrial antibodies.

Fernandez-Shaw et al., stated that the presence of antiendometrial antibodies (AEA) was mainly associated with endometriosis [19].

A study showed that the serum levels of antiendometrial antibodies showed a statistically significant difference between control and endometriosis groups, and can be used as a potential bio-marker for endometriosis [20].

Higher than the current study Gajbhiye et al., reported on almost 60% presence of IgG or IgM AEA in endometriosis patients [7] .

Two studies identified a potential correlation between IgG and endometriosis. IgG antibodies were identified in 56% of affected women and 5% of healthy controls [21, 22]. Another investigation highlighted the presence of IgG in 33% of cases, and of IgM in 27% of them [23].

Regarding oocytes retrieved, the current study showed that that 33 (97.05%) patients had successful oocytes retrieve. Mean number of oocytes retrieved was 8.29 ± 5.74. There were 18 (54.54%) patients had poor oocyte quality. 13 (39.39%) patients had fair oocyte quality. 2 (6.06%) patients had good oocyte quality.

However, Wafa et al., showed that the mean number of oocytes retrieved was 6.2±3.6 with Fertilization rate of 64.8% in endometriosis patients [12].

As well, another study revealed that the median number of oocytes retrieved was 10.5 (2–29) with Fertilization rate of 71 (0.0–100) % in endometriosis patients [14].

Also, Boucret et al., (2020) revealed that the mean number of oocytes retrieved was 7.0 ± 4.3 with Oocyte maturity rate of 68.6 ± 24.5 % in endometriosis patients [15].

The current study showed low prevalence of good oocyte quality among endometriosis patients. Suggesting the negative impact of endometriosis on the quality of oocyte.

Also, Borges et al., showed that the patients with endometriosis have significantly impaired oocyte quality compared to matched controls [24].

Regarding Embryo transfer, the current study showed that 29 (85.3%) patients had successful embryos transfer. Mean number of embryos collected was 4.88 ± 3.78. 18 (62.06%) patients had grade A embryo quality. 11 (37.9%) patients had grade B embryo quality. 18 (62.06%) patients had fresh cycle. 11 (37.9%) patients had frozen cycle.

However, Wafa et al., showed that 69.5% patients had successful embryos transfer and the mean number of embryos transferred was 2.24 ± 1.07 [12].

As well, Borges et al., (2015) showed that 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 [24].

Moreover, Boucret et al., showed that the women with endometriosis had a significantly lower number of oocytes and mature oocytes retrieved despite receiving higher gonadotropins doses, and a significantly lower number of embryos and top-quality embryos [15].

Regarding pregnancy test, it was revealed that out of 34 studied women there were 7 (24.1%) patients had positive pregnancy test, while 22 (75.86%) patients had negative pregnancy test.

Comparable to the current study Muteshi et al., showed that the pregnancy rate was 142 (26.7%) among endometriosis patients [25].

Higher than the current study Borges et al., showed that the pregnancy rate was 36.9% among endometriosis patients [24].

Also, Wafa et al., showed that the pregnancy rate was 19 (47.5%) among endometriosis patients [12].

The variation of pregnancy rate may be due to the difference in Infertility type and Grade of disease between studies.

There have been two primary theories for the proposed poor outcome after IVF in patients with endometriosis. First, the oocyte quality is poor, resulting in lower fertilization rates. Second, implantation is impaired either as a result of Endometrial dysfunction or combined with poor oocyte or embryo quality [12].

Regarding the correlation between Anti-endometrial Ab and Pregnancy test, it was revealed that there was significant nega-

tive correlation between Anti-endometrial Ab with pregnancy test and Oocyte quality. However, there was no significant correlation between Anti-endometrial Ab with Embryo quality.

This was supported by study which revealed that particular Anti-endometrial Antibodies were associated with in vitro fertilization (IVF) implantation failure [11].

Also, in concordance with the current study Randall et al., showed that the presence of serum and peritoneal fluid Anti-endometrial Antibodies significantly correlated with miscarriage in patients with endometriosis [26].

In contrast, the pilot study by Parry et al., suggest that presence of serum AEA does not appear to be a marker for early pregnancy loss [27].

Literature showed that serum anti-endometrial antibodies was elevated in for patient with endometriosis and was related to intracytoplasmic sperm injection cycles outcome [7, 11, 19, 21, 22, 23,26], small studies in literature have assessed the prognostic accuracy of serum anti-endometrial antibodies in the detection of implantation rate for patient with endometriosis undergoing intracytoplasmic sperm injection cycles.

Conclusions

Based on the results of the current study it serum anti-endometrial antibodies can be used as a biomarker to detect implantation rate for patient with endometriosis undergoing intracytoplasmic sperm injection cycles. Serum anti-endometrial antibodies was negatively correlated with outcome (pregnancy test and Oocyte quality). Patients with endometriosis and tested positive for anti-endometrial antibodies, have low oocyte quality and pregnancy rate.

Conflict of Interest

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

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