

## Apo-lipoprotein A1 in the Endometria of Patients with Polycystic Ovary Syndrome

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### Abstract

**Objective:** This clinical trial aimed at assessing the levels of apo-lipoprotein A1 in the endometria of patients with polycystic ovary syndrome (PCOS).

**Setting:** El-Demerdash Hospital, over a 2 years period, between September 2015 and January 2017.

**Patients:** this clinical trial involved 50 patients (age range 20-35 years) arranged into two equal groups. Group I (25 patients) which includes women with PCOS and were collected from the infertility outpatient clinic while group II (25 patients) parous women, they were presented to us due to any cause other than inability to conceive as a control group. Methods: Endometrial brushing was performed to get endometrial samples from all consented women. ELIZA was used to detect the expression of Apo-lipoprotein A1 (Apo A1) in the endometrial samples. Two endometrial samples were gathered from every patient, the first one was collected when the largest ovarian follicle is  $\geq 20$  mm (proliferative phase) while the second one was collected 5 days following the first one (secretory phase).

**Results:** Interestingly, endometria of infertile women with PCOS had expressed apo-lipoprotein A1 in higher levels than the endometria of infertile women. Also, this study proved that the expression of this protein was more in the proliferative rather than secretory phase of the menstrual cycle (P value<0.05).

**Conclusion:** It is apparent that there is an inverse relationship between apo-lipoprotein A1 and the degree of receptivity of the endometria in women with PCOS. Also, this clinical trial found a fluctuation of the level of this protein all through the menstrual cycle, being higher in the proliferative phase and less in the secretory phase when the endometrium is receptive for embryos (window of implantation).

**Keywords:** Apo-lipoprotein A1; Polycystic ovary syndrome; Endometrium

This study tries to find out the suggested and potential relationship between the Apo A1 and the receptivity of the endometrium.

### Introduction

Metabolic syndrome (MS) and cardiovascular diseases (CVD) are common in patients with PCOS due to the occurrence of hypertension, dyslipidemia and insulin resistance [1,2]. These abnormalities start in the adolescent period, and continues all through the patient life. It is well known that few adolescent females complaining of PCOS, have MS but other hormonal and metabolic aberrations are common with presence of at least two criteria of MS which is called pre-MS. There is increased potentiality of developing MS, DM, ischemic heart disease in patients with pre MS. Early detection and management of pre-MS would be beneficial to avoid the undesired fate of the disease [3].

ApoA1 is part of the protective lipoprotein; high-density lipoprotein (HDL) and plays a prominent role in the reverse transportation of cholesterol, as well as anti-inflammatory and antioxidant processes. Hence, the ApoB/ApoA1 ratio reflects the status of pro- and anti-atherogenic lipoproteins, and is a marker of MS and CVD [4-10].

### Patients and Methods

This study was done, after the approval of the Research Ethics Committee, in El-Demerdash Maternity Hospital during the period between September 2015 to January 2017 and involved 50 patients. Two equal groups were arranged, group I (n=25) suffering from PCOS who were recruited from the infertility clinic and group II (n=25) parous fertile women as a control group. Brushing of the endometrium was done for all consented women (ages ranged from 20 to 35 years). ELIZA was utilized to detect the expression of endometrial apo-lipoprotein A1 in the endometrial samples of all participants. Two samples were taken from every woman; the first was taken in the preovulatory period when the dominant follicle was equal to or more than 20 mm by TVUS, while the second sample was taken 5 days following the first one during the receptive window of the secretory phase.

All included women did not use an intra-uterine device or administer any hormonal therapy during the last 3 months. Women with polycystic ovary were diagnosed by anovulation, apparent

hyperandrogenism by clinical and/or biochemical evidences, and those with ultrasound characters of polycystic ovaries.

The samples were stained after paraffin preparation for presence of apoA-I. A buffered apoA-I antigen was put in special plates and given time to allow for the expected adherence and interactions then a bovine serum albumin or any solution of non-reacting protein is added to the plate. ELISA was performed either in a qualitative or quantitative methods. Qualitative method aims at giving a positive (yea) or negative (no) result. A cut-off between positive/negative results is assessed. It is needed to differentiate positive and negative results to get 2 or 3 times the SD (standard deviation in a test). In the quantitative method, a standard curve is used with the optical density of the endometrial samples is assigned to it.

### Statistical methods

IBM, SPSS, Statistics V 22 was used for analysis of data, (IBM, Corp., Armonk, NY, USA) and XLSTAT, V 2014.5.03 (Addinsoft, NY, USA).

### Results

This current study was conducted in El-Demerdash Maternity Hospital during the period between September 2015 to January 2017 a total of 50 women were included in the study (Tables 1 and 2).

	Group I (25)	Group II (25)	P-value
Age	27.3 ± 4.4	27.5 ± 4.1	>0.005
Menarche age	11.1 ± 2.9	11.7 ± 1.9	>0.005
Body mass index (kg/m <sup>2</sup> )	26.8 ± 4.1	26.3 ± 3.9	>0.005
Previous gravidity	1.1 ± 0.3	4.1 ± 1.5	< 0.005 S
Previous abortions	1.3 ± 0.2	1.2 ± 0.1	> 0.005

**Table 1:** The clinical and demographic criteria of participants (\* NS=Non-Significant, S=Significant).

	Group I (25)	Group II (25)		P-value
Menstrual type				
Regular	8	16		<0.005 S
Irregular	17	9		
LH (mu/ml)	9.1 ± 2.3	4.9 ± 1.8		<0.005 S
FSH (mu/ml)	5.2 ± 3.2	9.1 ± 3.1		<0.005 S
LH/FSH	2.2 ± 1.3	0.7 ± 1.2		<0.005 S
Progesterone level	3.9 ± 1.3	11.2 ± 2.2		<0.005 S
Testosterone (ng/ml)	4.2 ± 0.74	1.9 ± 0.56		<0.005
ELIZA for EAPO-a		Proliferative	Secretory	
	0.42 ± 0.2	0.23 ± 0.04	0.15 ± 0.03	<0.005 S

**Table 2:** The hormonal and clinical parameters of PCOS and control women.

### Discussion

In women with PCOS, metabolic abnormalities are common including dyslipidemia or lipoprotein abnormalities [11]. Apo-lipoprotein A1, a pivotal protein component of high-density lipoprotein (HDL) had been previously involved in many disorders as pregnancy induced hypertension, endometriosis, and also in repeated implantation failure [12,13]. Very few clinical trials were examining endometrial apo-lipoprotein A1 function in women with PCOS.

Recently, it had been reported, after various trials on human endometria, that increased apo-lipoprotein A1 level is linked to recurrent miscarriages and also unexplained infertility [2,14]. It was revealed that apo-lipoprotein A1 is exhausted by pre-implantation

embryos. This consumption is demonstrating a feasible function in implantation and pregnancy. Actually, embryos that have highest probability of implantation exhaust or consume apo-lipoprotein A1, which compose an encouraging microenvironment in the endometrium with less apo-lipoprotein A1 values for probable implantation. Apo-lipoprotein A1 is more manifested in non-decidualized endometria when compared to a decidualized stroma [14]. So, crucial negative impacts might be anticipated for apo-lipoprotein A1 in augmenting and maintaining an implantation window.

Apo-lipoprotein A1 has an additional anti-inflammatory actions involving suppressing the interleukin 1 (IL-1) and expressing the

tumor necrosis factor alpha, and inhibiting the degranulation of neutrophils [15]. Inflammation is involved in the pathogenesis of endometriosis. Endometrial apo-lipoprotein A1 upregulation is clear in those with clinical stigmata of endometriosis [16].

We examined the presence of endometrial apo-lipoprotein A1 as a possible stigma of non-receptivity in those with PCOS without therapeutic regimens. The conclusion revealed a more endometrial apo-lipoprotein in PCOS when compared to parous women. Our work showed that endometrial apo-lipoprotein A1 expression was increased in PCOS compared to normal subjects.

Indeed, it was found an acute inflammation reaction in the endometria during the secretory phase especially at the receptive window of implantation [17]. A successful interaction between the embryo and the endometrium is required for implantation to occur, and this interaction needs the presence of cytokines and adhesive molecules which arise from the previously mentioned inflammatory reaction [18].

Apo-lipoprotein A1 is able to block the production of cytokines and adhesive particles, as selectins, which have crucial functions in implantation [19]. Apo-lipoprotein A1 possibly shares in the implantation failure which might be through preventing angiogenesis. Tissue remodeling with angiogenesis play an important function in implantation and decidualization [20]. Apo-lipoprotein A1 inhibits angiogenesis and remodeling through decreasing metalloproteinases, endothelial growth factor/fibroblast growth factor expression [21].

We demonstrated that endometrial apo-lipoprotein A1 expression is changed through the cycle with a minimum is in the secretory phase, simultaneous with the window of implantation. This is clear that estrogens and progesterone regulate the occurrence of apo-A1 with a reverse manner. It is obvious that apo-lipoprotein A1 is increased by estrogen and is decreased by progesterone which might prevent the deleterious effects of apo-A1 in the crucial phase of the receptivity. Endometrial apo-lipoprotein A1 manifestation is blocked with the increase of human chorionic gonadotropin from the implanted embryo, this is a prerequisite for implantation [22,23] So, human chorionic gonadotrophin regimens might increase the receptivity and consequently pregnancy rates in in vitro fertilization women with PCOS by reducing apo-A1 values.

## Conclusion

The pathogenesis of implantation failure and subsequently subfertility appears to be linked to PCOS condition. Increased Apo-A1 values could be evaluated as a beneficial biomarker for non-receptive endometria of women suffering from PCOS. More clinical trials are required to explore the possible clinical applications of this protein to increase the implantation rate in these patients.

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