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The Relationship Between Serum Adrenomedullin, Pentraxin3 Levels and Successful Implantation in Assisted Reproductive Techniques Cycles

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ABSTRACT

Background & Objective: A competent embryo, receptive endometrium and a series of highly coordinated molecular events between them are all essential for successful implantation. Evaluation of certain molecules which may be used as biomarkers may help to predict pregnancy outcome and detect subtle implantation defect. The present study was conducted with aim to assess the relationship between serum concentrations of adrenomedullin (ADM) and pentraxin3 (PTX3) measured at the day of embryo transfer and successful implantation in assisted reproductive technique cycles.

Materials & Methods: This prospective cohort study included 88 frozen embryo transfer (FET) cycles. All patients received sequential oestrogen & progesterone medications. Embryo transfer (with a minimum of one top quality embryo) was scheduled after 4 days (D3 embryo), 6 days (D5 embryo) of progesterone administration. The serum ADM and PTX3 levels were analyzed 1 hour before the embryo transfer (ET) using ELISA kits. A possible association between these two markers levels and embryo implantation was evaluated.

Results: Overall, biochemical pregnancy rate was 25% (22/88). Data were then categorized into pregnant (22/88) & non-pregnant (66/88). No significant difference were found between the two groups regarding female age, endometrial thickness, number of oocyte collected, oestradiol level (E2), FSH level, grade and number of embryo transferred (P>0.05). The ADM levels were higher on the day of ET, although was not significant in pregnant group (254.60 pg/ml vs 248.18pg/ml). PXT3 levels (pg/ml) were lower in pregnant compared to non-pregnant group (25.396±11.78 vs 28.431±16.51, P=0.428).

Conclusion: Higher ADM and lower PTX3 levels at the day of embro transfer may be associated with successful implantation.

Keywords: Implantation, Adrenomedullin, Pentraxin3, Embryotransfer, Assisted Reproductive Technique Cycles

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Introduction

Although many human infertility problems have been overcome by in vitro fertilization and embryo-transfer techniques; implantation rates remain low **(1)**. A receptive endometrium and a functionally normal blastocyst, as well as an exquisitely coordinated cross-communication between them, are required for implantation **(2)**.

With regard to endometrial receptivity, defects probably represent a range of molecular changes, making it imperative that a large panel of biomarkers is available **(3)**. One of the suggested biomarkers is adrenomedullin (ADM): a vasodilatory, angiogenic and anti-inflammatory protein which belongs to the calcitonin/calcitonin gene-related peptide family. ADM is highly expressed in female reproductive system including the uterine endometrium **(4)**. Estrogen, progesterone and hypoxia are known to dramatically upregulate either ADM or AM receptor gene expression in several human female reproductive tissues **(5)**. ADM may have a role in the gonadotropin's secretion, growth and luteinization of ovarian follicles **(6)**. It aids in the transport of fertilized embryo through fallopian tubes by enhancing ciliary activity **(7)**.

Additionally, it had a pivotal role in the embryo attachment and implantation **(8)**. In mice, ADM administration results in a higher embryo implantation rate **(9)**. Also, ADM secretion by the trophoblastic cells, play a role in uNK cell recruitment **(10)**. Another possible biomarker is Pentraxin3 (PTX3): a soluble (pattern recognition receptor) protein (PRR) with multiple functions. It had a significant role as regulator of innate immunity and is involved in many aspects of human reproduction **(11)**. It is produced by variety of cells including dendritic cells, endothelial cells, monocytes, polymorphonuclear cells, fibroblasts, and smooth muscle cells **(12)**. PTX3 might be a biomarker for oocyte quality and fertilization **(13)**. PTX3 gene is highly expressed during implantation **(12)**.

Understanding of the molecular basis of endometrium may guide us to diagnose defective implantation to treat specific molecular defects by replacement or genetic modifications **(14)**. Therefore, the present study was conducted with aim to investigate the value of serum ADM and PTX3 levels at the time of embryo transfer as markers of implantation in patients undergoing IVF/ICSI cycles.

Methods

This prospective cohort study was conducted at multiple IVF centres in Iraq (Al-Saader centre for fertility and IVF/ Al Najaf Al ashraf city, High institute for infertility diagnosis and assisted reproductive technology, Al-Nahrain University/Baghdad) between June 2022 and January 2023. The study was approved by the Institutional Review of Arab Board of Medical Specializations and from Iraqi Fellowship of Reproductive Medicine.

A total of 88 FET cycles were enrolled in this study. Informed verbal consent was obtained from all the participants. Infertile women aged 18 to 42 years old who underwent frozen embryo transfer (FET) cycle with single or multiple embryo transfer (with a minimum of one top-quality embryo) of a cleavage stage (Day 3) or a blastocyst stage embryo/s (Day 5) were included.

The exclusion criteria were patients with any type of endocrinopathies (such as diabetes or thyroid disease), endometriosis, polycystic ovarian syndrome, uterine fibroid, uterine malformation, fresh embryo transfers, and patient prone to difficult transfer.

The participants were interviewed & assessed on Day 2 or 3 of menstrual cycle. Controlled ovarian hyperstimulation was started using appropriate type of gonadotropin like recombinant FSH (gonal f®, Serono, Germany), HMG (Merional®, IBSA, India) according to the patient's condition. Pituitary downregulation was achieved using GnRH antagonist (flexible protocol), cetrorelix acetate (cetrotide®:0.25mg; Serono, Germany) which was given when the diameter of the follicle reached 14mm. Once three or more follicles reached 17-18mm in diameter, oocyte maturation was triggered by Human chorionic gonadotropin (choriomon®:10.000iu, IBSA, India). Oocytes were collected 36 hr later, then sperm was directly injected into the egg. Vitrification of the remaining available embryos was carried out.

For endometrial preparation, artificial cycle protocol was used. On cycle Day 2-3, after initial transvaginal ultrasonographic evaluation of the endometrium and ovaries, estrogen (Estrofem®:2mg; NovoNordisk, Denmark) was started: 4mg/day on day 1-5, then 6mg/day from Days 6 onward with the dose adjusted according to the endometrial thickness.

Endometrial thickness (ET) was measured on day 10-12 of E_2 administeration. ET $\geq$ 8 mm was considered as an ideal thickness. Embryo transfer then scheduled and progesterone was administered as oral dydrogesterone (duphaston®:10mg;bid;Abbott,Netherland), micronized progesterone (cyclogest®:400 mg bid; Actavis Uk Ltd) vaginal suppositories with intramuscular progesterone (Progesterone® Injection USP 50 mg/ml once daily; Watson) for up to 4 days for cleavage stage embryo & 6 days for blastocyst stage embryos.

The quality of embryos were scored according to their morphology; they were given a score between 1 (top), 2 (average) and 3 (poor) in terms of blastomere number, regularity and the percentage of fragmentation. Gardner grading system was used for blastocyst stage embryo **(15)**.

A top-quality (D3) embryo was defined as having 7-8 blastomeres and fragmentation $\leq$ 20-30%. D5 Blastocyst with blastocoel filling the whole blastocyst, inner cell mass (score A or B) and a trophectoderm layer (score A or B) was regarded as a top-quality embryo. Most of the cryopreserved and transferred embryos were cleavage stage. The number of embryos transferred was determined by the women's age, cryosurvival and grade of cryopreseved embryos post-thawing. The embryos were put in an ET catheter (COOK®) that was introduced through the cervix under ultrasound guidance and the embryos were safely deposited just below the uterine fundus. All patients were advised to rest at least 1hr after the procedure before discharge. They all were instructed to continue with their hormonal supplementation until 10th weeks if they get pregnant.

Prior to embryo transfer, 2ml of venous blood samples were taken from all women and were allowed to clot for 1hour at room temperature, then centrifugation was done at 1000xg for 15 min. The supernatant was collected and stored at -80c° till the time of the study when the samples were allowed to thaw at room temperature for subsequent ADM and PTX3 assay.

Adrenomedullin and pentraxin 3 (PTX3) were assessed using the Elabscience Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Catalog No: E-

EL-H0275, E-EL-H6081 respectively, United States). Test specifics for ADM: sensitivity 9.38pg/ml, detection range 15.63-1000pg/ml with coefficient of variation (CV)<10%. PTX3: sensitivity 4.12pg/ml, detection range 6.86-5000pg/ml with coefficient of variation (CV)< 10%.

Serum βhCG >25 mIU/ml at 2 weeks following embryo transfer was used to detect the presence of biochemical pregnancy. Serial trans-vaginal ultrasound scans were done and presence of gestational sac/s with positive heartbeat at around 5-6th week of amenorrhea confirmed clinical pregnancy. Miscarriage was defined as the loss of clinical pregnancy before 12th week of gestation. Pregnancy continued beyond 12 weeks was considered as ongoing.

Statistical analysis

Data analysis was performed using the statistical package of SPSS-28 (Statistical Packages for Social Sciences- version 28). Data were presented in simple measures of frequency, percentage, mean, standard deviation, median, and range (minimum-maximum values). The significance of difference between different means was measured using Students t-test and ANOVA test. The significance of difference between different percentages was assessed using Pearson Chi-square test (χ^2-test). P≤0.05 was considered statistically significant. Correlation between the two continuous variables was assessed by Pearson correlation (ralue) with its t-test for testing the significance of correlation. It could be either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, and >0.7 strong correlation.

Results

A total of 88 frozen embryo transfer cycles were analyzed. As shown in (Table 1), the biochemical pregnancy rate was 25% (n=22), clinical pregnancy rate 23.8% (n=21), ongoing pregnancy rate 17.04% (n=15), miscarriage rate 27.2% (n=6) and ectopic pregnancy rate was 4.5% (n=1).

Table 1. Reproductive outcome per embryo transfer

		No	%
Outcome	Pregnant	22/88	25.0
	No implantation (not pregnant)	66/88	75.0
Pregnancy outcome	Clinical	21/88	23.8
	Ongoing	15/88	17.04
	Miscarriage	6/22	27.2
	Ectopic	1/22	4.5

Table 2. Demographic and clinical characteristics of the pregnant and non-pregnant group

		Pregnant		Non pregnant		P value
		No	%	No	%	
Age (years)	<30y	11	50.0	38	57.6	0.536
	=>30y	11	50.0	28	42.4	
Reason of infertility	Male factors	12	54.5	49	74.2	0.083
	Others	10	45.5	17	25.8	
Parity	Para0	18	81.8	52	78.8	0.760
	Para1+	4	18.2	14	21.2	
Number of failed previous ICSI/IUI trials	No	17	77.3	35	53.0	0.045*
	Yes	5	22.7	31	47.0	
Endometrial thickness (ET) (mm)	8.0---	8	36.4	27	40.9	0.931
	9.0---	9	40.9	25	37.9	
	=>10.0mm	5	22.7	14	21.2	
Number of oocytes	<10oocytes	9	40.9	10	15.2	0.063

		Pregnant		Non pregnant		P value
		No	%	No	%	
FSH (IU/L)	10---	2	9.1	16	24.2	
	15---	4	18.2	13	19.7	
	=>20oocytes	7	31.8	27	40.9	
	<4.0IU/L	2	9.1	9	13.6	0.597
	4.0---	10	45.5	26	39.4	
	6.0---	5	22.7	22	33.3	
	=>8.0IU/L	5	22.7	9	13.6	
Pretriger E2 (pg/ml)	<1000pg/ml	6	27.3	6	9.1	0.065
	1000---	8	36.4	22	33.3	
	=>2000pg/ml	8	36.4	38	57.6	
Grade I No. (n=159)	GI	41	59.42	118	59.29	0.337
Grade II No. (n=86)	GII	25	36.23	61	30.65	
Grade III No. (n=22)	GIII	3	4.3	19	9.54	
Number of transferred embryos	1	1	4.5	7	10.6	0.634
	2	6	27.3	11	16.7	
	3	8	36.4	27	40.9	
	4+	7	31.8	21	31.8	

***Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.**

Cycles were sorted into pregnant and non-pregnant groups. Table 2 represents the demographic and clinical characteristics of the two groups in the study population. No significant difference was detected between the pregnant and the non-pregnant group in terms of age, endometrial thickness, number of oocyte collected, oestradiol level (E2) and FSH level (p>0.05).

The total number of embryo in the pregnant group was 69 (25.7%), GI: 41 (59.42%), GII: 25 (36.23%), and GIII: 3 (4.3%), while the total number of embryo in non-pregnant group was 199, GI: 118 (59.29%), GII: 61 (30.65%), and GIII: 19(9.54%). There was significant difference between pregnant and non-pregnant women regarding history of no previous failed trial of ICSI/IUI cycles (17/22, 77.3% versus 35/66, 53%, p<0.05).

The distribution of adrenomedullin and pentraxin 3 level among the whole study population are shown in Table 3 and Figure 1 and 2.

The mean ADM was (263±120.9 pg/ml, range 61.014-588.06).

The mean pentraxin3 was (27.67±15.4 pg/ml, range 8.830-84.114).

Table 3. The mean of Adrenomedullin and Pentraxin 3 levels in the study population

		No	%
Adrenomedullin (ADM) (pg/ml)	<100pg/ml	7	8.0
	100---	21	23.9
	200---	33	37.5
	300---	14	15.9
	400---	8	9.1
	=>500pg/ml	5	5.7
	Mean±SD (Range)	263.607±120.902	(61.014-588.062)
	<10pg/ml	3	3.4

		No	%
Pentraxin3 (PTX3) (pg/ml)	10---	32	36.4
	20---	23	26.1
	30---	15	17.0
	40---	7	8.0
	=>50pg/ml	8	9.1
	Mean±SD (Range)	27.672±15.459	(8.830-84.114)

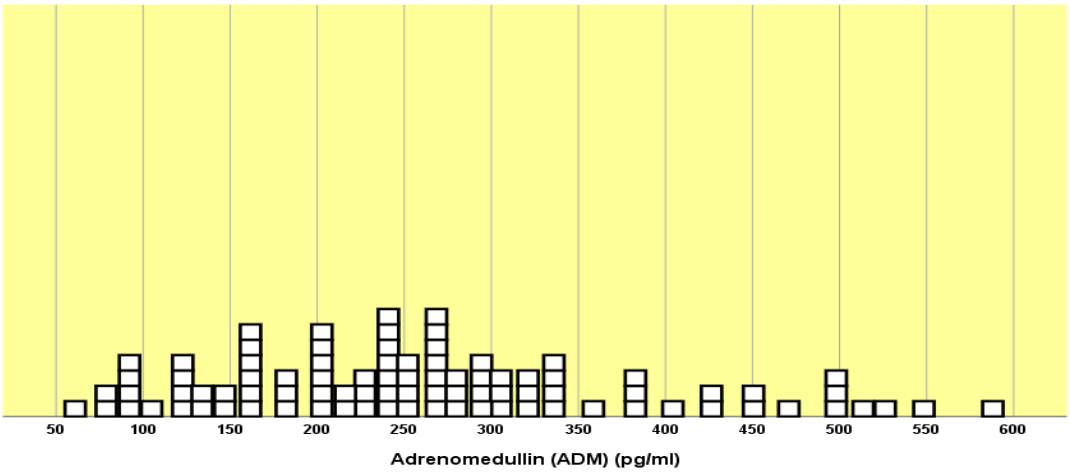


Figure 1. Adenomedullin distribution in the study population

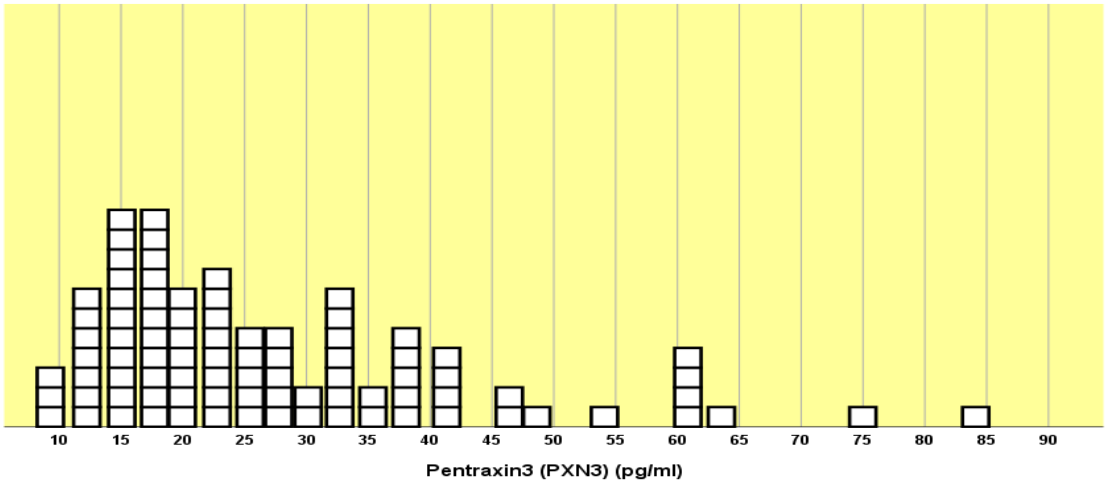


Figure 2. Pentraxin 3 distribution in the study population

Table 4 shows the mean levels of Adrenomedullin and pentraxin 3 in the pregnant and non-pregnant groups. Although the mean of pentraxin3 level was found to be lower in the pregnant group than the non-pregnant group (25.396±11.78pg/ml vs 28.431 ±16.51pg/ml,p value 0.428), the difference was not statistically significant. The median value of pentraxin3 was lower in the pregnant group than the non-pregnant group (22.142pg/ml vs 23.551pg/ml). Also, the mean of ADM level in the pregnant and non-pregnant group were (256.13±111.01pg/ml vs 266.10±124.734pg/ml, pvalue 0.740) respectively, the difference was not statistically significant. The median value of ADM in the pregnant group was higher than the non-pregnant women (254.60pg/ml vs 248.18pg/ml).

Table 5 shows the correlation coefficients among continuous parameters.

Significant positive correlation was found between pre-trigger E2 and the number of oocyte collected (r=0.573, p=0.001). Also, significant inverse correlation was observed between the number of retrieved oocyte & FSH level (r=0.363, p=0.001),

between female age and the number of oocytes collected (r=0.266, P=0.012), and between FSH level and pre-trigger E2 (r=0.325, P=0.002). On the other hand, there was no significant correlation between ADM and PTX3 levels and other parameters (P>0.05).

Table 4. Mean of Adrenomedullin & pentraxin3 level in pregnant and non-pregnant women

		Pregnant		Non pregnant		P value
		N	%	No	%	
Adrenomedullin (ADM) (pg/ml)	<100pg/ml	1	4.5	6	9.1	0.899
	100---	7	31.8	14	21.2	
	200---	7	31.8	26	39.4	
	300---	4	18.2	10	15.2	
	400---	2	9.1	6	9.1	
	=>500pg/ml	1	4.5	4	6.1	
	Mean±SD	256.13±111.01		266.10±124.734		0.740
	Median	254.60		248.18		
Pentraxin3 (PXN3) (pg/ml)	<10pg/ml	1	4.5	2	3.0	0.766
	10---	7	31.8	25	37.9	
	20---	8	36.4	15	22.7	
	30---	4	18.2	11	16.7	
	40---	1	4.5	6	9.1	
	=>50pg/ml	1	4.5	7	10.6	
	Mean±SD	25.396±11.78		28.431±16.51		0.428
	Median	22.142		23.551		

***Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.**
#Significant difference between two independent means using Students-t-test at 0.05 level.

Table 5. Correlation between continuous parameters

		Number of oocytes	FSH (IU/L)	Adrenomedullin (ADM) (pg/ml)	Pentraxin3 (Ptx3) (pg/ml)
Age (years)	r	-0.266*	0.164	0.155	-0.053
	P	0.012	0.126	0.149	0.622
Endometrial thickness (ET) (mm)	r	0.072	-0.036	0.002	0.014
	P	0.508	0.738	0.985	0.898
Number of oocytes	r	-	-0.363**	0.047	0.023
	P	-	0.001	0.660	0.829
FSH (IU/L)	r	-0.363**	-	-0.005	0.045
	P	0.001	-	0.966	0.676
Pre-trigger E2 (pg/ml)	r	0.573**	-0.325**	0.155	0.078
	P	0.0001	0.002	0.151	0.473
Adrenomedullin (ADM) (pg/ml)	r	0.047	-0.005	-	0.047
	P	0.660	0.966	-	0.664
Pentraxin3 (Ptx3) (pg/ml)	r	0.023	0.045	0.047	-
	P	0.829	0.676	0.664	-

***Correlation is significant at the 0.05 level. **Correlation is highly significant at the 0.01 level.**

Discussion

Implantation represents the key rate-limiting step in assisted reproductive technology (ART). It is still the least understandable process because normal implantation steps in human being cannot be assessed directly. So, searching for factors that lead to IVF treatment failure provides clues into the essential events that determine the implantation success **(16)**.

The purpose of the present study was to highlight the role of certain novel multisystemic peptides (Adrenomedullin and Pentraxin3) in assisted reproductive technique cycles. Frozen embryo transfer cycles were enrolled in this study to avoid the negative impact of higher esrtradiol levels during fresh cycles which could lead to structural changes in the endometrium **(17)**.

All of the following studies, although animal based, signify ADM involvement in the process of implantation and placentation. Matson, et al. **(9)** had demonstrated the positive effect of ADM on the number of pinopodes, water dynamics, and cellular communication in the endometrium during implantation window as shown by their observation that infusing AM into the mouse womb prior to embryo transfer improves the implantation rate **(9)**. Other studies had found that infusion of the ADM antagonist was detrimental to implantation and placentation in rat animal model **(18, 19)**. Li, et al. **(19)** using mouse models had shown that ADM gene and its receptor were essential to stimulate sufficient recruitment of maternal uNK cells to the site of placentation and thus promote uterine spiral arteries remodeling **(19)**.

The results of the current research study showed that the median level of ADM was higher in the pregnant than the non-pregnant women (254.60 pg/ml vs 248.18 pg/ml), but the difference was not significant. Our results were comparable to another study conducted by Karli et al. in 2020 which show higher serum level of ADM in pregnant than the non-pregnant (641.38 vs 639.12 ng/ml) at the day of embryo transfer, the difference was also not statistically significant **(20)**.

Another marker which has been investigated in the present study was Pentraxin 3 which has an important role in the regulation and as a marker of inflammatory process that is involved in the etiology of pathologies such as sepsis and preeclampsia **(21)**. Popovici, et al. **(22)** in 2006 and Hass et al. in 2006 had shown that Ptx3 gene was one of the upregulated gene involved in immune response at implantation site **(22, 23)**. Tranguch, et al. **(24)** showed that deletion of Pentraxin3 gene in mice results in both defective implantation and decidualization **(24)**. Agostinis, et al. **(25)** emphasized that Ptx3 ligand Clq play important role in trophoblast invasion and placentation **(24)**. On the other hand, some other studies reported that abnormal PTX3 expression had been involved in adverse reproductive outcome Cruciani, et al. **(26)** found that the maternal plasma PTX3 concentration is significantly high during term and preterm labor suggesting that the high Ptx3 levels is part of the pro-inflammatory process in the maternal circulation which could be physiologic or pathologic response **(26)**. Rovere-Querini, et al. **(27)** reported that serum levels of PTX3 were strikingly higher in preeclampsia compared with normal control pregnancies **(27)**.

Ibrahim, et al. in found positive correlation between plasma PTX3 and primary recurrent pregnancy loss **(28)**. Similar result was expressed by Zeybek, et al. **(21)** in when they had found higher placental PTX3 expression in women with idiopathic recurrent miscarriage **(21)**.

In the present study, the serum PTX3 level was measured at the day of embryo transfer. The findings were consistent with above studies although the results were not statistically significant. The mean PTX3 value was lower in those who achieved pregnancy compared with non-pregnant group (25.396±11.78 pg/ml vs 28.431±16.51pg/ml) (i.e., implantation failure was associated with higher PTX3 level).

Our results also were in agreement with that of Irani, et al. **(29)** who measured ptx3 level in early follicular phase of natural frozen embryo transfer cycle involving euploid blastocyst embryo. Women with successful pregnancy outcome (live birth) had significantly lower serum ptx3compared to those who did not get pregnant **(29)**. In the present study, cleavage stage embryo was also included in the study. PTX3 is upregulated by estrogen and progesterone (hormonally prepared cycles). So this may explain the statistical insignificance of our results.

Nerveless our results, although not statistically significant, might be closer to the results of in Freis, Von Horn which showed that pregnant women had significantly lower serum ptx3 levels at the day of embryo transfer compared to those without implantation **(30)**. Although our results were consistent with their finding, they were not statistically significant since the transfers were done in frozen cycles suggesting the fact of altered inflammatory and immune milieu between fresh and frozen cycles.

Regarding the limitations of the present study, the ADM and PTX3 levels at start of the IVF cycles are lacking. The ploidy status of the embryos was not evaluated. Finally, the local ptx3 and AM levels were not measured. So, more research with larger sample size would be invited to afford satisfactory evidence to help the physician in making the decision regarding embryo transfer in current cycle or defer it to another cycle. Also, further research are advised to see if it would be possible to utilize intrauterine infusion of ADM to enhance implantation in human.

Conclusion

As evidenced by the results of the present study, higher ADM and lower PTX3 levels at the day of embryo transfer may be associated with successful implantation. Abnormal levels of adrenomedullin and pentraxin3 might reflect an aberrant inflammatory and immunological signaling that may contribute to impairment of uterine receptivity and subsequent failure of implantation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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