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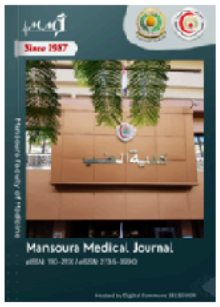

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INTERCELLULAR ADHESION MOLECULE-1 & REACTIVE OXYGEN SPECIES IN FEMALES WITH UNEXPLAINED INFERTILITY

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INTERCELLULAR ADHESION MOLECULE-1 & REACTIVE OXYGEN SPECIES IN FEMALES WITH UNEXPLAINED INFERTILITY

By

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INTRODUCTION

The uterine cervix appears to have several important role in reproduction and is often considered the gateway to upper reproductive tract. The primary physiologic function is the secretion of cervical mucus which functions as biologic barrier between the microbial colonized vagina and the sterile upper reproductive tract (Glatstein et al., 1995).

Moghissi et al., (1980) and Kenneth & Ross, (1995), described several functional properties of the cervix and its secretions that are important for sperm migration, capacitation and impair the transport of abnormal spermatozoa. Any disturbance in these functions can participate in infertility which comprise about 5 % of infertile cases.

Dimarzo et al., (1992), defined unexplained infertility as involuntary infertility of at least 12 months as female partner had regular, spontaneous ovulation and normal pelvis at both hysterosalpingography and laparoscopy, normal post coital test and the male partner has normal semen profile. It affects approximately 10 -15 % of couples in the reproductive age group which makes it an important of the practices of many physicians (Michael & Alan, 1997).

The diagnosis of unexplained infertility is one of exclusion and is made only after an infertility evaluation has failed to reveal abnormalities. The diagnostic tests which are included by all investigators as a part of standard infertility evaluation include semen analysis of male partner, dem-

onstration of tubal patency by hysterosalpingography or laparoscopy, laboratory assessment of ovulation, postcoital test, and antisperm antibodies analysis in sera and cervical mucus of female partner (Crosignani et al., 1993 & Naz et al., 1995).

Despite advances in the diagnostic assessment of infertility many couples have no explanation for their problem. It possibl arise from shortcoming in our knowledge of fertilization and from our inability to utilize all current knowledge (Crosignani et al., 1991).

One of the most important causes of unexplained infertility reported by Witkin et al., (1992) and Tanba et al., (1995), is sperm dysfunction as defects in capacitation, sperm motion, binding spermatozoa to zona pellucida, acrosome reaction and inability of spermatozoa to penetrate the zona free hamster oocyte. Subclinical infection may be of relevance in cases of unexplained infertility (Fedel et al., 1989).

The, possibility that reactive oxygen species, generated by leukocytes within male and / or female genital tracts, may by responsible for alteration in sperm functions (Kovalski et al., 1992).

Hydrogen peroxide (H_2O_2) is a reactive oxygen species that inhibit not only sperm viability but also the acrosome reaction, gamets binding and oocyte penetration (Lapointe et al., 1998).

Intercellular adhesion molecule - 1 (ICAM-1), an important marker of immune activation, is a member of the immunoglobulin superfamily (Springer, 1990). In general, inflammatory and immune stimulation can induce the expression of ICAM-I on various cell types, which in turn leads to an increase in leukocyte emigration at inflammatory sites and enhances antigen-specific cell interaction (Kishimoto et al., I989).

The soluble form of ICAM- 1 is regarded as a useful parameter in diagnosis and monitoring of various inflammatory, neoplastic and immune disorders (Seth et al., 1991).

Wu et al., (1998) hypothesized that sICAM-I may be used as an effective indicator in diagnosis of endometriosis and may be used to predict the treatment of this illness.

From the previous observation, this study was conducted as a trial to evaluate the role of sICAM-I and reactive oxygen species in unexplained infeltile women through measuring their levels in serum and cervical mucus which acts as incubator and transport media for sperm.

MATERIAL & METHODS

(30) couples were selected from those patients attending Fertility Unit of Gynecology & Obstetric Department, Mansoura University Hospital.

(15) couple s were complaining of infertility one year at least after marriage without offspring, these selected couples have no explained causes for infertility and they were diagnosed as unexplained infertility, this diagnosis is explained according to the following criteria:

A- Male Partner :

1- All male partners are apparently healthy without any organic lesion as endocrine disturbances (e.g. hyperprolactinemia, varicocele, congenital factors, testicular failure), anatomical abnormalities or debilitating diseases as T.B., diabetes, chronic renal impairment and chronic hepatitis.
2- Normal seminogram based on semen analysis according to WHO criteria (1992).
3- Normal sexual history, normal levels of blood sex hormones.

B- Female Partner :

All selected female partners were normal without any apparent organic diseases as well as gynecological abnormalities. The selection was based on the following criteria :

I- General selection criteria :

1- Normal hysterosalpingography: to exclude blocked tubes.
2- Secretory endometrium : by premenstrual endometrium biopsy for exclusion of ovulatory dysfunction.
3- Good results of post coital test: for in vivo assessmet of sperm and cervical mucus interaction depending on satisfactory postcoital test parameter assessed by WHO criteria (1992).
4- Normal laparoscopic finding: to exclude cases of endometriosis or peritoneal factors of infertility.
5- Negative antisperm antibodies: to exclude immunological factors of infertility.

II- Specific selection criteria :-

1- No evidience of abnormal vaginal

or cervical discharge to eliminate the possibility of local infection as a cause of errors in the results.

2- Spontaneous (non induced) menstrual cycles as some ovulatory drugs as clomphin citrate which has antiestrogenic action on cervical mucus.

3- Ovulatory monitoring by transvaginal sonography.

4- Normal body temperature to exclude fever as a cause of errors in the results.

Our study includes two groups :-

Group I : included (15) apparent healthy fertile females with offspring. They were slected as control group.

Group II: included (15) females with unexplained infertility according to the previous investigation.

Preparation of serum and cervical mucus. samples :

Blood and cervical mucus (C.M.) samples were taken at the same time at midcycle (13 days from the first day of menstruation). Female partners were instructed to avoid sexual intercourse prior to cervical mucus collections by 2-3 days to prevent contamination of samples (Naz & Butler, 1996).

Blood samples were collected by venipuncture and sera separated.

Cervical mucus samples were aspirated from the endocervical canal using pasture pipette the bloody samples will be excluded. C.M. were diluted 1:4 with phosphate- buffered saline. The samples were thorouhly mixed to allow solublization of cervical mucus according to Menge et al., (1982) .

Sera and diluted cervical mucus were kept frozen at - 20^{O}C till used in the assay.

Serum and cervical mucus will be assayed for :

1- Malondialdehyde (lipid peroxidation products) :

Serum and cervical mucus proteins were precipitated by addition of trichloroacetic acid (TCA). Then thiobarbituric acid (TBA) reacts with malondialdehyde (MDA) to form thiobarbituric acid reactive products which measured at 532 nm according to Draper & Hadley, (1990).

2- Soluble inter cellular adhesion molecule-1 (sICAM-1):

The quantitative detection of soluble ICAM-1 in serum and cervical mu-

cus was performed using a commercial available solid phase sandwich enzyme linked-immuno-sorbent assay (ELISA) kit, The kit was provided from Diaclone Research, Besancon Cedex, France.

Statistical Analysis :-

Data analysis were performed by Mann Whitney U-Wilcoxon Rank Sum W-test for evaluation of differences as appropriate for data type and distribution. The correlation coefficient (r) between various parameters was determined by analysing for Kendall correlation test using SPSS (Statistical Pakage for Social Science) program version 8, 1998. Results were expressed as mean ± SEM. P values <0.05 were considered as statistically significant.

RESULTS

Results obtained in the present investigation demonstrate that :

1 - There is a highly significant increase in serum sICAM-1 ($P<0.005$) and cervical mucus sICAM-1 ($P< 0.0005$) (tab. 1) with significant increase in serum MDA ($P <0.05$) and cervial mucus MDA ($P<0.05$) in unexplained infertile group when compared with fertile group (tab. 2).

2 - There is a positive correlation with significant result ($P<0.05$) between cervical mucus sICAM-I and cervical mucus MDA in unexplained infertile group (tab. 3).

3 -There is a positive correlation with insignificant results between serum sICAM-land cervical mucus sICAM-I($P = 0.372$) and between serum MDA and cervical mucus MDA ($P = 0.1$) in unexplained infertile group (tab. 3).

Table (1) : Shows the levels of serum and cervical mucus (C.M.) sICAM-1 (ng/ml) in fertile and unexplained infertile groups (n=15) .

	Fertile group		unexplained infertile group	
	Serum	C. M.	Serum	C. M.
Mean	507.4	52.6	792.067	152.933
Median	500	45	822	175
Range	322-810	30 - 105	325-980	40 - 202
S E of Mean	± 26.77	± 5.79	± 49.047	± 12.99
Z			3.422	4.15
P			< 0.005***	< 0.0005***

Mann-Whitney U- Wilcoxon Rank Sum W test .

*** Extremely significant .

Table (2) : Shows the levels of serum and cervical mucus (C.M.) malondialdehyde (MDA) (n mol/ml) in fertile and unexplained infertile groups (n=15) .

	Fertile group		unexplained infertile group	
	Serum	C. M.	Serum	C. M.
Mean	0.849	0.759	1.628	1.725
Median	0.790	0.510	1.72	1.133
Range	0.513-1.71	0.083-1.98	0.306-2.9	0.280-4.680
S E of Mean	± 0.078	± 0.170	±0.214	± 0.372
Z			2.51	2.447
P			< 0.05	< 0.05

Mann-Whitney U- Wilcoxon Rank Sum W test .

Table (3) : Shows the correlation study between different variables in unexplained infertile group. .

	Serum MDA		Serum sICAM-1		C.M. MDA	
	r	p	r	p	r	p
Serum sICAM-1	0.165	0.397				
C.M. MDA	0.32	0.1	0.0286	0.882		
C.M. sICAM-1	0.117	0.55	0.172	0.372	0.383	0.047*

* Significant .
r= correlation coefficient .
sICAM-1 levels ng/ml.
MDA levels nmol./ml.

DISCUSSION

Infertility affects approximately 10 - 15% of couples in the reproductive age goup (Michael & Alan, 1997). Failure to ovulate is the major problem in approximately 40% of female infertility, another 40% is due to tubal pathology and about 10% is due to other problems as anatomic abnormalities or thyroid disease, the remaining 10% is called unexplained infertility (Luciano et al., 1990).

The diagnois of unexplained infertility is one of exclusion and is made only after an infertility evaluation has failed to reveal abnormalities. The diagnostic tests which are included by all investigators as part of standard infertility evaluation include semen analysis of male partner, demonstration of tubal patency by hysterosalpingography or laparoscopy, laboratory assessment of ovulation, postcoital test, and antisperm antibodies analysis in sera and cervical mucus of female partner (Crosignani et al., 1993 & Naz et al., 1995).

Despite advances in the diagnostic assessment of infertilit'y many couples have no explanation for their problem. It possibly arise from shortcoming in our knowledge of fertilization and from our inability to utilize all current knowledge

(Crosignani et al., 1991).

Numerous studies have suggested that abnormalities of follicular development, ovulation and corpus luteum function occur in women with unexplained infertility. Ultrasound permits detailed assessment of follicular growth patterns related to profiles of pituitary gonadotropins and ovarian steroids. Ultrasound monitoring may identify anomalies of follicular growth and the leutinized unruptured follicle syndrome (Castelbaum et al., 1994).

Although fertilization can be achieved in most couples, the main oocyte fertilizatian rate during subsequent cycles in cases of unexplained infertility is low. This suggests an underlying undiagnosed pathology of oocyte T- sperm interaction in some cases of unexplained infertility (Lipitz et al., 1993).

Templeton et al., (1990), reported that menstrual disturbances can occur as a result of stress and these are possibly mediated through disturbances in the neuroendocrine control of ovulation. Tubal motility and gamete transport may also be altered in stress-related infertility.

The conventional semen analysis represents a crude method of assessing the fertility of the male. Studies in patients with unexplained infertility have reported defects in capacitation and sperm motion characteristics, binding of spermatozoa to zona pellucida, acrosome reaction and the ability of the spermatozoa to penetrate zona free hamster oocyte. These observations suggested that methods for assessing the fertilizing capacity of spermatozoa have to be incorporated in the evaluation of couple with unexplained infertility in order to amplify the scope of the workup and to better decide the appropriate treatment for these couples (Witkin et al, 1992).

Lower sperm motility and lower cleavage rates was seen in the unexplained infertile group indicating gamete defects as possible causes of infertility (Tanba et al., 1995).

The results obtained in the present study demonstrated that there is a highly significant increase in serum sICAM-1 and cervical mucus sICAM-I in unexplained infertile group when compared with fertile group. These results may be attributed to infiltration of cervical tissues with leukocytes and induction of its secretion by proinflam-

matory cytokines through out th'e body. This suggestion is in alliance with the reports of other investigators.

Wah et al., (1990), reported that in vivo it is possible that leukocytes, microorganisms and other antigens present in seminal fluid may elicit immune responses that could- impair normal reproduction through immune cell activation culminating in the release of soluble factors detrimental to sperm viability or function. Thls heory is supported by evidence of increased leukocyte number in cervical tissues in female with unexplained infertility in comparison with controls.

Under normal conditions, human reproductive tissues contain many types of immune and inflammatory cells capable of secreting soluble products. Cytokines are secreted proteins of activated macrophages, T lymphocytes, natural killer cells and a host of somatic cells throughout the body. Cytokines may be cytotoxic and affect the differentiation and regulation of other cells including reproductive cells (Best & Hill, 1997)

Several cytokines have been detected in human cervical tissues. Gene expression for cytokines IL-Iα, IL-6, IFN-γ and TNF-α has been detected in human cervical tissues (Pao et al., 1995). TNF-α, IL-Iβ and IL-6 have been detected in cervicovaginal secretions (Belec et al., 1995).

Intercellular adhesion molecule-1 (ICAM-I), an important marker of immune activation, is a member of immunoglobulin superfamily (Springer, 1990). Activation studies in human demonstrated that inflammatory mediators including IL-1, IFN-γ and TNF-α caused strong induction of ICAM- 1 in a wide variety of tissues (Vigano et al., 1997).

A soluble form of ICAM-I has been described recently and believed to be released as an indirect consequence of inflammation or tissue damage in certain inflammatory and autoimmune diseases including asthma, diabetes, rheurnatoid artheritis and malignant melanoma (Becker et al., 1991; Gearing & Newman, 1993 and Roep et al., 1994).

Moreover, it has been suggested that the fast detection and measurement of circulating ICAM-I, would not only facilitate early diagnosis of many immunologic disorders but also would allow monitoring of thrapy and intervention (Rothlein et al., 1991 and Vi-

gano et al., 1998).

The source of sICAM-I in cervical mucus may be via local production in cervix and / or exudation from serum. The general non significant correlation of serum levels with cervical mucus ICAM-I, suggests the local production of sICAM-I by cervical tissues.

Although reactive oxygen species (ROS) have been implicated in a variety of pathological processes, the generation of higly reactive oxygen species is an integral feature of normal cellular metabolism as mitochondrial respiratory chain, phagocytosis, arachidonic acid metabolism, ovulation and fertilization. However, their production can multiply during pathological circumstances (Rth, 1997).

Mani et al., (1994), illustrated that nitric oxid (NO), an active free radical formed duriing conversion of arginine to citruline by the enzyme NO synthase (NOS), mediates vasorelaxation, cytotoxicity and neurotransmission. Neuron containing NOS are located in hypothalamus . These neurons control the release of several hypothalamic peptides. Release of NO from these neurons stimulate pulsatile release of luteinizing hormone-releasing hormone (LHRH) in vivo which induces LH release that induce ovulation.

Reyes et al., (1998), suggested that the peroxidation products, the free radicals, and the antioxidants compounds increase during ovulation, implantation and pregnancy evolution. Superoxide anion is connected with the increase of fluidity and polarity of the membranes during the implantation. At the end of pregnancy the antioxidants exceed peroxidation phenomena. By the other hand, NO radical has gained great importance during pregnancy because it is considered one of the most powerful relaxants of smooth muscles.

Aitken, (1995), reported that although excessive exposure to ROS may be harmful to spermatozoa, in physiological amounts these molecules are of importance in the control of normal sperm function.

The capacity of human sperm fertilization is principally dependent on sperm motility and membrane integrity. Oxygen derived free radicals, such as superoxide anion, are known to impair sperm motility and membrane integrity by inducing membrane lipid

peroxidation. NO, a biologically active free radical, has recently been shown to inactivate superoxide and increase intracellular cGMP (Zhang & Zheng, 1996).

Hydrogen peroxide (H2O2) is a reactive oxygen species that inhibits not only sperm viability but also the acrosome reaction, sperm binding and oocyte penetration (Aitken et al., 1993).

Catalase enzyme activates the decomposition of H2O2, thus removing an initiator of free radical chain reaction leading to lipid peroxidation. Since the oviduct is known to enhance sperm survival, Lapointe et al., (1998), hypothesized that it might secrete catalase enzyme which increased during cycle and reached its maximal level just before ovulation. They found that catalase activity was also detected in porcine oviductal fluid, human oviductal fluid, and cervical mucus, and this enzyme may play an important role in sperm survival within the female tract and any disturbance in this defense mechanism will lead to infertility.

This fact can explain the highly significant increase in cervical mucus malondialdehyde (MDA), an index of lipid peroxidation, illustrated in table (2). The highly significant increase in serum MDA demonstrated in table (2) may be attributed to the defect in the fundamental defense against ROS. This defense includes scavenger enzymes (superoxide dismutase, catalase, glutathion peroxidase) and lipid and water soluble antioxidants (ascorbic acid, glutathion, albumin, transferrin) as reported by Rth, (1997).

The source of MDA in cervical mucus may be via local production by the cervix and / or exudation from serum. The general non-significant correlation of serum levels with cervical mucus levels as illustrated in table (3), suggested the local production of ROS by cervical mucus.

The results obtained from table (3) demonstrated that there is a positive correlation with significant results between cervical mucus sICAM-1 and cervical mucus MDA. This correlation may be attributed to the fact that ROS function as second messenger molecules in the activation of trascription nuclear factor (NF)-kappa B which indue the expression of ICM- 1 while inhibit the expression of VCAM- 1 and E-selectin (Khan et al., 1996).

From the results of this study , it may be concluded that the fast detection and measurement of cervical mucus sICAM and cervical mucus MDA will facilitate early diagnosis and early treatment of female with unexplained infertility before progressed to immunologic infertility.

SUMMARY & CONCLUSION

This study was designed to evaluate the role of sTCAM-I and reactive oxygen-species in unexplained infertile female. This study included (30) couples. They were selected from those patients attending Fertility Unit of Gynecology & Obstatric Department, Mansoura University Hospital. The selected subjects were divided into 2 groups. Group (I) included (15) apparent healthy fertile females with offspring. They were selected as control group. Group (II) included (15) female with unexplained infertility.

The diagnosis of unexplained infertility is one of exclusion and is made only after an infertility evaluation has failed to reveal abnormalities. The diagnostic tests which are included by all investigators as a part of standard infertility evaluation include semen analysis of male partner, demonstration of tubal patency by hysterosalpingography or laparoscopy, laboratory assessment of ovulation, postcoital test, and antisperm antibodies analysis in sera and cervical mucus of female partner.

Blood and cervical mucus (C.M.) samples were taken at the same time at the midcycle (13 days from the first day of menstruation). Female partners were instructed to avoid sexual intercouse before C.M. sampling by 2-3 days .

The sera were separated from the collected blood samples. C.M. were solubilized in phosphate-buffered saline. The sera and C.M. samples were kept frozen -20°C till time of assessment of malondialdehyde (MDA) and soluble intercellular adhesion molecule (sICAM- 1) .

Serum and C.M. MDA were assayed by reaction with thiobarbituric acid (after precipitation of their protein content) to form thiobarbituric acid reactive products which measured at 532 nm. Serum and C.M. sICAM-1 were assayed by available commercial ELISA kit provided from Diaclone Research, Besancon Cedex, France.

The results of this study showed that there is a highly significant increase in serum and C.M. sICAM- 1 with significant increase in serum and C.M. MAD in unexplained infertile group when compred with fertile group. There is a positive correlation with significant results between C.M. sICAM-I and C.M. MAD in unexplained infertile group.

From the results of this study, it may be concluded that cervical mucus sICAM-1 and cervical mucus MAD can be used as diagnostic marker of early diagnosis of unexplained infertile female which can help in early treatment of these cases of infertility before progressed to immunologic type of infertility.

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الجزيئات الملتصقة التى بين الخلايا-١ والشقوق الحرة فى حالات العقم الغير مفسر عند السيدات

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تم إجراء هذا البحث لدراسة دور كل من الجزيئات الملتصقة التى بين الخلايا-١ والشقوق الحرة فى السيدات اللاتى يعانين من العقم الغير مفسر. ويشمل هذا البحث على ٣٠ سيدة تم إختيارهن بناء على الفحص الاكلينيكى والتحاليل الشاملة. وقد تم تقسيم الحالات المختارة إلى مجموعتين. المجموعة الأولى وتشمل على ١٥ سيدة غير العقيمات وتمثل المجموعة الضابطة. المجموعة الثانية وتشمل على ١٥ سيدة يعانين من العقم الغير مفسر بعد إجراء كل الفحوصات اللازمة مثل نتيجة تحليل طبيعة السائل المنوى الخاص بالزوج - عمل منظار للرحم والحوض - عمل أشعة بالصبغة على الرحم والبوقين - إختبار التبويض وإختبار بعد الجماع .

وقد تم أخذ عينات الدم وإفرازات عنق الرحم فى اليوم الثالث عشر من بدء حدوث الطمث وبعد عملية فصل سيرم الدم وذوبان إفرازات عنق الرحم بعد تخفيفة بنسبة ٤:١ فى محلول الفوسفات الملحى تم تعيين نسبة كل من الجزيئات الملتصقة التى بين الخلايا-١ والشقوق الحرة فى كل منهما. وكانت نتائج البحث كالآتى :-

زيادة نسبة الجزيئات الملتصقة التى بين الخلايا-١ فى السيرم وإفرازات عنق الرحم زيادة ذات دلالة إحصائية عالية. وكذلك زيادة نسبة الشقوق الحرة فى السيرم وإفرازات عنق الرحم ذات دلالة إحصائية فى المجموعة الثانية عند مقارنتها بالمجموعة الأولى وهى المجموعة الضابطة .

كما أنه توجد علاقة إيجابية موجبة ذات دلالة إحصائية بين الجزيئات الملتصقة التى بين الخلايا-١ والشقوق الحرة فى إفرازات عنق الرحم فى المجموعة الثانية. كما أنه توجد علاقة إيجابية موجبة ليست ذات دلالة إحصائية بين الجزيئات الملتصقة التى بين الخلايا-١ فى السيرم ونظيرتها فى إفرازات عنق

الرحم وكذلك بين الشقوق الحرة فى السيرم وإفرازات عنق الرحم فى المجموعة الثانية.

وبناء على نتائج هذه الدراسة يمكن القول أنه بتعيين مستوى كل من الجزيئات الملتصقة التى بين الخلايا-١ والشقوق الحرة فى إفرازات عنق الرحم قد يساعد فى التشخيص المبكر لحالات العقم الغير مفسر وعلاجه قبل أن يتحول إلى العقم المناعى .