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Herpes Simplex Virus & Cytomegalovirus inflicted semen substantiates infertility among men.

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Abstract: *Infertility is a growing challenge worldwide that cause many affiliated socio-psychological problems in many cultures that carry a negative impact on many families.*
As a last resort, many physicians engage certain drugs to over stimulate the gonadotropins to hope for the production of healthy Sperms and Ovum to materialize the fertility. Also, fertilization in vitro is a growing solution for the affording but many patients are not able to afford expensive interventional procedures. Over stimulation of the sperms or ovum does not constitute the chromosomal DNA to amicably contribute to the successful fertility, normal fetus development, uneventful pregnancy and/ or normal delivery.
Many scientists have linked the Cytomegalovirus and Herpes Simplex Virus to the infertility but complete understanding of the pathogenesis remains elusive.
We studied the prevalence and the role of herpes simplex virus (HSV), cytomegalovirus (CMV) in the semen of infertile men. Data was collected from sixty nine infertile men. Serum Anti- HSV IgG & IgM, CMV IgG & IgM from the blood and Polymerase chain reaction (PCR) test were performed on the semen to detect the presence of HSV & CMV in these infertile subjects. Anti- CMV IgG was found in 44 (62.9%), CMV IgM in 4 (5.9%), HSV IgG in 22 (31.4%), HSV IgM in (0%) and PCR showed presence of CMV in 26 (37.1%), HSV PCR was positive in 13 (18.8%). Overall, results revealed that CMV was relatively more prevalent in the semen of infertile men but how its presence leads to infertility requires further investigation.
Key Words: *Infertility, HSV, CMV, HSV & CMV PCR*

Objective:

To test the hypothesis that Herpes Simplex virus & Cytomegalovirus inflicted semen substantiates infertility among men.

Introduction:

Infertility is considered to be a big human challenge worldwide. Couples in most societies and cultures deal with this challenge in many different ways. It has been observed clinically that among infertile couples the relationship tends to become strenuous leading to metabolic syndrome, hypertension, stress, depression, isolation anxiety, lower self-esteem, psychological distress, as well as guilt feelings and suicidal ideation. Infertility becomes a stressful experience for both of the partners, effect relationships with each other and family members, occupational issues, helplessness and marital instability [1].

In many societies men's infertility is just stereotypically associated with women problem. Females are stigmatized for this issue not only in Asian cultures but also western societies without knowing the core cause for infertility. Females are not only psychologically abused but also physically traumatized due to not be capable to produce baby [2]. Different researches have identified the physiological causes of infertility, based on that different treatment strategies like In vitro fertilization (IVF), Zygote intrafallopian transfer (ZIFT), Gamete intrafallopian transfer (GIFT) and many others have been introduced but the actual cause behind the pathology is still unknown [3].

Therefore, the aim of our clinical study was to find the pathological link and possible solution to this growing challenge. Great many scientists looked at this challenge in many different ways. Taiwanese, Malaysian's and Greek's particularly looked at the involvement of the herpes family of viruses and hypothesized the phenomenon of its involvement in the infertility [4], [5], [6].

There are 8 herpes family of viruses recorded to have been involved in many prominent diseases, yet there are 48 viruses those are uncategorized. These viruses have the ability to persist latently in the host cell and

give rise to recurrent infections. The herpes class of viruses have been divided into three subfamilies (α, β, and γ) based on both virologic and biological properties [7].

Herpes Simplex Virus and Cytomegalovirus are well known for their chronic isolation in humans after first intraction. To see its prevalence, one has to look at the Chronicity by tracing the level of IgG and the acuteness or recurrence of the infection through IgM in the serum. Human cytomegalovirus (CMV) belongs to the β family, has been known to contribute in the physical or mental retardation, hearing or vision impairment as well as neurologic impairments. When a person gets infected with this virus, it remains latent in individual's body for life. Under specific conditions as viral infections become active, deprive the related functions of controlled area [8].

Materials & Methods:

Sixty nine (69) documented infertile men participated in this study. Participants were informed with the scope of the study and the integrity of the overall project. Serum evaluation of Herpes simplex virus [Anti HSV-IgG & IgM], Cytomegalovirus [Anti CMV IgG & IgM] were conducted to determine exposure to the virus and PCR reactions were performed using standard molecular biology techniques using semen samples.

Prior to the laboratory testing, informed consent was taken from the participants. Subjects were assured to maintain the confidentiality, right to voluntarily participation and withdrawal from the participation at any given time. Participants were given full privacy to draw their sample in a container. All the measures were concluded one by one for the participants under the International standards and controlled conditions. At the end, all the participants were informed about the results.

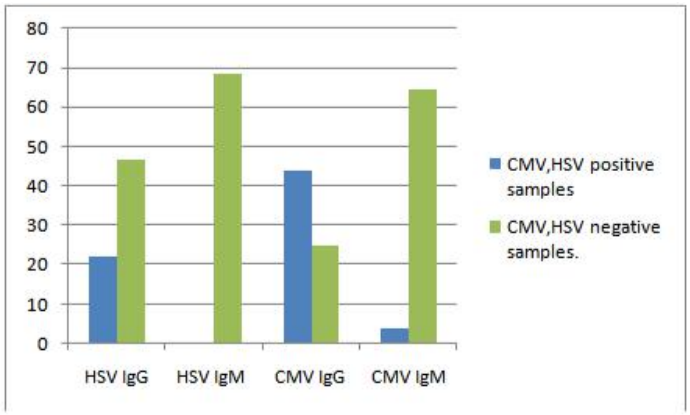
All the samples were taken under the supervision of medical scientists, to ensure quality. World Health Organization (WHO) and Clinical Laboratory Standardization Institute (C.L.S.I) guidelines were followed. All the samples were sent to laboratory within 15 minutes of the ejaculation and the blood draw. All the semen samples were stored at minus $80C^0$ before analysis.

Enzyme linked immuno-sorbent assays (ELISA)/ chemiluminescent assays were performed using commercially available research grade kits, on blood samples for CMV IgM, CMV IgG, HSV IgM and HSV IgG. Real time PCR technique was used to detect nucleic acid of the target viruses using commercially available primers. Data was analysed using SPSS 20.

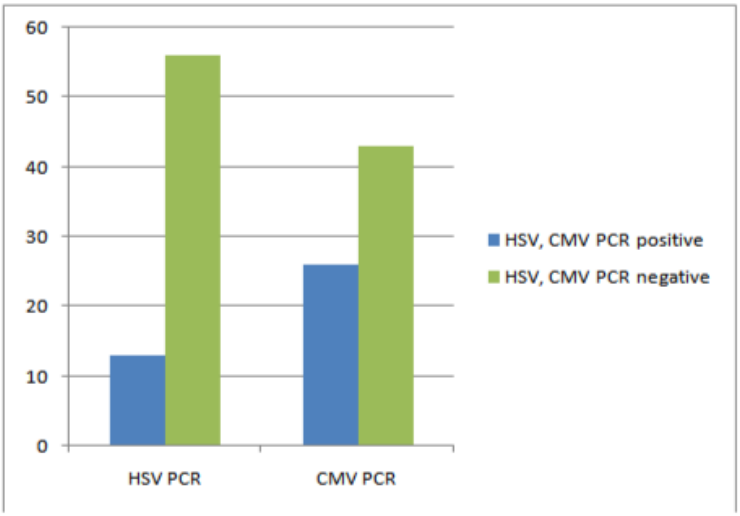
Results:

Descriptive statistical analyses were carried out including frequencies, means, and standard deviations. A total sample of 69 candidates were selected, CMV IgG antibodies were found positive in 44 males 63.8%, on the other hand, CMV IgM antibodies were found positive only in 4 infertile males were positive that is 5.8% candidates were positive for CMV IgM. For HSV IgG antibodies, 22 males were found positive and none of the candidate was found positive for HSV IgM antibodies. It precipitated 39.9 % and zero percent respectively. Total sero positivity for CMV, HSV was 69.6% and 39.9% respectively.

PCR showed 56.5% positivity in total for HSV and CMV, out of which 18.8 % male were positive for HSV nucleic acid compared with 37.7% for the CMV nucleic acid in the semen samples. Comparing CMV PCR results with HSV showed that CMV positivity was 50% greater in the semen samples. Independent 2 tail T-Test showed a highly significant value, $p^{***} < 0.0001$



Graph1: Frequencies of the HSV, CMV antibodies in blood.



Graph. 2> Frequencies of the HSV, CMV PCR in semen samples.

Discussion:

Chronic inflammation of the testicular tissues related to the viral infection in not well understood but overall effects of the inflammation and immune interactions are well known for local cell damage. Therefore, the presence of the HSV & CMV antibodies in the serum has been found due to the antibodies war against the viral genome proliferating in the seminal fluid. This substantiates the very potential of the infection process taking place within the neospermogenesis, may leaving a variety of conditions of the spermatozoa.

According to Late Dr. Edward Wagner of University of California at Irvine in 2004 reported that viral proliferation takes place continuously in Central nervous system under three major conditions (high heat, internal injury and downtrend of immunity) [9]. Because, the heat plays a significant role in the viral genome proliferation, therefore, the atmospheric and environmental heat may play a significant role in the enhancement of this Pathophysiology. Heat factor may acts as a complimentary effect in view of the local atmospheric conditions and its influence on spermogenisis and viral genome proliferation in the testes of male.

A Study carried out on 250 infertile men in Taiwan concluded that Anti- CMV IgG was present in 249 (99.6%) of the 250 male serum samples and in 247 (98.9%) of the 250 female serum samples. Viral shedding was detectable in 83 (33.5%) of 248 semen samples and 83 (33.7%) of 246 cervical mucus samples. It is concluded that the seroprevalence and genital tract viral shedding were relatively high in infertile couples in Taiwan [4]. This study is very close to our study in respect of viral shedding among the infertile population though we have not included the female participents.

A descriptive clinical study to investigate the prevalence of herpes simplex virus cytomegalovirus and Epstein-Barr virus in the semen of men with fertility problems was reported. This study concluded that Herpes simplex virus plays a significant role in male Infertility [5]. Our present study do compliment the mentioned study in terms that HSV plays a role in the infertility. At the same time we concluded that HSV is of lesser prevalence compared with the CMV. Another study reported in literature reveal that, if CMV does not contribute to infertility then in future it gives rise to other obstetric complications. Study result of the serum samples from 125 apparently healthy pregnant women proved that Cytomegalovirus plays significant role in later challenges in fertile women. CMV IgG was found in 84% of the cases and CMV IgM in 7.2%. Both CMV IgM and IgG were also found in another 37 women with various obstetric complications that included 17 cases of spontaneous abortions, 15 cases of fetus anomalies, 1 case of incomplete abortion, 3 cases with premature delivery of infant with congenital anomalies and 1 case of infertility [6]. This study signifies total CMV sero-positivity 91.2% for the infertility. Whereas we have concluded it is 68.8% infertility due to CMV total sero-positivity. Scientist have reported a variety of sero-positivity of CMV & HSV in relation to the Infertility.

From the overall literature review, it can be concluded that Cytomegalovirus (CMV) in relation to infertility has rarely been reported in the literature. Not even a single study is reported from Pakistani context. So, further studies in that dimension are required, for not only enlightenment of knowledge but also to make the therapeutic services more effective and beneficial for the human beings.

Conclusion:

Significant presence of the antibodies against any virus is the direct reflection of the war against that viral nucleic acid at the least. Presence of the virus in the absence of the IgM indicates chronic infection and possible seroconversion that can make clinical decision of using antivirals a debateable topic. We believe that integration of the molecular tools to detect the viral genome can help reach the decision but using molecular approaches for such investigations are not clinically used routinely so far. This study is a paradigm shift in understanding of the aetiology and viral patho-physiology of infertility. We suggest that presence of chronic viral pathogens in the semen can be associated with the inflammation which may lead to the cascade of the sperm deterioration and subsequently infertility.

Future Guidelines:

Further studies are required in order to find out the role of viral pathogenesis in infertility. Role of antiviral therapy shall be studied among infertile patients.

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