




TORCH, Anti-cardiolipin, and Anti-phospholipids in Women with Repeated Miscarriage in Mosul City

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Abstract

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BACKGROUND AND OBJECTIVE: The present study aimed to identify a connection between common viral infections and women who had repeated miscarriages.

MATERIAL AND METHODS: This study is a retrospective study which has been carried out on 2010 records in Mosul city/Iraq, and the patients were all women of child-bearing age (20–35 years old). All of the women had suffered from an abortion at least once before. The target viruses in charge for this study include Toxoplasma gondii, Cytomegalovirus, Rubella virus, and Herpes virus. The patient's records include tests for detection of serum antiphospholipid, and anticardiolipin, together with cutoff values of Toxoplasma gondii, Cytomegalovirus, Rubella virus, and Herpesvirus as a positive result for the presence of these infectious diseases.

RESULTS: The analysis is based on the detection of the antibodies which confirmed a negative correlation between antibodies level and active viral infection, together with no clear association between the presence of active infectious status and miscarriage. In addition, only a few positive cases for each patient were positive for viral infection.

CONCLUSION: The outcome confirmed no clear association between the presence of infectious agents and repeated miscarriage. Nonetheless, rubella and cytomegalovirus have shown the highest contribution in this regard.

Introduction

Miscarriage is officially defined as the loss of pregnancy within the first 12 weeks. Late miscarriage is defined as the loss of pregnancy from 12 to 24 weeks [1], [2]. It is fairly common since it occurs in one of five pregnancies. It can have considerable physiological and psychological implications for the patient [3], [4]. Infection can cause nearly 15% of early miscarriages and 66% of all later miscarriages [5]. Reports increasingly accumulating regarding the association between abortion and the presence of viral infections; including Herpes virus [6], [7], human papillomavirus [8], [9], Parvoviruses [10], Cytomegalovirus [8], [9], Rubella virus [11], [12], [13], or protozoal infection, such as Toxoplasma Gondi [14], [15] and bacterial infection [16].

Anti-cardiolipins are antibodies that are directed against cardiolipin which is found in several diseases including syphilis and anti-phospholipid syndrome. The presence of these antibodies in a pregnant woman's body could result in spontaneous abortion or miscarriages. Anti-phospholipid syndrome is a disorder of the immune system which can cause

an increased risk of blood clots within the body. This means that those with this condition are at greater risk of developing deep vein thrombosis which results in blood clots in the leg. This has also been linked to pregnancy complications and recurrent miscarriages. It can also result in late miscarriage which is caused after 12 weeks of pregnancy [17], [18], [19], [20].

Although abortion seems to be the most prevalent unfavorable pregnancy result, global statistics are unavailable. Hence, it is a very significant factor to watch out for when handling the treatment and care of women who have miscarried before. Several publications have associated anti-phospholipid syndrome with retarded intrauterine growth and others have associated it with pre-eclampsia. The present study focuses on analyzing the prevalence of miscarriage in pregnancy in our locality since such statistics are lacking.

Patients and Methods

This study is a retrospective study where data were collected from the main gynecological department

in the city hospital. Records of all miscarriage mothers were considered regarding the presence of viral infection. The patients were all women of childbearing age (20–35 years old) and suffered from abortion at least once before. No interference was conducted to select patients' data, the included data were kept in the same order as they were conducted and recorded by the laboratory staff.

The included tests were the measurement of anti-*Toxoplasma Gondii* IgM antibodies and the measurement of anti-*HSV* IgM antibodies in a patient's serum by ELISA as referred by the specialized obstetrician; IgM antibodies represent the marker of active infection rather than IgG antibodies which represent an old or latent infection. All ELISA kits were from bioMerieux Company and the ELISA BioTek ELX-800 instrument was used as instructed by the kit insert. The accuracy rate of anti-*Toxoplasma Gondii* IgM antibodies and anti-*HSV* IgM antibodies kits is 97.4% and 97%, respectively [12], [13], [14], [15], [16], [17], [18], [19], [20]. Routine tests for miscarriage women also include detection of serum concentration of anti-cardiolipin and antiphospholipid as a confirmative technique for the presence of infectious diseases including these mentioned viruses.

Statistical analysis in this study was conducted using *Microsoft Excel* spreadsheets version 14.0. 2010, using a T-test at $p \leq 0.05$ was considered significant.

Results

Correlation between infectious agent and measured antibody parameters

The study found that there were no significant instances of anti-phospholipid and anti-cardiolipin within the patients who had either of the four viruses. This showed that since the antibodies were absent, this meant that the patients had been infected. As a result, these viruses likely affected repeated miscarriages within the few correlated patients. The lowest occurrences of the antibodies were within patients who had either the Rubella or the Herpes virus. Not only are these common viruses, but are known to be explicitly deadly against unborn babies. Table 1 results show the correlation between infectious agents such as *Toxoplasma Gondii*, Cytomegalovirus, Rubella Virus, and Herpes Virus. This table has also defined a set of values to understand the data more precisely.

Table 1: The correlation between infectious agents and measured antibody parameters

Correlation	Anti-phospholipid	Anti-cardiolipin
<i>Toxoplasma Gondii</i>	0.16	0.033
Cytomegalovirus	0.018	0.01
Rubella Virus	0.01	0.001
Herpes Virus	0.03	0.015

Correlation between presence of infectious microorganisms and patients

The prevalence of infectious microorganisms or viruses among patients who repeatedly miscarried was also very low. This is in line with the statistics which say that 60% of all miscarriages remain unexplained. However, it also lines up with the statistics that 15% of all early-stage miscarriages are caused by infections. One clear observation here is that the prevalence of *Toxoplasma Gondii* among the patients was the lowest, at 2.45%. That lines up with the correlation between infectious diseases and the prevalence of antibodies. As we can see, the prevalence of antibodies was highest in patients with *Toxoplasma Gondii*. This shows that the patients with the highest resistance to the infectious microorganisms had *Toxoplasma Gondii*. This either shows that *Toxoplasma Gondii* is not as prevalent within the region, or that it is not nearly as fatal as the other viruses in the study (Table 2).

Table 2: The percentage prevalence of infectious agents among enrolled subjects

Between infectious	Prevalence (%)
<i>Toxoplasma Gondii</i>	2.453386
Cytomegalovirus	11.57998
Rubella Virus	14.22964
Herpes Virus	11.57998

Causative factors measured in women who repeatedly miscarried

The chart shows potential causative factors measured in miscarried women. The results here are expressed as a visualization of the mean with the standard errors added in. The addition of the standard errors is done to offset the 2.6%–3% inaccuracies within the testing kits employed in the study as well as to account for any unseen and unaccounted for variables within the study.

The chart shows that the highest instances of miscarriages occurred for the patients who had the cytomegalovirus or the Rubella Virus. Both the Herpes and the *Toxoplasma Gondii* viruses had smaller effects overall on the pregnant women experiencing miscarriages.

However, *Toxoplasma Gondii* seems to be the weakest virus associated with the miscarriage in women in Mosul. This result is concurrent with the previous results in the study which showed that patients with the *Toxoplasma Gondii* virus had the highest number of antibodies within their systems. The previous results also showed that *Toxoplasma Gondii* was prevalent in a much lower number of patients than all the other viruses (Figures 1 and 2).

Discussion

Herpes is viral DNA and investigators have confirmed that this virus enters the host and remains dormant lifelong with potential reactivation [21]. In a study

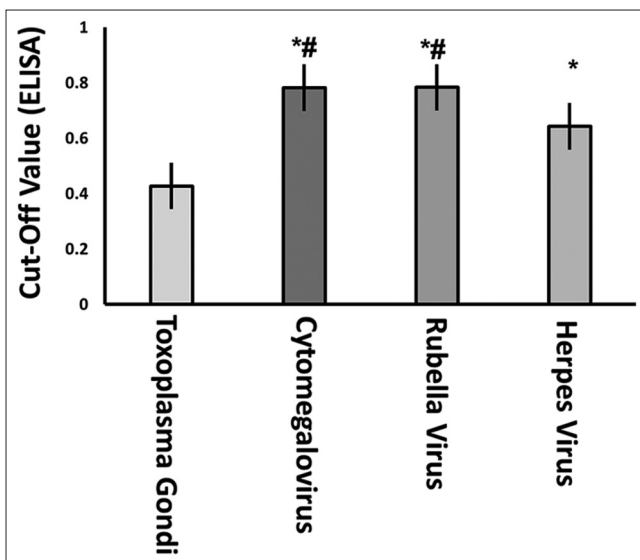


Figure 1: Overall data analysis of the potential causative factors measured in miscarriage women. The results were expressed as mean \pm SE. *^{#p} < 0.05. *As compared to toxoplasma positive cases. [#]As compared to herpes virus-positive cases

conducted by Kapranos and Kotronias, 2009 [6], using DNA hybridization of sera samples of women undergoing recurrent spontaneous abortion compared to a lower rate of elective abortion. Similarly, Kim *et al.*, 2012b reported that an analysis of sera of pregnant women for HSV found a relatively high positivity (17%) [7]. Rubella has been partially studied and inconclusive outcomes reported by researchers. Rubella has coexisted with other virus infections such as HSV [7]

In a study conducted by Hadar *et al.*, 2010 who has tested a group of women with CMV positive before pregnancy [22]. Only four out of 59 women enrolled in the study had miscarriage other underwent normal delivery or elected abortion making the outcome inconclusive. These controversial results were recorded in another more detailed study conducted by Saraswathy *et al.* 2011 who has shown the presence of CMV IgG antibody in their serum [23].

The protozoal infection has been increasingly linked to miscarriage. Toxoplasmosis has been investigated in all miscarriages studied population. In a study conducted on 100 serum samples from 55%

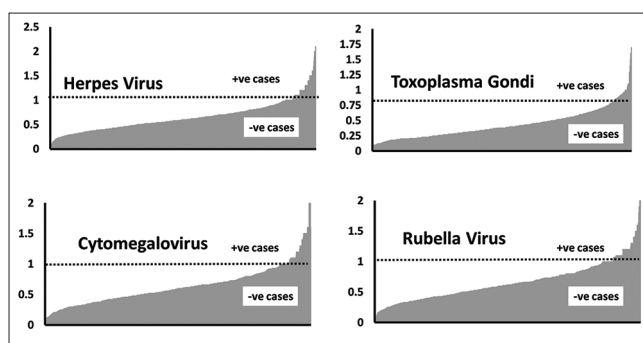


Figure 2: The clustering cutoff value of roughly two in the study's cases of subjects that were recruited. The cutoff value between positive and negative situations is shown by a dotted line.

toxoplasma seropositive subjects, most of them were in the first trimester, however, the study lacked comparison to the control group [24]. Similarly, Alvarado-Esquivel *et al.* 2014, study lacked comparison to control and confirmed a slightly high exposure to toxoplasma Gondi among miscarriage women [25]. In alternative meta-analysis studies conducted over 132 studies, the outcome has shown a higher infection rate among miscarriage women [26]. Nonetheless, epidemiological studies have confirmed that the link between Toxoplasma infection rate and miscarriage differs across the world and varies from 40 % to 70% between UK/USA and tropical countries, respectively [27].

The immune system's participation in a good pregnancy is critical. While the semi-allogeneic fetus' immunological responsiveness is established, various components of the immune system perform their assigned duties in preparation for implantation as well as during gestation [28], [29]. In the fetomaternal interface, natural killer (NK) cells, macrophages, and dendritic cells have all been found [30], [31], [32]. Cytokines such as interleukin (IL-10) and colony-stimulating factor (CSF-1) have been connected to the implantation process and are present in uterine cells [30], [33]. Due to the obvious infiltration and injury to the maternal tissue, implantation causes an inflammatory reaction, with several cells suffering apoptosis [34], [35].

In contrast, inflammatory cytokines like interferon- γ and tumor necrosis factor- α (TNF- α) are not normally produced in the placenta and have been linked to miscarriage in mice models [28]. Stillbirth is hypothesized to be caused by abnormal implantation, placentation, or blood vessel change [4], [36]. An active infection might disturb the pregnancy by interfering with any of the above-mentioned processes as well as disrupting the immunological homeostasis, even if it never culminated in maternal and fetal infection.

The mechanism of maternal-fetal transfer of infectious agents has been studied carefully. Some of these infectious agents are transferred to the fetus through maternal circulation, such as plasmodium Malaria [37], [38]. Other infectious agents are using surface protein to internalize into the placenta such as *Listeria monocytogenes* [39], [40], [41] using invasion mechanism of internalization through placenta.

Since the cause of miscarriage is yet unknown, many factors have been regarded as contributing to the increase in the chance of miscarriage, these include genetic, mother stress and psychological status, mother's high/low BMI, mother malnutritional, alcoholics, smoking, and use of NSAIDs [2], [42], [43], [44], [45], for these aforementioned causes, sequential miscarriage is considered in women with previous history of first miscarriage [46]. Finally, reports also indicated the reciprocal link to presence of infectious agents [47], [48], [49], [50], [51], [52]. However, no single infectious agent was conclusively agreed to be responsible, moreover, bacterial, viral, and protozoal

are believed to be equally involved, thereby, no single infectious agent could be ruled out [5]

Conclusion

The data analysis of this study has shown that while there was a significant presence of each of the four viruses mentioned within the sample population of female patients, none could be singled out as a decisive factor for repeated miscarriages. The statistical truth wills out in this study, that 60% of all miscarriages are unexplained; however, many can be explained by the occurrence of infectious diseases or the presence of infectious microorganisms; with rubella and cytomegalovirus seeming to be the main causative agents in this regard. Underestimation of miscarriage's physical and psychological number of casualties are common. The direction from diagnosis through professional management to supportive aftercare can be difficult. The rate of robust toxoplasmosis and HSV infectivity in frequently aborted females shows no link to weather changes. The active HSV infectivity is more associated with abortion than toxoplasmosis in this set of experienced females. Varying terms and inclusion criteria hamper comparison of treatment options for miscarriage in studies, multiple doses and routes of administration of drug treatment, and different definitions of treatment failure. Other infectious diseases need to be aligned together and further studies need to be assessed.

We do recommend routine screening tests to be conducted in our local teaching hospitals to identify positive cases if any. These screening tests will improve the follow-up for those positive cases which might reduce the rate of continuous abortion in this context.

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Authors Contributions

Conceptualization, K.A.A. and M.K.J.A.; methodology, K.W.A; software, K.W.A.; formal analysis, K.W.A.; investigation, M.K.J.A.; resources, K.W.A.; data curation, K.W.A.; writing—original draft preparation,

K.A.A.; writing—review and editing, M.K.J.A.; visualization, M.K.J.A.; project administration, K.A.A.; and funding acquisition, M.K.J.A.

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