REVIEW ARTICLE

Seroepidemiology of *Toxoplasma gondii*, Rubella, Cytomegalovirus and Herpes Simplex Virus Type -2 in Women with Abnormal Pregnancy Outcomes: A Review

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Received: 7/1/2019   Accepted: 16/03/2019   Published:1st May, 2019

Abstract

**Background:** The role of *T. gondii*, rubella, cytomegalovirus and herpes simplex virus type -2 was not fully understood as the range of Seroepidemiology of these agents was with a wide range. The reported studies results were affected by study design and patients selection criteria.

**Aim:** To determine the role of ToRCH agents on pregnancy outcomes

**Materials and methods:** Published articles on the role of ToRCH agents in women with bad obstetrics history retrieved from Google and reviewed. For *T. gondii* 19 global studies and 36 Arab countries were reviewed, while for rubella 24 global studies and 16 Arab countries were included. In addition, 19 global and 18 Arab countries for CMV, while 14 HSV-2 global and 6 Arab countries studies were reviewed.

**Results:** *T. gondii* IgG and IgM seroprevalence range in global studies were 5.33% - 91.2% and 1.2% - 84.4% respectively. While the corresponding values in Arab countries studies was 6.8% - 81.5% and 0.79% and 58.1% respectively. Rubella IgG seroprevalence range was 3.6% - 91.2% in global studies and 1.05% - 93.3% in Arab countries studies. Additionally, rubella IgM seroprevalence was 1.2% - 98.4% in global studies and 1.5% - 62.3% in Arab countries studies. CMV IgG seroprevalence range was 8.3% - 99.4% in global studies and 4.8% - 97.8% in Arab countries studies. While CMV IgM seroprevalence range in global studies was 0% - 81.1% and 0% - 65% in Arab countries studies. HSV-2 IgG seroprevalence range was 6.66% - 97.6% in global studies and 29.1% - 60.6% in Arab countries studies. While HSV-2 IgM seroprevalence range was 0% - 76.2% in global studies and 3.1% - 73.9% in Arab countries studies.

**Conclusions:** This review indicated that IgG and IgM seroprevalence ranges for ToRCH agents in global, Arab countries and Iraqi studies were with a wide range and indicated that ranges were affected by sample size of study population.
Key words: T. gondii, Cytomegalovirus, Rubella, Herpes simplex virus, Global, Arab countries, Bad obstetrics history, Bad obstetrics outcome.

1. Introduction

Bad obstetrics outcome is health problem with psychological and social impact. The etiology of bad obstetrics outcome is attributed to multiple etiology which included genetic, immunological and/or infections [1]. The frequency of each of the causal group factors varies in developing from developed countries [2-5]. Although in developing countries genetic and immunological factors may play a role as a cause of bad obstetrics history, however, infection is the main cause of such health problem [2-16]. ToRCH agents infection is extensively studied globally and indicated a geographical variations in the seroprevalence of T. gondii, cytomegalovirus (CMV), rubella and herpes simplex virus type 2 (HSV-2) [17,18]. Probably, due to increased health awareness, the prevalence of ToRCH infection may be reduced with time. Thus this review was conducted and compared with a previous one [17,18] to illustrate if there is a change in pattern of ToRCH agents infections in women with bad obstetrics outcome. The sample size was determined for T. gondii, rubella, cytomegalovirus and HSV-2 according to the following equation:

\[ N = \frac{Z^2 \times P(1-P)}{e^2} \]

N= Sample size,
Z= Z score of the confidence level and 95% level used, thus Z=1.96
P= Proportion of the population which has the attribute in the question and estimated from seroprevalence of the previously reported studies for the 4 tested agents,
e= Margin of error, 5% and 10% used to determine the accepted sample size for both error margins.

2. Toxoplasma gondii

A 19 articles of global T. gondii infection [19-37] and 36 articles of infection in Arab countries [14,38-72] (27 studies from Iraq) in women with bad obstetrics history was reviewed, Table 1. For error margin of 10%, the sample size accepted for T. gondii was 92 subjects, while for 5% error margin the accepted sample size was 368 subjects. Thus 42.1% of the reported global studies, 25% of the Arab countries and 25.9% of the Iraqi were their sample sizes below the accepted value. While if ≥ 300 subjects is regarded as the cut-off of accepted sample size, 68.4%, 83% and 88.9% of the reported studies were under the accepted sample size for 5% error margin for global, Arab countries, and Iraqi studies respectively. This do explain the wide range of seroprevalence of T. gondii in the reported studies.

* T. gondii* IgG seroprevalence range in global studies was 5.33% (India, 75 women) [31] to 91.2% (Ethiopia, 176 women) [35], which wider to that reported before [17]. Exclusion of the studies with sample size of < 100 women, the seroprevalence range was 19.44% - 91.2%, while the exclusion of studies with sample size of < 300 women the seroprevalence range was 19.44%-55.2%. This findings indicated that T. gondii seroprevalence is influenced by the study sample size and thus the sero-epidemiology of toxoplasmosis interpreted with caution. The acute T. gondii infection range as determined by IgM detection was 1.2% (Iran, 81 women) [28] to 84.8% (Bangladesh, 91 women) [29] and this rage was wider to previously reported study [17]. However, the exclusion of sample size studies of < 100 women reduced the IgM seroprevalence range to 6%-72.3%, while range of
acute infection was 6%-20.7% if the studies with sample size of < 300 women were excluded, Table 2.

In Arab countries studies the *T. gondii* IgG seroprevalence was 6.8% (Iraq, 190 women) [60] to 81.5% (Iraq, 81 women) [50], which is wider to previously reported studies range [17]. The range was 6.8% - 77.1% after the exclusion of studies with sample size of <100 women and 17.9% - 45% when studies of sample size of < 300 women were excluded. The acute infection was with range of 0.97% (Iraq, 310 women) [38] to 58.1% (Iraq, 122 women) [48] and was the same when the studies of <100 women sample size were excluded and the range decreased to 0.97% to 17.6% after the exclusion of <300 women sample size studies. The present review indicated an increase in the prevalence of remote *T. gondii* in Arab countries, while the acute infection stay with the same pattern. The pattern of increase in the remote infection seroprevalence may be attributed to the presence of latent infection and not a new cases.

In Iraq, *T. gondii* IgM seroprevalence range was 0.97% - 58.1%, while IgG was with 6.84%-81.5% seroprevalence. Additionally, in Iraq, Kirkuk, recent study [71] which included 547 women with history of BOH indicated remote infection seroprevalence of 23% and acute infection of 1.3%. Another study, Duhok, [68] with sample size of 1275 shows IgM seroprevalence of 2.82%. The prevalence reported in these two studies are the most reasonable as the study population within the accepted sample size of ≥ 368 women, Table 3.

3. Rubella

A 24 articles of global rubella infection [23-28,30-37, 73-82] and 16 articles from Arab countries [6,8,41,43,44,60,61,64,67-69,83-87] (14 from Iraq) in women with bad obstetrics outcome were reviewed, Table 1. For error margin of 10%, the sample size accepted for rubella was 94 subjects, while for 5% error margin the accepted sample size was 375 subjects. Thus 25% of the reported global studies, 25% of the Arab countries studies and 28.6% of the Iraqi were their sample sizes below the accepted value. While if ≥ 300 subjects is regarded as the cut-off of accepted sample size, 79.2%, 68.7% and 78.6% of the reported studies were under the accepted sample size for 5% error margin for global, Arab countries, and Iraqi studies respectively. This do explain the wide range of seroprevalence of rubella in the reported studies.

In global studies, rubella IgG seroprevalence range was 3.6% (India, 2007, 1115 women)[75] to 91.2% (Iran,2011, 220 women)[79] indicating a wide range of susceptibility to rubella infection. The lower rubella susceptibility rate was 8.8% in Iran [79] and higher rate (96.4%) was in India [75], which is the same of that reported previously [17]. The same range pattern was achieved following exclusion of sample size of <100 women, however, the range was much less (3.6%-61.3%) when <300 women studies were excluded. The range upper limit of rubella seroprevalence was higher in the present study (91.2%) as compared to previously reported one (78.9%)[17].

The IgM rubella seroprevalence was 1.2% (Iran,2016, 81 women) [28] to 98.4% (India,2018, 200 women)[32] and thus the lower limit was less while the upper limit was higher than the previously reported range [17]. While the acute infection range was 3% -98.4% when <100 women studies were excluded and 3% - 26.8% when <300 women studies exclusion. It is interesting to note that range of acute infection was reduced following exclusion of studies with sample size of <300 women. This indicated that acute infection reported by different studies are under the influence of sample size.
In Arab countries, rubella remote infection was with range of 1.05% [60](Iraq,2011, 190 women) to 93.3% [64](Libya,2008, 692 women). The same range pattern demonstrated when studies of <100 women sample size were excluded, while the range was 67.6% - 93.3% if <300 women sample size studies exclusion. Thus high susceptibility rate was higher in Thi Qar, Iraq (98.95%)(2011) [60], 93.5% in Baghdad (2009) [41, Iraq, and 91.12% in Kirkuk (2007)[61], Iraq. However, other studies in Iraq show susceptibility rate of 65.8% in Baghdad (2009) [83], 45.7% in Waset (2011)[43], 41.3% in Duhok (2015)[69], 24.5% in Kirkuk (2016) [6], 23% in Najaf (2009)[86], 12% in Kirkuk (2015)[87], 10.9% in Kirkuk (2013) [8]. The variability in rubella none immune rate in different Iraqi Governorates may attributed to the disruption of vaccination programs by military activities and population displacement. 

The acute rubella infection range in Arab countries was 1.5% in Kirkuk, (Iraq,2016, 547 women)[6] to 62.3% in Waset ( Iraq,2011, 162 women) [43]. The same range pattern was demonstrated when the studies of <100 women sample size were excluded, however, the range is reduced to 1.5% - 7% when only the studies of ≥300 women included in the analysis. Acute rubella infection rate was 16% in Mousel (Iraq,2010,100 women) [44], 7% in Palestine [67],(2010,1954 women); 4.8% in Baghdad [41](2009, 119 women); 4.66% in Najaf [86], (2009, 300 women); 1.73% in Duhok [68],( 2019, 1275 women); 1.7% in Kirkuk [8],(2013, 293 women); 1.6% in Duhok [69],(2015, 184 women) and 1.5% in Kirkuk [6], (2016, 547 women). Thus the acute rubella infection range between 1.5 and 4.8% in Iraqi community with the exception of Jasim [43] study in Waset which is too much higher than studies in other regions in Iraq, Table 5.

4. Cytomegalovirus.

A 19 articles of global cytomegalovirus infection [23-28,30-34,36,37,75,76,81,88-90] and 18 articles from Arab countries [7,11,41,43,44,51,52,53,60,61,63,68,69,91-95] (15 from Iraq) in women with bad obstetrics outcome were reviewed, Table 1. For error margin of 10%, the sample size accepted for CMV was 90 subjects, while for 5% error margin the accepted sample size was 361 subjects. Thus 36.8% of the reported global studies, 16.7% of the Arab countries studies and 13.3% of the Iraqi studies were their sample sizes below the accepted value. While if ≥ 300 subjects is regarded as the cut-off of accepted sample size, 78.9%, 77.8 and 86.6% of the reported studies were under the accepted sample size for 5% error margin for global, Arab countries, and Iraqi studies respectively. This do suggest that the reported seroprevalence may not present the right rate of infections and explain the wide range of seroprevalence of CMV in the reported studies.

CMV IgG seroprevalence range was 8.3% in Nepal [24](2011,12 women) to 99.4% in China [90](2014,527 women) which is not differ from the previously reported studies [18]. When the studies of sample size of <100 women were excluded, the lower limit of the seroprevalence range increased to 11% [75](India, 2007, 1115 women), while the upper limit is the same. The same pattern demonstrated when the studies of sample size of <300 women were excluded. The acute CMV infection range in global studies was 0% [25](India,2012,86 women) to 81.1% [76](Russia, 2001,127 women) and the lower limit increased to 3.2% [32](India, 2018, 200 women] when studies of sample size of <100 women were excluded while the upper limit not changed. However, after the exclusion of studies with sample size of <300 women only 3 studies remain with IgM seroprevalence of
3.8% [90] in China (2014, 527 women), 4% in India [37] (2015, 1158 women) and 8.4% [26] in India (2003,380 women).

In Arab countries studies, the CMV seroprevalence range was 4.8% in Iraq [41] (2009, 119 women) to 97.8% in Sudan [95](2015, 89 women) with same pattern of the previously reported studies [18]. The range was 4.8% in Iraq [41] to 96.6% in Iraq [7](2014, 293 women) after exclusion of studies with sample size of <100 women. However, after the exclusion of studies with sample size of <300 women, only two studies remain with seroprevalence of 91.2% in Kirkuk, Iraq [11](2014, 547 women) and 95% in Jordan [94](2000, 898 women).

The CMV IgM seroprevalence range in Arab studies was 0% in Sudan [95](2015, 89 women) to 65% in Thi Qar, Iraq [93](2011, 60 women), which is about the of the previously reported range [18]. However, the range was 2.27% in Duhok, Iraq [68](2019, 1275 women) to 60.2% in Waset, Iraq [43](2011, 162 women) after the exclusion of studies with sample size of <100 women. While the CMV acute infection was 1.4% in Jordan [94](2000, 898 women), 3.8% in Kirkuk, Iraq [11](2014, 547 women) and 6 % in Palestine [63](2009, 1954 women) after exclusion of <300 women sample size studies.

5. **Herpes simplex virus type -2**

A 14 articles of global HSV-2 infection [23-26,28,30-35,36,37,88,96] and 6 articles from Arab countries [9,10,41,43,44,69] (5 from Iraq) in women with bad obstetrics outcome were reviewed, Table 1. For error margin of 10%, the sample size accepted for HSV-2 was 96 subjects, while for 5% error margin the accepted sample size was 384 subjects. Thus 42.8% of the reported global studies, 0% of the Arab countries studies and 0% of the Iraqi studies were their sample sizes below the accepted value. While if ≥ 300 subjects is regarded as the cut-off of accepted sample size, 78.6%, 83.3 and 83.3% of the reported studies were under the accepted sample size for 5% error margin for global, Arab countries, and Iraqi studies respectively. This do suggest that the reported seroprevalence in about 2/3 of the reported studies to be interpreted with caution.

In the global, HSV-2 IgG seroprevalence was 6.66% in India [33](2015, 120 women) to 97.6% in India also [32](2018,200 women). The lower limit of this range was lower than previously reported studies, while the upper limit was higher than that reported in earlier studies [18]. The same pattern was demonstrated when the studies of <100 women were excluded. However the exclusion of studies with sample size of <300 women one study show 33.58% seroprevalence, India, (2003, 380 women [26] and second one with 64% seroprevalence, India [37](2015, 1158 women). HSV-2 IgM seroprevalence range was 0% in Iran [28] (2016, 81 women) and India [33](2015, 120 women) to 76.2% in India [36] (2016, 130 women) and thus the upper limit of seroprevalence were much higher that previously reported [18]. Exclusion of studies with sample size of <100 women not change the range, while the exclusion of studies with sample size of <300 women, the seroprevalence was 3% in India [37](2015,1158 women); 3.6% in India [26](2003, 380 women) and 16.8% in India [96](2011, 450 women).

In Arab countries, the HSV-2 IgG seroprevalence range was 29.1% in Iraq [9](2014, 547 women) to 60.6% in Iraq [43](2011, 162 women) and the range was the same even after the exclusion of studies with sample size of <100 women. Only one study reported a prevalence of remote infection of 29.1% [9] which included a sample size of 547 women with BOH from Kirkuk, Iraq. The acute HSV-2 infection in women with BOH range was 3.1% in Kirkuk, Iraq [9] to 73.9% in Waset, Iraq [43] and this indicated that IgM seroprevalence was reduced from 73.9% in 2011 to
3.1% in 2014 in Iraqi population. The acute HSV-2 infection was 11% in Mousel [44] in 2010, 10.9% in Duhok [69] in 2015, 8.1% in Baghdad [41] in 2009, 5.8% in Kirkuk [10] in 2013. Thus a single study that reported high rate of acute HSV-2 of 73.9% and this may not reflected the accurate frequency since all other studies performed in Iraq are with range of 3.1% to 11%. This high seroprevalence may be attributed to cross reaction between HSV-1 and HSV-2 strains rather than accurate HSV-2 acute infection. Both strains are with variable prevalence between primary and recurrent herpetic infections and HSV-2 infection is mostly presented as herpes genitalis and this disease not reach such high prevalence in Iraqi community [97]. Additionally, sequential HSV-1 and HSV-2 infections may interfere with immune response and lead to a variable results which may be influenced by avidity and affinity of the immunoglobulin's [98] and HLA antigens [99]. However, the seroprevalence of HSV-2 acute infections should interpreted with caution since the limited studies number in Iraqi women with BOH and small size number in the performed studies (100-293 women). Hassan et al [9], study in Kirkuk, Iraq which included 547 women with BOH (study population exceeded the lower limit of 384 subjects for HSV-2) indicate a prevalence of 3.1% of acute HSV-2 infection. The prevalence of acute and remote HSV infections may be underestimated due to social reason or may be misinterpreted because of the influence study population selection criteria and study cohort sample size.

6. Conclusions
This review indicated that IgG and IgM seroprevalence ranges for ToRCH agents in global, Arab countries and Iraqi studies were with a wide range and indicated that ranges were affected by sample size of study population.

7. Recommendations
Due to a wide ranges of seroprevalence for both acute and remote T. gondii, rubella, CMV and HSV-2 infections a large scale studies with a minimum sample size of 368 women for T. gondii, 375 women for rubella, 361 women for CMV and 384 women for HSV-2 are warranted. Sound interpretation results and conclusions for the role of these four microorganisms are achieved in a systematic review and meta-analysis and thus the performance of such review is recommended. As bad obstetrics outcome is with high prevalence in Iraqi community and represent a psychological, medical and social health problem illustrate the need to set up a national screening program to clarify the health impact of the problem.

Table.1. Sample size of studies population

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<td>%</td>
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<td>Global (24)</td>
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### Table 2. Seroprevalence of T. gondii, Rubella, CMV, HSV-2 IgG antibodies in women with bad obstetric history in global studies.

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Prevalence Limit</th>
<th>All studies</th>
<th>&lt;100 exclusion</th>
<th>&lt;300 exclusion</th>
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<td></td>
<td>Prevalence %</td>
<td>Country</td>
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<td>Prevalence %</td>
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<td>India</td>
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<tr>
<td></td>
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<td>India</td>
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### Table 3. Seroprevalence of T. gondii, Rubella, CMV, HSV-2 IgM antibodies in women with bad obstetric history in global studies.

<table>
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<tr>
<th>Microbe</th>
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<td>Prevalence %</td>
<td>Prevalence %</td>
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<td>Iran</td>
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### Table 4. Seroprevalence of T. gondii, Rubella, CMV, HSV-2 IgG antibodies in women with bad obstetric history in Arab countries

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<th>Prevalence Limit</th>
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<td></td>
<td>Prevalence %</td>
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<td>Prevalence %</td>
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Table 5. Seroprevalence of T. gondii, Rubella, CMV, HSV-2 IgM antibodies in women with bad obstetric history in Arab countries

<table>
<thead>
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<th>Microbe</th>
<th>Prevalence Limit</th>
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References


