

## INFLUENCE OF *TOXOPLASMA GONDII* INFECTION ON SYMPTOMS AND SIGNS OF PREMENSTRUAL SYNDROME: A CROSS-SECTIONAL STUDY

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Infection with *Toxoplasma gondii* in brain may cause some symptoms that resemble those in women with premenstrual syndrome. To determine the association of *T. gondii* infection with symptoms and signs of premenstrual syndrome, we examined 489 women aged 30–40 years old. Sera of participants were analyzed for the presence of anti-*Toxoplasma* IgG and IgM antibodies using enzyme-linked immunoassays (EIA) and *T. gondii* DNA by polymerase chain reaction (PCR).

Anti-*T. gondii* IgG antibodies were found in 38 (7.8%) of the women studied. Anti-*T. gondii* IgM antibodies were found in 13 (34.2%) of the 38 IgG seropositive women. Logistic regression showed two variables associated with seropositivity to *T. gondii*: presence of diarrhea (odds ratio [OR] = 6.10; 95% confidence interval [CI]: 1.37–27.85;  $P = 0.01$ ) and weight gain (OR = 2.89; 95% CI: 1.37–6.07;  $P = 0.005$ ), and two variables associated with high (>150 IU/ml) levels of IgG against *T. gondii*: presence of diarrhea (OR = 7.40; 95% CI: 1.79–30.46;  $P = 0.006$ ) and abdominal inflammation (OR = 3.38; 95% CI: 1.13–10.10;  $P = 0.02$ ). Positivity to EIA IgG and PCR was positively associated with obesity and negatively associated with joint pain by bivariate analysis.

Our study for the first time reveals a potential association of *T. gondii* infection with clinical manifestations of premenstrual syndrome.

**Keywords:** *Toxoplasma gondii*, seroprevalence, premenstrual syndrome, cross-sectional study

### Introduction

It is estimated that about one third of humanity is infected with the protozoan parasite *Toxoplasma gondii* [1, 2]. Infection with *T. gondii* is zoonotic, and it is most frequently acquired by the ingestion of raw or undercooked meat of *T. gondii*-infected animals containing tissue cysts, or ingestion of food or water contaminated with *T. gon-*

*dii* oocysts shed by cats [3, 4]. Other routes of *T. gondii* infection are vertical [5], organ transplantation [6], and blood transfusion [7]. Most infections with *T. gondii* are asymptomatic [3]. However, some infected individuals develop clinical manifestations of the disease called toxoplasmosis [5]. Individuals suffering from toxoplasmosis may have involvement of lymph nodes, eyes, or central nervous system [3, 8]. A life-threatening toxoplasmosis

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may occur in immunocompromised patients [9]. Infection with *T. gondii* has been linked to psychiatric illnesses, i.e., schizophrenia [10, 11], obsessive-compulsive disorder [10], intermittent explosive disorder [12], depression [13], and generalized anxiety disorder [14]. A number of general symptoms of toxoplasmosis have been described including headache [15, 16], pain and weakness of muscles [16–18], fatigue [16, 19, 20], difficulty concentrating [19], and confusion [13].

Premenstrual syndrome is characterized by recurrent affective, physical, and behavioral symptoms that develop during the luteal menstrual cycle and disappear within a few days of menstruation [21, 22]. A severe form of this syndrome is called premenstrual dysphoric disorder [22, 23]. Clinical manifestations of premenstrual syndrome include fatigue, impaired concentration [24, 25], confusion [24], headache [26], and depression [27]. These clinical features are also observed in toxoplasmosis. It is possible that infection with *T. gondii* in brain might cause or influence some symptoms in women during the premenstrual period. In a recent study, infection with *T. gondii* was associated with out of control feeling or overwhelmed in women suffering from premenstrual dysphoric disorder [28]. However, it is unknown whether *T. gondii* infection might influence symptoms in premenstrual syndrome. Symptoms of premenstrual syndrome might be not only hormonal but also nervous in nature. Infection with *T. gondii* in brain might be linked to clinical manifestations in premenstrual syndrome as occurred in menopause [29]. Since the link of *T. gondii* infection and clinical manifestations of premenstrual syndrome has not been investigated in the past, we investigated the association of *T. gondii* infection with clinical characteristics of premenstrual syndrome in women in the northern Mexican city of Durango.

## Materials and methods

### *Study design and study population*

We performed a cross-sectional study of 489 women who attended general consultations in two public primary healthcare centers: Centro de Salud #2 of the Secretary of Health ( $n = 327$ ) and Clinic of Family Medicine of the Institute of Security and Social Services of State Workers ( $n = 162$ ) in Durango City, Mexico. All women were examined from February to April 2016. Inclusion criteria for enrollment were women aged 30–40 years old who accepted to participate in the study. Socioeconomic status and occupation of the women were not restrictive criteria for enrollment. Pregnancy was an exclusion criterion. Mean age in women studied was  $35.27 \pm 3.47$ .

### *Clinical characteristics of women*

We used a face-to-face questionnaire to record the symptoms and signs of premenstrual syndrome in the women

studied. Clinical data studied were presence of irregular periods, severity of menstruation, suffering from mental illness, vaginal infections, thyroid disease, obesity, arterial hypertension, sleep problems, fatigue, memory lapses, difficulty concentrating, confusion, judgment problems, mood changes, low self-esteem, depression, guilty feeling, increase of fears, panic attacks, anxiety, tension, nervousness, irritability, aggressiveness, lack of interest in daily activities, lack of interest in social relations, out of control feeling or overwhelmed, reduced tolerance to noises and lights, dizziness, headache, migraine, allergy, breast pain, bouts of rapid heartbeat, decrease in muscle power, joint pain, low back pain, muscle tension, clumsiness, tingling extremities, electric shock sensation, bruises, painful periods, edema in ankles, hands or feet, decreased libido, increased libido, dyspareunia, abdominal bloating, gas, abdominal pain, constipation, diarrhea, nausea, abdominal inflammation, appetite disturbance, desire to eat certain food or eat a lot, weight gain, presence of acne, presence of herpes labialis, and respiratory problems.

### *Detection of anti-T. gondii antibodies*

We obtained a serum sample from each woman. Sera were frozen at  $-20\text{ }^{\circ}\text{C}$  until analyzed. Anti-*T. gondii* IgG antibodies were detected in sera with the commercially available enzyme immunoassay (EIA) kit “*Toxoplasma* IgG” (International Immuno-Diagnostics, Foster City, CA, USA). Anti-*T. gondii* IgG antibody levels were expressed as International Units (IU)/ml, and a cut off of  $\geq 8$  IU/ml was used for seropositivity. Sera with anti-*T. gondii* IgG antibodies were further analyzed for anti-*T. gondii* IgM antibodies by the commercially available EIA “*Toxoplasma* IgM” kit (Diagnostic Automation Inc., Calabasas, CA, USA). All assays were performed according to the manufacturer’s instructions.

### *DNA extraction and T. gondii polymerase chain reaction*

Women with positive EIA for *T. gondii* IgG antibodies were further examined to detect *T. gondii* DNA by nested polymerase chain reaction (PCR). Extraction of DNA was performed from whole blood according to a protocol described by Iranpour and Esmailizadeh (<http://www.protocol-online.org/prot/Protocols/Rapid-Extraction-of-High-Quality-DNA-from-Whole-Blood-Stored-at-4-C-for-Long-Period-4175.html>). We used a PCR protocol and two pairs of primer directed against the B1 gene of *T. gondii* as described elsewhere [30]. This protocol was previously tested and showed high specificity and sensitivity: 0.01 to 0.02 fg of the target DNA in the presence of 1  $\mu\text{g}$  of contaminating negative human DNA was detected by PCR [31]. PCR products were electrophoresed with agarose gels, stained with ethidium bromide, and visualized by ultraviolet transillumination.

### Statistical analysis

Analysis of results was performed by using the following software: SPSS 15.0 (SPSS Inc. Chicago, Illinois), Microsoft Excel, and Epi Info 7. For calculation of the sample size, we used: a) a reference seroprevalence of 6.1% [32] as the expected frequency for the factor under study, b) 200,000 as the population size from which the sample was selected, c) a 2.2% of confidence limits, and d) a 95% confidence level. The result of the sample size calculation was 454 subjects. We assessed the association of *T. gondii* seropositivity and the clinical characteristics of women with the Pearson's chi-squared test or the two-tailed Fisher's exact test (when values were small). We included in the multivariate analysis only variables with a *P* value  $\leq 0.10$  obtained in the bivariate analysis. Odds ratio (OR) and 95% confidence interval (CI) were calculated by multivariate analysis using logistic regression with the Enter method. Statistical significance was set at a *P* value  $< 0.05$ .

### Ethical aspects

This study was approved by the Ethics Committee of the General Hospital of the Secretary of Health in Durango City, Mexico. Participation was voluntary, and the purpose and procedures of this study were explained to all participants. Furthermore, a written informed consent was obtained from each participant.

## Results

Anti-*T. gondii* IgG antibodies were found in 38 (7.8%) of the 489 women studied. Of the 38 anti-*T. gondii* IgG positive women, 22 (57.9%) had IgG levels  $> 150$  IU/ml, 1 (2.6%) between 100 and 150 IU/ml, and 15 (39.5%) between 8 and 99 IU/ml. Anti-*T. gondii* IgM antibodies were found in 13 (34.2%) of the 38 IgG seropositive women. DNA of *T. gondii* was detected in six (15.8%) of the 38 women with IgG antibodies against *T. gondii*.

Seropositive women showed from four to 41 (mean:  $15.1 \pm 8.5$ ) signs or symptoms of premenstrual syndrome. Seronegative women ( $n = 451$ ) had from one to 45 (mean:  $16.7 \pm 9.1$ ) signs or symptoms of premenstrual syndrome. Mean number of signs or symptoms in seropositive women was similar to that found in seronegative women ( $P = 0.28$ ).

Bivariate analysis of clinical characteristics of premenstrual syndrome and IgG seropositivity to *T. gondii* showed ten variables with a *P* value less than 0.10: confusion, allergy, low back pain, tingling extremities, electric shock sensation, increased libido, abdominal bloating, gas, diarrhea, and weight gain. Other clinical characteristics of premenstrual syndrome showed *P* values equal to or higher than 0.10 by bivariate analysis. *Table 1* shows results of bivariate analysis of a selection of clinical data of premenstrual syndrome and IgG seropositivity to *T. gondii*. Further analysis by logistic regression of variables with *P* value less than 0.10 obtained by bivariate analysis

**Table 1.** Results of bivariate analysis of a selection of premenstrual clinical characteristics of women and IgG seropositivity to *T. gondii*

Characteristic	Women tested		Prevalence of <i>T. gondii</i> infection		<i>P</i> value
	No.	No.	%		
<b>Obesity</b>					
Yes	192	18	9.4	0.28	
No	297	20	6.7		
<b>Arterial hypertension</b>					
Yes	46	6	13.0	0.14	
No	441	31	7.0		
<b>Confusion</b>					
Yes	99	3	3	0.04	
No	389	35	9		
<b>Irritability</b>					
Yes	240	15	6.3	0.21	
No	249	23	9.2		
<b>Reduced tolerance to noises and lights</b>					
Yes	131	6	4.6	0.11	
No	358	32	8.9		
<b>Dizziness</b>					
Yes	172	9	5.2	0.12	
No	317	29	9.1		

**Table 1.** (cont'd)

Characteristic	Women tested		Prevalence of <i>T. gondii</i> infection		P value
	No.	No.	%		
<b>Headache</b>					
Yes	278	23	8.3		0.63
No	211	15	7.1		
<b>Migraine</b>					
Yes	124	7	5.6		0.30
No	365	31	8.5		
<b>Allergy</b>					
Yes	118	5	4.2		0.10
No	371	33	8.9		
<b>Breast pain</b>					
Yes	234	15	6.4		0.28
No	255	23	9		
<b>Bouts of rapid heart beat</b>					
Yes	115	5	4.3		0.11
No	373	33	8.8		
<b>Decrease in muscle power</b>					
Yes	176	10	5.7		0.19
No	313	28	8.9		
<b>Joint pain</b>					
Yes	217	13	6		0.23
No	270	24	8.9		
<b>Low back pain</b>					
Yes	308	18	5.8		0.03
No	181	20	11		
<b>Tingling extremities</b>					
Yes	200	10	5		0.05
No	289	28	9.7		
<b>Electric shock sensation</b>					
Yes	131	5	3.8		0.04
No	358	33	9.2		
<b>Edema in ankles, hands, or feet</b>					
Yes	111	7	6.3		0.49
No	375	31	8.3		
<b>Decreased libido</b>					
Yes	151	9	6		0.30
No	334	29	8.7		
<b>Increased libido</b>					
Yes	34	0	0		0.09
No	449	38	8.5		
<b>Abdominal bloating</b>					
Yes	108	6	5.6		0.00
No	381	32	8.4		
<b>Gas</b>					
Yes	30	5	16.7		0.07
No	459	33	7.2		

**Table 1.** (cont'd)

Characteristic	Women tested	Prevalence of <i>T. gondii</i> infection		P value
	No.	No.	%	
Constipation				
Yes	123	6	4.9	0.16
No	366	32	8.7	
Diarrhea				
Yes	14	3	21.4	0.08
No	475	35	7.4	
Abdominal inflammation				
Yes	48	6	12.5	0.24
No	441	32	7.3	
Weight gain				
Yes	219	23	10.5	0.03
No	267	14	5.2	

showed that only two variables were associated with seropositivity to *T. gondii*: presence of diarrhea (OR = 6.10; 95% CI: 1.37–27.85;  $P = 0.01$ ) and weight gain (OR = 2.89; 95% CI: 1.37–6.07;  $P = 0.005$ ) (Table 2).

Bivariate analysis of clinical characteristics of premenstrual syndrome and high (>150 IU/ml) IgG levels to *T. gondii* showed only six variables with a  $P$  value less than 0.10: low self-esteem, irritability, low back pain, tingling extremities, diarrhea, and abdominal inflammation. Further analysis by logistic regression of these variables

with  $P$  values less than 0.10 obtained by bivariate analysis showed that two variables were associated with high levels of IgG against *T. gondii*: presence of diarrhea (OR = 7.40; 95% CI: 1.79–30.46;  $P = 0.006$ ) and abdominal inflammation (OR = 3.38; 95% CI: 1.13–10.10;  $P = 0.02$ ) (Table 3).

With respect to the association of premenstrual clinical manifestations and seropositivity of both IgG and IgM anti-*T. gondii*, bivariate analysis showed no significant associations, and only the variables tingling extremities and diarrhea showed borderline ( $P = 0.05$ ) associations.

**Table 2.** Multivariate analysis of selected premenstrual clinical characteristics of women and their association with *T. gondii* infection

Characteristic	Odds ratio	95% confidence interval	P value
Confusion	0.38	0.11–1.34	0.13
Allergy	0.50	0.18–1.38	0.18
Low back pain	0.48	0.23–1.02	0.05
Tingling extremities	0.78	0.33–1.86	0.58
Electric shock sensation	0.52	0.17–1.58	0.25
Abdominal bloating	0.89	0.33–2.34	0.81
Gas	2.60	0.79–8.57	0.11
Diarrhea	6.10	1.37–27.85	0.01
Weight gain	2.89	1.37–6.07	0.005

**Table 3.** Multivariate analysis of selected premenstrual characteristics and their association with high (>150 IU/ml) levels of IgG to *T. gondii*

Characteristic	Odds ratio	95% confidence interval	P value
Low self-esteem	0.58	0.19–1.74	0.33
Irritability	0.67	0.24–1.86	0.44
Low back pain	0.53	0.20–1.36	0.18
Tingling extremities	0.62	0.21–1.81	0.38
Diarrhea	7.40	1.79–30.46	0.006
Abdominal inflammation	3.38	1.13–10.10	0.02

To avoid bias and due to a small number of cases with IgM seropositivity, no further regression analysis with these variables was performed.

Concerning the results of the positivity to both IgG antibodies against *T. gondii* and DNA of *T. gondii* by PCR, women with obesity showed a significantly ( $P = 0.03$ ) higher prevalence of *T. gondii* (5/192: 2.6%) than women without obesity (1/297: 0.3%) whereas women with joint pain showed a significantly ( $P = 0.03$ ) lower prevalence of *T. gondii* (0/217) than women without joint pain (6/270: 2.2%).

## Discussion

Premenstrual syndrome has a number of signs and symptoms also observed in toxoplasmosis. Therefore, we hypothesized that *T. gondii* infection may have an influence on clinical manifestations of premenstrual syndrome. As far as we know, the association between *T. gondii* infection and signs and symptoms of premenstrual syndrome has not been assessed yet. Therefore, this study aimed to determine whether infection with *T. gondii* was associated with clinical characteristics of premenstrual syndrome in women in Durango City, Mexico. We found that women seropositive for *T. gondii* had a similar mean number of signs or symptoms of premenstrual syndrome than seronegative women. Results suggest that infection with *T. gondii* does not influence on the number of clinical manifestations of premenstrual syndrome in general. However, logistic regression showed in particular that infection with *T. gondii* is associated with specific clinical characteristics of premenstrual syndrome. Thus, results suggest that *T. gondii* infection may influence qualitatively on clinical manifestations of premenstrual syndrome. Remarkably, both IgG seropositivity to *T. gondii* and high levels of IgG against *T. gondii* were associated with the presence of diarrhea. It is not clear why infection with *T. gondii* was associated with diarrhea during the premenstrual period. Diarrhea is a well-known clinical sign included within the physical features of premenstrual syndrome [33]. In a Chinese study about prevalence of premenstrual syndrome in women at reproductive age, researchers found diarrhea as the fourth most frequent clinical characteristic in premenstrual syndrome just after irritation, depression, and anxiety [33]. In addition, in a prevalence study about the menstrual cycle and its effect on inflammatory bowel disease and irritable bowel syndrome, Kane et al. found that women with Crohn's disease were more likely to report increased gastrointestinal symptoms during menstruation, being diarrhea the clinical feature reported most often [34]. In a recent study, Zhang et al. reported that Chinese women suffering from both diarrhea-predominant irritable bowel syndrome and premenstrual syndrome had more severe bowel symptoms [35]. On the other hand, infection with *T. gondii* may lead to diarrhea in humans and animals [36]. Presence of diarrhea in *T. gondii* infected individuals has been unusually reported. However, the link between

infection with *T. gondii* and diarrhea in humans has been scantily studied. A case of gastric toxoplasmosis with diarrhea in a man with acquired immunodeficiency syndrome was reported [37]. Similarly, a case of toxoplasmic colitis with diarrhea where microorganisms were identified in the colonic mucosa and confirmed by immunohistochemistry was reported [38]. In animals, severe or fatal toxoplasmosis cases with diarrhea have been reported in cats [39, 40] and a valley quail [41]. It is unclear how frequent diarrhea occurs in immunocompromised and immunocompetent subjects. We may hypothesize that *T. gondii* may affect intestines of women during the premenstrual period perhaps under a hormonal influence leading to diarrhea. It is also possible that *T. gondii* causes diarrhea by affecting enteric neurons. Experiments in rats have shown that infection with *T. gondii* causes changes in myenteric neurons of the jejunum, i.e., atrophy of myenteric neurons along with increased weight gain in rats at 30 days of infection, or hypertrophy of myenteric neurons along with normal weight gain in rats at 90 days after infection [36]. Interestingly, IgG seropositivity to *T. gondii* was associated with weight gain. It is not clear why women who have gained weight had a higher seroprevalence of *T. gondii* infection than those without weight gain. Experimental infections of *T. gondii* have showed weight gain in rats after 30 days of infection [36]. In humans, *T. gondii* infection has been associated with weight gain in pregnant women [42]. In addition, both *T. gondii* seroprevalence and high IgG anti-*T. gondii* antibody levels have been associated with obesity [43]. In fact, results of the positivity to both IgG antibodies against *T. gondii* and DNA of *T. gondii* in this study showed that women with obesity had a significantly higher prevalence of *T. gondii* than women without obesity. On the other hand, women with joint pain showed a significantly lower prevalence of *T. gondii* than women without joint pain. This finding suggests that *T. gondii* was not an important factor for joint pain in the women studied.

Logistic regression analysis also showed that high levels of IgG against *T. gondii* were associated with abdominal inflammation. *T. gondii* may cause inflammation in organs and tissues in the abdomen, as observed in experimental infections in mice [44]. Therefore, the presence of this clinical feature may suggest an active immune reaction against *T. gondii* in abdomen.

Limitations of our study included small sample size of the women studied and a low prevalence of IgG, IgM, and PCR positivity. However, strengths of our study include that women were studied from two health centers of Durango City and that we used detection of DNA of *T. gondii* to increase the evidence of *T. gondii* exposure.

## Conclusions

The present study for the first time points towards an association of *T. gondii* infection with clinical manifestations of premenstrual syndrome, i.e., physical symptoms. Re-

sults warrant further research of the role of *T. gondii* on clinical manifestations of premenstrual syndrome.

## Competing interests

The authors declare that no competing interests exist.

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