The association between *Toxoplasma gondii* infection and postpartum blues

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Abstract

Introduction and Aim: *Toxoplasma gondii* is an intracellular protozoan parasite infecting approximately 30% of the global human population. It has often been suggested that chronic infection with *T. gondii* is related to personality changes and various mental disorders including depression. It is not known whether this includes post-partum blues or depression. In this study, we test the hypothesis that there is a relationship between *T. gondii* infection and post-partum blues by measuring the association between infection and postpartum blues.

Methods: A total of 475 Chinese women who have just given birth were detected serology for *Toxoplasma* IgG and IgM antibodies, and evaluated the degree of depression by Hamilton Depression Scale (HAMD) score. Data were analyzed by Chi-square or Fisher's Exact tests using SPSS software.

Results: We found an overall *Toxoplasma* seroprevalence of 5.68% (27/475; 95% CI: 3.59 - 7.77) which was broken down into a prevalence of 6.60% (7/106; 95% CI: 1.80 – 11.41) in mothers with post-partum blues and 5.42% (20/369; 95% CI: 3.10 – 7.74) in non-affected mothers. There was no significant association between infection and post-partum blues ($p = 0.64$).

Conclusion: The results suggest that there is no relationship between *T. gondii* infection and postpartum blues, at least in this sample of patients from China.

Key words: *Toxoplasma gondii*, postpartum blues, seroprevalence, newborn, puerpera, Hamilton Depression Scale

1. Introduction

Toxoplasma gondii, which infects 30% to 50% of the global population, is one of the most common parasites affecting both healthy and immunocompromised humans (Furtado et al., 2011; Klaren and Kijlstra, 2002; Prandota, 2014). It is believed that *T. gondii* infection, termed toxoplasmosis, in immunocompetent individuals is generally considered asymptomatic (Halonen and Weiss, 2013). However, considering an extended set of disease conditions, evidence is accumulating that strongly suggests that this parasite may be implicated in neurodegenerative diseases and are gradually emerging as a global health threat (Nissapatorn, 2010; Furtado et al., 2011; Torgerson and Mastroiacovo, 2013). For example, chronic infection with *T. gondii* is more frequent in individuals with schizophrenia than in psychiatrically healthy controls, as indicated in several studies from different countries (Torrey and Yolken, 2001, 2003; Torrey et al., 2007). In addition, a number of studies have also demonstrated that *T. gondii* seropositivity is related to personality changes and various mental disorders including development of suicidal tendencies, obsessive compulsive disorder, bipolar disorder, and depression (Sutterland et al., 2015; Arling et al., 2009; Hinze-Selch et al., 2010; Ling et al., 2011; Okusaga et al., 2011; Tedla et al., 2011).

Depressive disorder, also known as clinical depression, is a mood disturbance characterized by changes in mood, and loss of interest, pleasure, cognitive function, sleep, appetite, or energy level (Pratt and Brody, 2008). Furthermore, clinical depression is commonly associated with significant morbidity and mortality (Hsu et al., 2014). It has been reported that, during 2009-2012, about 7.6% Americans aged 12 and over had

depression (Pratt and Brody, 2014). However, the prevalence of mood disorders in China appears to be lower than that found in North America and Western Europe. Data indicated that the prevalence of major depressive disorders in China was at 1.96% in Kunming, 5.3% in Beijing, 3.6% in Shenyang and 1.15% in Jiangsu, respectively (Hu, 2003; Lu et al., 2008; Ma et al., 2009; Qin et al., 2008). Moreover, depression is also considered a common mental health problem among women of childbearing age, with a higher prevalence rate ranging from 10 to 32% (Ertel et al., 2011; Wang et al., 2011). Postpartum nonpsychotic depression is the most common complication of childbirth, affecting approximately 10-15% of women, and represents a considerable health problem affecting women and their families. A mother's ongoing depression can contribute to later emotional, behavioral, cognitive and interpersonal problems in the offspring. Because of these serious consequences, exploring potential factors, early diagnosis and intervention treatment of postpartum illnesses are imperative for the health and well-being of mother and child (Robertson et al., 2004). Previous studies have consistently demonstrated common significant predictors of postpartum depression as follows: experiencing depressed moods or anxiety during pregnancy, life events, no social support and socioeconomic status (Patel et al., 1999; Bartley, 1994; Beck, 2001; Brugha et al., 1998; Neter et al., 1995). Furthermore, studies have shown that latent *T. gondii* infection is associated with symptoms of depression during pregnancy (Groer et al., 2011).

Post partum blues are self-limiting depression commonly found within one week soon after delivery, and are considered as important indicators of depression (Maliszewska et al., 2016; Reck et al., 2009). However, it remains unknown whether

parasite infection may play an important role in postpartum blues. We are interested in the relationship between chronic latent *T. gondii* infection and the development of postpartum blues in new mothers. Using a cohort of new mothers in China, we aim to investigate this globally important question and to test the hypothesis that *T. gondii* infection may be more frequent and/or more intense in patients with major postpartum depression compared with psychiatrically healthy controls.

2. Materials and Methods

Participants and Questionnaires

In this study, blood samples were collected from 475 women one week after delivery (puerpera) in the First Affiliated Hospital of Guangzhou Medical University, China. Mothers were randomly selected for this study and all those selected were tested by a psychiatrist irrespective of any obvious signs of depression. Due to the low prevalence of *Toxoplasma* infection in China, the sample size needed to ensure sufficient statistical power (minimum n=442) was calculated using a previously published prevalence of 7.8% (ONIHPDCSS, 2005). Furthermore, this value concurred with our previous studies (collated from greater than 120000 pregnant women (1990 - 2010)) that recorded the seroprevalence of *Toxoplasma* to be less than 10% in this demographic group (Gao et al., 2012). Sera were separated by centrifugation and stored at -80 °C until serological testing. All participant information was obtained (usually 2-3 days postpartum) through questionnaires and

recorded. These included participants' age, occupation, relevant eating habits (consumption of raw or undercooked meat – past and current) and cat contact (current and past cat ownership, cats in the same household, playing closely with cats, cleaning cat litter).

Ethical Approval

This study was approved by the Medical Science Ethical Committee of Sun-Yet San University and the First Affiliated Hospital of Guangzhou Medical University. All enrolled participants were informed about the objectives of the study, and written informed consent was obtained from all of them.

Hamilton Depression Scale (HAMD) score

Psychiatrists evaluated the degree of depression according to the HAMD (Hamilton, 1967) depression scale score, clinical symptoms and the exclusive criteria. A HAMD score of <8, was considered normal; 8-19, indicated mild depression; 20-34, indicated medium depression; and ≥35, was considered as severe depression. All patients with mild, medium and severe depression were considered as postpartum blues cases according to their clinical signs.

Serological Tests

All serum samples were tested for anti-*T. gondii* antibodies - both IgM (indicator of acute infection) and IgG (indicator of chronic infection) using a commercially available

enzyme-linked immunosorbent assay (ELISA) kit (Modern Gaoda Biotechnology Company, Beijing) according to the manufacturer's instructions (accuracy > 96.7%, detection limit of 5 IU/ml and coefficient of variation < 15%.). Positive, negative and cutoff serum controls were included in every plate. The optical densities (ODs) were measured at 450 nm in a microplate reader (Thermo Scientific Multiskan FC, Thermo Scientific, China). All serum samples were run in triplicate. Samples with ODs above the cutoff value were considered as serologically positive.

Statistical Analysis

Data on the prevalence of anti-*T. gondii* antibodies and depression symptoms in population groups were analyzed by Chi-square or Fisher's Exact tests using SPSS software. Risk factors of occupation, serolopositivity for *T. gondii*, raw meat consumption and a significant contact with cats were evaluated by using odds ratios (ORs), together with their corresponding 95% confidence intervals (95% CIs). Bias corrected ORs were obtained by adding 0.5 to each data point.

3. Results

The collection of 475 serum samples taken from the new mothers was examined for anti-*T. gondii* IgG and IgM antibodies using enzyme-linked immunosorbent assay (ELISA). All 475 puerpera samples were IgM negative, suggesting that no current infection of the parasite was occurring. Anti-*Toxoplasma* positive IgG was detected in

158 27 (5.68%; 95% CI: 3.59 - 7.77) of the 475 serum samples as shown in Table 1.

159 Hamilton Depression Scale scores in the same set of new mothers were
160 determined. All patients with mild, medium and severe depression were considered as
161 true cases having postpartum blues according to their clinical signs. There was no
162 significant association between *T. gondii* seropositivity and postpartum blues (p =
163 0.643; n = 475). When broken down, the seroprevalence of *T. gondii* was slightly
164 higher in the new mothers with postpartum blues (6.60%, 7/106; 95% CI: 1.80 –
165 11.41) than that in the remaining normal group (5.42%, 20/369; 95% CI: 3.10 – 7.74)
166 but this was not significant (p = 0.643, OR = 1.234[0.507-3.002]) – see Table 1.

167

168 To further explore the hypothesis that *T. gondii* infection is related to postpartum
169 depression, it is possible that there is a quantitative influence on the relationship. For
170 example, *T. gondii*-positive new mothers might show higher scores on the depression
171 scale when compared to their uninfected counterparts. To examine that, we further
172 analyzed the relationship between *T. gondii* immunoglobulin G (IgG) optical densities
173 (ODs) and the Hamilton Depression Scale (HAMD) scores. We found that depression
174 scores were not significantly different (p = 0.873) between the positive and negative
175 *T. gondii* optical density (ODs) groups in the entire population of new mothers
176 (n=475) (Figure S1A). In addition, as shown in Figure S1B, the *T. gondii* positive
177 group (n = 27) did not show a positive correlation of *T. gondii* ODs (serointensity)
178 with the Hamilton Depression Scale (HAMD) scores (p = 0.214). Although we
179 recognize that the sample sizes in this breakdown are small, these analyses further

support the prevalence data that suggests there is no significant association between infection and postpartum blues.

According to previous reports, the probability of becoming infected with *T. gondii* increases with age because the infection is ubiquitous and the probability of being exposed to infection increases with age (Hinze-Selch et al., 2007). Therefore, we analysed the seroprevalence of *T. gondii* in the 475 pregnant women in different age groups (Table 2) and the results demonstrated that there was no significant correlation between *T. gondii* seroprevelence and age ($p = 0.872$). Therefore, the results from our current study demonstrate that anti-*T. gondii* seropositivity is not age dependent in this sample of mothers. One possible reason for the results is that the age range of pregnant women is too narrow to reveal this effect and we also recognize that the sample sizes in this breakdown are small. We also found that the incidence of postpartum blues did not show a significant relationship with age of the mothers ($p = 0.610$) (Table 2) although again our numbers of individuals were small.

To investigate whether there was any association between the prevalence of either post-partum blues or *T. gondii* seropositivity, analyses were conducted on a breakdown of occupational status of the participants based on the questionnaire data (Table 3). The participants were categorized into 10 occupational type groups: farmers (most are less well educated and live in rural areas), workers (born in the city, most are less well educated and tend to be employed in factories and companies), medical staff (well-educated, with a good understanding of health and hygiene),

managers (born in the city and most are well-educated but may not have an understanding of health issues), teachers (well-educated, have health awareness but may not have detailed knowledge), business staff (may or may not be well-educated, most of them do not have an understanding of health issues), self-employed (may or may not be well-educated, most of them do not have an understanding of health issues), housewives (most are less well educated and are responsible for the routine work in the family), unemployed (most are less well educated and have been out of work for the past few years) and others (no details of their working status). There was no significant difference in anti-*T. gondii* seroprevalence ($p = 0.971$) and incidence of postpartum blues ($p = 0.918$) between the different occupational groups. We again recognize that there are small numbers of individuals sampled in this analysis.

We also investigated traditional risk factors associated with the seroprevalence of *T. gondii* and prevalence of postpartum blues in new mothers (Table 4). Surprisingly, our analyses showed that contact with cats and consumption of raw or uncooked meat, two generally well established risk factors, were not associated with *T. gondii* seropositivity ($p = 0.766$ and 0.357, respectively). By contrast, consumption of raw or uncooked meat was significantly associated with increased prevalence of postpartum blues among new mothers ($p = 0.007$) albeit based on small numbers. The prevalence of postpartum blues in the group of participants that consumed raw meat was significantly higher than the group that did not consume raw meat (32.97% [30/91] vs 19.79% [76/394], OR: 1.993, 95% CI: 1.204-3.229). In addition, the association between cat contact and prevalence of postpartum blues in new mothers is

close to significance at $p = 0.061$ suggesting that a larger sample size would be useful to explore this further. The prevalence in the cat-contact group (29.47%, 28/95) is slightly higher than that of the non-cat-contact group (20.53%, 78/380; OR: 1.618; 95%CI: 0.975-2.685).

4. Discussion

Depression during the perinatal period does not only have a significant impact on quality of life of the mother (Darcy et al., 2011), but also influences the developmental outcomes of their children (Ertel et al., 2011; Turney, 2012). Many previous studies have tried to identify the role of *T. gondii* in general neurological and psychiatric conditions in humans (Torrey et al., 2007; Arling et al., 2009; Groer et al., 2011; Hinze-Selch et al., 2010; Prandota, 2014; Sutterland et al., 2015). Clear associations seem to be emerging for schizophrenia (Torrey et al., 2007, Sutterland et al., 2015) and probable associations with attempted suicide (Arling et al., 2009) and personality disorders (Hinze-Selch et al., 2010). A major detailed meta-analysis provided convincing evidence of an association between *T. gondii* infection and schizophrenia but also suggested links with bipolar disorder, obsessive-compulsive disorder, addiction but not for major depression (Sutterland et al., 2015). Several other studies also demonstrated no link with major depression (Gale et al 2014; Gale et al 2016; Suvisaari et al 2017). Some studies have focused specifically on prenatal depression. Groer et al (2011) conducted a study on women during pregnancy and showed that there was no significant difference in *T. gondii* seroprevalence between

mothers with prenatal depression and controls. However, they observed that higher titers of *T. gondii* IgG antibody were positively correlated with increased measures of depression and anxiety (as measured by the Profile of Mood States –POMS – method). Furthermore, other studies have shown no association between the seroprevalence of *T. gondii* and prenatal depression in both low (5.25%) (Alvarado-Esquival et al., 2017) and in high (59%) (Nourollahpour Shiadeh et al., 2016) seroprevalence of infection. The latter study demonstrated that there was an association of increasing *T. gondii* IgG titer with increasing depression score (as measured by the Iranian version of the Edinburgh Post-Partum Depression Scale (EPDS) (Nourollahpour Shiadeh et al., 2016) however, no such association was found in the former one (EPDS, Mexican version) (Alvarado-Esquival et al., 2017). The consensus seems to be emerging that there is no association of *T. gondii* seroprevalence and prenatal depression although conflicting evidence exists with regard to association between serointensity and depression severity score. To our knowledge, no studies have been conducted that investigate any possible association between *T. gondii* infection and postpartum depression or postpartum blues, the latter being considered as sa elf-limiting mild depression commonly found in new mothers a few days after delivery (Maliszewska et al., 2016). In our study, we report the first investigation addressing this question. Using a cohort of 475 participants, we analyzed the association between *T. gondii* infection and postpartum blues. Our results show clearly that overall there was no significant association between seropositivity of *T. gondii* and new mothers with postpartum blues. This lack of

association, between seroprevalence and postpartum blues, follows the same pattern revealed by studies on prenatal depression during pregnancy, described above, and supports a consensus that there may be no general association with perinatal depression. Furthermore, when we broke our data down further, we found no evidence of association between increasing IgG titer and depression severity score (as measured by the Hamilton Depression Scale). Although we do recognize that the low prevalence of *T. gondii* infection and prevalence of postpartum blues in our cohort reduces the power of such a detailed analysis. Again, though, our data, on the quantitative association between *T. gondii* IgG titer and depression score, is consistent with some other studies (Alvarado-Esquival et al., 2017). However, both our results and those of Alvarado-Esquival et al. (2017) conflict with those of Nourollahpour Shiadeh et al. (2016) on this quantitative association. This could be due, in part, to differences in either depression scoring methods or due to differing backgrounds of the prevalence of parasite infections. The former is unlikely, since both the studies of Alvarado-Esquival et al (2017) and Nourollahpour Shiadeh et al (2016) used variants of the EPDS. However, the background of prevalences in each study differed considerably (5.25% and 59%) with the former corresponding to our reported prevalence in our cohort (5.68%) suggesting that this could be a factor. In China, the seroprevalence of *T. gondii* in the Chinese population (~10%) is much lower than that in some parts of South America and Europe (50%-80%) (Fromont et al., 2009; ONIHPDCSS, 2005). In pregnant mothers in China, the prevalence is also low (~10%) and corresponds to the general population levels (Gao et al., 2012). In this

290 study, the prevalence followed the typical low level found in China (5.68%). The
291 correspondence between the background prevalence in the study of Alvarado-
292 Esquival et al (2017) and our study, both finding no quantitative association between
293 *T. gondii* IgG titer and depression scores, supports a view that the conflict with the
294 study of Nourollahpour Shiadeh et al (2016) could be related to prevalence. This also
295 raises the issue that studies conducted in areas of low parasite prevalence may need
296 substantially larger samples sizes to achieve the required power to conduct more
297 detailed breakdowns of interactions. The question is clearly complex and it is
298 possible that other interacting factors may confound any role that *T. gondii* may
299 possess in perinatal depression.

300 If *T. gondii* infection is not the main factor causing postpartum blues nor
301 depression in new mothers, are there any other factors, such as age, which could
302 influence the seroprevalence of *T. gondii* or baby blues. Seroprevalence of *T. gondii*
303 has been shown to that increase with age (Hinze-Selch et al., 2007). For instance, in
304 the Israeli population, the seroprevalence rate of *T. gondii* is 7.6% in the 10-19 years
305 group, 31.4% in the 50-59 years group, followed by a sharp increase to 58.1% in the
306 ≥ 60 years group (Markovich et al., 2014). In addition, similar results have been
307 observed in pregnant women in Poland, where mean prevalence of IgG antibodies
308 was seen at 40.6% and increased with age with a yearly seroconversion rate of 0.8%
309 (95% CI: 0.6-1.0, $p< 0.001$) (Nowakowska et al., 2014). However, in an older study,
310 Ye and Zou (1993) reported that seroprevalence of *T. gondii* in new mothers in China
311 did not increase with age. In our study of Chinese new mothers, no age prevalence

312 increase was observed (p = 0.610). These latter studies may be explained by bias due
313 to a relatively narrow age window found in cohorts of new mothers/women in
314 pregnancy.

315 In our study, we investigated the influence of occupation, association with cats
316 and consumption of raw meat on the relationship between *T. gondii* infection and
317 postpartum blues. Our data shows no significant association between these risk
318 factors and infection or postpartum blues. However, we recognise that once our data
319 was broken down to these levels of detail, sample sizes were small and future studies
320 may be needed with increased statistical power to dissect these questions.

321 To our knowledge, this is the first study that has investigated the association of
322 *T. gondii* infection with postpartum blues in new mothers. We found no association
323 between the seroprevalence of *T. gondii* and clinically depressed participants. Other
324 studies, that have focused on prenatal depression during pregnancy, have also failed
325 to detect significant association with *T. gondii* seroprevalence. We propose, therefore,
326 that, the current studies are tending towards a consensus that shows little support for
327 the involvement of this parasite in perinatal depression in general. However, perinatal
328 depression has a complex etiology and future larger scale studies may be required to
329 unpick further detail and to investigate specific epidemiological interactions.

330

331 **Authors' contributions**

332 Jiang-Mei Gao and Zhao-Rong Lun they were responsible for designed research;
333 Jiang-Mei Gao and Yi-Ting Xie conducted research; Zhi-Hui He provided essential

materials; De-Hua Lai conducted analyzed data or performed statistical analysis; Jiang-Mei Gao, Geoff Hide, De-Hua Lai and Zhao-Rong Lun wrote paper.

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Conflict of interest

The authors report no conflict of interest.

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Table 1. Detection of anti-*Toxoplasma gondii* IgM and anti-*T. gondii* IgG antibodies in new mothers with baby blue and in the control group.

	Toxoplasma gondii IgM	*Toxoplasma gondii* IgG		
	Total	Total	postpartum blues	Normal
No. examined	475	475	106	369
No. positive	0	27	7	20
Prevalence(95% CI), %	0	5.68(3.59-7.77)	6.60(1.80-11.41)	5.42(3.10-7.74)
OR (95% CI)	—	—	Ref.	1.234[0.507-3.002]
P-value	—	—	0.643	

Table 2. Association between age, seropositivity of *Toxoplasma gondii* and prevalence of post-partum blues in new mothers. * Figures in brackets indicate the number of cases of new mothers with both depression and *T. gondii* seropositivity.

Age	*Toxo* IgG					post-partum blues				
	No. examined	No. positive (cases with depression *)	Prevalence (95% CI), %	OR (95% CI)	*P*-value	No. examined	No. positive (cases with depression *)	Prevalence (95% CI), %	OR (95% CI)	*P*-value

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<25	57	2 (0)	3.51(0-8.43)	Ref.	0.872	57	14	24.56 (13.04-36.08)	Ref.	0.610

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25-30	274	17 (5)	6.20(3.33-9.08)	(1.81 (0.40 8-8.102)		274	63	22.99 (17.98-28.01)	0.917 (0.47 1-1.784)	

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30-35	113	6 (2)	5.31(1.11-9.51)	1.542(0.301-7.894)		113	25	22.12(14.35-29.90)	0.873(0.413-1.845)
>35	31	2 (0)	6.45(0-15.61)	1.897(0.254-14.167)		31	4	12.90(0.40-25.40)	0.455(0.136-1.527)
All	475	27 (7)	5.68(3.59-7.77)			475	106	22.32(18.56-26.07)	

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Table 3. Occupation demographics associated with seropositivity of *Toxoplasma gondii* and prevalence of postpartum blues in new mothers.

Occupation	*Toxoplasma gondii* IgG					post-partum blues				
	No. examined	No. positive	Prevalence(95% CI),%	OR(95% CI)	*P*-value	No. examined	No. positive	Prevalence(95% CI),%	OR(95% CI)	P-value
Farmer	22	2	9.09(0-22.14)	Ref.	0.971	22	5	22.73 (3.71-41.75)	Ref.	0.918
Worker	51	2	3.92(0.408-9.44)	0.401 (0.054-3.101)		51	11	21.57 (9.89-33.25)	0.935 (0.284-3.104)	

Medical staff	36	2	5.56(0.588-13.42)	(0.077-4.507)	36	6	16.67(3.88-29.46)	0.680(0.180-2.565)	
Manager	14	1	7.14(0-22.57)	0.769(0.063-9.371)	14	2	14.29(0-35.25)	0.567(0.094-3.423)	
Teacher	18	1	5.56(0-17.28)	0.588(0.049-7.067)	18	4	22.22(0.95-43.50)	0.971(0.218-4.323)	
Business staff	66	3	4.55(0.476-9.71)	(0.074-3.055)	66	14	21.21(11.09-31.34)	0.915(0.287-2.916)	
Self-employed	69	6	8.70(1.88-15.51)	(0.178-5.097)	69	18	26.09(15.46-36.71)	1.200(0.387-3.725)	
Housewives	7	0	0.00(0.000-0.000)	(0.023-)	7	3	42.86(0-92.29)	2.550(0.422-)	

			12.750)*				15.406)	
Unemployed	47	3	6.38(0-13.64)	0.682(0.106-4.405)	47	9	19.15(7.47-30.83)	0.805(0.234-2.765)
Others	145	7	4.83(1.30-8.36)	0.507(0.098-2.615)	145	34	23.45(16.47-30.43)	1.041(0.358-3.032)

Table 4. Risk factors associated with the seropositivity of *Toxoplasma gondii* and prevalence of postpartum blues in new mothers.

Risk factor	*Toxoplasma gondii* IgG	No. examined	No. positive (with depression)	Prevalence(95% CI),%	OR(95% CI)	*P*-value
Cat Contact	No	380	21 (4)	5.53(3.22-7.83)	Ref.	0.766
	Yes	95	6(3)	6.32(1.33-11.3)	1.152(0.452-2.940)	
Raw Meat	No	384	20(2)	5.21(2.98-7.44)	Ref.	0.357
	Yes	91	7(5)	7.69(2.17-13.27)	1.51(0.621-3.704)	

Figure legends.

Figure S1A. Quantitative comparison between *Toxoplasma gondii* immunoglobulin (IgG) optical density (OD) and Hamilton Depression Scale (HAMD) score in all new mothers (n=475). There is no significant correlation between IgG optical density and HAMD score ($p = 0.872$).

Figure S1B. Quantitative analysis of all *Toxoplasma gondii* seropositive new mothers (n=27) by comparison of immunoglobulin (IgG) optical density (OD) and Hamilton Depression Scale (HAMD) score in the same mothers. There is no significant correlation between IgG optical density and HAMD score ($p= 0.214$).

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