



Explore the association between *Toxoplasma gondii* infection and stress, depression in pregnant women in Makkah, Saudi Arabia

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Toxoplasmosis is one of the zoonotic diseases caused by *Toxoplasma gondii*; the hosts included warm-blooded animals and human. People may remain to stay asymptomatic and may infect for life. The prevalence is estimated between 25% and 30% globally. The main aim of the current study was to explore the association between depression, stress and latent infection of toxoplasmosis in pregnant women in Saudi Arabia. The current study was the case-control to compare between two target groups. The first group was pregnant women in various trimesters of pregnancy with latent toxoplasmosis, and the second group was pregnant women also in different stages of pregnancy without *T. gondii* infection. There was a significant correlation between pregnant women with latent toxoplasmosis and depression (defined by cortisol level) ($P < 0.05$) but the non-significant correlation with stress (defined by testosterone level) ($P > 0.05$). Latent toxoplasmosis in Saudi pregnant women may increase the cortisol and may cause depression among the pregnant women.

Keywords: Latent toxoplasmosis, Cortisol, Testosterone, Stress, Depression, Pregnant

INTRODUCTION

As coccidian and obligate parasite; *Toxoplasma gondii* (*T. gondii*) infected third of the people around the world (Dubey, 2009). The main route of transmission via tissue cysts of *T. gondii* is eating raw or undercooked meat containing these cysts or oocysts of the parasite contaminated the drinking water (Montoya and Liesenfeld, 2004; Guo et al. 2015). Vertical transmission may happen from pregnant woman to her foetus which may lead to abortion or malformation to the foetus (Montoya and Liesenfeld, 2004; Kravetz, 2013). The signs and symptoms in primary acquired infection are asymptomatic in more than 80% of immunocompetent people in European countries and North America (Montoya and Liesenfeld, 2004; Robert-Gangneux and Dardé, 2012). In the other cases, people may develop fever, lymphadenopathy, myalgia, asthenia, and others nonspecific symptoms (Robert-Gangneux and Dardé, 2012). In some study done in the United States, confirmed that about 48% of congenital toxoplasmosis mother could pass the infection to the birth and recall typical clinical signs matching with toxoplasmosis acquired during pregnancy (Boyer et al. 2005). Latent

toxoplasmosis characterized by the bradyzoites or tissue cysts of the parasite has life-long in the different tissues of the host included the nervous system and the presence of IgG antibodies in the serum indicated this stage (Flegr and Striz, 2011). Several studies were published indicated the importance and the effectiveness of latent toxoplasmosis. Of these studies, latent toxoplasmosis found to be increased the infected by schizophrenia (Toney et al. 2007; Flegr and Striz, 2011), can increase Parkinson's disease (Miman et al. 2010; Flegr and Striz, 2011), changes the behavior and human personality (Flegr and Striz, 2011; Flegr, 2007; Lindová et al. 2010), impairs the performance of psychomotor, increases the risk of suicide (Arling et al. 2009; Flegr and Striz, 2011).

Some study done in Saudi pregnant women was found that the prevalence of antenatal depression was varied from mild (18.6%) and severe (11.7%), and the study recommended early detection of depression and causes and treatment to avoid the complications of the outcomes to the mother and her child (Moawad et al. 2015).

Therefore, the main goal of the current study was to explore the association between depression and stress

and latent infection with *T. gondii* in pregnant women in Saudi Arabia

MATERIALS AND METHODS

Study Design

The present study was the case-control to compare between two target groups. The first group was pregnant women in various trimesters of pregnancy with latent toxoplasmosis (+ IgG & -IgM), and the second group was pregnant women also in different stages of pregnancy without *T. gondii* infection (- IgG & -IgM).

Data Collection and Consent

Information from participants was collected using questionnaire after obtained their agreement and signed the consent. The interview was done with each participant before sample collection.

Sampling Process

The blood sample from the vein collected from each pregnant woman participated in the present study. Blood samples were put in the EDTA tubes and centrifuged at 5,000g for 10 minutes. Plasma separated and transferred into cryotube and stored at -80°C until analysed.

ELISA IgM and IgG

ELISA IgM and IgG was performed to detect anti-*Toxoplasma* antibodies and to differentiate between recent infection and latent toxoplasmosis. In ELISA procedures, researchers follow the manufacturing instructions (Humans®).

Measure testosterone & cortisol

Detection of testosterone and cortisol were done by using ELISA kit (Diaplus Inc. kit, America) and ELISA reader.

Statistical Analysis

Statistical analysis was carried out using the SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). For quantitative variables the mean ± SD was used, and for qualitative variables, we used number and %. The group of *T. gondii* positive (N=65) was matched to the group of negative (N=64) by Independent Samples t-test. The positive group of *T. gondii* was separately evaluated, and correlation analyses by Pearson correlation coefficient were performed between *T. gondii* titers and depression (defined by cortisol level) and stress (defined by testosterone level) in this group. Linear regression analyzed the effect of demographic characteristics on this relationship. The P value of less than 0.05 was considered statistically significant.

RESULTS

About 129 pregnant women were contributed in the present study; half of them have IgG against *T. gondii*,

and all participants have IgM negative against *T. gondii*. As clarified in Table (1) the average of participants' age was 29.9 ± 6.2 years, most of the participants were Saudi with Arab race (79.8%). Although few of participants were uneducated (3.9%), and most of them resident in the urban area (79.1%) but the majority of them were the housewives (82.9%). The average weight and height of participants were 69.5 ± 15.5 kg and 155.1 ± 5.4 cm as seen in the Table (1).

Table 1: General characteristics & measurements of participants

Variables		Participants (No. = 129)	
		No.	%
Age (years)	Mean ± SD	29.9 ± 6.2	
	Min – Max	17 – 45	
	≤ 30 years	76	58.9
	> 30 years	53	41.1
Nationality	Saudi	103	79.8
	Non-Saudi	26	20.2
Race	Arab	103	79.8
	Asian	15	11.6
	African	6	4.7
	Others	5	3.9
Education	Illiterate	5	3.9
	Primary	21	16.3
	Intermediate	18	14.0
	Secondary	41	31.8
Occupation	Graduate	44	34.1
	Housewife	107	82.9
	Employee	18	14.0
Residence	Students	4	3.1
	Urban	102	79.1
	Rural	27	20.9
Address	North Makkah	27	20.9
	South Makkah	32	24.8
	East Makkah	36	27.9
	West Makkah	13	10.1
	Outside Makkah	21	16.3
Weight (kg)	Mean ± SD	69.5 ± 15.5	
	Min – Max	40 – 142	
Height (cm)	Mean ± SD	155.1 ± 5.4	
	Min – Max	137 – 176	

The social characteristic of participants included the average duration of marriage was 29.9 ± 6.2 years the majority of women have more than five years of marriage (55%). The average size of the family was 4.4 ± 2.1, and most of the family consist of 3 to 5 individuals (52.8%). The number of boys and girls in the family were very similar as mentioned in Table (2).

The obstetric characteristics of participants indicated

that more than half of participants were grandmultigravida (51.9%), most of the women in the third trimester (45%) and few of them were in the first pregnancy (14.7%). Almost, 67.4% of participants have no history of abortion, and few of them have the history of stillbirth (3.9%) as clarify in Table (3).

In the Table (4) there was a significant correlation between pregnant women with latent toxoplasmosis and depression (defined by Cortisol level) but the non-significant correlation with stress (defined by testosterone level).

Table (2) Family characteristics of participants.

Variables		Participants (No. = 129)	
		No.	%
Years of Marriage	Mean ± SD	29.9 ± 6.2	
	Min – Max	17 – 45	
	< 1 year	17	13.2
	1 – 5 years	41	31.8
	> 5 years	71	55.0
No. of family members	Mean ± SD	4.4 ± 2.1	
	Min – Max	2 – 15	
	2	20	15.5
	3 – 5	68	52.8
	> 6	26	20.2
No. of boys	Mean ± SD	1.3 ± 1.4	
	Min – Max	0 – 7	
	0	37	28.7
	1 – 2	61	47.3
	≥ 3	15	12.5
No. of girls	Mean ± SD	1.1 ± 1.1	
	Min – Max	0 – 5	
	0	41	31.8
	1 – 2	59	45.8
	≥ 3	14	10.9

Table 3: Obstetric characteristics of participants.

Variables		Participants (No. = 129)	
		No.	%
Gravidity	Primigravida	26	20.2
	Multigravida	36	27.9
	Grandmultigravida	67	51.9
Month of pregnancy	First trimester	34	26.4
	Second trimester	37	28.7
	Third trimester	58	45.0
No. of previous pregnancies	0	19	14.7
	1 – 3	59	45.8
	4 – 6	34	26.4
	≥ 7	17	13.2
History of abortion	Yes	1	19
		2	13
		≥ 3	10
	No	87	67.4
History of stillbirth	Yes	5	3.9
	No	124	96.1

Table 4: Relation between cases and controls regarding hormonal levels among participants

	Cases	Control	t	P-value
<i>T. gondii</i> IgG (IUs)	2.99 ± 1.6	0.23 ± 0.18	13.75	0.001 *
Depression (Cortisol level)	368.2 ± 219.7	267.1 ± 130.6	6.33	0.03*
Stress (Testosterone level)	0.71 ± 0.56	0.63 ± 0.46	0.94	0.349

t: Independent Samples t-test. *: Significant.

DISCUSSION

The current study is performed to explore the relation between the infection with *T. gondii* and the stress hormones from one side, and the testosterone changes, from the other side. The relationship between the level of these hormones and related complications (extreme stress caused by high cortisol levels), and high blood testosterone and *T. gondii* infection was demonstrated in our study.

It is well known that behavioral changes can result from *T. gondii* infection in its host and these changes were studied in different models of mice (Groër et al. 2011; Duffy et al. 2015). The results showed that the titer of cortisol in individuals infected with the parasite has a significant negative correlation between pregnant women with toxoplasmosis and depression (defined by cortisol level). The increase of cortisol is a person significant stress symptom, and if it were still high for a long period, it would result in the induction of behaviors and anxiety because of stress.

From another side, damage to different parts of the nervous system may take place as a result of an increase in the titer of this hormone. Also, it is well known that the increase of cortisol level (stress hormone) affect the individuals and they suffer from anxiety, paranoia, and depression (Cox and John-Alder, 2005; Karrer-Voegeli et al. 2009). Regarding to the present research findings, there was no significant correlation detected between *T. gondii* infection and the depression in pregnant women.

From the different point of view, latent *T. gondii* infection can affect different behavioral and hormonal alterations in rodents and humans (Flegr, 2013) and participate in different psychotic etiology disorders (Dalimi and Abdoli, 2012; Flegr, 2013). The increase in testosterone concentration in men infected with chronic toxoplasmosis in comparison to the testosterone in negative men for *T. gondii* was reported in different studies (Flegr et al. 2008; Shirbazou et al. 2011).

Elevated testosterone levels were confirmed in a model of the animal infected with latent toxoplasma infection (Lim et al. 2013). Also, different non-direct pieces of evidences present for excessive social hormone (testosterone) levels can result in anxiety and depression in latent toxoplasmosis. The discrepancy in levels of testosterone between uninfected and infected people gives rise to differences in behavior (Flegr, 2007). Other

researches mention that *T. gondii* infection may elevate son height and number of infected men and change the factors of women and men personality. (Flegr et al. 1996)

Groër et al. (2011), who have suggested the relationships between cytokines in pregnancy, depression, *T. gondii* IgG titers, and immunity that could be translated into considerable health risks for fetus and mother, did the preliminary work. Also, *T. gondii* may indirectly change the anxiety-like behaviors, through the immune response of the hosts. Cytokine production played an essential role in latent *T. gondii* infection of the cysts (Carruthers and Suzuki, 2007).

Arling et al. (2009) have supposed that toxoplasmosis seropositivity will be related to past suicide trials, that sero-intensity will be higher between suicide attempters than non-attempters. Also, the suicide history attempters have widely studied (Arling et al. 2009; Yagmur et al, 2010; Ling et al. 2011). Modified serotonergic function, besides its association with aggression, impulsivity, and depression (suicide risk factors) has been published to be accomplished with the behavior of suicide (Mann, 2003).

In contrast to these studies, the current study has shown that no significant correlation between latent *T. gondii* infection, and testosterone levels which suggest more work are needed to study this correlation and we conclude that the link between sero-intensity and suicide attempts and depression as strong relationship have a right to replicate in more considerable prospective researches.

People infected with *T. gondii* perform to have high testosterone levels. In infected pregnant women, the levels of testosterone may be higher, and immune responses may be suppressed by testosterone. Also, testosterone may participate in depression in females. Because of their higher incidence of depression and high incidence of *T. gondii* IgGs, these effects have often appeared at risk in Hispanic women (Groër, 2011).

This early work indicates that there are linkages between cytokines in pregnancy, *T. gondii* IgG titers, immunity, and depression that could be translated to remarkable health risks for fetus and mother (Groër, 2011).

There are fragmentary and occasionally conflicting results about the *T. gondii* infection association and depression (García and Perdomo 1980; Misra, 2004; Pearce et al. 2012).

Results of previous studies have shown that

psychiatric patients suffering from depression have a higher significant *T. gondii* infection seroprevalence than control individuals without depression in the common population of the same city (Alvarado-Esquivel et al. 2016). In a study of 70 women veterans, significant associations among *T. gondii* seropositivity and the Center for Epidemiologic Studies Depression score, Profile for Mood States – depression, and total mood disturbance score were found (Duffy et al. 2015). In another study of pregnant women in the USA, prenatal depression was linked with higher titers of *T. gondii* in infected women (Groër et al. 2011).

Alvarado-Esquivel et al. (2016) assessed the linkage of depression and infection with *T. gondii* in a sample of psychiatric patients and control subjects without depression. The results of their study suggested a potential relationship between depression and infection with *T. gondii*. It is well known that elevated titers of *T. gondii* IgG in infected women were linked to depression and anxiety during pregnancy. *T. gondii* reactivation or immunological reaction to *T. gondii* may change the pregnant women mood (Groër, 2011).

On the other hand, the relation of depression and anxiety with *T. gondii* IgGs in pregnancy is important for different reasons. More than 30% of the world populations have *T. gondii* positive antibodies (Montoya and Liesenfeld, 2004). Anxiety and prenatal depression are also common and are related to fetal outcomes and negative pregnancy (Bansil et al. 2010). It is also a predictor for postpartum depression.

Old studies have shown that none of the cases seropositive to *T. gondii* had IgM antibodies, suggesting that depression and anxiety might be associated with latent infection. This association may be explained as a result of tachyzoites of *T. gondii* invade many cells in the brain (Fond et al. 2013) and it is possible that *T. gondii* causes mood disorders via alterations in the brain levels of serotonin and dopamine (Groër et al. 2011).

CONCLUSION

Latent toxoplasmosis in Saudi pregnant women may increase the cortisol and may cause depression among the pregnant women.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEDGEMENT

The authors would like to thank Institute of Scientific Research and Revival of Islamic Heritage at Umm Al-Qura University (project # 43309004) for the financial support.

AUTHOR CONTRIBUTIONS

KM wrote the proposal, designed the experiments, interpreted the results, and wrote the first draft. ND collected the samples and performed the experiments. MA

reviewed the draft and approved the final one. MJ performed the experiments and approved the final draft. HK analyzed the data and prepared the tables.

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REFERENCES

- Alvarado-Esquivel C, Rascón-Careaga A, Hernández-Tinoco J, Corella-Madueño MAG, Sánchez-Anguiano LF, et al. (2016) Seroprevalence and Associated Risk Factors for *Toxoplasma gondii* Infection in Healthy Blood Donors: A Cross-Sectional Study in Sonora, Mexico. *BioMed Research International*, Article ID 9597276, 8 pages <http://dx.doi.org/10.1155/2016/9597276>.
- Arling TA, Yolken RH, Lapidus M, Langenberg P, Dickerson FB, et al. (2009) *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. *J Nerv Ment Dis.* 197: 905-08.
- Bansil P, Kuklina EV, Meikle SF, Posner SF, Kourtis AP, et al. (2010) Maternal and Fetal Outcomes among Women with Depression. *Journal of Women's Health.* 19(2):329-34.
- Boyer KM, Holfels, E, Roizen, N, Swisher, C, Mack, D, et al. (2005) Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am. J. Obstet. Gynecol.* 192:564 –71.
- Carruthers, VB, and Suzuki, Y. (2007) Effects of *Toxoplasma gondii* infection on the brain. *schizophr. Bull.* 33: 745–51.
- Cox, RM, and John-Alder, HB, (2005) Testosterone has opposite effects on male growth in lizards (*Sceloporus spp.*) with opposite patterns of sexual size dimorphism. *J. Exp. Biol.*, 208: 4679-87.
- Dalimi A, and Abdoli A, (2012) Latent Toxoplasmosis and Human. *Iran. J. Parasi.* 7(1):1-17.
- García DG, Perdomo RE, (1980) Reactivity of toxoplasmin intradermal test in neurotic and manic-depressive patients *Rev Cubana Med Trop.* 32(1):35-9.
- Duffy AR, Beckie TM, Brenner, LA, Beckstead, JW, Seyfang, A, et al. (2015) Relationship between *Toxoplasma gondii* and mood disturbance in women veterans. *Mil Med* 180: 621–25
- Dubey JP (2009) History of the discovery of the life cycle of *Toxoplasma gondii*. *Int J Parasitol*; 39, 877–882.
- Flegr J, Zitkova, S, Kodym, P, Frynta, D, (1996) Induction

- of changes in human behavior by the parasitic protozoan *Toxoplasma gondii*. *Parasitology* 113:49-54.
- Flegr J (2007) Effects of *Toxoplasma* on human behavior. *Schizophr Bull.* 33:757-760.
- Flegr J, Lindova J, Kodym, P, (2008) Sex-dependent toxoplasmosis-associated differences in testosterone concentration in humans. *Parasitology*, 135: 427-431.
- Flegr J, Striz I, (2011) Potential immunomodulatory effects of latent toxoplasmosis in humans. *BMC Infectious Diseases*; 11:274.
- Flegr J, Preiss M, Klose J, (2013) Toxoplasmosis-associated difference in intelligence and personality in men depends on their Rhesus blood group but not ABO blood group. *PLoS One* 8(4):e61272. doi:10.1371/journal.pone.0061272
- Fond G, Loundou A, Hamdani N, Boukouaci W, Dargel A, et al (2014) Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*, 264(8): 651–60.
- Groër MW, Yolken RH, Xiao JC, Beckstead JW, Fuchs D, et al (2011) Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. *Am J Obstet Gynecol* 204(5):433.e1-7. doi: 10.1016/j.ajog.2011.01.004.
- Guo M, Dubey JP, Hill D, Buchanan RL, Gamble et al (2015) Prevalence and risk factors for *Toxoplasma gondii* infection in meat animals and meat products destined for human consumption. *J Food Prot* 78, 457–76.
- Kar N, Misra B, (2004) *Toxoplasma* seropositivity and depression: a case report. *BMC Psychiatry* 4, 1
- Karrer-Voegeli S, Rey F, Raymond MJ, Meuwly JY, Gaillard RC et al, (2009) Androgen dependence of hirsutism, acne and alopecia in women: Retrospective analysis of 228 patients investigated for hyperandrogenism. *Medicine*, 88(1):32-45. doi: 10.1097/md.0b013e3181946a2c.
- Kravetz J, (2013) Congenital toxoplasmosis. *BMJ Clin Evid* 0906.
- Lim A, Kumar V, Hari Dass SA, Vyas A, (2013) *Toxoplasma gondii* infection enhances testicular steroidogenesis in rats. *Mol. Ecol.* 22, 102–110. doi:10.1111/mec.12042
- Ling VJ, Lester D, Mortensen PB, Langenberg PW, Postolache TT (2011) *Toxoplasma gondii* seropositivity and suicide rates in women. *J. Nerv. Ment. Dis.* 199, 440–44.
- Lindová J, Kubena AA, Šturcová A, Křivohlavá R, Novotná et al (2010) Pattern of money allocation in experimental games supports the stress hypothesis of gender differences in *Toxoplasma gondii* -induced behavioural changes. *Folia Parasitol (Praha)*, 57 (2): 136-42.
- Mann JJ, (2003) Neurobiology of suicidal behaviour. *Nat Rev Neurosci.* 4 (10):819-28.
- Miman O, Kusbeci OY, Aktepe OC, Cetinkaya Z, (2010) The probable relation between *Toxoplasma gondii* and Parkinson's disease. *Neurosci Lett* 475: 129-31.
- Moawed SA, Gemaey EM, Al-Mutairi HA, (2015) Prevalence of Depression among Saudi Pregnant Women. *Journal of Nursing and Health Science (IOSR-JNHS)* 4(2):61-8.
- Montoya JG, Liesenfeld O, 2004: Toxoplasmosis. *Lancet* (2004) 363, 1965–76.
- Pearce BD, Kruszon-Moran D, Jones JL (2012) The relationship between *Toxoplasma gondii* infection and mood disorders in the third National Health and Nutrition Survey. *Biol Psychiatry* 72, 290–95.
- Robert-Gangneux F, Dardé M, (2012) Epidemiology of and Diagnostic Strategies for Toxoplasmosis. *Clinical Microbiology Reviews* 25(2):264–96.
- Shirbazou SS, Abasian L, Meymand FT, (2011) Effects of *Toxoplasma gondii* infection on plasma testosterone and cortisol level and stress index on patients referred to Sina hospital, Tehran. *Jundishapur J. Microbiol.*, 4: 167-73.
- Steven E, Schmitt B, Golovko A, Mehdi E, Santanu K, (2008) Toxoplasmosis, Chap 2.9.10. In: Barry ON (ed) *Terrestrial Manual*. OIE Scientific Publications, Paris.
- Toney EF, Bartko JJ, Lun ZR, Yolken RH, (2007) Antibodies to *Toxoplasma gondii* in patients with schizophrenia: A meta-analysis. *Schizophr Bull* 33:729-36.
- Yagmur F, Yazar S, Temel HO, Cavusoglu M, (2010) May *Toxoplasma gondii* increase suicide attempt – preliminary results in Turkish subjects? *Forensic Sci. Int.* 199, 15–17.