Research Article

The Impact of Gonadotropin Hormones on Toxoplasma Gondii Infection in Women With Polycystic Ovarian Syndrome

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ABSTRACT

Recent research tell us that infectious pathogens may play a role in the development of polycystic ovarian syndrome (PCOS), especially through immunological dysregulation. Toxoplasma gondii (T. gondii), an intracellular protozoan parasite, has been linked to various immune-mediated diseases. This study looked at the connection between gonadotropin hormones and a T. gondii infection in PCOS-affected individuals. The study had 90 women with PCOS and toxoplasmosis and 90 healthy controls. The serum levels of estrogen (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (TST), immunoglobulin G (IgG), and immunoglobulin M (IgM) were measured. Women with PCOS and toxoplasmosis had considerably greater levels of LH, E2, TST, LH/FSH ratio, IgG, and IgM, as well as significantly lower FSH levels, compared to controls ($p = 0.001$). Furthermore, positive relationships were found between the LH/FSH ratio and factors such as LH, IgG, and IgM levels, as well as age and number of abortions in infected PCOS patients, while a significant negative association was found with FSH levels. These data imply that T. gondii infection may worsen hormonal and immunological problems in PCOS patients.

Keywords: Polycystic ovarian syndrome (PCOS), Gonadotropin hormone, Female hormones**,** Toxoplasma Gondii Infection.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine diseases among women of fertile age, with symptoms including hyperandrogenism, recurrent anovulation, and polycystic ovaries [1, 2]. As well as reproductive dysfunction, PCOS has been linked to metabolic problems and immune response changes [3, 4], which may increase the chances of getting infected. Toxoplasmosis is a parasitic disease that affects around one-third of the world population [5, 6]. It is caused by the parasite Toxoplasma gondii (T. gondii), which was first discovered by Nicol and Manso in 1908. This parasite was discovered in the tissue of a hamster named gondii. At the same time, Alfonso Splendor found T. gondii in a rabbit in Brazil [7]. T. gondii was called by its shape. The term "Toxoplasma" comes from the Greek word "toxon," which means bow, and refers to the crescent form of the organism during its rapid growth phase. The rodent from whence the name "Gondi" originated is the source of the species' nickname, Janko was the first to discover the T. gondii parasite in humans when he noticed tissue cysts on a hydrocephalic child's retina in 1923 [8].

Toxoplasmosis usually shows no symptoms, but it can cause reproductive health problems such as miscarriage, infertility, and pregnancy difficulties [6,9]. T. Gondii has a complex life cycle, including many developmental stages and a broad range of hosts and environments. Infection is usually serious if transmitted in the early first stages of pregnancy, but the risk of vertical transmission is higher in the last stages. Toxoplasmosis is typically asymptomatic in immunocompetent adults, but in immunocompromised patients, it can cause encephalitis and chorioretinitis [10]. The parasite can be transmitted to the child during pregnancy, which may lead to miscarriage, chorioretinitis, cerebral calcifications, and hydrocephalus [11, 12]. The relationship between hormonal imbalance and the possibility of infection in women with PCOS is not fully understood, yet.

Recent data suggests that gonadotropic hormones, especially luteinizing hormone (LH) and follicle-stimulating hormone (FSH), play an important role not only in ovarian function but also in immune system regulation [12]. Disruption of these hormones in women with PCOS may change the host and parasite interaction, redirecting the danger of the toxoplasmosis infection. Moreover, the interaction between endocrine and immunological pathways may provide to the clinical variation seen in women with PCOS [13, 14]. The objective of this study is

to know the correlation of gonadotropin and toxoplasmosis in PCOS-affected women. It strives to link the gap between endocrine dysfunction and infectious disorders, providing a better knowledge of reproductive and metabolic health in women with PCOS.

MATERIALS AND METHODS

SAMPLE COLLECTION:
From July11, 2024, to 20 September 2024, the study was done in a hospital Azadi Teaching Hospital/Azadi Infertility and In Vitro Fertilization (IVF) Centre in Duhok, Iraq, with the Ethics Approval Code: (210)/R.A. D, on Jun 6, 2024, and was performed in accordance with the Rules of Helsinki.

GROUP OF PCOS WITH TOXOPLASMOSIS PATIENTS:
This study dealt with 90 women with PCOS and Toxoplasmosis who were diagnosed by specialists. Their ages were from 18 to 43 years. The clinical data from each case was written into a test particularly prepared for this purpose.

CONTROL GROUP:
The control group was formed of 90 women who seemed to be in good health and showed no signs nor symptoms of systemic disorders like diabetes, hypertension, or obstetric difficulties. Their ages were between 17 and 48 years. All control subjects tested negative for both IgM and IgG antibodies to Toxoplasma infection.
Blood samples were obtained for luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen (E2), testosterone (TST), immunoglobulin G (IgG), and immunoglobulin M (IgM) in both groups after 12 hours of fasting at the start of the follicular phase (period day two or three). Blood samples (5 ml) were taken in test tubes, centrifuged within an hour to separate the serum, and stored in a deep freezer container. Before being examined, samples were given the opportunity to reach room temperature.

PROCEDURE:
The study used a kit from Minividas (France) and Cobas c311(German) to assess LH, FSH, E2 and TST levels. The Minividas system evaluated the results using the Enzyme-Linked Fluorescent Assay (ELFA) technique.
Kits for the detection of IgG and IgM antibodies against T. gondii antigens in human serum (Roche Diagnostics GmbH, Mannheim, Germany) were used according to the manufacturer's instructions. Detection of anti-Toxoplasma IgM and IgG antibodies was used to evaluate the patients' serologic status for T. gondii infection. The sera were analyzed using the automated Cobas® 4000 platform (Cobas e 411 analyzer), a fully automated immunoassay system controlled by dedicated software. The software automatically handled the transmission of information to and from the analyzer, as well as result evaluation, documentation, and quality control.

STATISTICAL ANALYSIS:
Statistical analysis was performed using SPSS version 27 (IBM). Data were analyzed using statistical procedures such as standard deviation and mean. A t-test was used to compare the total number of patients and the total number of controls, and it was significant at $p \leq 0.05$ [15].

RESULTS COMPARING HORMONAL LEVELS IN PCOS PATIENTS INFECTED WITH TOXOPLASMOSIS AND THE CONTROL GROUP:
Table (1) demonstrates that women with PCOS infected with toxoplasmosis had significantly higher levels of LH, E2, TST, LH/FSH ratio, IgG and IgM compared to the control group (p=0.001). In contrast, they showed significantly lower levels of FSH (p=0.001).

Table (1): Comparing hormonal levels in PCOS patients infected with toxoplasmosis and the control group

Parameters	PCOS Patients with Toxo Mean ± SD No. = 90	Control group Mean ± SD No.= 90	p-value
LH (mlU/ml)	5.90 ± 0.54	3.84 ± 0.20	0.001
FSH (mlU/ml)	3.87 ± 0.78	6.86 ± 1.82	0.001
E2 (pg/ml)	76.15 ± 2.43	49.28 ± 0.13	0.001
TST (mlU/ml)	1.42 ± 0.23	0.56 ±0.61	0.001
LH/FSH	1.80 ± 0.02	0.62 ±0.04	0.001
IgG (IU/ml)	1.43 ± 0.07	0.76 ± 0.08	0.001
IgM (IU/ml)	1.19 ± 0.24	0.60 ± 0.04	0.001

THE RELATIONSHIP INVOLVING THE LH/FSH RATIO AND THE LEVELS OF SEXUAL HORMONES AND IMMUNOLOGICAL MARKERS:

Table (2) demonstrates a strong positive correlation between LH/FSH Ratio and LH, IgG, IgM, and as well as with age and number of abortions in PCOS patients infected with toxoplasmosis. In contrast, a significant negative correlation was observed with FSH levels in the same group.

Table (2) The association between the LH/FSH ratio and levels of sex hormones and immunological markers

Parameters	r-value	p-value
Age	0.44	0.01
PCOS	0.235	0.05
abortion	0.331	0.01
LH (mlU/ml)	0.67	0.05
FSH (mlU/ml)	- 0.56	0.01
E2 (pg/ml)	- 0.039	N
TST (mlU/ml)	0.039	N
IgG (IU/ml)	0.96	<0.001
IgM (IU/ml)	0.85	<0.001

N=No significant differences

RELATIONSHIP BETWEEN IGG AND IGM LEVELS AND MISCARRIAGES NUMBER IN PCOS PATIENTS WITH TOXOPLASMOSIS:

The Figure (1) demonstrates the relationship between IgM and IgG levels and the number of miscarriages in PCOS patients infected with Toxoplasmosis. The results show that the number of miscarriages increased to three when IgG and IgM levels attained 1.39 and 1.27, respectively. In comparison, two miscarriages were recorded at IgG and IgM levels of 1.53 and 1.10, while one miscarriage occurred when IgG and IgM levels were 1.27 and 1.23, respectively. These findings suggest a possible association between elevated antibody levels and increased rate of miscarriage among affected PCOS patients.

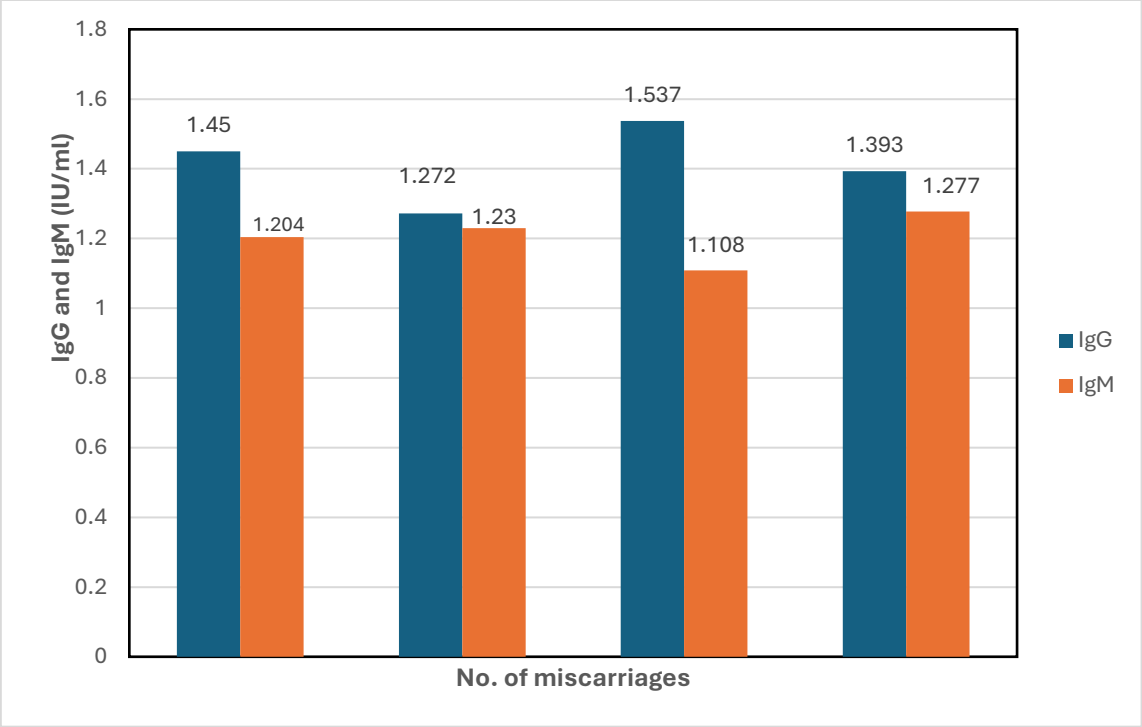


Figure (1): Relationship between IgG and IgM levels and miscarriages number in patients PCOS with toxoplasmosis

MISCARRIAGE RATE AMONG PCOS PATIENTS INFECTED WITH TOXOPLASMOSIS:

The Figure (2) shows the rate of miscarriage of patients with polycystic ovary syndrome (PCOS) infected with Toxoplasmosis. It was noticed that the miscarriage rate was up to 50% in cases with three miscarriages, 33% in cases with two miscarriages, and 17% in cases with one miscarriage.

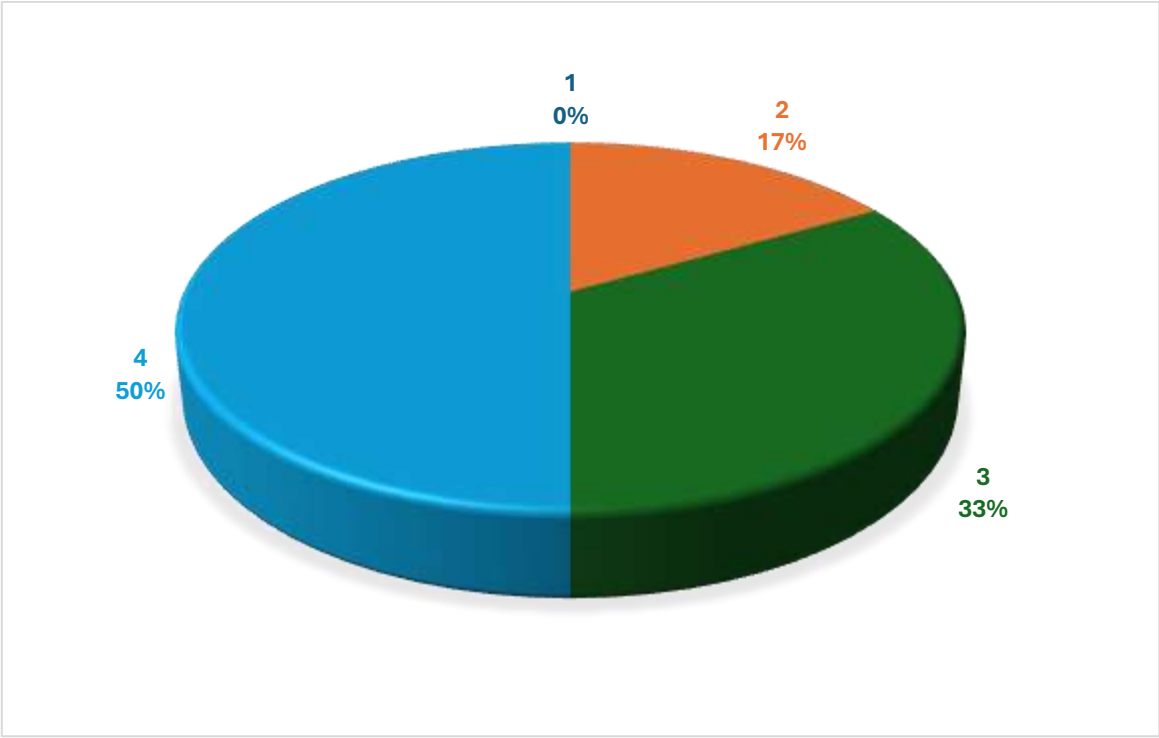


Figure (2): The rate of miscarriages in PCOS patients with toxoplasmosis

DISCUSSION

Toxoplasmosis is a parasitic disease with a broad range around the world. The parasite can cross the placenta barrier and create serious difficulties for the fetus [16]. Table (1) indicates that women with polycystic ovarian syndrome (PCOS) who were infected with Toxoplasmosis had noticeably higher levels of LH, E2, testosterone (TST), LH/FSH ratio, IgG, and IgM than the control group. FSH levels were significantly lower in the group. These hormonal fluctuations may affect the immune system, increasing the exposure to Toxoplasmosis infection [17].

The T. gondii has been associated to the activation of the hypothalamic-pituitary-adrenal (HPA) stress axis, which in turn moderates the hypothalamic-pituitary-gonadal (HPG) axis, leading to disturbances in the secretion of gonadotropins such as LH and FSH. These neuroendocrine pathways may account for observed changes in LH levels during infection [18]. The immunological and endocrine systems are inseparably linked, with sex hormones that have an importance in controlling immune responses. Hormonal alternatives, especially in testosterone and estradiol levels, can affect the exposure levels and severity of T. gondii infection by directly changing immune cell function. [4].

During toxoplasmosis in women, proliferative tachyzoites may invade female reproductive organs, specifically the oviducts, leading to the formation of tissue cyst and tubule dysfunction, which can cause hormonal abnormalities and secondary infertility [7,8].

The increase in IgG and IgM levels proves the existence of an active or recent immunological response to T. gondii. This immunological stimulation may cause inflammatory alterations that can weaken ovarian function and have reproductive consequences. Reduced FSH levels can contribute to poor follicular growth, intensifying anovulation and infertility in PCOS patients [19]. The interaction between T. gondii infection and hormonal imbalance in PCOS can produce a compounding effect (Cumulative effect), in which parasitic infection not only activates immune responses but also changes the reproductive hormonal environment, potentially aggravating PCOS clinical symptoms. T. gondii infection can induce abortion and various symptoms, including neurological and neurocognitive impairments, as well as chorioretinitis in fetuses [20]. These parasites use the infected host's immune system to sustain a prolonged infection, producing an environment conducive to their multiplication, this method works by regulating host gene transcription, which disrupts inflammatory signaling pathways and leads to leukocyte mobility, modification of endothelial cell adhesion, release of immunoregulatory cytokines, and cell death [21,22].

Table (2) shows substantial correlations between hormonal, immunological, and clinical markers among PCOS patients infected with T. gondii. There was a considerable positive correlation between the LH/FSH ratio and factors such as LH, IgG, IgM, age, and number of abortions. This shows that hormonal abnormalities are common aspects of PCOS and have been linked to chronic low-grade inflammation and reproductive issues. The development of a pro-inflammatory chronic condition in women with this syndrome may interfere with normal ovarian function, compromising sexual hormone production and release, follicular maturation, and eventual ovulation [23]. In contrast, a substantial negative correlation was found with FSH levels in the same population. These results emphasize the role of immune activation and chronic inflammation in disease pathogenesis and reproductive difficulties.

The results in Figure (1) show that greater IgM and IgG levels were linked with an increased frequency of miscarriages, with a maximum of three pregnancy losses at 1.39 and 1.27, respectively. High IgG levels could illustrate determined parasite exposure or persistence, leading to long-term immune activation. This chronic inflammatory condition, when paired with hormonal and metabolic abnormalities, can increase the chance of miscarriage, and studies have shown that stronger anti-Toxoplasma antibodies are linked with a higher probability of stillbirth. T. gondii appears to function as a secondary component, changing hormonal balance and stimulates egg implantation and embryo survival, as well as increasing other variables such as cytokines [24]. In response to T. gondii infection, inflammatory monocytes cause proinflammatory cytokines such as IL-1 and IL-1β. This diverse cytokine response adds to inflammation, which then affects ovulation, implantation, and fertilization processes [25].

The results illustrated in Figure (2) indicate the rate of miscarriage between patients with polycystic ovary syndrome (PCOS) infected with T. gondii. This distribution indicates an raise in miscarriage frequency among

affected patients, implying a possible link between T. gondii infection and recurrent pregnancy loss in women with PCOS. Toxoplasmosis could stimulate the hypothalamic-pituitary-adrenal (HPA) stress axis, which then affects the hypothalamic-pituitary-gonadal (HPG) axis, leading to gonadotropin secretion abnormalities and an increased inflammatory response at the maternal-fetal interface. This imbalance may compromise placental growth and function, increasing the risk of recurring miscarriages [17].

CONCLUSION:

Overall, our data suggest that Toxoplasma gondii infection is linked to significant hormonal and immunological problems in PCOS patients.. The T. gondii infection may contribute to or worsen reproductive complications in women with PCOS, as evidenced by elevated levels of LH, estrogen, testosterone, LH/FSH ratio, and anti-T. gondii IgG and IgM, as well as reduced FSH levels, emphasizing the importance of taking infectious and immunological factors into account in clinical management of affected women, thus, contributing to achieving Sustainable Development Goal 3 (SDG3). More research is needed to determine the causative pathways that link toxoplasmosis and unfavorable reproductive outcomes.

ACKNOWLEDGMENTS

The patients' involvement in this study is much appreciated by the researchers., as well as the University of Mosul and the University of Nineveh for their support.

ETHICAL CONSIDERATIONS

The Authors' Review Committee and our company (Code: (210)/R.A. D, on Jun 6, 2024) authorized this study. The study was carried out in compliance with the Declaration of Helsinki's tenets, corporate policy, and all applicable national legislation.

CONFLICT OF INTEREST

The authors attest that they have no competing interests with relation to the information in this study.

REFERENCE:

[1]. Z. A. M. Al-Jawadi and F. K. Al-Taie, "Clinical study of the role of thyroid stimulating hormone on polycystic ovary synsyndrome", Health Biotechnology and Biopharma, 9, 85–98 (2025).
[2]. Z. A. M. Al-Jawadi, "Effect of Vitamin D Deficiency on Women with Polycystic Ovary Syndrome (PCOS)", Egypt. J. Chem, 64, 4417–4424 (2021).
[3]. S. F. de Medeiros, B. B. Barbosa, A. K. L. W. Yamamoto, M. M. W. Yamamoto, M. A. S. de Medeiros, J. M. Soares Junior et al., "The interplay between androgens and adipocytes: The foundation of comorbidities of polycystic ovary syndrome", Gynecol. Reprod. Endocrinol. Metab., 1, 2–8 (2020).
[4]. K. H. Zghair, B. N. Al-Qadhi and S. H. Mahmood, "The effect of toxoplasmosis on the level of some sex hormones in male blood donors in Baghdad", J. Parasit. Dis., 39, 393–400 (2013).
[5]. H. F. Escobar-Morreale, M. Luque-Ramírez and F. González, "Circulating inflammatory markers in polycystic ovary syndrome: A systematic review and meta-analysis", Fertil. Steril., 95, 1048–1058.e2 (2011).
[6]. R. Moghaddami, K. Moradi, M. Mahdipour, A. S. Pagheh, J. Razeghi, N. Nazdikbin Yamchi, A. Khordadmehr, A. Nematollahi, B. Ghorbanzadeh and E. Ahmadpour, "Strain-dependent effects of Toxoplasma gondii on ovarian health and inflammation in a rat model", BMC Infect. Dis., 25, 690 (2025).
[7]. Y. J. Salman, "Chlamydia trachomatis antibodies cross reaction with seropositive Toxoplasma gondii and cytomegalovirus among women with abortion and outcomes of congenital abnormalities in Kirkuk City", Tikrit J. Pure Sci., 21, 1–6 (2016).
[8]. C. Charlier and M. Lecuit, "Maternal–fetal infections: Why do they matter?", Virulence, 11, 398–399 (2020).
[9]. Z. A. M. Al-Jawadi, "Effect of selenium level of serum and semen in infertile Iraqi men", Biochem. Cell. Arch., 20 (Suppl. 2), 3619–3622 (2020).
[10]. S. Ait Hamou, B. Lamhamdi, I. Hayah, I. Belbacha, A. Sadak and M. Laboudi, "The level of knowledge about toxoplasmosis among university students in Rabat, Morocco", J. Parasitol. Res., 2021, 1–7 (2021).
[11]. B. Bodaghi, V. Touitou, C. Fardeau, L. Paris and P. LeHoang, "Toxoplasmosis: New challenges for an old disease", Eye, 26, 241–244 (2012).

[12]. J. W. Ajioka and N. S. Morrissette, "A century of Toxoplasma research", Int. J. Parasitol., 39, 859–860 (2009).
[13]. J. P. Dubey, "History of the discovery of the life cycle of Toxoplasma gondii", Int. J. Parasitol.,39, 877–882 (2009).
[14]. M. Zamaniyan, M. Fakhar, R. Tabaripour, S. Peivandi, M. Keighobadi, S. Ghasemi and M. Montazeri, "Credible serological evidence of latent Toxoplasma gondii infection among women with primary infertility: A ten-year registry-based study", Acta Parasitol., 68, 400–405 (2023).
[15]. L. Kirkpatrick and B. C. Feeney, A Simple Guide to IBM SPSS Statistics for Version 18.0 and 19.0, 11th ed., Wadsworth Cengage Learning, Belmont, CA, 2012.
[16]. A. Rostami, S. M. Riahi, D. G. Contopoulos-Ioannidis, H. R. Gamble, Y. Fakhri, M. N. Shiadeh et al., "Acute toxoplasma infection in pregnant women worldwide: A systematic review and meta-analysis", PLoS Negl. Trop. Dis., 13, e0007807 (2019).
[17]. F. B. Mikaeel, "The effect of Toxoplasma gondii infection in women on some biochemical and hormonal parameters in Duhok province, Iraq", Int. J. Res. Med. Sci., 8, 3508–3512 (2020).
[18]. W. Ibrahim and K. E. A. Abdelsalam, "Levels of FSH, LH, SHBG, total testosterone, and LH/FSH ratio in Sudanese patients with polycystic ovary syndrome in relation to body mass index", Int. J. Curr. Res., 7, 11919–11922 (2015).
[19]. M. L. Galván-Ramírez, A. F. Gutiérrez-Maldonado, F. Verduzco-Grijalva and J. M. Dueñas-Jiménez, "The role of hormones on Toxoplasma gondii infection: A systematic review", Front. Microbiol., 5, 503 (2014).
[20]. Z. D. Wang, H. H. Liu, Z. X. Ma, H. Y. Ma, Z. Y. Li, Z. B. Yang et al., "Toxoplasma gondii infection in immunocompromised patients: A systematic review and meta-analysis", Front. Microbiol., 8, 389 (2017).
[21]. T. S. Lima and M. B. Lodoen, "Mechanisms of human innate immune evasion by Toxoplasma gondii", Front. Cell. Infect. Microbiol., 9, 103 (2019).
[22]. P. V. dos Santos, D. N. M. de Toledo, D. M. S. de Souza, T. P. Menezes, L. O. Perucci, Z. M. Silva et al., "The imbalance in the relationship between inflammatory and regulatory cytokines during gestational toxoplasmosis can be harmful to fetuses: A systematic review", Front. Immunol., 14, 1074760 (2023).
[23]. L. M. Velez, M. Seldin and A. B. Motta, "Inflammation and reproductive function in women with polycystic ovary syndrome", Biol. Reprod., 104, 1205–1217 (2021).
[24]. S. Shojaee, A. Teimouri, H. Keshavarz, S. J. Azami and S. Nouri, "The relation of secondary sex ratio and stillborn history with Toxoplasma gondii infection", BMC Infect. Dis., 18, 10–15 (2018).
[25]. A. F. Alkhuriji, S. Y. Al Omar, Z. A. Babay, M. F. El-Khadragy, L. A. Mansour, W. G. Alharbi and M. I. Khalil, "Association of IL-1β, IL-6, TNF-α, and TGFβ1 Gene Polymorphisms with Recurrent Spontaneous Abortion in Polycystic Ovary Syndrome", Dis. Markers, 2020, 6076274 (2020).