The Effect of Toxoplasma IGG Antibodies on Folliculometry and Luteinizing Hormone Level in Unexplained Infertility

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Abstract: Background: *Toxoplasma gondii* (T. gondii) is an obligate intracellular protozoan parasite.1 It has a complex life cycle with asexual reproduction taking place in diverse tissues of mammals and birds (secondary hosts) and sexual reproduction taking place in digestive epithelium of cats (primary host). Primary infection of *T. gondii* in pregnant women can cause vertical transmission of the parasite and result in miscarriage, stillbirth, premature birth, malformations and other adverse pregnancy outcomes. **Objective:** The present study was designed to correlate the effect of toxoplasma Ig G antibodies on folliculometry and LH level in seropositive versus sero-negative infertile women. **Patients and Methods:** The study is a cross section study that was done on 100 infertile females patients attending the infertility clinic at Al-Azhar University Hospital (New Damietta) from May 2016 to October 2017. **Results:** There were a statistical significant differences between positive and negative studied cases regarding toxoplasmosis IgG, follicular development on 9th day, 11th day and 14th day and urinary LH level on 6th, 9th and 12th level. There was negative correlation between positive toxoplasmosis and follicular growth with statistically significant difference and also negative correlation between positive toxoplasmosis and LH surge with statistically significant difference. There was positive correlation between LH surge and follicular growth with statistically significant difference.

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Key words: Infertility, Toxoplasma gondii, LH

1. Introduction

Toxoplasmosis is a disease caused by an obligate intracellular protozoan parasite Toxoplasma gondii **(Dubey et al., 2009)**. Approximately one third of the world population is infected with this parasite **(Pappas et al., 2009)**.

Infertility is a disease of the reproductive system defined by failure to achieve a clinical pregnancy after twelve months **(Zegers-Hochschild, 2009).** Human infection is acquired through ingestion of food or water contaminated with oocysts shed in the feces of cats or viable tissue cysts in undercooked or raw meat **(Dubey, 2007)**.

Infection with Toxoplasma gondii is very common. Postnatal acquired toxoplasmosis is usually asymptomatic. However, clinical disease is greatly confined to risk groups, including infants and immunocompromised individuals. Level of seroprevalence for toxoplasmosis ranged from 8-77% worldwide **(Tentera et al., 2000)**.

Several studies have examined the causes of infertility in the Middle East. A high proportion of secondary infertility and a great contribution of the female factor was the major finding in most of these studies **(Oostrum et al., 2013)**.

Aral et al. (2011) suggested that toxoplasmosis has some unfavorable effects on reproductive capacity in both men and women concerning infertility mechanisms due to T. gondii in females include development of endometritis and fetal rejection due to local release of T. gondii from latently located cysts in endometrial tissue on stimulation during placenta formation and noticed impaired folliculogenesis in ovaries and endometrial atrophy and reproductive failure due to hypothalamic dysfunction as a result of chronic toxoplasmosis.

So, the aim of our study was to correlate the effect of toxoplasma Ig G antibodies on folliculometry and LH level in seropositive versus sero-negative infertile women.

2. Patients and Methods

The present cross sectional study was done on 100 infertile females patients attending the infertility clinic at Al-Azhar University Hospital (New Damietta) from May 2016 to October 2017 and has the following inclusion criteria; female with primary or secondary infertility, age between18 - 40 years and women with unexplained infertility.

The selected 100 infertile cases divided into two groups.

- **Seropositive group:** (IGg toxoplasmosis ≥ 160 Iu/ml): cases positive for toxoplasmosis IgG (37 cases).
- **Seronegative group:** cases negative for toxoplasmosis IgG (63 cases).
- Then two groups exposed to further examination through transvaginal ultrasound for folliculometry done at 9th, 11th and 14th day of menstrual cycle and the two groups were evaluated for LH surge by using urinary LH kits to measure LH levels in urine started at 6th, 9th and 12th day of menstrual cycle.

The Toxoplasma IgG estimated according to **Voller et al. (1976)** and Luteinizing hormone level was determined by quantitave colorimetric method using Biodiagnostic laboratory kit according to **Vlaisavljevic and Došen (2007).**

1- Full history taking: included age, parity, history of infertility and its type, duration of infertility and any other medical or surgical history. The history used to check for inclusion and exclusion criteria according to standardized research protocol.

2- Menstrual History was taken to ask about any menstrual irregularities, post menstrual spotting and dysmenorrhea.

3- Each woman was asked about any previous uterine surgery and any operative procedure was taken in consideration.

4- Past history including medical diseases (DM, Hypertension, Coagulopathies, cardiac and pulmonary diseases….), previous operations, previous dilatation and curettage, previous abortion or others.

Examination:

1- General examination:

Full general examination was done with special concern to

- Vital signs: Blood pressure, Pulse, temperature and respiratory rate.
- Pallor and signs of anemia.
- Chest and Heart examination.

2- Abdominal examination:

- Liver, spleen and loin

3- Semen analysis was done to their husband to exclude any disorder that leading to infertility.

4- Ultrasound examination:

Trans abdominal and Trans vaginal ultrasound were be used.

- Ultrasonography: ultrasound scan was performed using a Voluson 730 Pro machine (GE, Milan, Italy) equipped with a multifrequency volume endovaginal probe. The ovary could be described as a relatively small, paired organ with a complex, mosaic-like, constantly changing structure, which has a central role in reproduction as it is the only source of ova and the main site of sex steroid hormone production in females.

Ethical consent

The nature of the study was clearly explained to each patient. An informed written consent was obtained.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 22 (SPSS Inc, Chicago, USA), running on IBM compatible computer. For qualitative data, frequency and percent distributions were calculated. For quantitative data, mean, standard deviation (SD), minimum and maximum were calculated. For comparison between two groups, the independent samples (t) test was used. Pearson correlation co-efficient (r-test) was used for correlating different variables. For all tests p value <0.05 were considered significant. For all tests p value >0.05 were considered insignificant.

3. Results

The present cross-sectional study was done on 100 infertile females patients attending the infertility clinic at Al-Azhar university hospital in New Damietta.

The present work was done on women with mean age (25.04 ± 4.85 years), mean body weight (72.13 ± 4.66 Kg) and mean duration of marriage (3.07 ± 1.85 years) **(Table I).**

Table (I): Demographic data of the studied cases

Variable (No)	Studied cases (100)
Age (years)	
Mean± SD	25.04 ± 4.85
Minimum - Maximum	18 - 37
Body weight (Kg)	
Mean± SD	72.13 ± 4.66
Minimum - Maximum	65 - 83
Duration of marriage (years)	
Mean± SD	3.07 ± 1.85
Minimum - Maximum	1 - 8

The present study classified according to toxoplasmosis IgG into positive cases 37% and negative cases 63% **(Table II).**

Table (II): Classification of the studied cases.

Variable (No)	Studied cases (100)	
	Number	% ratio
Positive cases	37	37
Negative cases	63	63

Age, body weight and duration of marriage were nearly comparable between positive and negative studied cases (age; 24.79 ± 4.76 Vs 25.19 ± 4.85 years, body weight; 72.06 ± 4.7 Vs 72.17 ± 4.6 Kg and duration of marriage; 3.12 ± 1.9 Vs 3.04 ± 1.8 years) respectively **(Table III).**

The mean toxoplasmosis IgG was 0.99 ± 0.77, mean follicular developments by folliculometry were 10.44 ± 2.39, 13.61 ± 2.61 and 16.41 ± 3.6 on the 9th, 11th, and 14th days respectively and also the mean levels of urinary LH were 0.02 ± 0.01, 0.099 ± 0.23 and 0.37 ± 0.51 mIU/ml on the 6th, 9th and 12th days respectively **(Table IV).**

Table (III): Comparison between positive and negative studied cases regarding demographic data.

Variable Number	Positive cases (37)	Negative cases (63)	T test	P value
Age (years) Mean± SD Minimum - Maximum	 24.79 ± 4.76 18 - 37	 25.19 ± 4.85 18 - 36	0.38	0.7
Body weight (Kg) Mean± SD Minimum - Maximum	 72.06 ± 4.7 65 - 81	 72.17 ± 4.6 65 - 83	0.11	0.91
Duration of marriage (years) Mean± SD Minimum - Maximum	 3.12 ± 1.9 1 - 7	 3.04 ± 1.8 1- 8	0.21	0.83

There were a statistical significant differences between positive and negative studied cases regarding toxoplasmosis IgG (1.82 ± 0.49 Vs 0.5 ± 0.39), follicular development on 9th day, 11th day and 14th day (8.88 ± 1.89 Vs 11.35 ± 2.18, 11.62 ± 2.15 Vs 14.76 ± 2.12 and 13.16 ± 2.59 Vs 18.29 ± 2.67 respectively) and urinary LH level on 6th, 9th and 12th level (0.015 ± 0.007 Vs 0.03 ± 0.01, 0.026 ± 0.01 Vs 0.14 ± 0.27 and 0.063 ± 0.16 Vs 0.37 ± 0.51 respectively) **(Table V).**

There were statistical significant differences between follicular development of the positive studied cases on the 9th day and 11th day, on the 9th day and 14th day and also on the 11th day and 14th day **(Table VI).**

There were statistical significant differences between urinary LH levels of the positive studied cases on the 6th day and 9th day and on the 6th day and 12th day associated with non-statistical significant differences on the 9th day and 12th day **(Table VII).**

In the present study, there was negative correlation (r= -0.55) between positive toxoplasmosis and follicular growth with statistically significant difference and also negative correlation (r= -0.611) between positive toxoplasmosis and LH surge with statistically significant difference. There was positive correlation (r= 0.36) between LH surge and follicular growth with statistically significant difference **(Table VIII).**

Table (IV): Toxoplasmosis IgG, folliculometry and urinary LH level of the studied cases

Variable (No)	Studied cases (100)
Toxoplasmosis IgG Mean± SD Minimum - Maximum	 0.99 ± 0.77 0.1 – 2.89
Folliculometry on 9th day Mean± SD Minimum - Maximum	 10.44 ± 2.39 6.1 – 17.1

Variable (No)	Studied cases (100)
Folliculometry on 11th day Mean± SD Minimum - Maximum	 13.61 ± 2.61 7 - 19
Folliculometry on 14th day Mean± SD Minimum - Maximum	 16.41 ± 3.6 8.3 – 26.7
Urinary LH level on 6th day (mIU/ml) Mean± SD Minimum - Maximum	 0.02 ± 0.01 0.008 – 0.06
Urinary LH level on 9th day (mIU/ml) Mean± SD Minimum - Maximum	 0.099 ± 0.23 0.01 – 1.1
Urinary LH level on 12th day (mIU/ml) Mean± SD Minimum - Maximum	 0.37 ± 0.51 0.01 – 1.4

Table (V): Comparison between positive and negative studied cases regarding toxoplasmosis IgG, folliculometry and LH level.

Variable Number	Positive cases (37)	Negative cases (63)	T test	P value
Toxoplasmosis IgG Mean± SD Minimum - Maximum	 1.82 ± 0.49 0.75 – 2.89	 0.5 ± 0.39 0.1 – 1.51	14.17	<0.001*
Folliculometry on 9th day Mean± SD Minimum - Maximum	8.88 ± 1.89 6.1 – 14.0	11.35 ± 2.18 8.2 – 17.1	5.64	<0.001*
Folliculometry on 11th day Mean± SD Minimum - Maximum	11.62 ± 2.15 7 – 16.5	14.76 ± 2.12 12 - 19	6.69	<0.001*
Folliculometry on 14th day Mean± SD Minimum - Maximum	13.16 ± 2.59 8.3 – 18.7	18.29 ± 2.67 13.2 – 26.7	8.85	<0.001*
LH level on 6th day (mIU/ml) Mean± SD Minimum - Maximum	 0.015 ± 0.007 0.008 – 0.03	 0.03 ± 0.01 0.01 – 0.06	5.8	<0.001*
LH level on 9th day (mIU/ml) Mean± SD Minimum - Maximum	0.026 ± 0.01 0.01 – 0.06	0.14 ± 0.27 0.03 - 1.1	2.41	0.002*
LH level on 12th day (mIU/ml) Mean± SD Minimum - Maximum	0.063 ± 0.16 0.01 – 0.94	0.37 ± 0.51 0.01 – 1.4	4.85	<0.001*

* indicate significant.

Table (VI): Comparison between follicular development on the 9th and 11th days, on the 9th and 14th days and on the 11th and 14th days of the positive studied cases

Variable	Follicular development on 9th day	Follicular development on 11th day	Follicular development on 14th day
Mean± SD Minimum - Maximum	8.88 ± 1.89 6.1 – 14.0	11.62 ± 2.15 7 – 16.5	13.16 ± 2.59 8.3 – 18.7
P value		<0.001*	<0.001*
P value			0.01#

* indicate significant compared to development on 9th day. # indicate significant compared to development on 11th day.

Table (VII): Comparison between urinary LH levels on the 6th and 9th days, on the 6th and 12th and on the 9th day and 12th day of the positive studied cases

Variable	LH level on 6th day	LH level on 9th day	LH level on 12th day
Mean± SD	0.015 ± 0.007	0.026 ± 0.01	0.063 ± 0.16
Minimum - Maximum	0.008 – 0.03	0.01 – 0.06	0.01 – 0.94
P value		<0.001*	0.04*
P value II			0.19

* indicate significant compared to LH level on 6th day.
P value II indicate comparison compared to LH level on 9th day

Table (VIII): Correlation between positive toxoplasmosis, follicular growth and LH surge.

Variables	Follicular growth		LH surge	
	r	P	r	P
Positive toxoplasmosis	-0.55	0.001*	-0.611	<0.001*
LH surge	0.36	<0.001*	-	-

4. Discussion

Infertility is defined as a condition of the reproductive system in which there is a failure to achieve clinical pregnancy after 12 months of regular unprotected sexual intercourse **(Zegers-Hochschild et al., 2009).**

Infertility affects approximately 15–20% of reproductive aged couples. Primary infertility is a term used to describe a couple that has never been able to conceive a pregnancy after a minimum of 1 year of attempting to do so through unprotected intercourse. The infertility causes may be wide range of physical as well as emotional factors (**Rouchou, 2013**).

The incidence of ovarian ailments such as premature ovarian failure (POF) and polycystic ovary syndrome (PCOS) has risen in recent years, constituting a major cause of female subfertility in the modern world. Determination of ovarian status and follicle monitoring are important first steps in evaluating infertile females, making ovarian imaging the most common diagnostic approach for female infertility (**Goodarzi et al., 2011).**

Toxoplasma gondii is an obligate intracellular parasite, which affects a wide-range of mammals including human. Based on serological studies, T. gondii is one of the most prevalent protozoan parasites. Primary infection during pregnancy may cause spontaneous abortion or stillbirth **(El-Tantawy et al., 2014).**

Toxoplasma gondii test is a routine test for the infertile couples especially those with unobvious cause of infertility. Toxoplasma infection can cause severe damage in cases of congenitally acquired infection, serology is the only method to determine if the female has been infected by Toxoplasma gondii (recent or chronic infection) **(Jabbar, 2012).**

Thus, the aim of this work is to correlate the effect of toxoplasma Ig G antibodies on folliculometry and LH level in seropositive versus sero-negative infertile women.

In the present work, age, body weight and duration of marriage were nearly comparable between positive and negative studied cases (age; 24.79 ± 4.76 Vs 25.19 ± 4.85 years, body weight; 72.06 ± 4.7 Vs 72.17 ± 4.6 Kg and duration of marriage; 3.12 ± 1.9 Vs 3.04 ± 1.8 years) respectively.

The risk of abortion also increases as age progresses. Spontaneous miscarriage rates in natural conception cycles are generally low and stable before age 30 **(Fritz and Speroff, 2011)** so the age of the present study at range 25 years.

El-Tantawy et al. (2014) found the prevalence of anti- T. gondii IgG antibodies in the older age group (30-39 years) was more than other age groups reporting 65.65% in female infertility patients and 65% in pregnant females. There was a study carried in Menoufia governorate, Egypt among pregnant women reporting higher prevalence of anti-T. gondii IgG antibodies in older ages than younger ages with a percentage of 88.4 and 58.8 respectively **(El Deeb et al., 2012).** It is logic that seropositive cases for toxoplasmosis increase with age as older ones have more chance to be exposed to parasite infection (**Fan et al., 2003**).

Abdul-Aziz (2014) revealed an increase in the prevalence of toxoplasmosis infection at age group 43-60 years toxoplasmosis in hemodialysis patients in Baghdad.

Zain and Norman (2008) and Adesiyun (2012), reported that obesity contributes to anovulation and menstrual irregularities, reduced conception rate and a reduced response to fertility treatment. It also increases miscarriage and contributes to maternal and perinatal complication. Obesity and overweight are also associated with increased requirements for gonadotrophins and a

higher miscarriage rate. These differences are evident at a BMI over 25.

Homan et al. (2012) also reported that female fertility may be enhanced by losing weight through enhancing ovulation and improving pregnancy rate. The level of obesity in young women has been increasing, which leads to increased rates of anovulation and polycystic ovary syndrome (PCOS), as well as poorer response to fertility treatment.

Sharma et al. (2013) reported that for women, being underweight and having extremely low amounts of body fat are associated with ovarian dysfunction and infertility. The risk of ovulatory infertility increases in women with a BMI below 17. **Veleva et al. (2008),** found that obese and underweight women have an increased risk of miscarriage after IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection).

The Latex test was used to detect toxoplasmosis in serum because it is relatively simple, cheap and specific but less sensitive than other serological. Hence, ELISA IgG tests were used to more reliable results **(Abdul-Aziz, 2014).**

The present study classified according to toxoplasmosis IgG into positive cases 37% and negative cases 63% this results agree with **Siddiqui et al. (2014)** who done their work on patients suffered from infertility and reported that 55.1% had IgM and 44.9% had low IgG avidity antibodies. **Aral et al. (2011)** reported that 28.8% in infertile women had toxoplasmosis. **Zhou et al. (2002)** noticed that 34.8% of women with toxoplasmosis had relationship between this women and infertility.

Zakai and Bisharah (2015) noticed a significant positive correlation between the presence of IgG antibodies to Toxoplasma gondii and having problems in conceiving a child normally.

In contradiction **Elsheikha et al. (2009)** which reported 59.6% seroprevalence of anti-T. gondii IgG antibodies among blood donors in Mansoura University Hospital, Dakahlia governorate, Egypt. This high prevalence is due to lake of health education and exposure to risk factors including contact with cats, agricultural activities, eating raw unwashed vegetables, drink insufficiently boiled milk, eating insufficiently cooked meat like luncheon and shawerma (**El Deeb et al., 2012**).

Li et al. (2011) reported high prevalence (15.9%) of anti-T. gondii IgG antibodies using ELISA among female infertility patients in comparison to 5.6% among pregnant–puerperant women. The hypothesized mechanisms for this positive correlation between infertility and chronic Toxoplasma infection include development of endometritis and fetal rejection due to local release of T. gondii from latently located cysts in endometrial tissue on stimulation during placenta formation (**Akarsu et al., 2011**), impaired folliculogenesis in ovaries, uterine atrophy and reproductive failure due to hypothalamic dysfunction as a result of chronic toxoplasmosis **(El-Tantawy et al., 2014).**

Urinary luteinizing hormone predicts LH surge, the urinary LH surge usually occurs about 12 to 60 hours before ovulation. A shorter range is 22 to 44 hours, with a mean of 30 hours. The most sensitive use of the test requires a woman to empty her bladder in the morning, restrict fluids and then perform the test between 10 AM and 12 PM **(Anwar and Anwar, 2016).**

The mean levels of urinary LH were 0.02 ± 0.01, 0.099 ± 0.23 and 0.37 ± 0.51 mIU/ml on the 6^{th}, 9^{th} and 12^{th} days respectively. Determination of ovarian status and follicle monitoring are common methods of diagnosing female infertility (**Amy-Lin et al., 2016).**

Dvorakova-Hortova et al. (2014) found low levels of luteinizing hormone in urine of mice infected with toxoplasmosis. Toxoplasmosis may affect the level of different hormones in the body. This may have a secondary effect resulting in infertility, so the presence of anti-Toxoplasma antibodies in serum of young females as an indicator for possible future infertility **(Zakai and Bisharah, 2015)**.

The level of LH in urine was tested to address the first hypothesis, which suggests that T. gondii may activate the hypothalamo-pituitary-adrenal (HPA) stress axis and consequently modify the hypothalamo-pituitary-gonadal (HPG) axis resulting in an altered release of gonadotropins (**Terpsidis et al., 2009**). LH level was significantly decreased in positive toxoplasmosis groups and the decreased LH level disturb spermatogenesis process because of LH is one of the main regulators for germ cell development and released from hypophysis that is regulated by the hypothalamic GnRH (**Vyas, 2013**), the modification of HPA axis by the infection can result in an altered gonadotropin level due to the decrease of GnRH secretion by the hypothalamus or by the decrease of sensitivity of the hypophysis towards the GnRH (**Wistuba et al., 2007**).

Theca cells in the ovary respond to LH stimulation and ovulation of mature follicles on the ovary is induced by a large burst of LH secretion. The rapid increase in LH levels at mid-cycle (LH surge) causes a suspension of further granulosa cell mitosis and permits final oocyte maturation to begin and luteinization of the cumulus-oophorus to occur. The high levels of LH prevent further growth of the non-dominant follicles. LH plays critical roles in the control of folliculogenesis and ovarian function in humans **(Kumar and Sameer, 2012).** 139.

Metwally et al. (2007) reported that a patient's weight has a significant influence on follicular size

during ovarian steroidal stimulation. Obese women had lower peak estradiol level and require higher doses of gonadotrophins to achieve ovulation. Moreover, it has been suggested that weight loss regularizes menstrual cycles and increases the chance of spontenous ovulation and conception in anovulatory, overweight and obese women (**Nohr et al., 2009**).

Conclusions

This study revealed high seropostivity of IgG antibodies for toxoplasmosis among females in child bearing age. The infertile females had a significant higher prevalence of T. gondii infection than the controls. These data highlight the possible correlation between Toxoplasma infection and infertility. Toxoplasmosis can cause temporary impairment on the reproductive parameters.

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Recommendation

We recommended that the screening of young females of reproductive age before marriage for Toxoplasma antibodies using ELISA (IgG) and treat them is important to prevent infertility caused by it.

Further researches still needed to clarify the mechanism of association between toxoplasmosis and infertility.

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