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Researcher of Guizhou Rural Economic and Social Development Research Institute, China
yingwen0806@163.com

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Ph.D.
University of Glasgow, UK
Email Id: Lizihan1992@gmail.com

Gabriela Cioca

Pharmacology Department, Faculty of Medicine, Lucian Blaga University
of Sibiu, Lucian Blaga street, no 2A, Sibiu, Romania,

gabriela.cioca@ulbsibiu.ro

Dariusz Nowak

Municipal Hospital, Mickiewicza street no 12, 42-200 Czestochowa,

Poland

dariuszandrzejnowak@wp.pl

Aleksandra Zyska

Department of Physiology, Faculty of Medicine, University of Opole,

Oleska street no 48, 45-052 Opole, Poland

aleksandra.zyska@uni.opole.pl

Katarzyna Sznajder

Clinical Department of Diagnostic Imaging, Faculty of Medicine, University of Opole,

Oleska street no 48, 45-052 Opole, Poland

katarzyna.sznajder@uni.opole.pl

Jacek Jóźwiak

Department of Family Medicine and Public Health, Faculty of Medicine, University of Opole,

Oleska street no 48, 45-052 Opole, Poland,
jacek.jozwiak@uni.opole.pl

Luciano Benedini

Universidad Nacional del Sur, Bahía Blanca 8000,

Argentina

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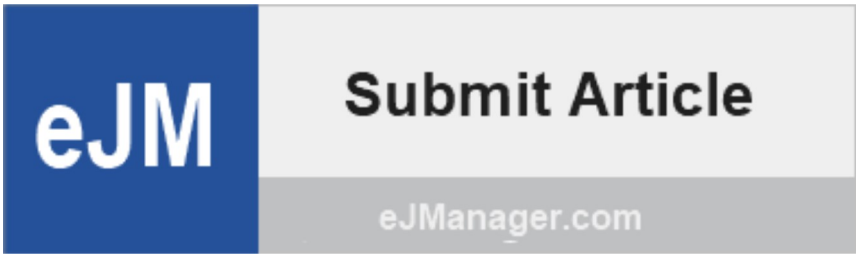
Departamento de Biología, Bioquímica y Farmacia,



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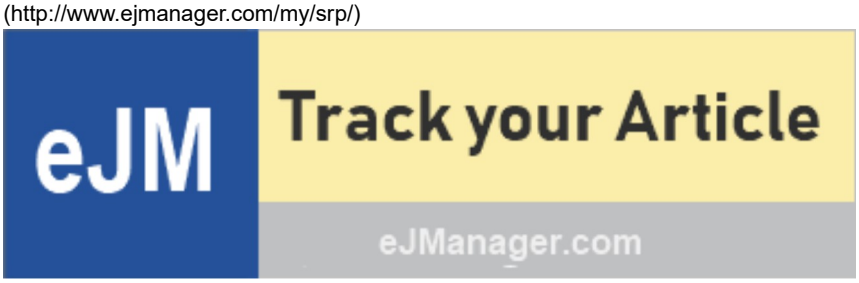

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Effects of Hyperbaric Oxygen Therapy on Il-17, Fetal Body Weight and Total Fetus in Pregnant Rattus Norvegicus Infected With Tachyzoite Toxoplasma Gondii

Arif Rahman Nurdianto[1,2], Aryati Aryati[3*], Muhammad Guritno Suryokusumo[4,5], Mufasirin Mufasirin[6], Lucia Tri Suwanti[6], Sunarjo[7], Teguh Wahju Sardjono[8], Erry Gumilar Dachlan[9]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
[2]Public Health Office of Sidoarjo - STIKES Anwar Medika Hospital, Sidoarjo 61262, Indonesia
[3]Department of Clinical Pathology, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
[4]Aquatic and Hyperbaric Medicine Academie Nationale de Medicine, Paris 75006, France
[5]Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, Jakarta, 12450, Indonesia
[6]Department of Parasitology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
[7]Departement of Public Health, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
[8]Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, Malang 65145, Indonesia
[9]Departement of Obstetric and Gynecology, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

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ABSTRACT

IL-17 in Toxoplasma gondii infection has an important role in miscarriage and low birth weight with many negative effects. This study explains the effect of hyperbaric oxygen (HBO2) administration on fetal body weight and IL-17 pregnant female rat levels. Rattus norvegicus were divided into four groups. IL-17 concentration was measured by serum ELISA. There was statistically significant reduction of IL-17 levels (79.42±30.36, 125.46±60.05, 201.17±70.33, 158.76±58.48, p = 0.001 for pregnant rats infected by Tachyzoite with HBO2 group, pregnant rats non-infected by Tachyzoit with HBO2 group, pregnant and infected without HBO2 group, and negative control, respectively). Although, there was no significant difference in the number of fetuses among groups (p = 0.096). The HBO2 treatment group had the heaviest of fetal weight among groups (0.98 [0.30 – 6.22] gram, p = 0.046). The results of the Spearman correlation test showed that only group B had a significant negative relationship between IL17 concentration and the mean fetal weight (p = 0.001). HBO2 therapy was found to be able to reduce IL-17 levels and result in rising of fetal weight in pregnant Rattus norvegicus and might prevent the occurrence of abortion.

Keywords: Toxoplasma gondii, Tachyzoite, HBO2, IL-17, Fetal Weight, Pregnant Rats.

Correspondence:
Aryati Aryati
Department of Clinical Pathology, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
E-mail: dr_aryati@yahoo.com

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INTRODUCTION

Toxoplasma gondii (*T. gondii*) often causes severe congenital toxoplasmosis through placental transmission and results in abortion, stillbirth, or congenital abnormalities in humans and mammals.(1,2) The maternal mortality rate in Indonesia in 2015 is 305 per 100,000 live births. Maternal mortality was caused, among others, by bleeding for 30.3%, hypertension for 27.1%, infection for 7.3%, 0% abortion, and others for 40.8%.(3)

The causes of abortion are divided into fetal factors and maternal factors.(4) Abortion from fetal factors caused by abnormalities in genetic development in the first quarter ranged from 60%, while maternal factor abortion which plays a role in genetic disorders is an infection in pregnancy, one of which is toxoplasmosis. The prevalence of *T. gondii* infection in Indonesia is 2–63%. The prevalence of *Toxoplasmosis* in East Java, especially in Jakarta and Surabaya, reached 70% and 58%.(5,6) As similiar with other infection such as *Helicobacter pylori*,(7,8) *T. gondii* associated with hygiene and sanitation.

Hyperbaric oxygen (HBO_2) can reduce the formation of TLR4, NF-κB and other inflammatory factors, such as TNF-α, IL-6, IL-1β, and ICAM-1.(9–11) Increased dissemination of transplacental *Tachyzoite* is associated with elevation of IFN-γ and ICAM-1 molecules that facilitate monocyte migration.(10,12) Monocytes are dominant cells infected by *tachyzoite* and facilitate tachyzoite migration to the placenta. Monocytes can actively penetrate the placental tissue with its gliding movements and transmigration capabilities.(13) However, this high infectious ability by the *Tachyzoite* will make it easier to infect a fetus resulting in abortion.

With the mechanism of HBO2 through decreasing IL-17 concentration and decreasing expression of ICAM-1, it was expected to be able to reduce the chance of *Tachyzoite* infecting the placenta through the interaction between monocytes infected by ICAM-1. The previous studies found an increase in the expression of Bcl2 in spiral arteries which also occurred in the administration of HBO_2 therapy. In addition, administration of HBO_2 can also prevent abortion.(14,15)

IL-17 concentration increased at the beginning of *T. gondii* infection. It was aimed at the development and recruitment of neutrophils which are useful for eliminating infections. Besides, the increase of IL-17 was also triggered by IL-6, IL-23, and TGF-β.(16) IL-17 also has a function in innate immunity to increase neutrophil recruitment for the elimination of *T. gondii*.(17) IL-17 can also increase the expression of anti-apoptotic Bcl-2 and decrease apoptotic factor Bax through signal transducer and activator of transcription 3 (STAT3) because of STAT3 functions for distinguishing Th17.(18)

Monocytes are cells that often getting infected by *Tachyzoites*. These cells can become vehicles for the

Tachyzoite to infect the placenta in pregnancy. In toxoplasmosis, excessive IFNγ production can trigger the expression of intracellular-1 (ICAM-1) adhesion molecules in the placenta. Monocytes infected by *Tachyzoite* will be easily attached then the *Tachyzoite* will easily infect the placenta by ICAM-1 intermediary, thus the incidence of infection in toxoplasmosis is very large because of this infected monocyte.(12,19,20)

IL-17 stimulates the production of IL-16, IL-18 and stimulate the formation of the ICAM-1. The administration of HBO_2 will be able to suppress proinflammatory cytokines such as TNF-α etc.(21–25) It is expected that by giving HBO_2, IL-17 concentration will be reduced so that the production of ICAM-1 can be suppressed and the possibility of *Tachyzoite* infection in the placenta increased We examined the effect of HBO_2 administration on fetal body weight and IL-17 pregnant female rat levels.

METHODOLGY

Animal Model

Rats were placed at the room with a temperature of 20-23ºC to increase pregnancy probability. Rats copulated at night, and the next day, the female rats' vaginas were examined for the presence of a vaginal plug. If the vaginal plug was positive, it means that the rats have been pregnant for 0.5 days.

The female rats with a vaginal plug were sent to the Bio-Safety Level 2 Lab (BSL2), Faculty of Veterinary, Universitas Airlangga to get inoculated using Tachyzoite. Before injecting tachyzoite, the abdomen was examined around the uterus to determine whether the rat was genuinely pregnant. The first day of the pregnancy was calculated based on the first day the rats having vaginal plug. Rats which were not found to be pregnant were left uninfected.

This was an animal study with a post-test only design with 49 *Rattus norvegicus Sprague Dawley*. Rats were separated into four groups with twelve rats in every group. Group A consisted of infected rats and treated with HBO2. In Group B rats were not infected and given with HBO_2. Group C consisted of infected rats without treatment. Whereas in Group D rats were uninfected and not treated. Rats in Groups A and C were given with 10^3 *Tachyzoite* through intraperitoneal injection. Examinations of IL-17 and fetal body weight were performed on day-5 after HBO_2 (HBO twice a day). Blood rats were taken by intracardiac technique. IL-17 concentration were measured by serum ELISA examination and the amount of the fetus was calculated then weighed before being put into formalin solution.

ELISA Procedure

Rats' blood was taken to Surabaya Tropical Infection Hospital from the *Toxoplasma gondii* Laboratory at the Faculty of Veterinary Medicine, Universitas Airlangga, to examine IL-17 concentration using the Bioassay Technology Laboratory rat IL-17 ELISA (Cat. No. E0115Ra, Lot. no.1807009, Bioassay Technology Laboratory, Shang Hai, China). Briefly, plasma was incubated for 15 minutes on the plate, washed, and labeled with biotinylated antibodies. After incubation for 30 minutes at room temperature, streptavidin-HRP was added, then reacted with 3.3', 5.5'-Tetramethylbenzidine. Measurements were made with a spectrophotometer set at 450 nm.

All procedures have been acknowledged by the Animal Care and Use Committee (ACUC) of the Faculty of Veterinary Medicine, Universitas Airlangga, with the ethical number 777-KE.

HBO_2 Protocol

HBO_2 with 100% oxygen pressure 2.4 ATA for 3 x 30 minutes with 5-minute relaxation intervals (2 sessions) per day for ten sessions in 1 chamber. The administration of HBO_2 was carried out in different cages in every group. During the administration of HBO2, the experimental animal still got ad libitum food and drink, except in the last session.(26,27) All data were processed using SPSS 21 for the normality test with saphiro Wilk, ANOVA Test, Kruskal Wallis test, ANOVA and then the data were examined using Spearman correlation statistical test.

RESULT

IL-17 concentration in group C experienced a significant increase compared to Group A given with Tachyzoite infection and HBO_2. This increase explains that administration of HBO_2 in pregnant rats infected by Tachyzoite can reduce IL-17 concentration in their blood serum. There was no abortion found in all rats during therapy.

The data normality test results using the Shapiro Wilk test showed IL17 data, and the number of fetuses in the four groups were normally distributed ($p > 0.05$), while the mean data in the four groups in the mean of fetal weight were not normally distributed ($p < 0.05$). Differences in IL17 and the number of fetuses among groups were analyzed using analysis of variance (Table 2), while differences in the mean of fetal were analyzed using the Kruskal Wallis test. IL-17 statistical test results with the SPSS 21 ANOVA program showed that there were significant differences between Group D and Group C ($p < 0.001$, Table 1), and Group D with Group C ($p < 0.001$). Variance Analysis Results showed that there were significant differences in IL-17 among groups ($p < 0.05$). The post hoc Anova results with LSD test showed that Group A was different from the other three groups; Group B was different from Group C. The results of the analysis of variance showed no significant difference in the number of fetuses among groups ($p > 0.05$). It can be concluded that the administration of HBO_2 can reduce IL-17 concentration in Group A. Whereas increases in IL-17 concentration occurred in group C (pregnant and infected only).

Kruskal Wallis test results showed that there were significant differences in mean of fetal weight among groups ($p = 0.046$), so it was necessary to do further tests to find out which groups were different. Mann-whitney test results showed Groups A and B differed from Group D (Table 3).

The results of the Spearman correlation test were only group B which showed a significant relationship between IL17 concentration and mean fetal weight ($p = 0.001$, Table 4). The relationship between IL17 and mean fetal weight had

negative relationship direction with the strength of a strong relationship. The results of the analysis of variance showed no significant difference in the number of fetuses among groups ($p > 0.05$).

DISCUSSION AND CONCLUSION

The results of the mean IL-17 level and the results of statistical tests showed that there was a significant decrease in IL17 concentration between all groups. With these results, the administration of HBO_2 has a significant effect on IL-17 concentration in pregnant rats infected with *Tachyzoite T. gondii*. There was no significant difference in number of fetuses among group. There was significant difference in fetal weight among groups, and there was negative relationship correlation between IL-17 serum concentration with fetal weight.

IL-17 expressing CD4+ and CD8+ T lymphocyte might have a function in the inflammatory response to *Tachyzoite*, so this cytokine plays a role in *Tachyzoite* exposure in pregnancy and control of parasitic invasion and replication. Cells involved in the IL-17 production are associated with abortion (28) and one of the causes of abortion is excessive apoptosis, especially in pregnancy with toxoplasmosis.(15) The number of CD4 + cells producing IL-17 in Rats infected by *T. gondii* was significantly higher.(28) This can be seen in the results of IL-17 concentration in the group of infected rats (Group C), found to be high.

Th17, which is a subset of T cells that produce cytokines IL-17, IL-21 and IL-22, contributes to the initial infection of parasites. Tc17 does not express perforin and granzyme B and was unable to mediate the target cell lysis process in vitro experiments. (28) Low concentration of IL-17 by giving HBO2 benefited group A rats because IL-17 could stimulate the production of IL-16 and IL-18 and stimulate the formation of the Intracellular Adhesion Molecule-1 (ICAM-1) in fibroblast cells. By suppressing IL-17 concentration by giving HBO_2, the expression of ICAM-1 could be suppressed so that it can reduce the number of macrophages infected by *Tachyzoite*s as not to infect placenta trophoblast cells and the other cells, such as myometrium and spiral arteries, so apoptosis does not occur from the spiral arteries and can prevent fetal weight loss and abortion.(15)

IL-17 has a harmful effect when its concentration is high, such as tissue damage and tissue degeneration during inflammation. IL-17 also induces the production, often synergistically, of cytokines IL-1, IL-6, TNF-α, chemokine, NOS, and matrix metalloproteinases (MMPs) by fibroblasts, macrophages, and endothelial cells.(29) Low IL-17 concentration after the administration of HBO_2 could also reduce the risk of monocytes infected by *Tachyzoite* to infect placenta because we know before in patients with Rheumatoid Arthritis (RA), IL-17 is strongly associated with increased monocyte migration activity and Monocyte Chemoattractant Protein-1 (CCL2/MCP-1) concentration.(30)

Another study also stated that the administration of HBO_2 could also reduce the formation of TLR4, NF-κB and other inflammatory factors, such as TNF-α, IL-6, IL-1β, and ICAM-1.(9) Increased dissemination of transplacental *Tachyzoite* is associated with increased IFN-γ secretion and ICAM-1 molecules that facilitate monocyte migration.(12) On the other hand, monocytes are permissive and dominant cells infected by *Tachyzoit*[4] and facilitate *Tachyzoit* migration to the placenta and the other cells. Although monocytes will not enter the fetal circulation, it can actively penetrate the placental tissue with its gliding movements and transmigration capabilities.(13) This high infectious ability by the *Tachyzoite* will make it easier to infect a rat fetus and result in fetal weight reduction and abortion. With the mechanism of HBO_2 through decreasing IL-17 concentration and decreasing expression of ICAM-1, it was expected to reduce the chance of *Tachyzoite* infecting the placenta through the interaction between monocytes infected with ICAM-1. With a great opportunity to infect the fetus, fetal body weight in Group C was lower than those in the other groups.

ROS production due to HBO administration increased. ROS could induce IDO production in rats which would increase so that the amount of tryptophan amino acids in the environment around cells decreased and finally stimulated Foxp3 + Tregs cell expansion as well as inhibited cell differentiation from Th17 so that IL-17 production would decrease.(31,32)

IL-17 concentration increased at the beginning of *T. gondii* infection. It was aimed at the development and recruitment of neutrophils, which are useful for eliminating infections. This could be seen in Group C. Besides, the increase of IL-17 was also triggered by IL-6, IL-23, and TGF-β.(16) IL-17 also has a function in innate immunity to increase neutrophil recruitment for the elimination of *T. gondii*.(17) IL-17 can also increase the expression of anti-apoptotic Bcl-2 and decrease apoptotic factor Bax through signal transducer and activator of transcription 3 (STAT3) because of STAT3 functions for distinguishing Th17.(18) Whereas in this study, administration of HBO_2 could reduce IL-17 so that apoptosis in the spiral arteries could be decreased as indicated by an increase in the expression of Bcl2 spirals arteries(15), and decreased apoptosis could prevent fetal rats weight loss.

In an in-vitro study, high concentration of IL-17 with TNF-α and IL-1 cytokines could cause bone damage and bone resorption. With the addition of these three anti-cytokines in an experiment, it reduces the rate of bone damage. Therefore IL-17, in this case, has a high role in tissue damage with TNF-α and IL-1. In other cases, additional IL-17 with TNF-α together triggered platelet aggregation and thrombosis. From the explanation above, it can be explained that IL-17 and TNF-α synergize to cause inflammatory effects on tissues that have infection or inflammation. Whereas in this study low IL-17 concentration were found in the group given HBO2 (group A) compared to group C, and in group B there was also low IL-17 level compared to that in Group D.(33) Low IL-17 concentration with HBO_2 administration was not followed by an increase in TNF-α. It can be seen in previous studies because it was found that TNF-α and IFN-γ concentration were also high with HBO_2 administration in pregnant rats infected by *T. gondii*.(14) Low concentration of IL-17 can control the occurrence of over inflammation in cases of toxoplasmosis in pregnancy.

Weight loss can occur if prostaglandin and TNF-α production can cause parasitic infections in the placenta so that it can interfere with placental function as a food supplier for the fetus. In addition, high IL-17 can also cause macrophage infiltration in the placenta, and the accumulation can interfere with intervillous fetomaternal compartment, which can ultimately interfere with fetal nutrition intake until the occurrence of preterm birth or abortion.(34,35) This explains that high levels of IL17 can cause weight loss in Groups C and A compared to those in Groups B and D. Statistical results also showed that there was significant relationship of decreasing IL-17 levels with the administration of HBO_2 in normal pregnancy, which can reduce the mean fetal weight fetus.

This study has limitations on the use of the number of samples and applications in humans so that it was done first in rats. Based on the results of this study, researchers tried to research other variables before doing at the human stage. This study aimed to look for adjuvant therapy for patients with toxoplasmosis during pregnancy as well as patients who would plan to become pregnant and infected by *T. gondii*. Cases of *T. gondii* infection in Indonesia are often found when pregnant women visit, and there have been cases of abortion in the babies. By doing this study, the authors expected that pregnant women who are at risk of being infected by *T. gondii* are screened for *T. gondii* infection before pregnancy or during pregnancy, so congenital abnormalities in the fetus can be prevented.

Researchers expected that providing health services to pregnant women, such as *T. gondii* screening before and during pregnancy, can reduce the rate of low birth weight, disability and abortion of pregnant women in the world. With this preventive effort, it was expected to reduce the rate of low birth weight, abortion and infant disability due to infection of *T. gondii* because we know that material losses in patients due to abortion and infant defects are higher and have social and economic impacts on patients and families. Therefore, if there are pregnant women infected by *T. gondii*, adjuvant therapy in the form of HBO_2 can be given.

The administration of HBO_2 in pregnancy has been carried out by several previous researchers in humans and proven to be safe and can provide an increase in hemoglobin concentration in pregnant women with anemia.(36)

Administration of HBO_2 2.4 ATA for 3x30 minutes in ten sessions can reduce serum IL-17 concentration in pregnant *Rattus norvegicus* infected by *Tachyzoite T. gondii*. The reduction of IL-17 concentration, in turn, will provide protection for pregnancy, especially fetuses because decreased IL17 production of pregnant rat serum can prevent fetal weight loss, low birth weight dan abortion in pregnant rats infected with *T. gondii*.

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Table 1. Different test results IL-17 in four groups

Groups	N	Mean±SD	P value
Infection +, HBO_2 +	12	79.42±30.36[a]	<0.001
Infection -, HBO_2 +	13	125.46±60.05[b]	
Infection +, HBO_2 -	12	201.17±70.33[c]	
Infection -, HBO_2 -	12	158.76±58,48[bc]	

Note: Different superscripts show significant differences

Table 2. Differences in the number of fetuses among groups

Groups	N	Mean±SD	p value
A	12	8.92±1.881	0.096
B	13	8.54 ± 2.184	
C	12	7.58 ± 1.929	
D	12	9.58 ± 1.676	

Table 3. Mean fetal weight differences among groups

Group	N	Median (min – max)	P value
A	12	0.98 (0.30 – 6.22) [a]	0.046
B	13	0.68 (0.1 – 5.13) [a]	
C	12	0.52 (0.31 – 6.55) [ab]	
D	12	2.43 (1.20 – 21.02) [b]	

Note: Different superscripts show significant differences

Table 4. The results of the relationship between the concentration of IL17 with the mean of fetal weight in each group

Groups	N	Spearman Correlation Coefficient	P value
A	12	-0.399	0.198
B	13	-0.786	0.001
C	12	0.410	0.186
D	12	-0.448	0.145