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Toxoplasma gondii and Male Reproduction Impairment: A new Aspect of Toxoplasmosis Research

Abdolhossein Dalimi [1,*], Amir Abdoli [1]

[1]Department of Parasitology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, IR Iran

*Corresponding author: Abdolhossein Dalimi, Department of Parasitology, Faculty of Medical Sciences, Tarbiat Modares University, P. O. Box: 14115-331, Tehran, IR Iran. Tel: +98-2182883838, Fax: +98-2182884555, E-mail: dalimi_a@modares.ac.ir.

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Introduction: *Toxoplasma gondii* is one of the most important pathogen that has adverse effect on reproductive function.
Evidence Acquisition: Recent studies revealed that infection with *T. gondii* not only affect female reproduction, also cause male reproductive impairment. In clinical studies, high prevalence of toxoplasmosis in sterile men has been reported. In animal models, toxoplasmosis is associated with male reproductive impairment. Moreover, there are some evidences about venereal transmission of *T. gondii*. Drugs used for treatment of toxoplasmosis may cause adverse effects on male reproductive function.
Results: In present article, effect of *Toxoplasma* infection on male reproductive system of human and animal was reviewed.
There are several reports expressing association between Toxoplasmosis and male genital tract impairment in both human and animals.
Conclusions: These findings suggest that *T. gondii* infection can cause temporary impairment on the reproductive parameters of human or animal male as well as impairment of different hormones which may cause insufficient male reproductivity.

Keywords: Toxoplasma gondii; Reproductive function; Sterility

1. Introduction

Toxoplasma gondii is an intracellular protozoan that infected approximately one-third of the world's population. Feline including domestic cat act as definitive host and various warm-blooded animals as well as human, act as an intermediate host. The infection in human generally occurs through consuming food or drink contaminated with oocysts or tissue cysts. Congenital transmission and organ transplantation are other routes of the infection (1). Human toxoplasmosis is spreading in different parts of the world including Iran (2, 3). Seroprevalence rate of the infection is estimated between 20 - 80%. The most common form of the infection in humans is latent (asymptomatic) but in some conditions like immune-compromised patients and congenitally infected fetuses and newborns, the infection may cause severe disease (4, 5).

In life cycle of *Toxoplasma*, after ingestion of parasite and proliferation of tachyzoites during acute stage, the parasite is usually localized in different organs (6, 7) including male and female reproductive organs of intermediate hosts (8-14). So, the infection may cause some adverse effects on reproductive function. In the recent years profound adverse effects of *Toxoplasma* infection on female reproductive functions have been reported by some workers (15); but the reports on male reproductive parameters are little. In the present paper the effect of *Toxoplasma* infection on reproductive system in male human and animal is reviewed.

2. Evidence Acquisition

A comprehensive search of PubMed and SIRUS was performed with the following MeSH term search keywords: *T. gondii*, male reproduction, sterility, infertility, semen, spermatogenesis, pyrimethamine, sulfadiazine, Sulpha-trimethoprim. All published data from 1945 until Dec 2011, have been included in this study. The inclusion criteria for the study are; toxoplasmosis and/or pyrimethamine, sulfadiazine, Sulpha-trimethoprim affecting human or animal reproductive function, sterility, infertility, spermatogenesis.

3. Results

3.1. Male Sterility and T. gondii Infection

A few clinical studies have reported that *T. gondii* affect reproductive parameters of men. In this regard; Zhou et al. (16) showed that, infection with *T. gondii* in infertile couples is significantly higher than fertile couples

Implication for health policy/practice/research/medical education:
This review is about pathological effects of *Toxoplasma gondii* which may be used as an effective target for prevention and controlling toxoplasmosis.

(34.83% versus 12.11% respectively, P < 0.01) and level of anti-sperm antibody is significantly higher in *Toxoplasma* infected than non-infected couples. Another study was done in Chinese infertile men that shown among 100 cases of man's sterility, 36% of them were serologically *Toxoplasma* positive, while the seropositivity of *Toxoplasma* infection in fertile men was 11% (17). Moreover, there are several reports express association of male genital tract impairment with special feature of testicular Toxoplasmosis (8-11), *Toxoplasma* orchitis (12, 13) and hypogonadotropic hypogonadism caused by congenital Toxoplasmosis (14). These evidences suggest *Toxoplasma* infection in men may be associated with male sterility.

3.2. Evidences From Animal Models

Rats are considered as the best model for human Toxoplasmosis investigation, whereas chronic form of Toxoplasmosis in human is similar to rat (18). Abdoli et al. (19) conducted different sperm parameters (including: sperm motility, viability, concentration and number of normal spermatozoa) along with various fertility parameters like fructose levels in seminal vesicle, coagulating gland, testosterone in serum and testes were significantly decreased temporary up to 70 days after infection with *T. gondii*. These findings suggest that, Toxoplasmosis can cause temporary impairment on the reproductive parameters of male rats. Also, other studies in rat model revealed that different sperm parameters (20, 21), testes weights, serum testosterone and total antioxidant capacity were significantly decreased in infected animals compared to control cases (21).

Further studies on mice showed acute *T. gondii* infection significantly decreased various reproductive parameters such as testicular LDH-X, sperm concentration, motility and number of normal spermatozoa in infected animals compare to control group (22). Moreover, acute Toxoplasmosis in male mice can induce pathological changes in different reproductive organs such as testes, epididymis, vas deferens and prostate (23-25). These data propose that, acute *T. gondii* infection can cause severe impairment on the reproductive parameters of male rats. Lopes et al (25) observed in larger animals such as sheep no alteration in sperm parameters experimentally infected with *T. gondii*, However, various histopathological changes in testicles, prostate and seminal vesicles in infected animals observed.

3.3. Venereal Transmission of T. gondii

Transmission of *T. gondii* occurs via oral rout, congenital transmission, organ transplantation and rarely through blood transfusions (3). In different studies *T. gondii* detected in semen and reproductive organs of experimentally infected male rat (27), rabbit (28, 29), dog (30), goat (31, 32), sheep (33-37), cattle (38) and pig (39). There are some evidence propose that *T. gondii* can transmit with semen to female animals (28, 30, 36). In this regard, data obtained by Arantes et al. has clearly shown that *T. gondii* is transmitted through semen to female dog (30). In their study, *T. gondii* detected in testicle, epididymis and seminal samples of experimentally infected male dogs. Moreover, the infected seminal samples were injected to *Toxoplasma*-negative female dogs with artificial insemination. They observed all of the female dogs were infected. In two of the female dogs fetal reabsorption occurred at the beginning of gestation, likewise numerous Toxoplasmic cerebral cysts were isolated from four puppies of the dogs (30).

In rabbit, presence of *T. gondii* DNA in semen and blood of experimentally infected male has been observed at 7 to 88 days post infection (28). The infection in some *Toxoplasma*-negative female rabbits resulted from artificial insemination of infected semen has been reported by Liu et al. (29). A recent study conducted by de Moraes et al. showed that in sheep artificial insemination of semen experimentally contaminated with *T. gondii* tachyzoites was capable to infect sheep that suggested the possibility of venereal transmission of *T. gondii* in sheep (36, 37). Furthermore, persistent anestrus, hydrometra, mucometra and follicular cysts along with histopathological lesions in placentas were observed in female sheep that infected with contaminated semen (36, 37).

A remarkable study conducted by Dass et al. revealed that *T. gondii* could transmit sexually in rats (27). In this study, *T. gondii* cysts were observed in epididymis and semen of infected male rats eight weeks post-infection. The cysts also observed in vaginal lavage of female rats 12 hours after mating with infected male rats resulting infection in female rats. In addition, Parasite cysts were detected in some pups of mated females. These observations confirm sexually transmission of *T. gondii* in rats. Moreover, comparison of mating behavior in infected and non-infected rats showed *T. gondii* enhanced sexual attractiveness of infected animals with manipulation of mating behavior; that means uninfected females preferred infected males. So, *T. gondii* gained greater opportunities for venereal transmission.

Hormonal manipulations of *T. gondii* may lead to male reproductive impairment. Impairment of different hormones was reported during *T. gondii* infection (40-49). This impairment may cause insufficient male reproductivity. Testosterone is one of the most important hormones that play a critical role in male fertility. Recently, Kanˇková et al. reported that the level of testosterone was decreased in *T. gondii* infected male and female mice than uninfected control animals (40). Similarly, the study conducted by Khaki et al and Abdoli et al. revealed that impairment of reproductive functions of *T. gondii* infected male rats was along with testosterone reduction (19, 21). Furthermore, Oktenli et al. reported that serum FSH, LH and total and free testosterone were decreased in

male patients with acute Toxoplasmosis; in contrast, IL-1β increased in these patients and negatively correlated with the levels of FSH, LH and total and free testosterone (41). They concluded that acute *Toxoplasma* infection may cause temporary hypogonadotrophic gonadal insufficiency regardless to the course of the disease.

Hypothalamic–pituitary axis dysfunction was also observed in murine Toxoplasmosis (42-45), for instant Stahl et al. reported female mice a few weeks after infection with *T. gondii* developed hypogonadotrophic hypogonadism resulting hypothalamic dysfunction (42-44). Additionally they concluded that, the edematous changes particular in thalamus and hypothalamus may cause malfunctioning of supra and intrahypothalamic centers regulating the pulsatility and release of GnRH. Furthermore, two case reports of pituitary adenoma associated with *T. gondii* infection have been published by Zhang et el. (46).

On the other hand, hypothalamic–pituitary axis dysfunction affect on thyroid and sex steroid hormones which influence on male reproduction (47, 48). Thyroid dysfunction (hypothyroxinaemia) as a result of thyrotropin-releasing hormone impairment (TRH), thyroid-stimulating hormone (TSH) and decreasing serum thyroxine (T4) levels reported in *T. gondii* infected mice by Stahl et al. (49, 50). Normal thyroid hormone levels play an important role in testicular development and its function (48). Alteration in thyroid hormones (particular hypothyroidism) negatively affects gonadotropin secretion (like testosterone) and semen quality (48, 51-54). To consider the effects of *Toxoplasma* infection on thyroid function; impairment of male reproductive function within this indirect mechanism is plausible.

3.4. Drugs use in Treatment of Toxoplasmosis Affects Male Reproductive Function

Treatment of Toxoplasmosis in immunocompetent individuals is usually administered with combination of pyrimethamine, sulfadiazine, and folinic acid for 4–6 weeks. Also, in immunocompromised individuals, trimethoprim/sulfamethoxazole prophylaxis is highly effective antibiotic (1).

Several reports indicated that anti- *Toxoplasma* drugs, particularly pyrimethamine, have adverse effects on male reproductive function (55-63). According to experimental studies in male mice and rats, different fertility parameters, like sperm motility and sperm counts were significantly decreased in pyrimethamine treated animals. In addition, structure of testes and epididymis were altered in treated animals compare to control group (55-57). Other studies suggested, pyrimethamine have mutagenesis effects in germ cells of mice testes and can cause reduction in synthesis of DNA in spermatogonia cells (58, 59). Different studies suggested that drugs with antifolate effects or anti-dihydrofolate reductase (DHFR), affects the availability of purines and pyrimidines of DNA synthesis and may have antifertility effects (56). Antifertility effects of other anti-*Toxoplasma* drugs such as sulfadiazine and combination of trimethoprim/sulfamethoxazole have also been considered in further studies (60-63).

Although antifertility effects of toxoplasmosis and anti-*Toxoplasma* drugs have been reported in various studies, there is not any report that reveal whether combination of the disease and drugs have synergic adverse effect on male reproductive functions or not? This question is very serious and unpredictable.

4. Conclusions

These findings suggest that *T. gondii* infection can cause temporary impairment on the reproductive parameters of human or animal male as well as impairment of different hormones which may cause insufficient male reproductivity. Furthermore, the parasite is able to transmit with semen to female animal. As most of the investigations in this matter concentrated on animals, the outcome of this review may be applied to human Toxoplasmosis. However, to increase our knowledge about the outcome of the disease on human reproductive system, more researches should be done in this area.

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Authors' Contribution

Both authors contributed in preparing and editing the manuscript.

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References

1. Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet.* 2004;**363**(9425):1965–76.
2. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. *Int J Parasitol.* 2000;**30**(12-13):1217–58.
3. Shahmoradi A, Rezaian M, Dalimi A. Sheep an important reservior of human toxoplasmosis in Iran. *Med J IR.Iran.* 1993;**7**(3):173–174.
4. Weiss LM, Dubey JP. Toxoplasmosis: A history of clinical observations. *Int J Parasitol.* 2009;**39**(8):895–901.
5. Hill D, Dubey JP. Toxoplasma gondii: transmission, diagnosis and prevention. *Clin Microbiol Infect.* 2002;**8**(10):634–40.
6. Sharifian M, Dalimi A, Kazemi B. Early diagnosis of toxoplasmosis by PCR method in the blood of experimentally infected rats. *J Vet Res.* 2003;**58**(4):323–327.

7. Zare F, Dalimi A, Ghaffarifar F. Detection of active Toxoplasma godii (RH strain) in the different body tissues of experimentally infected rats. *Modares J Med Sci.* 2006;**9**(1):19–23.
8. Martinez-Garcia F, Regadera J, Mayer R, Sanchez S, Nistal M. Protozoan infections in the male genital tract. *J Urol.* 1996;**156**(2 Pt 1):340–9.
9. Nistal M, Santana A, Paniaqua R, Palacios J. Testicular toxoplasmosis in two men with the acquired immunodeficiency syndrome (AIDS). *Arch Pathol Lab Med.* 1986;**110**(8):744–6.
10. Barreto F, Hering F, Dall'oglio MF, Martini Filho D, Campagnari JC, Srougi M. [Testicular toxoplasmosis: a rare case of a testicular mass]. *Actas Urol Esp.* 2008;**32**(6):666–8.
11. De Paepe ME, Guerrieri C, Waxman M. Opportunistic infections of the testis in the acquired immunodeficiency syndrome. *Mt Sinai J Med.* 1990;**57**(1):25–9.
12. Crider SR, Horstman WG, Massey GS. Toxoplasma orchitis: report of a case and a review of the literature. *Am J Med.* 1988;**85**(3):421–4.
13. Haskell L, Fusco MJ, Ares L, Sublay B. Disseminated toxoplasmosis presenting as symptomatic orchitis and nephrotic syndrome. *Am J Med Sci.* 1989;**298**(3):185–90.
14. Suresh Babu PS, Nagendra K, Navaz RS, Ravindranath HM. Congenital toxoplasmosis presenting as hypogonadotropic hypogonadism. *Indian J Pediatr.* 2007;**74**(6):577–9.
15. Jones J, Lopez A, Wils NM. Congenital Toxoplasmosis. *Am Famil Phys.* 2003;**67**:2131–2138.
16. Zhou YH, Lu YJ, Wang RB, Song LM, Shi F, Gao QF, et al. [Survey of infection of Toxoplasma gondii in infertile couples in Suzhou countryside]. *Zhonghua Nan Ke Xue.* 2002;**8**(5):350–2.
17. Qi R, Su XP, Gao XL, Liang XL. [Toxoplasma infection in males with sterility in Shenyang, China]. *Zhonghua Nan Ke Xue.* 2005;**11**(7):503–4.
18. Dubey JP, Frenkel JK. Toxoplasmosis of rats: a review, with considerations of their value as an animal model and their possible role in epidemiology. *Vet Parasitol.* 1998;**77**(1):1–32.
19. Abdoli A, Dalimi A, Movahedin M. Impaired reproductive function of male rats infected with Toxoplasma gondii. *Andrologia.* 2012;**44 Suppl 1**:679–87.
20. Terpsidis KI, Papazahariadou MG, Taitzoglou IA, Papaioannou NG, Georgiadis MP, Theodoridis IT. Toxoplasma gondii: reproductive parameters in experimentally infected male rats. *Exp Parasitol.* 2009;**121**(3):238–41.
21. Khaki A, Farzadi L, Ahmadi S, Ghadamkheir E, Saedeh SS, Sahizadeh R. Recovery of spermatogenesis by Allium cepa in Toxoplasma gondii infected rats. *Afr J Pharm Pharmacol.* 2011;**5**(7):903–907.
22. Sun LH, Fan F, Wang JJ, Gong J. [Acute Toxoplasma gondii infection affects the reproductive function of male mice]. *Zhonghua Nan Ke Xue.* 2008;**14**(1):55–7.
23. Shen L. [Pathology and pathogenetic study of the Toxoplasma gondii acute infection mice testis]. *Chin J Zoonos.* 2001:17:75–77.
24. Lu M, Yang LD, Chen CY, Wu XZ, Gong F. [Infertility experiment on male mice infected with Toxoplasma]. *Chin J Zoonoses.* 2005;**21**:592–594.
25. Lopes WD, Costa AJ, Souza FA, Rodrigues JD, Costa GH, Soares VE, et al. Semen variables of sheep (Ovis aries) experimentally infected with Toxoplasma gondii. *Anim Reprod Sci.* 2009;**111**(2-4):312–9.
26. Lopes WD, Santos TR, Luvizotto MC, Sakamoto CA, Oliveira GP, Costa AJ. Histopathology of the reproductive system of male sheep experimentally infected with Toxoplasma gondii. Parasitol Res. 2011;109(2):405-9.
27. Dass SA, Vasudevan A, Dutta D, Soh LJ, Sapolsky RM, Vyas A. Protozoan parasite Toxoplasma gondii manipulates mate choice in rats by enhancing attractiveness of males. *PLoS One.* 2011;**6**(11).
28. Liu SG, Zhang HZ, Li X, Zhang Z, Hu B. Dynamic observation of polypide in semen and blood of rabbits infected with Toxoplasma tachyzoites. *Chin Med J (Engl).* 2006;**119**(8):701–4.
29. Liu SG, Qin C, Yao ZJ, Wang D. Study on the transmission of Toxoplasma gondii by semen in rabbits. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi.* 2006;**24**(3):166–70.
30. Arantes TP, Lopes WD, Ferreira RM, Pieroni JS, Pinto VM, Sakamoto CA, et al. Toxoplasma gondii: Evidence for the transmission by semen in dogs. *Exp Parasitol.* 2009;**123**(2):190–4.
31. Dubey JP, Sharma SP. Prolonged excretion of Toxoplasma gondii in semen of goats. *Am J Vet Res.* 1980;**41**(5):794–5.
32. Santana LF, da Costa AJ, Pieroni J, Lopes WD, Santos RS, de Oliveira GP, et al. Detection of Toxoplasma gondii in the reproductive system of male goats. *Rev Bras Parasitol Vet.* 2010;**19**(3):179–82.
33. Spence JB, Beattie CP, Faulkner J, Henry L, Watson WA. Toxoplasma gondii in the semen of rams. *Vet Rec.* 1978;**102**(2):38–9.
34. Teale AJ, Blewett DA, Miller JK. Experimentally induced toxoplasmosis in young rams: the clinical syndrome and semen secretion of toxoplasma. *Vet Rec.* 1982;**111**(3):53–5.
35. Lopes WD, da Costa AJ, Santana LF, Dos Santos RS, Rossanese WM, Lopes WC, et al. Aspects of toxoplasma infection on the reproductive system of experimentally infected rams (ovis aries). *J Parasitol Res.* 2009;**2009**.
36. de Moraes EP, Batista AM, Faria EB, Freire RL, Freitas AC, Silva MA, et al. Experimental infection by Toxoplasma gondii using contaminated semen containing different doses of tachyzoites in sheep. *Vet Parasitol.* 2010;**170**(3-4):318–22.
37. Moraes EP, Freitas AC, Gomes-Filho MA, Guerra MM, Silva MA, Pereira MF, et al. Characterization of reproductive disorders in ewes given an intrauterine dose of Toxoplasma gondii tachyzoites during the intrauterine insemination. *Anim Reprod Sci.* 2010;**122**(1-2):36–41.
38. Scarpelli L, Lopes WDZ, Migani M, Bresciani KDS, Costa AJd. Toxoplasma gondii in experimentally infected Bos taurus and Bos indicus semen and tissues. *Pesq Vet Bras.* 2009;**29**(1):59–64.
39. Moura AB, Costa AJ, Jordão Filho S, Paim BB, Pinto FR, Di Mauro DC. Toxoplasma gondii in semen of experimentally infected swine. *Pesq Vet Bras.* 2007;**27**(10):430–434.
40. Kankova S, Kodym P, Flegr J. Direct evidence of Toxoplasma-induced changes in serum testosterone in mice. *Exp Parasitol.* 2011;**128**(3):181–3.
41. Oktenli C, Doganci L, Ozgurtas T, Araz RE, Tanyuksel M, Musabak U, et al. Transient hypogonadotrophic hypogonadism in males with acute toxoplasmosis: suppressive effect of interleukin-1 beta on the secretion of GnRH. *Hum Reprod.* 2004;**19**(4):859–66.
42. Stahl W, Dias JA, Turek G. Hypothalamic-adenohypophyseal origin of reproductive failure in mice following chronic infection with Toxoplasma gondii. *Proc Soc Exp Biol Med.* 1985;**178**(2):246–9.
43. Stahl W, Kaneda Y, Noguchi T. Reproductive failure in mice chronically infected with Toxoplasma gondii. *Parasitol Res.* 1994;**80**(1):22–8.
44. Stahl W, Dias JA, Turek G, Kaneda Y. Etiology of ovarian dysfunction in chronic murine toxoplasmosis. *Parasitol Res.* 1995;**81**(2):114–20.
45. Antonios SN, Ismail HI, Essa T. Hypothalamic origin of reproductive failure in chronic experimental toxoplasmosis. *J Egypt Soc Parasitol.* 2000;**30**(2):593–9.
46. Zhang X, Li Q, Hu P, Cheng H, Huang G. Two case reports of pituitary adenoma associated with Toxoplasma gondii infection. *J Clin Pathol.* 2002;**55**(12):965–6.
47. Achermann JC, Jameson JL. Fertility and infertility: genetic contributions from the hypothalamic-pituitary-gonadal axis. *Mol Endocrinol.* 1999;**13**(6):812–8.
48. Choksi NY, Jahnke GD, St Hilaire C, Shelby M. Role of thyroid hormones in human and laboratory animal reproductive health. *Birth Defects Res B Dev Reprod Toxicol.* 2003;**68**(6):479–91.
49. Stahl W, Kaneda Y. Impaired thyroid function in murine toxoplasmosis. *Parasitology.* 1998;**117 (Pt 3)**:217–22.
50. Stahl W, Kaneda Y. Aetiology of thyroidal dysfunction in murine toxoplasmosis. *Parasitology.* 1998;**117 (Pt 3)**:223–7.
51. Wagner MS, Wajner SM, Maia AL. The role of thyroid hormone in testicular development and function. *J Endocrinol.* 2008;**199**(3):351–65.
52. Buitrago JM, Diez LC. Serum hormones and seminal parameters in males with thyroid disturbance. *Andrologia.* 1987;**19**(1):37–41.
53. Krassas GE, Papadopoulou F, Tziomalos K, Zeginiadou T, Pontikides N. Hypothyroidism has an adverse effect on human spermatogenesis: a prospective, controlled study. *Thyroid.* 2008;**18**(12):1255–9.
54. Corrales Hernandez JJ, Miralles Garcia JM, Garcia Diez LC. Pri-

mary hypothyroidism and human spermatogenesis. *Arch Androl.* 1990;**25**(1):21–7.
55. Cosentino MJ, Pakyz RE, Fried J. Pyrimethamine: an approach to the development of a male contraceptive. *Proc Natl Acad Sci U S A.* 1990;**87**(4):1431–5.
56. Kalla NR, Saggar SK, Puri R, Mehta U. Regulation of male fertility by pyrimethamine in adult mice. *Res Exp Med (Berl).* 1997;**197**(1):45–52.
57. Awoniyi CA, Chandrashekar V, Hurst BS, Kim WK, Schlaff WD. The effects of chronic administration of pyrimethamine on spermatogenesis and fertility in male rats. *J Androl.* 1993;**14**(3):174–9.
58. Egeli U, Aydemir N, Akpinar G, Cimen C, Ergul E, Tutar G, et al. In vivo dominant lethal effect of pyrimethamine in male mouse germ cells. *Mutagenesis.* 1999;**14**(1):67–9.
59. Lee SK, Lee JS, Kim KA, Cho JS. Effect of Pyrimethamine on DNA Synthesis of Germ Cells in Mice Testis. *Korean J Urol.* 1995;**36**(4):386–391.
60. Osenkop RS, Macleod J. Sulfadiazine; its effect on spermatogenesis and its excretion in the ejaculate. *J Urol.* 1947;**58**(1):80–4.
61. Guillebaud J. Sulpha-trimethoprim combinations and male infertility. *Lancet.* 1978;**2**(8088):523.
62. Merino G, Carranza-Lira S. Infection and male infertility: effect of different antibiotic regimens on semen quality. *Arch Androl.* 1995;**35**(3):209–12.
63. Lange D, Schirren C. [Studies on the influence of trimethoprim/sulfamethoxazole on the quality of sperm in andrologic patients and a contribution to the pharmacological testing of a drug on the spermatogenetic activity of the testis]. *Z Hautkr.* 1974;**49**(20):863–78.