*Arşiv Kaynak Tarama Dergisi*
**Archives Medical Review Journal**

**DERLEME/REVIEW**

# Prevention of Oxidative Stress in Ovarian Torsion Detorsion: Data from Experimental Studies

## Over Torsiyon Detorsiyonunda Oksidatif Stresin Önlenmesi: Deneysel Çalışmalardan Elde Edilen Veriler

Yurdun Kuyucu[1], Samet Kara[1], Kezban Kartlaşmış[2], Ayşe Nur Çakır Güngör[3]

[1]Cukurova University Faculty of Medicine, Department of Histology and Embryology, Adana, Türkiye
[2]Cukurova University, Institute of Health Sciences, Adana, Türkiye
[3]Cukurova University Faculty of Medicine, Department of Obstetrics and Gynecology, Adana, Türkiye

**ABSTRACT**
Ovarian torsion is twisting of the ovary around the ligaments that support it. It is a rare, but an important gynecological emergency. Detorsion of the ovary surgically is preferred in patients to preserve the fertility. Ovarian detorsion causes tissue damage in response to excessive reactive oxygen species and accumulation of the activated neutrophils. In this review, antioxidant and anti-inflammatory agents that have been investigated in the literature to prevent the ovarian injury due to oxidative stress are summarised.
**Keywords:** Ovary, torsion detorsion, oxidative stress.

**ÖZET**
Over torsiyonu, overin kendisini destekleyen ligamentler etrafında dönmesidir. Nadir görülen ancak önemli bir jinekolojik acil durumdur. Doğurganlığı korumak için hastalarda overin cerrahi olarak detorsiyonu tercih edilir. Over detorsiyonu, aşırı reaktif oksijen türlerinin ve aktif nötrofillerin birikimine yanıt olarak doku hasarına neden olur. Bu derlemede, oksidatif strese bağlı over hasarını önlemek için literatürde araştırılan antioksidan ve antienflamatuvar ajanlar özetlenmiştir.
**Anahtar kelimeler:** Over, torsiyon detorsiyon, oksidatif stres.

## Introduction

Ovarian torsion is the twisting of the ovary around the ligaments that support it. It is a rare, but significant gynecological emergency, especially for fertility preservation. Ovarian torsion is observed relatively rare in pediatric age compared to adults. In premenarchal girls infundibulopelvic ligaments are elongated so that eases the torsion, however, they shorten in puberty[1]. Although spontaneous torsion can be seen, ovarian masses or cystic lesions may lead to torsion[2]. Ovarian torsion, usually associated with ovarian cysts, is also reported in fetuses and neonates[3].

Torsion of the ovary leads to ovarian edema, as a result arterial flow decreases, eventually ischemic injury, and even infarction occure. Early diagnosis and treatment are crucial in these patients[4]. Congestion, interstitial edema, hemorrhage, leukocyte infiltration, and follicular degeneration are observed in histopathological investigations[5,6].

Although oophorectomy or adnexectomy are the treatment options for extensive tissue necrosis, gross infection, malignancy, and postmenopausal patients, detorsion of the ovary is preferred in patients to preserve the fertility. Cystectomy if present, and oophoropexy to prevent recurrence may be applied during the detorsion operation[7].


2024;33(4):262-266
doi:10.17827/aktd.1604053

## Reperfusion injury after ovarian torsion detorsion (T/D)

Emboli occurrence due to thrombus formation at the pedicle, complete necrosis and underlying malignant process are still potential risks after detorsion[8]. However normal ovarian function following detorsion has been reported in the literature, the oxygenation of the ischemic tissues may produce reactive oxygen molecules that cause reperfusion injury[4]. Hypoxia due to ovarian torsion results in ischemic tissue. After surgical detorsion reperfusion causes a new histopathological process that is called reperfusion injury. Following ovarian detorsion, excessive reactive oxygen species (ROS) and cytokines are produced in tissues, and induce cell membrane damage, lipid peroxidation, endothelial cell damage, inactivation of antioxidant enzymes, and accumulation of the activated neutrophils which contribute to tissue damage (Fig.1)[9,10].

Ischemia causes intracellular ATP breakdown that results in hypoxanthine increase. With reperfusion and the increased oxygen in the tissue, xanthine oxidase converts hypoxanthine to uric acid and superoxide radicals. In addition, calcium influx into neutrophils because of ischemia leads to respiratory burst by neutrophils, and NADPH oxidase converts oxygen to the superoxide anion[11]. Oxidative stress is also accompanied by decreased levels of antioxidant enzymes, like catalase and glutathione peroxidase, and superoxide dismutase (SOD) enzyme activity[12-14]. The imbalance between free radical formation and antioxidant defense mechanisms results in tissue injury[15,16].

## Management of oxidative stress

Ischemia reperfusion animal model has been used to investigate the various antioxidant and anti-inflammatory agents with the intent of preventing the ovarian injury that develops in response to oxidative stress (Fig.1)[5,17].

Hascalik et al. studied resveratrol that is a red wine constituent and a derivative of natural phenol produced by several plants in a rat model. They demonstrated reduced lipid peroxidation products of ischemia with resveratrol administration[18]. Melatonin, pentoxifylline, amlodipine, and growth hormone have been reported in ovarian T/D. Edaravone that is a free radical scavenger, is shown to decrease free radicals and ROS, and to inhibit lipoxygenase activation[5].

Oral et al. studied the effect of montelukast that is a leukotriene receptor antagonist, an antioxidant and tissue protective agent. They concluded that montelukast at different doses could protect ovarian tissue injury by improving antioxidant enzyme levels[19].

L-Carnitine is a non-essential amino acid that is found naturally in mammalian tissues. It is involved in energy production from long-chain fatty acids, also takes part in the turnover of fatty acids peroxydated by free oxygen radicals. It shows anti-apoptotic effects by suppressing the mitochondrial permeability transition. Although L-carnitine is not an antioxidant agent or a free radical scavenger, it is reported as a protective agent against oxidative damage of cellular macromolecules like nucleic acids, proteins and lipids [20]. N-Acetyl cysteine is a precursor of glutathione and used as a mucolytic drug. It is reported as a thiol containing antioxidant and a scavenger of free oxygen radicals. It can easily penetrate cell membranes and has a lower toxicity compared to cysteine[20].

Statins are the inhibitors of the 3-hydroxy-3-methylglutarylcoenzyme A reductase, which catalyzes the rate-limiting step in the cholesterol biosynthesis. They are cholesterol-lowering agents and reveal atheroprotective effects. Their anti-inflammatory effects have been reported in recent studies. Atorvastatin, a synthetic statin, is reported to inhibit inflammatory mediators like IL-6 and NFkappaB. Atorvastatin also decreased oxidative markers, nitric oxide, and homocysteine in hypercholesterolemic rats and prevented angiotensin II-induced vascular remodeling and oxidative stress. Administration of atorvastatin is found effective in tissue damage induced by ischemia and ischemia-reperfusion in ovaries[21].

Oxytocin is a neurohypophysial nonapeptide that functions as a neurotransmitter, neuromodulator hormone. In addition, it is declared that oxytocin reveals antioxidant properties and modulates immune and anti-inflammatory responses. Consequently, oxytocin is suggested as a probable protective agent in ischemia reperfusion injury (IRI) in rat ovaries[22].

Phosphodiesterase inhibitors were found to be effective in reducing ovarian IRI. Among these, sildenafil and tadalafil were declared to be more effective than vardenafil in ovarian reserve protection[23].

Platelet-rich plasma is reported to improve tissue repair by stimulating stem cells and causing migration, proliferation, and differentiation[24].

Demir et al investigated the effect of monoacylglycerol lipase inhibitor JZL184 on ovarian IRI. They declared that JZL184 has antioxidant, antiapoptotic, anti-inflammatory, and ovarian reserve protective properties on ovarian IRI[4].

Urapidil is a vasodilator drug and decreases peripheral vascular resistance as an α1-adrenoceptor antagonist[25]. Güler et al. reported that urapidil demonstrated protective effects against ovarian T/D injury with its anti-oxidative, anti-inflammatory, and anti-apoptotic properties[25].

Metformin is a biguanide antidiabetic drug that is used to treat insulin resistance in type 2 diabetes mellitus. It has been shown that metformin has the capacity to decrease inflammation by reducing ROS. Dayangan Sayan et al. demonstrated the protective effect of metformin in IRI in rat ovary[26].

Türk et al. showed that hypothermia decreased oxidative stress markers and histopathological changes in ovarian torsion, and they recommended hypothermia to cope with oxidative stress in the ovarian T/D injury[27].

Etanercept administration following endotoxin injection is reported to neutralize the activity of TNF-α and inhibit the release of cytokines, chemokines, and stress hormones. Etanercept attenuated inflammation and related oxidative stress and DNA damage and also preserved ovarian reserve in ovarian I/R damage[28].

Researchers recommended hesperidin as an effective antioxidant flavonoid against ischemia-reperfusion injury[29,30].

The combination of the medical ozone therapy with conventional surgical ovarian detorsion is suggested in the protection of the ovarian reserve compared to surgical ovarian detorsion alone[31].

## Conclusion

Together with surgical approaches, medical therapies such as antiinflammatory and antioxidant free radical scavengers directed toward the mediators responsible for ischemic damage should be used for preventing tissue damage and irreversible changes in ovarian T/D. However, further studies are needed to elucidate the other protective mechanisms of I/R in ovarian tissue.

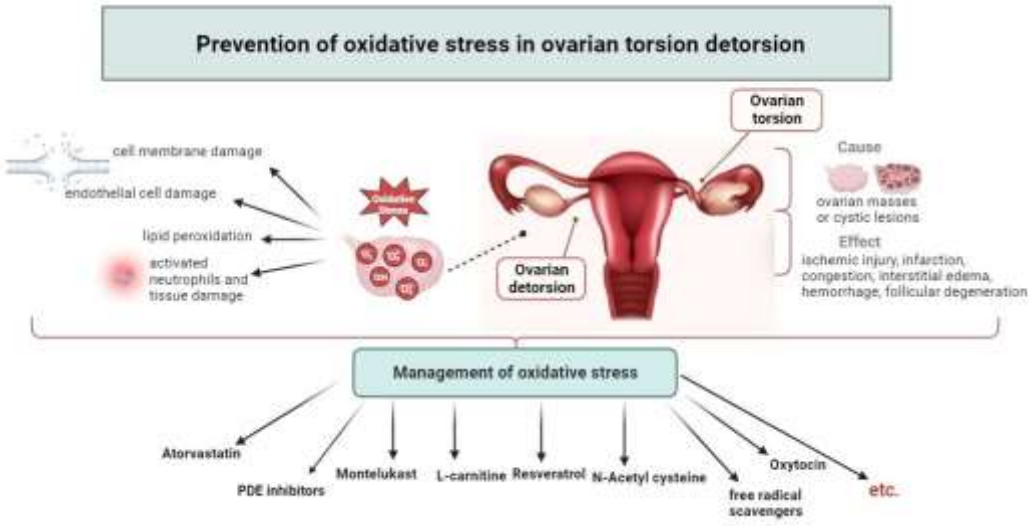


**Figure 1. Schematic diagram of oxidative stress in ovarian torsion detorsion and agents studied for management of oxidative stress in experimental studies (the image was generated using the Biorender application).**

# References


1. Huang C, Hong MK, Ding DC. A review of ovary torsion. Tzu Chi Medical Journal 2017;29:143-47.
2. Dasgupta R, Renaud E, Goldin AB et al. Ovarian torsion in pediatric and adolescent patients: A systematic review. Journal of Pediatric Surgery. 2018;53:1387–91.
3. Tielli A, Scala A, Alison M, et al. Ovarian torsion: diagnosis, surgery, and fertility preservation in the pediatric population. European Journal of Pediatrics. 2022;181:1405–11.
4. Demir Çaltekin M, Özkut MM, Çaltekin İ et al. The protective effect of JZL184 on ovarian ischemia reperfusion injury and ovarian reserve in rats. J Obstet Gynaecol Res. 2021;47:2692-2704.
5. Kara M, Daglioglu YK, Kuyucu Y, Tuli A, Tap O. The effect of edaravone on ischemia–reperfusion injury in rat ovary. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2012;162:197–202.
6. Gencer M, Karaca T, Güngör AN et al. The protective effect of quercetin on IMA levels and apoptosis in experimental ovarian ischemia-reperfusion injury. Eur J Obstet Gynecol Reprod Biol. 2014;177: 135-40.
7. Chang-Patel EJ, Palacios-Helgeson LK, Gould CH. Adnexal torsion: a review of diagnosis and management strategies. Curr Opin Obstet Gynecol. 2022;34:196-203.
8. A Kazez, SK Ozel, N Akpolat, M Goksu. The efficacy of conservative treatment for late term ovarian torsion. Eur J Pediatr Surg. 2007;17:110-4.
9. Bayir Y, Karagoz Y, Karakus E et al. Nigella Sativa reduces tissue damage in rat ovaries subjected to torsion and detorsion: oxidative stress, proinflammatory response and histopathological evaluation. Gynecol Obstet Invest 2012;74:41-9.
10. Trocha M, Merwid-Ląd A, Pieśniewska M et al. Age-related differences in function and structure of rat livers subjected to ischemia/reperfusion. Arch Med Sci. 2018;14:388–95.
11. Prillaman HM, Turner TT. Rescue of testicular function after acute experimental torsion. J Urol. 1997;157:340-5.
12. Laganà AS, Sofo V, Salmeri FM et al. Oxidative stress during ovarian torsion in pediatric and adolescent patients: changing the perspective of the disease. Int J Fertil Steril. 2016;9:416-23.
13. Trocha M, Merwid-Ląd A, Chlebda E, et al. Influence of ezetimibe on selected parameters of oxidative stress in rat liver subjected to ischemia/reperfusion. Arch Med Sci. 2014;10:817-24.
14. Quercetin protects against lipopolysaccharide-induced acute lung injury in rats through suppression of inflammation and oxidative stress. Arch Med Sci. 2015;11:427-32.
15. Barghi B, Shokoohi M, Khaki AA, Khaki A, Moghimian M, Soltani M. Eugenol improves tissue damage and oxidative stress in adult female rats after ovarian torsion/detorsion. J Obstet Gynaecol. 2021;41:933-38.
16. Turkler C, Kiremitli T, Onat T et al. Can pycnogenol prevent cisplatin-induced damage in uterus and ovaries? Arch Med Sci 2019;18:1364-71.
17. Gungor AN, Turkon H, Albayrak A et al. Does Omegaven have beneficial effects on a rat model of ovarian ischemia/reperfusion? Eur J Obstet Gynecol Reprod Biol. 2014;181:240-5.
18. Hascalik S, Celik O, Turkoz Y, Hascalik M, Cigremis Y, Mizrak B. Resveratrol, a red wine constituent polyphenol, protects from ischemia–reperfusion damage of the ovaries. Gynecol Obstet Invest. 2004;57:218–23.
19. Oral A, Odabasoglu F, Halici Z et al.Protective effects of montelukast on ischemia-reperfusion injury in rat ovaries subjected to torsion and detorsion: biochemical and histopathologic evaluation. Fertil Steril. 2011;95:1360-6.
20. Usta U, Inan M, Erbas H, Aydogdu N, Oz Puyan F, Altaner S. Tissue damage in rat ovaries subjected to torsion and detorsion: effects of L-carnitine and N-acetyl cysteine. Pediatr Surg Int. 2008;24:567-73.
21. Cadirci E, Oral A, Odabasoglu F, et al. Atorvastatin reduces tissue damage in rat ovaries subjected to torsion and detorsion: biochemical and histopathologic evaluation. Naunyn Schmiedebergs Arch Pharmacol. 2010;381:455-66.
22. Akdemir A, Erbas O, Gode F, et al. Protective effect of oxytocin on ovarian ischemia-reperfusion injury in rats. Peptides. 2014;55:126-30.
23. Sakin O, Anğın AD, Akalın EE, Cikman MS, Basak K, Kaptanagasi AO. Comparison of the protective effects of sildenafil, vardenafil and tadalafil treatments in ischemia-reperfusion injury in rat ovary. Ginekol Pol. 2019;90:513-19.
24. Bostancı MS, Budak Ö, Çakiroğlu H, Gök K, Köse O, Çokluk E. The effect of protection of platelet-rich plasma against experimental ischemia/reperfusion injury in the rat ovary on in vitro fertilization outcomes. J Obstet Gynaecol Res. 2022;48:1390-98.
25. Güler MC, Tanyeli A, Erdoğan DG et al. Urapidil alleviates ovarian torsion detorsion injury via regulating oxidative stress, apoptosis, autophagia, and inflammation. Iran J Basic Med Sci. 2021;24:935-42.
26. Dayangan Sayan C, Karaca G, Sema Ozkan Z et al. What is the protective effect of metformin on rat ovary against ischemia-reperfusion injury? J Obstet Gynaecol Res. 2018;44:278-85.
27. Türk E, Karaca İ, Ozcinar E, et al. The effect of hypothermia on adnexal torsion/detorsion injury in a rat ovary model. J Pediatr Surg. 2015;50:1378-81.
28. Eken MK, Ersoy GS, Kaygusuz EI et al. Etanercept protects ovarian reserve against ischemia/reperfusion injury in a rat model. Arch Med Sci. 2019;15:1104-12.
29. Celik E, Oguzturk H, Sahin N, Turtay MG, Oguz F, Ciftci O. Protective effects of hesperidin in experimental testicular ischemia/reperfusion injury in rats. Arch Med Sci. 2016;12:928-34.
30. Cakir Gungor AN, Gencer M, Karaca T et al. The effect of hesperetin on ischemia-reperfusion injury in rat ovary. Arch Gynecol Obstet. 2014;290:763-9.
31. Süzen Çaypınar S, Karakaş S, Kaya C, Sakız D, Sezer S, Ekin M. The effect of medical ozone therapy in addition to ovarian detorsion in ischemia reperfusion model. J Obstet Gynaecol. 2022;42:3164-71.

**Correspondence Address / Yazışma Adresi**
Yurdun Kuyucu
Cukurova University Faculty of Medicine
Department of Histology and Embryology
Adana, Türkiye
e-mail: ykuyucu@cu.edu.tr

**Geliş tarihi/ Received:** 19.12.2024
**Kabul tarihi/Accepted**: 25.12.2024