Ovarian Ischemia-Reperfusion Injury: A Brief Review

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Abstract

Pathological conditions such as cysts, neoplasm, long mesovarium and adnexal venous congestion may lead to the ovarian torsion. Early diagnosis and treatment of ovarian torsion is important to preserve ovarian functions and to prevent future infertility. This ovarian torsion-detorsion process is named as ischemia-reperfusion injury. Reperfusion leads to more severe injury in tissue than ischemia. Studies demonstrated that the agents with antioxidant or anti-inflammatory activities may be beneficial in reducing ovarian ischemia reperfusion injury. Also, studies revealed the beneficial effect of controlled reperfusion in the prevention of ovarian tissue damage. However, ischemia/reperfusion damage continues to be a serious problem clinically.

The ovarian artery supplies oxygenated blood to the ovary. Pathological conditions such as cysts, neoplasm, long mesovarium and adnexal venous congestion may lead to the ovarian torsion. Long-term arterial, venous or lymphatic obstruction of the ovary causes a critical reduction in tissue blood flow and permanent tissue damage [1]. So, early diagnosis and treatment of ovarian torsion is important to preserve ovarian functions and to prevent future infertility [2]. When adnexal torsion is detected, detorsion of the twisted adnexa and evaluation the tissue reperfusion is proposed to prevent future infertility even if tissues are cyanotic [2,3]. This ovarian torsion-detorsion process is named as ischemia-reperfusion (I/R) injury [4].

Reperfusion-related ovarian tissue damage is created by many factors including inflammation, leukocyte infiltration, neutrophil accumulation, large amounts of free-oxygen radical production and increased the levels of Malondialdehyde (MDA). Excessive production of Reactive Oxygen Species (ROS) and their toxic molecules interact with lipids and proteins; and this interaction leads to the cell damage [4,7]. Also, increased ROS and MDA levels lead to alkaline changes in nucleic acids and chain breaks in DNA; thus, DNA oxidative damage occurs [8]. The antioxidant defense system which includes enzymatic (glutathione peroxidase ‘GPx’, superoxide dismutase ‘SOD’, etc) and nonenzymatic (glutathione ‘GSH’, ascorbate, etc) components reduces free radical production and facilitates the neutralization of the formed free radicals. However, oxidative cell damage occurs in case of disruption of balance between oxidant-antioxidant systems in favor of oxidants [7].

Studies reported that reperfusion leads to more severe injury in tissue than ischemia [5,6]. Reperfusion-related ovarian tissue damage is created by many factors including inflammation, leukocyte infiltration, neutrophil accumulation, large amounts of free-oxygen radical production and increased the levels of Malondialdehyde (MDA). Excessive production of Reactive Oxygen Species (ROS) and their toxic molecules interact with lipids and proteins; and this interaction leads to the cell damage [4,7]. Also, increased ROS and MDA levels lead to alkaline changes in nucleic acids and chain breaks in DNA; thus, DNA oxidative damage occurs [8]. The antioxidant defense system which includes enzymatic (glutathione peroxidase ‘GPx’, superoxide dismutase ‘SOD’, etc) and nonenzymatic (glutathione ‘GSH’, ascorbate, etc) components reduces free radical production and facilitates the neutralization of the formed free radicals. However, oxidative cell damage occurs in case of disruption of balance between oxidant-antioxidant systems in favor of oxidants [7].

Various drugs with antioxidant or anti-inflammatory activities have been tested in order to minimize injury during the reperfusion of ischemic ovarian tissues [9-17]. Celik, et al. [10] investigated the effects of sildenafil (a selective and specific inhibitor of type V phosphodiesterase) on antioxidant enzyme activities, lipid peroxidation, and histopathologic changes in ovarian tissue after I/R injury in a rat model. They showed an increase in oxidant parameters including MDA levels and myeloperoxidase activities (an indicator of neutrophil infiltration) and a decrease in antioxidant enzymes including GPx and superoxide dismutase activities in ovarian tissue subjected to an I/R injury. They reported that sildenafil administration before reperfusion induces positive effects against I/R injury and decreases I/R induced histological damage in the ovaries. In another study, Aksak, et al. [18] researched the possible preventive effects of beta-carotene (precursor of Vitamin A) on oxidative damage via ischemia-reperfusion models in rat ovaries. They observed intense hemorrhagic areas, significantly increased MDA levels and, decreased SOD and GSH levels in the injury groups. But, beta-carotene treatment group had minimal hemorrhagic areas and normal MDA, SOD and GSH levels. Sayyah-Melli, et al. [12] performed a non-randomized single-blind clinical trial investigating the effect of recombinant erythropoietin on serum oxidants and the viability of ischemic ovaries after detorsion. Interventional group received recombinant erythropoietin 150 IU/kg subcutaneously during the operation and 72 h after detorsion while non-interventional group received no medication. They reported statistically significant different values of malondialdehyde, GSH, SOD, nitric oxide, and total antioxidants between groups 72 h after detorsion. They concluded that recombinant erythropoietin is effective in reducing the oxidative damage due to ovarian torsion. In another study Coşar, et al. [19] suggested that alpha-lipoic acid (an organosulfur compound derived from octanoic acid) pretreatment has beneficial
effects in the prevention of ischaemia-reperfusion injury of the rat ovaries. In another interesting study [20], researchers investigated the effect of enoxaparin (a low-molecular-weight heparin) on ovarian reserve and serum Anti-Müllerian Hormone (AMH) levels in a rat ovarian torsion model. They observed lower postoperative AMH levels in the control and detorsion-enoxaparin groups than in the detorsion-only group. But, vascular congestion and hemorrhage scores were higher in the detorsion-enoxaparin group compared to the other groups. Furthermore, a variety of agents including genistein (a phytoestrogen), trapidil (a platelet-derived growth factor antagonist), melatonin (a hormone secreted by the pineal gland in the brain), aprotinin (a small protein bovine pancreatic trypsin inhibitor), dehydroepiandrosteron and telnisartan (an angiotensin II receptor antagonist) were reported as effective in reversing tissue damage induced by ischemia/reperfusion in rat ovaries [21-26].

In a recent study; Bakacak, et al. [27] evaluated the efficacy of platelet-rich plasma (It contains many more platelets and growth factors than what is typically found in blood) in a rat ischemia/ reperfusion model. They found lower values of total oxidant status, oxidative stress index and total ovarian histopathological scores in rats subjected to the intraperitoneal platelet-rich plasma administration compared to the rats subjected to I/R injury without medication. In another recent study, Bostanci, et al. [28] investigated the effect of granulocyte colony-stimulating factor (G-CSF, a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells) on ischemia and ischemia/reperfusion-induced damage in rat ovary. They reported lower total histopathological scores, total oxidant status and oxidative stress index concentrations in rats treated with G-CSF compared to the control group.

Because of reperfusion leads to more severe tissue damage than ischemia, researchers designed reperfusion methods to improve the reperfusion damage. In one of these trials; Ozkisacik, et al. [29] showed the protective effect of gradual detorsion (the ovarian mesentery was detorsioned 360°, followed by a 5-min pause) for minimizing the reperfusion damage in a rat model of ovarian torsion. Ingec, et al. [15] also investigated whether controlled reperfusion is useful or not in the prevention of ovarian damage in ischemic conditions. They found highest GSH and SOD measurements and lowest malondialdehyde and DNA damage levels; and lower histopathological damage grade in ischemia/controlled reperfusion group compared to the ischemia and ischemia/reperfusion groups. In two recent studies [13,17]; we applied a controlled reperfusion procedure at different intervals after I/R injury in a rat model with or without unilateral oophorectomy. We reported that sterility and ovarian oxidative stress caused by I/R injury declines in parallel to the shortening of the controlled reperfusion duration. We also revealed the beneficial effect of controlled reperfusion in the prevention of damage in ovarian tissue ischemia biochemically and histopathological.

Conclusion

There are many studies in the literature about the improvement of ischemia reperfusion injury. Studies demonstrated that the agents with antioxidant or anti-inflammatory activities may be beneficial in reducing ovarian ischemia reperfusion injury. Also, studies revealed the beneficial effect of controlled reperfusion in the prevention of ovarian tissue damage. Although there are many studies in the literature; ischemia/reperfusion damage continues to be a serious problem clinically. Essentially, early diagnosis and treatment of ovarian torsion plays an important role to provide urgent protection against life-threatening complications from ischemia and to prevent future infertility.

References


References:


