Review Article

Oxidative Stress during Ovarian Torsion in Pediatric and Adolescent Patients: Changing The Perspective of The Disease

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Abstract

Among the different causes of gynecological acute pelvic pain, ovarian torsion represents a surgical emergency. It is a rare case in the pediatric/adolescent aged group that must be included in the differential diagnosis of any girl with abdominal pain or pelvic/abdominal mass. Current recommendations suggest that laparoscopic detorsion should be performed in order to preserve the integrity of the ovaries and fertility, although oophoropexy may be considered in case of severe necrosis. Nevertheless, maintaining the circulation of the ovary after detorsion deteriorates the tissue injury and leads to a pathologic process called ischaemia/reperfusion (I/R) injury, which is characterized by oxidative stress. During the detorsion process, an excess amount of molecular oxygen is supplied to the tissues, and reactive species of oxygen (ROS) such as superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH•), as well as reactive nitrogen species (RNS) are produced in excess. ROS, RNS and their toxic products cause DNA damage and lipid peroxidation in the cellular and mitochondrial membranes, leading to cell death. In spite of attention on this topic, currently there is no shared and clear evidence about the use of anti-inflammatory and antioxidant agents to prevent I/R damage after laparoscopic ovarian detorsion. Considering this element, future research should aim to develop shared protocols for the clinical use (route of application, dosage and time of application) of antioxidants after laparoscopic management of this condition.

Keywords: Paediatrics, Adolescents, Ischaemia/Reperfusion, Oxidative Stress, Antioxidants.

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Introduction

Ovarian torsion in pediatric and adolescent patients: what to do?

Among the different causes of gynecological acute pelvic pain, ovarian torsion (1) represents a surgical emergency. It occurs in 2.7% of all pediatric/adolescent population who presents with acute abdominal pain (2, 3). In this regard, torsion of the fallopian tube without torsion of the ipsilateral ovary, as known as Isolated Tubal Torsion (ITT), is an extremely rare event (4, 5) which may be caused by extremely large Morgagni hydatid (6). Furthermore, ovarian torsion must be considered in the differential diagnosis of any girl with abdominal pain or pelvic/abdominal mass (7, 8). Adnexal masses are uncommon events in the pediatric/adolescent population. The estimated incidence is approximately 2.6 per 100,000 girls younger than 18 years of age (9) and 10% of pediatric ovarian masses are found to be malignant (10-12).

According to Millar et al. (13) ovarian cysts are found in 2-5% of prepubertal females undergoing ultrasound scan , although they are mostly small (<1 cm) and insignificant. Considering only the neoplastic disease, it has been estimated that approximately 67% of ovarian cancers in childhood and adolescence are originated from germ cells (14), whereas the classic epithelial ovarian cancer occurs very rarely in pre-menarche (15). In the post-pubertal age, functional ovarian cysts could occur under several conditions: anovulation, excessive stimulation by follicle-stimulating hormone (FSH) or lack of normal luteinizing hormone (LH) peak, estrogens excess without corresponding progesterone influence (13, 16, 17).

Clinical presentation may comprise spotting of moderate vaginal bleeding and acute/chronic pelvic pain (18). In particular, the failure of luteolysis 14 days after the ovulation could cause persistence of theca-lutein cyst, and this condition could also occur in pregnancy for the high level of human chorionic gonadotropin (hCG) which cause hypertrophy of theca cells (19). About 3% of theca-lutein cysts are complicated by torsion or hemorrhage and 30% of these can cause hyperandrogenism (17). Furthermore, the other kind of ovarian cysts may be complicated with infarction and necrosis (20). Adnexal torsion in pediatric/adolescent population is most commonly (approximately 97%) caused by a benign ovarian cyst or teratoma (21). The size of an ovarian cyst has not been shown to correlate with an increased risk of ovarian torsion (22); moreover, ovarian torsions are more likely to result in the right side due to the protective effect of the sigmoid colon (23).

On ultrasound scan, an enlarged ovary and increased volume ratio in comparison to the contralateral ovary is indicative of an ovarian torsion (24). In this regard, ultrasound scan remains the most useful investigation (25-28), although in pediatric/adolescent population blood flow on Doppler examination does not exclude ovarian torsion (18, 23, 29) and sometimes computed tomography (CT) scan is needed (20). Current recommendations of treatment strongly support ovary conservation since macroscopic appearance of the ovary is not a reliable indicator of the degree of necrosis and potentiality for ovarian recovery (8). For children/adolescent with ovarian torsion, laparoscopic detorsion should be performed in order to preserve the integrity of the ovaries and fertility, although oophoropexy may be considered in case of severe necrosis (30, 31).

Nevertheless, in case of laparoscopic detorsion, it must be taken into account that the restoring of ovarian blood flow may be only partial and slow, and in addition to that, the ovarian damage could progressively increase for oxidative stress after reperfusion (32). Considering all these elements, early diagnosis and surgical intervention are essential, especially in adolescents, in order to preserve the anatomy and function of ovaries (1, 33).

Reactive oxygen species and cellular microenvironment: master and minion

Reactive oxygen species (ROS), derived from molecular oxygen, may present as free radicals or other forms; they have electronically unstable and ionized atomic structure, which interacts with biological macromolecules by capturing electrons and interfering with their biological functionality (34-37). There are several enzymatic activities involved in the generation of ROS: the reduction of dioxygen (O_2) in the mitochondria can lead to various intermediate forms of ROS; within peroxisomes, the reduction of amino acid oxidase trig-

gers the oxidative deamination in the α-keto acids and copper and iron ions generate ROS that may be released in to the blood flow by transferrin, albumin, and ceruloplasmin.

Finally, as well as intracellular nicotinamide adenine dinucleotide phosphate [NAD(P)H]-oxidase, cyclooxygenase, nitric oxide synthase (NOS) and xanthine oxidase produce ROS (38-40). Reactive nitrogen species (RNS) include nitric oxide (NO), nitrogen dioxide (NO_2) and non-reactive species such as peroxynitrite ($ONOO^-$), and nitrosamines (41). In mammals, RNS are mainly derived from NO, which is formed by NOS from O_2 and L-arginine using NADPH as an electron donor (42), and from its reaction with the superoxide anion, which forms peroxynitrite (43). Peroxynitrite could trigger lipid peroxidation and nitrosation of several tyrosine molecules, which play a key role in enzyme function and signal transduction pathways (41). Moreover, accumulating evidence suggests that the activity of endothelial NOS (eNOS) is increased in response to the LH surge and hCG (44). Moreover, animal models showed that eNOS expression is enhanced during chronic hypoxic conditions (45, 46).

Conversely, it has been demonstrated that hypertension in humans may occur due to suboptimal vascular endothelial production of NO (47). The physiological function of ROS has been widely studied in monocyte-macrophages, granulocytes, natural killer (NK) cells and neutrophils. Within these cells, there is a clear evidence that the NAD(P)H oxidase, the myeloperoxidase and the NOS produce anion superoxide, hypochlorous acid and nitrogen monoxide, triggering the cytotoxic responses of the immune system (38, 40). Furthermore, oxidizing agents play a key role in the phosphorylation and activation of protein kinases, and in the phospholipase signaling pathways mediated by Ca^{++}. In this regard, oxidative stress activates phosphorylated proteins. Considering the point that the activity of these protein kinases are strictly involved in the cell cycle regulation, it has been showed that the inhibition of these transduction cascades by ROS scavenger and antioxidant agents, such as superoxide dismutase (SOD), can inhibit the cell cycle progression (48).

Markers of oxidative stress: causes and effects

Since ROS are potentially harmful, the human body has evolved highly complex antioxidant defense systems, both enzymatic and non-enzymatic, which synergistically function in combination. Some antioxidants are produced directly in the intracellular microenvironment (enzymatic antioxidants), such as glutathione oxidase and peroxidase, ubiquinone (CoQ10), α-lipoic acid (ALA), SOD and superoxide catalase (49), while the non-enzymatic antioxidants consist of dietary supplements and synthetic antioxidants such as vitamin C, glutathione, taurine, hypotaurine, vitamin E, Zn, selenium (Se), betacarotene, and carotene (34, 50, 51).

Mechanism of antioxidants' action depends on their concentration, which is variably presented in fluids and tissues. Multiple redox reactions occur within cell metabolism which can lead to oxidative stress if unbalanced in homeostatic mechanisms. Although cells have several intrinsic antioxidant mechanisms, when ROS are present in large amount, the ability to rebalance homeostasis is exceeded and as a result cellular damage may occur (34-37). An excess of ROS may cause a cascade of events such as the release of Ca^{++}, which results in mitochondrial permeability and provokes mitochondrial membrane instability and consequent cessation of adenosine triphosphate (ATP) production; the lipid peroxidation, which increase the peroxyl radicals, damage of amino acids which leads to the formation of carbonyl groups. Oxidation of the mitochondrial DNA (mtDNA) without protection of histones, does not own any repair mechanisms (43). As result of this complex mechanisms , oxidative stress finally causes DNA damage and/or apoptosis of the cell (52). The total antioxidant status (TAS) was employed to assess the general antioxidative status (53).

Accordingly, total oxidant status (TOS) is obtained to ascertain the overall oxidation status. Represented as the ratio of TOS to TAS, the oxidative stress index (OSI) considered a precise index of oxidative stress (54). As meticulously reviewed by Agarwal et al. (49) oxidative stress seems to play a key role in the physiologic processes of menstrual cycle and ovulation, embryo implant, placental framework development, menopause. Conversely, accumulating evidence suggest that a breakdown in red-ox homeostasis occurs during several reproductive disease such as endometriosis, polycystic ovary syndrome, unexplained infertility, spontaneous abortion, recurrent pregnancy loss, preeclampsia, intrauterine growth restriction

and preterm labor. In particular, this review will try to shed light on the redo-ox process during the adnexal torsion in pediatric and adolescent patients.

Oxidative stress during ovarian torsion in pediatric and adolescent patients

The ovaries are organs of constantly predictable change during the reproductive cycle. Their arterial supply comes from two different vases that anastomose in the mesovarium: the ovarian artery, branch of the abdominal aorta, and the ovarian branch of the uterine artery, that ascends the uterus tortuously to reach the mesovarium. Although ovarian torsion may occur most often in the first 3 decades in normal ovaries, it is more frequent in association with pre-existing tubal/ovarian pathologies (55) for this reason it is a condition which rarely occurs in pediatric/adolescent patients. There might be more than one pathophysiological mechanism for ovarian torsion in these patients: the most important of which are growth of ovarian volume and excessive mobility of the tube and mesosalpinx with long ovarian ligaments (56).

Furthermore, several Authors (57, 58) suggest an average age of 10 years for occurring this condition. The time of the tissue's exposure to ischemia is critical. According to Macdougall (59), it is possible to have restitutio ad integrum of the adnexa following reperfusion within 18-24 hours after blood supply interruption. Moreover, ovarian torsion is not an isolated disease: Also unilateral torsion and ovariectomy affect the ovulation in contralateral ovary (60-62). Indeed, Akgur et al. (62) reported histological and ultrastructural changes in contralateral ovaries after ipsilateral ovarian ischaemia. This could be due, at least in part, to the stimulation of the sympathetic system by unilateral ovarian ischaemia, which may cause reduction of regional blood flow similar to testicular torsion. The tissue damage in the twisted ovary depends on one hand to direct damage caused by ischaemia during torsion and, on the other hand, to a secondary effect due to reperfusion during detorsion as a common mechanism to other organs such as kidney and brain (63, 64). Considering that because of release of thrombi from a thrombotic pelvic vein after detorsion of the twisted adnexa, thromboembolic phenomenon has never been demonstrated (65-67).

Nowadays to date laparoscopic ovarian detorsion is preferred with respect to ovariectomy especially in pediatric/adolescent patients (68-70). In particular, according to Galinier et al. (7) conservative approach of black-bluish ovaries after detorsion is safe and effective. Moreover, these authors also indicate that the size of abdominopelvic mass could be used as a good discriminating indicator to classify patients in the correct surgical procedure group before surgery. If it is lower than 75 mm, laparoscopy is preferred, whereas if it is equal to or greater than 75 mm, laparotomy is preferred. There is neither consensus about oophoropexy after untwisting, nor the preventive pexy on the opposite side (71, 72), even if it is advisable to perform this technique when the mesosalpinx is clearly loose (57).

Celik et al. (73) showed that after conservative treatment of 14 ovarian torsion, 13 of 14 ovaries that had been conserved. This procedure showed echographic imaging of follicullogenesis without ovarian atrophy. Others (74) underlined the lack of correlation between duration of symptoms and ovarian infarction. Finally, few pediatric observations of asynchronous bilateral torsions treated by ovarian removal and simple untwisting of the other have been published, although it could be considered a viable option in this condition (74-76). Nevertheless, maintaining the circulation of the ovary after detorsion makes the tissue injury worse and leads to a pathologic process called ischaemia/reperfusion (I/R) injury, characterized by oxidative stress (77). During the detorsion process, an excess amount of molecular oxygen is supplied to the tissues, and ROS such as superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH\bullet$), and NO are produced in excess. ROS, RNS and their toxic products cause DNA damage and lipid peroxidation in the cellular and mitochondrial membranes (77-79).

As reported by Ozat et al. (80), during I/R injury a massive influx of Ca^{++} into the cell occurs, caused by the action of sarcolemma and release of this cation from intracellular binding/sequestration sites (81, 82). Moreover, the excess of cytosolic Ca^{++} triggers several enzymatic pathways which provokes an inflammatory status and accumulation of free arachidonic acid and leads to the depletion of Ca^{++} from the endoplasmic reticulum lumen (64, 82-84). Following these events, the intracel-

lular excess Ca^{++} causes the release of cytochrome c from mitochondria and activation of caspase-dependent and caspase-independent cell death (8, 85, 86). During I/R injury, the most important mediator which is released in this process, and contribute as biomarkers of oxidative stress, is malondialdehyde (MDA) (87, 88). Till now, a number of anti-inflammatory and antioxidant agents have been used to prevent I/R injury, most of them in animal models (89, 90): SOD (91), curcumin (2, 92, 93), iloprost (a prostacyclin analogue) (80), melatonin (94), aprotinin (95), recombinant erythropoietin (rhEPO) (67, 96, 97), calcium channel blockers (98, 99) as 2-Aminoethoxydiphenyl borate (2-APB) (86, 100-102), growth hormone (GH) (103), ozone (O_3) therapy (104), dimethylsulfoxide (DMSO) (105), alpha-lipoic acid (LA, 1, 2-dithiolane-3-pentanoic acid) (106), genistein (107), marrubium cordatum (108) and amlodipine (109). Despite of the increasing attention to this topic, currently there is no shared and clear evidence about the use of anti-inflammatory and antioxidant agents to prevent I/R damage after laparoscopic ovarian detorsion. According to our literature review, future researches should focus on the correlation between I/R injury and consequent cellular/molecular events, especially by taking into account the role of the alterations in cellular immunity (110) and the apoptosis pathways (111, 112).

Conclusion

Current evidence suggests to performing laparoscopic ovarian detorsion, with respect to oophorectomy, in case of ovarian torsion in pediatric and adolescent patients. Although this procedure is acceptable, we must keep in mind that I/R injury can extend and make worse the ischemic and necrotic damage. Considering this element, future research should aim to develop shared protocols for the clinical use (route of application, dosage and time of application) of antioxidants after laparoscopic ovarian detorsion.

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