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The Co-Evaluation of Ovarian Epithelium Edema and Congestion after the Erythropoietin effect on Ovarian Ischemia Reperfusion Injury

C. Tsompos[1], C. Panoulis[2], K Toutouzas[3], A. Triantafyllou[4], CG.Zografos[5], K.Tsarea[6], M. Karamperi[7] A. Papalois[8]

[1.] *Constantinos Tsompos: Department of Gynecology, General Hospital of Thessaloniki "St. Dimitrios" Thessaloniki, Hellas*
[2.] *ConstantinosPanoulis: Department of Obstetrics & Gynecology, Aretaieion Hospital, Athens University, Athens, Attiki, Hellas*
[3.] *Konstantinos Toutouzas: Department of Surgery, Ippokrateion General Hospital, Athens University, Athens, Attiki, Hellas*
[4.] *AggelikiTriantafyllou: Department of Biologic Chemistry, Athens University, Athens, Attiki, Hellas*
[5.] *George C. Zografos: Department of Surgery, Ippokrateion General Hospital, Athens University, Athens, Attiki, Hellas*
[6.] *KalliopiTsarea: Experimental Research Centre ELPEN Pharmaceuticals, S.A. Inc., Co., Pikermi, Attiki, Hellas*
[7.] *Maria Karamperi: Experimental Research Centre ELPEN Pharmaceuticals, S.A. Inc., Co., Pikermi, Attiki, Hellas*
[8.] *ApostolosPapalois: Experimental Research Centre ELPEN Pharmaceuticals, S.A. Inc., Co., Pikermi, Attiki, Hellas*

***Corresponding Author:** Tsompos Constantinos, Department of Gynecology, General Hospital of Thessaloniki "St. Dimitrios" Thessaloniki, Hellas. E-mail: Tsomposconstantinos@gmail.com*

ABSTRACT

***Aim:** This study co-evaluated the 2 quoted histological variables after the erythropoietin (Epo) administration. The calculation was based on the results of 2 preliminary studies, each one evaluating a respective histological variable of ovarian epithelium edema (OE) or congestion (OC) in an induced ischemia reperfusion animal experiment.*

Materials and methods: The 2 main experimental endpoints at which the OE and OC scores were evaluated was the 60th reperfusion min (for the groups A and C)and the 120th reperfusion min (for the groups B and D). Specially, the groups A and B were processed without drugs, whereas the groups C and D after Epo administration.

***Results:** The first preliminary study showed that Epo non significantly recessed the ovarian epithelium edema (OE) within the "without lesions alterations" grade by0.1272727 [-0.4530022 - +0.1984567](p-value=0.4339)1. However, the second preliminary study showed that Eponon significantly enhanced the ovarian congestion (OC) within the "without lesions alterations" grade by0.1454545 [-0.1918887 - +0.4827978](p-value=0.3882)2. These 2 studies were co-evaluated since they came from the same experimental setting. This study investigated the combined diagnostic value of both variables together.*

***Conclusions:** Epo has a hardly deteriorating potency of these histologic parameters within the "without lesions alterations" grade by 0.0090909 [-0.2586031 -+0.2767849] (p-value=0.9456) since they were co-evaluated together.*

Keywords: *ischemia, ovarian epitheliumedema, congestion, erythropoietin, reperfusion*

INTRODUCTION

Erythropoietin (Epo) was investigated whether having antioxidant capacities. 2 histological variables in an ovarian ischemia reperfusion (OIR) experiment was tested for this purpose. The one variable was that of ovarian epithelium edema (OE), which was non significantly recessed within the "without lesions alterations"

grade by 0.1272727 [-0.4530022 - +0.1984567] (p-value=0.4339)1. The other variable was that of ovarian congestion (OC) but was significantly enhanced within the "without lesions alterations" grade by 0.1454545 [-0.1918887 - +0.4827978] (p-value=0.3882)2. Although Epo is met in over 30,606 published biomedical studies, only a 3.57% of them negotiate its antioxidant capacities. The present experimental work tried to co-evaluate these OE and OC variables together and to compare its outcome with each one separately, from the same rat induced OIR protocol.

Materials And Methods

Animal Preparation

This study received 2 ethics committee approvals under the 3693/12-11- 2010 & 14/10-1-2012 numbers fully following the tenants of the Declaration of Helsinki. The granting company, the experiment location and the Pathology Department are mentioned in preliminary references1,2. The human animal care of Albino female Wistar rats, the 7 days pre-experimental ad libitum diet, the non-stop intra-experimental anesthesiologic techniques, the acidometry, the electrocardiogram and the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16 – 18 weeks old. They were randomly assigned to four (4) groups consisted in N=10.

The stage of 45 min ischemia was common for all 4 groups. Afterwards, reperfusion of 60 min was followed in group A; reperfusion of 120 min in group B; immediate Epo intravenous (IV) administration and reperfusion of 60 min in group C; immediate EpoIV administration and reperfusion of 120 min in group D. The dose height assessment was described at preliminary studies as 10 mg/Kg body mass. Ischemia was caused by laparotomic clamping the inferior aorta over renal arteries with forceps for 45 min. The clamp removal was restoring the inferior aorta patency and reperfusion. After exclusion of the blood flow, the protocol of OIR was applied, as described above for each experimental group. Epo was administered at the time of reperfusion; through inferior vena cava catheter. The OE and OC scores were determined at 60th min of reperfusion (for A and C groups) and at 120th min of reperfusion (for B and D groups). Relation was rised between animals' mass with neither OE scores (p-value=0.8726); nor with OC ones (p-values=0.7816). The pathologic score grading was maintained the same as in preliminary studies: (0-0.499) without lesions, (0.5-1.499) the mild lesions, (1.5 -2.499) the moderate lesions and (2.5-3) the serious lesions damage.

Model of Ischemia-Reperfusion Injury

Control Groups

The 20 control rats were the same for preliminaries and this study.

Group A

Reperfusion which lasted 60 min concerned 10 controls rats of combined OE and OC (OE&OC) score as the mean of OE score and OC one (Table 1).

Group B

Reperfusion which lasted 120 min concerned 10 controls rats of combined OE&OC (cOE &OC) score as the mean of OE and OC one (Table 1).

Epo group

The 20 Epo rats were the same for preliminaries and this study.

Group C

Reperfusion which lasted 60 min concerned 10 Epo rats of cOE &OC score as the mean of OE score and OC one (Table 1).

Group D

Reperfusion which lasted 120 min concerned 10 L rats of cOE &OC score as the mean of OE score and OC one (Table 1).

Table1. *Ovarian epithelium edema(OE),ovarian congestion (OC) and their mean and SD scores*

	Mean OE score ±SD	Mean OC score ±SD	Mean OE&OC score ±SD
Group A	mildlesions0.7±0.8232726	moderate lesions 1.6±1.074968	mild lesions 1.15±0.7835106
Group B	mildlesions1.1±0.9944289	moderate lesions 1.9±0.9944289	mild lesions 1.5±0.8164966
Group C	mildlesions0.5±0.7071068	moderate lesions 2.1±0.5676462	mild lesions 1.3±0.5868939
Group D	mildlesions0.7±0.8232726	moderate lesions 2±0.8164966	mild lesions 1.35±0.5797509

Statistical Analysis

CoE & OC groups score was compared with each other from 3 remained groups applying Wilcox on signed-rank test (Table 2).Then, the

generalized linear models (glm) were applied with dependant variable the cOE & OC scores, and independent variables the Epo administration or no, the reperfusion time and their and the interaction.

Table2. *The values difference for groups (DG) after Wilcoxon signed-rank test for mean OE&OC scores.*

DG	Difference	p-value
A-B	+0.35	0.3513
A-C	+0.15	0.6787
A-D	+0.2	0.5009
B-C	-0.2	0.4914
B-D	-0.15	0.6009
C-D	+0.05	0.5994

Table3. *The alteration influence of erythropoietin in connection with reperfusion time p-values*

Recession	95% c. in.	Reperfusion time	Wilcoxon	Glm
without lesions alterations+0.15	-0.676883 +0.976883	1h	0.6787	
without lesions alterations +0.45	-0.1812485 +1.081249	1h		0.1515
without lesions alterations 0	-0.4439479 +0.4439479	1.5h		1.0000
without lesions alterations +0.05	-0.4048986 +0.5048986	1.5h	0.7916	
without lesions alterations +0.05	-0.604141 +0.704141	2h		0.8742
without lesions alterations -0.15	-0.7591045 +0.4591045	2h	0.6009	
without lesions alterations +0.2	-0.63224825+0.23224825	reperfusion	0.3623	0.3034
without lesions alterations +0.0090909	-0.2586031 +0.2767849	interaction		0.9456

RESULTS

Epo administration hardly non significantly deteriorated the cOE &OC scores within the "without lesions alterations" by0.025 [-0.42442325 - +0.47442325] (p=0.8958) after co-calculation by both Wilcox on signed-rank test and glm methods. Furthermore, reperfusion time hardly enhanced the cOE &OC scores within the "without lesions alterations" by 0.02 [-0.63224825 - +0.23224825] (p=0.3034) after co-calculation by the same methods. However, Epo administration and reperfusion time together also hardly deteriorated the cOE &OC scores within the "without lesions alterations" grade by 0.0090909 [-0.2586031 - +0.2767849] (p-value=0.9456) since they were co-evaluated together. A concise form of the above findings is depicted at table 4.

Table4. *Concise form of the table 3*

Recession	95% c. in.	Reperfusion time	p-value
without lesions alterations+0.3	-0.42906575 +1.029066	1h	0.4151
without lesions alterations+0.025	-0.42442325 +0.47442325	1.5h	0.8958
without lesions alterations-0.05	-0.68162275 +0.58162275	2h	0.7375
without lesions alterations+0.02	-0.63224825 +0.23224825	reperfusion	0.3034
without lesions alterations +0.0090909	-0.2586031 +0.2767849	interaction	0.9456

DISCUSSION

Kolusari A et al improved3 the survival of follicles, determined significantly higher levels of E2 in ovarian grafts most likely by reducing ischemic injury, by improving neoangiogenesis, and by its antioxidant effects. Follicle counts in the EPO group were significantly higher than those in the untreated group ($P \leq 0.05$) after condensated Epo administration in auto transplanted rat ovaries. Mahmoodi M et al found the mean total volume of ovary, cortex, medulla, the number of follicles, the follicle survival and function and the concentration of E2 increased4 whereas, apoptosis rate and the concentration of MDA decreased significantly in the auto grafted EPO-treated group than in the auto grafted placebo one ($P<0.01$) reducing the IR injury in grafted ovaries of Naval Medical Research Institute mice. Ma YS et al found the number of apoptosis cells decreased in rhEPO treated group ($P < 0.01$) than I/R group. rhEPO showed effects to inhibit the apoptosis of fetal neural cells and the expression of Caspase-3 protein due to intrauterine hypoxic-ischemic brain tissue injury. Ma YS et al found6 the expression of caspase-3, the death rate of fetal rats and the number of fetal rat brain cells apoptosis decreased in rhEPO treated groups ($P < 0.05$) than the I/R group in an intrauterine hypoxic-ischemic injury. Task in MI et al evaluated7 the tissue and serum TOS levels and OSI levels

markedly decreased. The ovarian protective effect of 2-APB appears to be mediated through its antiapopitotic and antioxidative effects in experimental I/R injury in rat ovaries.

Stanley JA et al have shown8 that edaravone mitigated or inhibited the effects of CrVI on follicle atresia, pubertal onset retardation, steroidogenesis hormone levels and AOX enzyme activity, as well as the expression of Bcl2 and Bcl2l1 in the ovary; whereas increased E_2 restored CrVI-induced depletion of glutathione peroxidase 1, catalase, thioredoxin 2, and peroxiredoxin 3 in the ovary of female Sprague Dawley rats. Yapca OE et al found9 that etoricoxib [a selective cyclooxygenase (COX)-2 inhibitor] prevented oxidative damage induced with I/R that may arise with reperfusion by detorsion in rat ovarian tissue. Yapca OE et al10 suggested that thiamine pyrophosphate may be useful in the prevention of IR-related infertility in diabetic rats. Celik M et al ameliorated11 I/R injury by sildenafil treatment in an ovarian tissue rat model. Gungor AN et al observed that omegaven improved12 the detrimental effects of ovarian I/R in torsioned - detorsioned ovaries. Kurt RK et al revealed13 that colchicine significantly reduced catalase activities and thus ovarian ischemia-reperfusion injury in experimental rat ovarian torsion model up to 5 days. Dokuyucu R et al found14 the numbers of primordial follicles (p=0.006) and primary follicles (p=0.036) increased whereas the mean levels of (Total Oxidant Status) TOS and (Oxidative Stress Index) decreased in groups that received erdosteine and/or alpha lipoic acid ALA than the detorsion group in an experimental rat ovarian IR torsion model injury. Keskin Kurt R et al revealed that zofenopril attenuated injury in an experimental model of ovarian IR torsion in rats. Guven S et al observed16 that the elevated serum ischemia-modified albumin IMA levels with high sensitivity-specificity values in women with ovarian torsion seem to have a potential role as a serum marker in the preoperative diagnosis of ovarian torsion in emergency settings and significantly distinguished patients with or without ovarian torsion. Yurtcu E et al found17 statistically significant dose-dependent decreased edema and follicle degeneration, with vascular congestion, hemorrhage and follicle degeneration in vardenafil treatment groups attenuating ischemia-reperfusion induced ovary injury in a rat model. Türk E et al considered18 hypothermia as effective in inhibiting inflammatory responses and also ischemia/reperfusion injury perhaps by inhibiting the production of oxidative stress in ovaries subjected to torsion/detorsion injury. Yıldırım Ş et al reduced19 hemorrhage, edema and vascular dilatation after proanthocyanidin administration known as free radical scavenger, antioxidant and protective against tissue damage induced by IR in rat ovaries Mete Ural Ü et al reversed20 the biochemical, histopathological and immune histochemical alterations, alleviated the injury and attenuated ovarian ischemia and ischemia/reperfusion injury after thymoquinone administration in rats. Aksak Karamese S et al normalized21 values after beta-carotene treatment which is a potent antioxidant in an experimental ischemia-reperfusion groups model. Sayar I et al suggested22 that ozone (O) and ellagic acid (EA) are effective against an ovarian torsion-detorsion I/R injury. Eser A et al showed23 that curcumin exerted no major significant protective effect on ischemia-reperfusion injury in the rat ovary female Wistar albino rats. Bayir Y et al concluded24 that aliskiren [a direct renin inhibitor] treatment is effective in reversing IR induced ovary damage via the improvement of cytokine and oxidative stress, reduction of inflammation and suppression of the renin-angiotensin aldosterone system in rat ovaries. Esteban-Zubero E et al proved25 melatonin as a potentially useful therapeutic tool in the reduction of graft rejection. Its benefits are based on its direct actions as a free radical scavenger as well as its indirect antioxidative actions in the stimulation of the cellular antioxidant defense system. Moreover, it has significant anti-inflammatory activity. Melatonin has been found to improve the beneficial effects of preservation fluids when they are enriched with the indoleamine.

Yao D et al described carthamus tinctorius26 in prescriptions and composite to promote blood circulation, remove blood stasis, regulate menstruation, alleviate pain, significantly promote ovarian granulosa cell proliferation with the effects of ant oxidation. Tuncer AA et al evaluated27 the combination of alpha-lipoic acid and coenzyme Q10 having beneficial effects on oxidative stress induced by ischemia-reperfusion injury related with rat model of ovarian torsion. Nayki UA et al significantly decreased28 severe hemorrhage, degeneration, inflammatory signs in the follicular cells and markedly ameliorated increased apoptosis, caused by IR in rats ovarian tissue. Ugurel V et al significantly retained29 severe acute inflammation, polynuclear leukocytes, macrophages, stromal edema, hemorrhage, degenerative changes in the ovary PCNA (+) cell numbers; decreasing lipid per oxidation products and leukocytes aggregation after treatment with erdosteine in adnexal torsion of ovarian IR injury in rats. Pınar N et al found

catalase levels significantly increased30 whereas MDA levels significantly lower in the I/R + tempoli.p. group. Tempol can be used for reducing ovarian I/R injury in female Wistar albino rats. Güleç Başer B et al found vascular congestion, hemorrhage, polymorph nuclear neutrophils interstitial edema and the number of apoptotic cells lower31 in PG group. Preoperative PG treatment might exert protective effects in ovarian IR injury through its anti-apoptotic and ant oxidative properties. Melekoglu R et al evaluated32 the serum follicle-stimulating hormone levels significantly reduced, the serum anti-Müllerian hormone levels significantly increased and the histopathological scores ameliorated in rats treated with Chrysin and Glycyrrhetinic Acid preventing I/R injury in rat adnexal torsion detorsion procedure. A numeric evaluation33 of the erythropoietin efficacies was provided by a meta-analysis of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion time coming from the same experimental setting (table 5).

Table5. *The erythropoietin influence (+SD) on the levels of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion (rep) time*

35 Variables	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of Epo and rep	p-value
Mean	+3.39%±12.15 %	0.5636	+4.44%±14.50 %	0.3711	+5.49%±18.55%	0.3496	+2.83%±7.13 %	0.4045

CONCLUSION

Epo has a slight deteriorating potency for ovarian epithelium edema and congestion together (p-values=0.9456) discouraging for beneficial usage in situations such as the survival of follicles in ovarian grafts, the follicle atresia, the pubertal onset retardation, the steroid genesis hormone levels, the follicle degeneration and inflammatory responses inhibition and the adnexal torsion detorsion procedure.

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REFERENCES

[1] C. Tsompos, C. Panoulis, K. Toutouzas, A. Triantafyllou, G. Zografos and A. Papalois. The effect of erythropoietin on ovarian epithelium edema during ischemia reperfusion injury in rats.Research Journal of Pharmacology and Toxicology 02[03] 2016: 8-11.

[2] Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G, et al. (2016) The Effect of Erythropoietin on Ovarian Congestion during Ischemia Reperfusion Injury in Rats. Int J Womens Health Wellness 2:010.

[3] Kolusari A, Okyay AG, Koçkaya EA. The Effect of Erythropoietin in Preventing Ischemia-Reperfusion Injury in Ovarian Tissue Transplantation. Report Sci. 2018 Mar;25(3):406-413.

[4] Mahmoodi M, SoleimaniMehranjani M, Shariatzadeh SM, Eimani H, Shahverdi A. Effects of erythropoietin on ischemia, follicular survival, and ovarian function in ovarian grafts. Reproduction. 2014 Apr 10;147(5):733-41.

[5] Ma YS, Zhou J, Liu H, Du Y, Lin XM. Protection effect of recombiant human erythropoietin preconditioning against intrauterine hypoxic-ischemic brain injury and its influence on expression of caspase-3 protein in brain tissue. Sichuan Da XueXueBao Yi Xue Ban. 2013 May;44(3):397-401.

[6] Ma YS, Zhou J, Liu H, Du Y, Lin XM. Effect of recombinant human erythropoietin on apoptosis of neural cells in fetal rats after intrauterine hypoxic-ischemic injury.Sichuan Da XueXueBao Yi Xue Ban. 2013 Jan;44(1):31-5.

[7] Taskin MI, Hismiogullari AA, Yay A, Adali E, Gungor AC, Korkmaz GO, Inceboz U. Effect of 2-aminoethoxydiphenyl borate on ischemia-reperfusion injury in a rat ovary model. Eur J ObstetGynecolReprod Biol. 2014 Jul;178:74-9.

[8] Stanley JA, Sivakumar KK, Arosh JA, Burghardt RC, Banu SK. Edaravone mitigates hexavalent chromium-induced oxidative stress and depletion of antioxidant enzymes while estrogen restores antioxidant enzymes in the rat ovary in F1 offspring. BiolReprod. 2014 Jul;91(1):12.

[9] Yapca OE, Turan MI, Yilmaz I, Salman S, Gulapoglu M, Suleyman H. Benefits of the antioxidant and anti-inflammatory activity of etoricoxib in the prevention of ovarian ischemia/reperfusion injury induced experimentally in rats. J ObstetGynaecol Res. 2014 Jun;40(6):1674-9.

[10] Yapca OE, Turan MI, Borekci B, Akcay F, Suleyman H. Bilateral ovarian ischemia/reperfusion injury and treatment options

in rats with an induced model of diabetes. Iran J Basic Med Sci. 2014;17(4):294-302.

[11] Celik M, Aksoy AN, Aksoy H, Aksoy Y, Halici Z. Sildenafil reduces ischemia-reperfusion injury in rat ovary: biochemical and histopathological evaluation. GynecolObstet Invest. 2014;78(3):162-7.

[12] Gungor AN, Turkon H, Albayrak A, Ovali M, Islimye M, Gencer M, Hacivelioglu S, Cevizci S, Cesur I, Cosar E. Does Omegaven have beneficial effects on a rat model of ovarian ischemia/reperfusion? Eur J ObstetGynecolReprod Biol. 2014 Oct;181:240-5.

[13] Kurt RK, Dogan AC, Dogan M, Albayrak A, Kurt SN, Eren F, Okyay AG, Karateke A, Duru M, Fadillioglu E, Delibasi T. Protective effect of colchicine on ovarian ischemia-reperfusion injury: an experimental study. Reprod Sci. 2015 May;22(5):545-50.

[14] Dokuyucu R, Karateke A, Gokce H, Kurt RK, Ozcan O, Ozturk S, Tas ZA, Karateke F, Duru M. Antioxidant effect of erdosteine and lipoic acid in ovarian ischemia-reperfusion injury. Eur J ObstetGynecolReprod Biol. 2014 Dec;183:23-7.

[15] Keskin Kurt R, Dogan AC, Dogan M, Albayrak A, Kurt SN, Eren F, Silfeler DB, Karateke A, Fadillioglu E, Delibasi T. Zofenopril attenuates injury induced by ischemia-reperfusion on rat ovary. J ObstetGynaecol Res. 2015 Jun;41(6):926-31.

[16] Guven S, Kart C, GuvendagGuven ES, Cetin EC, Menteşe A. Is the measurement of serum ischemia-modified albumin the best test to diagnose ovarian torsion? GynecolObstet Invest. 2015;79(4):269-75.

[17] Yurtcu E, Togrul C, Ozyer S, Uzunlar O, Karatas YH, Seckin KD, Caydere M, Hucumenoglu S, Cicek N. Dose dependent protective effects of vardenafil on ischemia-reperfusion injury with biochemical and histopathologic evaluation in rat ovary. J Pediatr Surg. 2015 Jul;50(7):1205-9.

[18] Türk E, Karaca İ, Ozcinar E, Celebiler A, Aybek H, Ortac R, Güven A. The effect of hypothermia on adnexal torsion/detorsion injury in a rat ovary model. J Pediatr Surg. 2015 Aug;50(8):1378-81.

[19] Yıldırım Ş, Topaloğlu N, Tekin M, Küçük A, Erdem H, Erbaş M, Yıldırım A. Protective role of Proanthocyanidin in experimental ovarian torsion. Med J Islam Repub Iran. 2015 Feb 23;29:185.

[20] Mete Ural Ü, BayoğluTekin Y, Şehitoğlu İ, Kalkan Y, CumhurCüre M. Biochemical, Histopathological and Immunohistochemical Evaluation of the Protective and Therapeutic Effects of Thymoquinone against Ischemia and Ischemia/Reperfusion Injury in the Rat Ovary. GynecolObstet Invest. 2016;81(1):47-53.

[21] AksakKaramese S, Toktay E, Unal D, Selli J, Karamese M, Malkoc I. The protective effects of beta-carotene against ischemia/reperfusion injury in rat ovarian tissue.ActaHistochem. 2015 Oct;117(8):790-7.

[22] Sayar I, Bicer S, Gursul C, Gürbüzel M, Peker K, Işik A. Protective effects of ellagic acid and ozone on rat ovaries with an ischemia/reperfusion injury. J ObstetGynaecol Res. 2016 Jan;42(1):52-8.

[23] Eser A, Hizli D, Haltas H, Namuslu M, Kosus A, Kosus N, Kafali H. Effects of curcumin on ovarian ischemia-reperfusion injury in a rat model. Biomed Rep. 2015 Nov;3(6):807-813.

[24] Bayir Y, Cadirci E, Polat B, KilicBaygutalp N, Albayrak A, Karakus E, Un H, Keles MS, KocakOzgeris FB, Toktay E, Karaca M, Halici Z. Aliskiren - a promising strategy for ovarian ischemia/reperfusion injury protection in rats via RAAS. GynecolEndocrinol. 2016 Aug;32(8):675-683.

[25] Esteban-Zubero E, García-Gil FA, López-Pingarrón L, Alatorre-Jiménez MA, Iñigo-Gil P, Tan DX, García JJ, Reiter RJ. Potential benefits of melatonin in organ transplantation: a review. J Endocrinol. 2016 Jun;229(3):R129-46.

[26] Yao D, Wang Z, Miao L, Wang L. Effects of extracts and isolated compounds from safflower on some index of promoting blood circulation and regulating menstruation. J Ethnopharmacol. 2016 Sep 15;191:264-272.

[27] Tuncer AA, Bozkurt MF, Koken T, Dogan N, Pektaş MK, Baskin Embleton D. The Protective Effects of Alpha-Lipoic Acid and Coenzyme Q10 Combination on Ovarian Ischemia-Reperfusion Injury: An Experimental Study. Adv Med. 2016;2016:3415046.

[28] Nayki UA, Nayki C, Cetin N, Cimen FK, CobanA, Mammadov R, Tas IH, Malkoc I. Effect of Kineret® on ovarian ischemia reperfusion injury in a rat model. J ObstetGynaecol Res. 2016 Nov;42(11):1525-1533.

[29] Ugurel V, Cicek AC, Cemek M, Demirtas S, Kocaman AT, Karaca T. Antioxidant and antiapoptotic effects of erdosteine in a rat model of ovarian ischemia-reperfusion injury. Iran J Basic Med Sci. 2017 Jan;20(1):53-58.

[30] Pınar N, SoyluKarapınar O, Özcan O, AtikDoğan E, Bayraktar S. Protective effects of tempol in an experimental ovarian ischemia-reperfusion injury model in female Wistar albino rats. Can J PhysiolPharmacol. 2017 Jul;95(7):861-865.

[31] GüleçBaşer B, İslimyeTaşkın M, Adalı E, Öztürk E, Hısmıoğulları AA, Yay A. Does progesterone have protective effects on ovarian ischemia-reperfusion injury? J Turk GerGynecol Assoc. 2018 Jun 4;19(2):87-93.

[32] Melekoglu R, Ciftci O, Eraslan S, Alan S, Basak N. The Protective Effects of Glycyrrhetinic Acid and Chrysin against Ischemia-Reperfusion Injury in Rat Ovaries. Biomed Res Int. 2018 May 14;2018:5421308.

[33] C. Tsompos, C. Panoulis, K. Toutouzas, A. Triantafyllou, G. Zografos, A. Papalois.The effect of erythropoietin on chloride levels during hypoxia reoxygenation injury in rats. Signa Vitae2017; 13(2):97-101.

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