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Ameliorative Effects of Omega-3 and Vitamin E Supplementation on the Histology of Placenta in Rats with Induced Preeclampsia

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ABSTRACT

Preeclampsia is a condition of pregnancy linked with placental failure; it is described by low levels of nitric oxide, oxidative stress, and abnormal remodeling of the spiral arteries. N(ω)-nitro-L-arginine methyl ester (L-NAME) is administered to mimic these effects in animals.

The present study will try to show beneficial effects, to what degree, of Omega-3 and vitamin E consumption on the placental histopathology in an experimental rat induced preeclampsia.

To study the effects of L-NAME preeclampsia and the protective roles of omega-3; and vitamin E, forty pregnant Wistar rats were divided into five groups. Doppler ultrasound, histological evaluation, and biochemical analysis as well as statistical calculation were integrated to measure maternal blood pressure, placental histology, and oxidative stress assessment.

Lethargy, rising mean arterial blood pressure (MABP), and increased placental oxidative stress—as elevated malondialdehyde (MDA) levels and significant histological damage—were consequences of L-NAME-induced preeclampsia during the course of this study. Individual omega-3 or vitamin E treatments lowered MDA with an improvement in placental structure. However, it is the combination treatment that indicated a preventive synergistic effect against preeclampsia by markedly increasing maternal activity, decreasing MABP, oxidative stress, and restoring placental histology to near normal.

Placental damage and oxidative stress resulted from L-NAME-induced preeclampsia. Vitamin E and omega-3 therapies markedly ameliorated the markers of oxidative stress as well as the degree of tissue degeneration, which implies therapeutic protective potential.

Keywords: Preeclampsia, Omega-3, Vitamin E, Placenta, Oxidative stress

Introduction

Usually appearing in the second and/or third trimester of pregnancy, preeclampsia (PE) is a slowly developing insult marked by elevated blood pressure. It affects 2–8% of all pregnancies in the world and is a major cause of perinatal and maternal morbidity and mortality (1). According to estimates from the World Health Organisation (WHO), pre-eclampsia prevalence is seven times greater in developing nations and 1.8% to 16.7% in industrialised nations (2). The pathophysiology of PE is believed to originate from the placenta, specifically because of abnormal remodelling of the spiral arteries and placental ischemia, which raises the level of circulating vascular endothelial growth factor receptor-1 (VEGFR-1) (3). However, the pathogenesis of PE is attributed to a complex combination of various genetic, environmental, and immunological factors. Significant changes in the placenta's appearance were noted based on the gestational period. Nevertheless, numerous distinctions between the placentas of humans and rats were found in terms of the appearance of the yolk sac and the maternofetal interface (4). Nonetheless, there are striking parallels between the two species, primarily in the deep invasion of trophoblasts and the remodelling of spiral arteries. Because the trophoblasts in both human and rat placentas come into direct contact with the mother's blood, the placentas are histologically categorised as hemochorial. They differ, however, in the quantity of trophoblast coatings: Humans have a hemomonochorial placenta, which has a single layer of trophoblast cells separating the maternal and fetal blood, whereas rats have a hemotrichorial placenta, which has three layers of trophoblast cells (two syncytiotrophoblast layers

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and one cytotrophoblast layer) between the maternal blood and the fetal capillaries (5).

According to histology, the rat placenta is made up of both maternal and fetal components. The maternal portion consists of the metrial gland and decidua, whereas the fetal portion consists of the yolk sac, the labyrinth zone, and the basal (or junctional) zone (6). A double layer of trophoblasts (cytotrophoblasts and syncytiotrophoblast I and II) underlie the outer cytotrophoblast cells that are immediately connected to the maternal blood. These cells control the transfer of substances through a variety of transporters that underlie their plasma membranes (7). The labyrinthine zone develops further during pregnancy and finally makes up the majority of the placental volume (8). Glycogen cells, spongiotrophoblasts, and trophoblastic giant cells comprise the basal zone, which reaches maximum development on day 15 before gradually regressing (9). As a structural barrier that separates the invading blastocyst from maternal uterine tissues, the decidua is classified into the decidua capsularis (located on the anti-mesometrial side), the decidua parietalis (located on the lateral side), and the decidua basalis (located on the mesometrial side). Additionally, because of the accumulation of glycogen and/or lipids, the decidua also functions as a source of nutrients (10).

Prior studies revealed that preeclamptic women produced more hydrogen peroxide than women with normal pregnancies, and others emphasised the importance of oxidative stress indicators in complex pregnancies, laying the foundation for further research on this topic (11). During a typical human pregnancy, the functional availability of nitric oxide (NO), which regulates regional blood flow and blood pressure, is increased. However, placental ischemia reduces nitric oxide synthase's (NOS) capacity to regulate blood pressure and vascular tone; consequently, preeclampsia pathogenesis has been associated with reduced NO synthesis (12).

When given in the middle to late stages of pregnancy, N-nitro-arginine methyl ester (L-NAME) decreases nitric oxide synthase irreversibly, which lowers the liberation of NO. Although it is yet unknown whether these alterations are the result of placental ischaemia and hypoxia or of NO inhibition, the use of L-NAME during the last stages of pregnancy (days 14–17) results in a substantial reduction in uteroplacental perfusion (13). On the other hand, pregnant rats given L-NAME in the middle of their gestation showed a prolonged rise in blood pressure, increased trophoblast apoptosis, the appearance of new biomarkers at the beginning of gestation and decreased NO production (14).

Through a chain-breaking lipid antioxidant action, vitamin E, the most important fat-soluble lipid-affinitive free radical-neutralising antioxidant, effectively scavenges peroxyl radicals in vivo, preventing the spread of peroxidation caused by free radicals (15).

Because it suppresses the activation of leukocytes and endothelial cells, prevents apoptosis in placental tissue, and has anti-inflammatory properties, vitamin E has been demonstrated in numerous trials to be particularly beneficial in preeclampsia (16). These factors may all play a role in the development of preeclampsia.

Because omega-3 fatty acids can inhibit endothelial cell migration, proliferation, and VEGF synthesis, they may be useful in the treatment of angiogenic illnesses such as cancer, chronic inflammation, and diabetic retinal problems. On the other hand, it might have adverse effects on vascular regeneration and arterial angioplasty (17).

In an experimental rat model of induced preeclampsia, the present study highlights the beneficial effects of vitamin E and Omega-3 intake on the placental histopathology.

Materials and Methods

Study Design and Animal Groups: The current experimental work was carried out in the Department of Anatomy, College of Medicine, University of Mosul, using a post-test control group design. According to the ethical approval report UOM/COM/MRECI dated 26/12/2022, it was approved by the College of Medicine's Medical Research Ethics Committee.

Forty mature male and forty adult Wistar albino rats (female), each weighing between 200 and 250 g, were part of the treatment group. These animals are obtained from the University of Mosul's Veterinary College's Animal House. The rats were allowed free access to food and water and standardised ideal housing circumstances for a week prior to the experiment. They were retained in plastic cages with bedding made of sawdust that was changed every day. Environmental conditions were closely monitored, with a 12-hour light/dark cycle, a room temperature of 25 ± 2°C, and a relative humidity of 60 ± 5%. Every step involved in the handling and care of the animals tracked the

rules delineated in the "Guide for the Care and Use of Laboratory Animals."

On day zero of pregnancy, female rats in the active phase of the oestrous cycle were paired with a male at a ratio of one male to four females in the same cage, awaiting fertilisation and pregnancy. The animals spent the night in cages made of wire mesh. The next morning, female vaginal lavages were examined for the existence of sperm and/or vaginal plugs using a tiny pipette and isotonic saline (18). When vaginal fluid was examined using a microscope and sperm appeared to be present, the female was presumed to be pregnant, marking the beginning of the first day of pregnancy.

Doses and drugs used:

- From the tenth to the end of pregnancy, a dose of 50 mg/kg of L-NAME per day, dissolved in distilled water, was administered orally via gastric lavage with a wide-bore tube to induce a state of hypertension similar to pre-eclampsia. (L-NAME) is available as a white powder from Sigma Aldrich, Germany®.
- The 300 mg total of the Omega-3 supplement, which contained 180 mg of EPA and 120 mg of DHA, was bought from NOW Foods Supplements.
- NOW Foods Supplements also supplies vitamin E in the form of 400 IU soft gel capsules.

Animal Groups: Forty pregnant Wistar albino rats were included in the study, and they were split equally into five groups of eight rats each:

- Group I: Normal pregnant rats that are not receiving any therapy are considered the control group.
- Group II: From day 10 until the end of pregnancy, the preeclampsia (PE) group received the vasoconstrictor L-NAME only orally at a dose of 50 mg/kg per day, or 0.5 ml, using an oropharyngeal cannula.
- Group III: oral intubation of L-NAME + omega-3 (180 mg EPA and 120 mg DHA) 300 mg capsules at a rate of 4 mg/kg/day, equivalent to 1 ml, from day 10 until the end of pregnancy.
- Group IV: oral intubation of L-NAME + vitamin E (400 mg capsule) at a dose of 3 mg/kg/day (0.6 ml) from day 10 till the end of pregnancy.
- Group V received the same doses of group III & IV from day 10 until the end of the pregnancy.

Throughout the study, the pregnant rats' activity and food intake were continuously monitored.

Doppler ultrasonography and Doppler parameters were used to automatically measure the end diastolic pressure of each spiral artery, the systolic pressure at the umbilical cord's insertion site, and the mean arterial blood pressure (MABP) in order to analyse hemodynamic changes and compare the groups (19).

The pregnancy was terminated on the 19th day of pregnancy. Ketamine (50 mg/kg) and Xylazine (5 mg/kg) were given intramuscularly into the pregnant rats to induce anaesthesia (20). The foetuses and umbilical cords were examined by opening the sacs after a lower midline abdominal incision was performed to reveal the gravid uterine horns. Samples were promptly preserved in 10% neutral buffered formalin for a full day after the placentas were gently removed. The placental tissues were then prepared for histological examination after being cleaned with tap water. Haematoxylin and Eosin were used to stain the placentas after they had been fixed in paraffin wax and cut into slices that were five microns thick.

Biochemical Test: The pregnancies ended on day 19 of gestation, and placental pieces of tissue and blood samples were taken. After removing any remaining blood with phosphate-buffered saline (PBS), the placentas were chopped into tiny pieces and mixed with PBS. After centrifugation and an overnight storage period below 20°C, the homogenates were stored at -80°C. ELISA kits were utilised to evaluate indicators of lipid peroxidation in the placental tissue homogenates. Colourimetric kits were used to quantify the amounts of malondialdehyde (Biodiagnostic, Giza, Egypt).

Statistical Analysis: The Statistical Package for the Social Sciences (SPSS) program, Windows Standard version 21, was used to analyse the data. Mean ± standard deviation (SD) was applied to represent continuous variables with a normal distribution. One-way ANOVA was used to assess differences between the five groups. Statistical significance was considered as a p-value of less than 0.05.

Results

Generally, the control group remained active and had a good appetite, while group II became drowsy and lethargic; groups III, VI, and V resumed their regular activities.

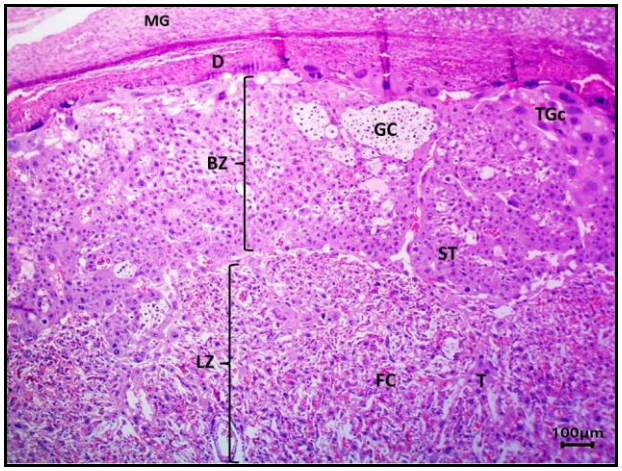

Fig. 1. Histological section of placenta from control group reveals metrial gland (MG), decidua (D), basal zone (BZ) with spongiotrophoblast (ST), trophoblastic giant cell (TGc), and glycogen cell (GC); labyrinth zone (LZ) with fetal capillary (FC) and trophoblast (T) (H&EX40)

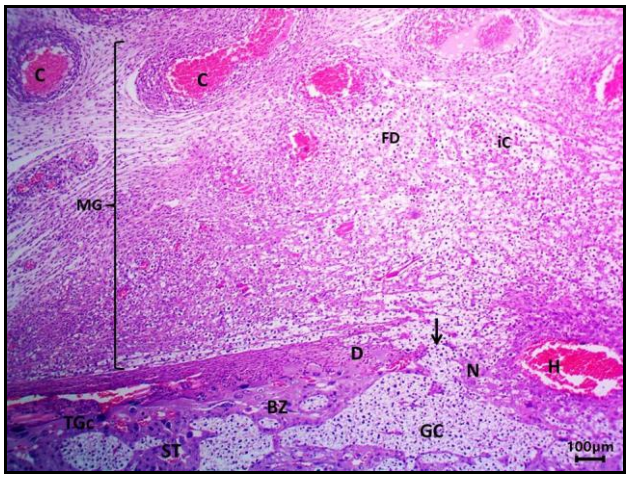

Fig. 2. Histological section of placenta from group II rats showed severe congestion (C) and haemorrhage (H) of maternal blood vessels, with damage to part of the decidua (arrow) and decreased numbers of spongiotrophoblast (ST), trophoblastic giant cell (TGc) and glycogen cell (GC) (H&EX40)

Measurement of Mean Arterial Blood Pressure (MABP): Table 1 showed that Group II (PE caused by L-NAME injection) had a significantly higher MABP (156.02 ± 1.04) than Group I (control group), which had an MABP of 96.01 ± 0.89. When Group III and Group IV received L-NAME combined with omega-3 and L-NAME mixed with vitamin E, respectively, the MABP decreased non-significantly in comparison to the

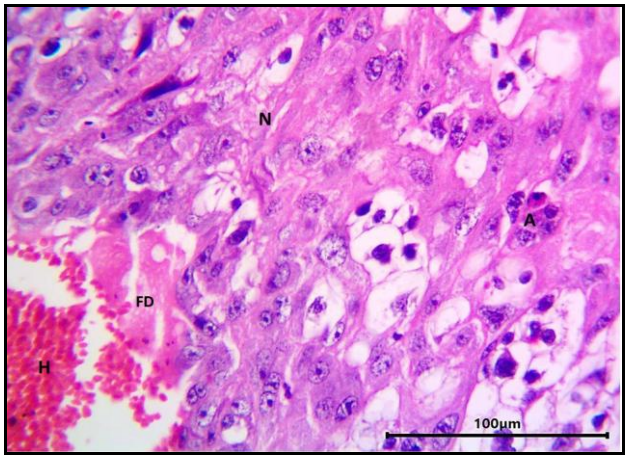

Fig. 3. Histological section of placenta from group II rats showed severe haemorrhage (H) of maternal blood vessels, vacuolar degeneration of glycogen cells (blue arrow), apoptosis of cells of tropospongium (black arrow) (H&EX400)

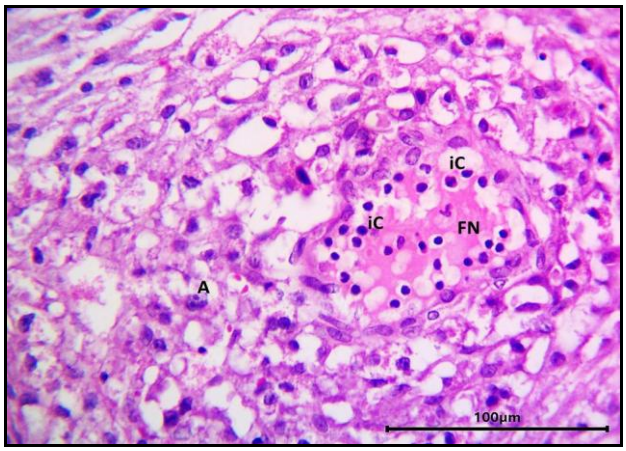

Fig. 4. Histological section of placenta from group II rats showed areas of fibrinoid deposition (FN), inflammatory cells infiltration (black arrow) (H&EX400)

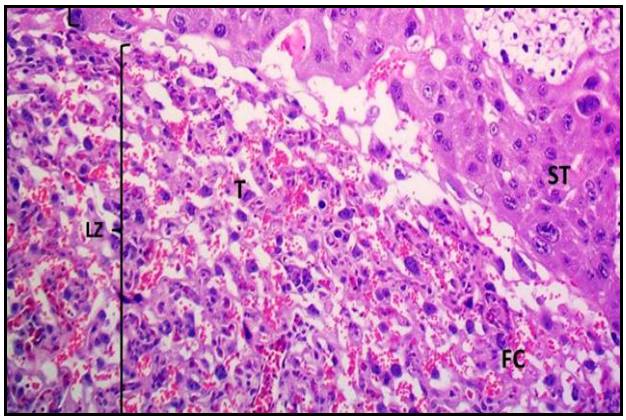

Fig. 5. Histological section of placenta from group II rats showed the labyrinth with deposition of homogenous acidophilic material in their lumen and narrowing of maternal blood sinusoids (arrow) (H&EX100)

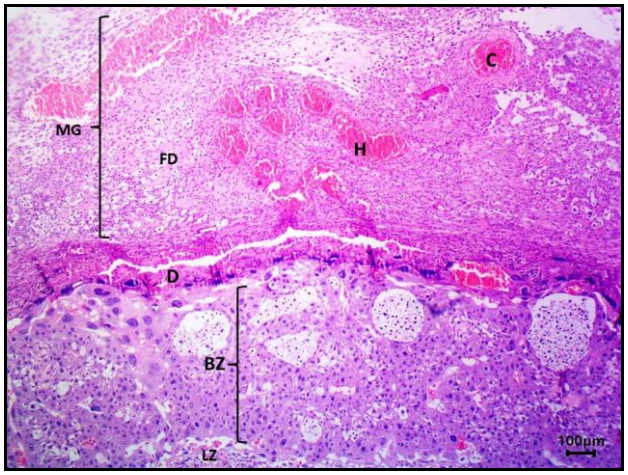

Fig. 6. Histological section of placenta from group III rats showed metrial gland (MG) with intact continuous decidua (arrow), congestion (C) and haemorrhage (H) of blood vessels, mild fibrin deposition (FD), unaffected trophoblastic giant cell (yellow arrow), and glycogen cell (GC)(H&EX40)

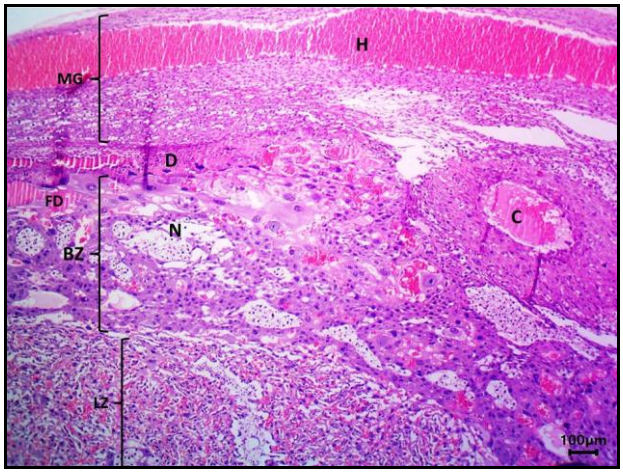

Fig. 7. Histological section of placenta from group IV rats showed metrial gland (MG) with severe haemorrhage (H) and congestion of blood vessels (C), integral decidua (D) and labyrinth zone (LZ) (H&EX40)

PE group. In contrast to the PE group, Group V, which received L-NAME, omega-3, and vitamin E treatment, showed a significant drop in MABP (see Table 1).

Measurement of Malondialdehyde (MDA): Table 2 shows the assessment of malondialdehyde (MDA) levels in placental tissue. When L-NAME was administered to Group II, placental MDA levels showed a very highly significant increase (5.4±0.1) in divergence to the control group (0.9±0.7). In comparison to Group II, placental MDA levels were significantly lower in Groups III, IV and V.

Histological findings:

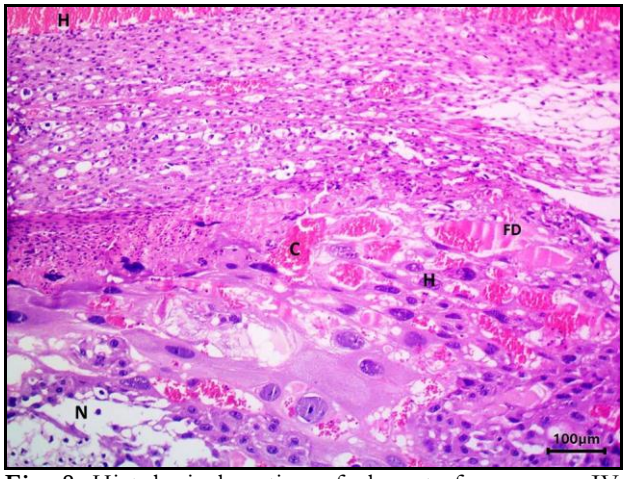

Fig. 8. Histological section of placenta from group IV rats showed mild fibrin deposition (FD), mild apoptosis of giant cells and glycogen cells of the basal zone (arrows) (H&EX100)

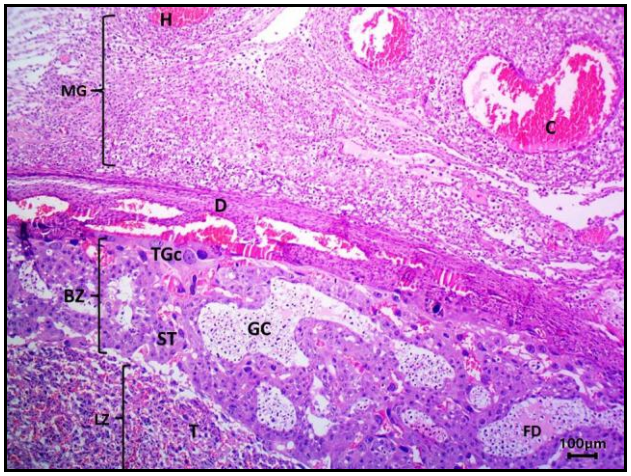

Fig. 9. Histological section of placenta from group V rats showed a near-normal appearance, intact decidua (D), basal zone (BZ) with spongiotrophoblast (ST), trophoblastic giant cell (TGc), and glycogen cell (GC), mild fibrin deposition, mild haemorrhage (H), congestion of blood vessels (H&EX100)

- Histological examination of H&E-stained placental sections from the control group showed the decidua and metrial gland in addition to the basal zone, which contained three different cell types: trophoblastic giant cells with basophilic cytoplasm, spongiotrophoblasts with basophilic cytoplasm, and glycogen cells with lightly stained cytoplasm. An interhaemal barrier composed of cytotrophoblast and syncytiotrophoblast cells separated the interdigitating fetal capillaries and maternal sinusoids that constituted the labyrinth zone (Fig. 1).
- On the other hand, placental slices from group II rats, in which L-NAME was used

Table 1: Means ± SD of MABP (mmHg) with Comparison Among the Five Groups

Groups	N	MABP (mmHg)	One-way ANOVA test	P-values
Group I Control group	8	96.01 ± 0.89	I vs. II	0.001
			I vs. III	0.001
			I vs. IV	0.001
Group II Preeclampsia group	8	155.02 ± 1.02	II vs. I	0.001
			II vs. III	0.2
			II vs. IV	0.4
Group III L-NAME + omega-3	8	154.02 ± 1.02	III vs. IV	0.6
Group IV L-NAME + vitamin E	8	154.01 ± 1.01	III vs. IV	0.6
Group V L-NAME + omega-3 + vitamin E	8	152.30 ± 5.21	III vs. V	0.040

SD=Standard deviation; underlined values = Significant (P≤0.05); vs.=versus.

Table 2: Means ± SD of Serum Level of MDA With Comparison Among The Five Groups

Groups	N	MDA (µmol/L)	One-way ANOVA test	P-values
Group I Control group	8	0.9 ± 0.7	I vs. II	0.001
			I vs. III	0.1
			I vs. IV	0.3
Group II Preeclampsia group	8	5.4 ± 0.1	II vs. I	0.001
			II vs. III	0.020
			II vs. IV	0.010
Group III L-NAME + omega-3	8	1.3 ± 2	III vs. IV	0.5
Group IV L-NAME + vitamin E	8	1.1 ± 0.2	III vs. IV	0.5
Group V L-NAME + omega-3 + vitamin E	8	1.3 ± 0.1	III vs. V	0.4

SD=Standard deviation; underlined values = Significant (P≤0.05); vs.=versus

- to induce preeclampsia (PE) showed significant maternal blood vessel constriction and bleeding. A decrease in the number of trophoblastic large cells, glycogen cells, and spongiotrophoblasts was observed together with clear injury to a portion of the decidua (Fig. 2). At increased magnification, the placenta showed apoptosis in the tropospongium cells and vacuolar degeneration of glycogen cells (Fig. 3), in addition to noticeable inflammatory cell infiltration and localised fibrinoid deposits (Fig. 4). Furthermore, the labyrinth's lumens showed a uniform, acidophilic substance accumulated within the constricted maternal blood sinusoids (Fig. 5).
- The placenta segment from group III that was treated with L-NAME + omega 3 showed intact continuous decidua, blood vessel congestion and haemorrhage, but only minimal fibrin deposition; the glycogen cell and trophoblastic giant cell seemed to be undamaged (Fig. 6).
- Severe bleeding and congestion of the blood arteries, integral decidua, and labyrinth zone were observed in the placenta of the group that received L-NAME+ vitamin E treatment (group IV) (Fig. 7). Nonetheless, large cells and glycogen cells in the basal zone continued to undergo apoptosis and moderate fibrin deposition (Fig. 8).
- While a mild fibrin deposition hemorrhage and blood vessel congestion were still observed, the placental sections from the L-NAME+omega3 + vitamin E recipient group (group V) showed a marked return of

histological architecture to a nearly normal appearance comparable to that of the control group, with intact decidua, basal zone, spongiotrophoblast, trophoblastic giant cell, and glycogen cell (Fig. 9).

Discussion

Rat and human placentas are both categorised as hemochorial placentas, which are distinguished by trophoblast-mediated remodelling of the uterine spiral arteries and deep invasion of intrauterine trophoblast cells. These two placentas share fundamental anatomical similarities. These similarities have prompted research on the maternal-fetal interface in hemochorial placentation, both in vitro and in vivo, using rats as a model (21). An essential organ for assessing developmental toxicity in embryos and the mechanisms underlying chemically induced toxicity is the placenta (22). Reactive oxygen species (ROS) are produced as a result of endothelial cell dysfunction and insufficient placental perfusion, the first pathogenic events in preeclampsia (23). Appropriate histological structure and function are essential to ensuring adequate maternal and fetal vascularisation because preeclampsia is one of the most severe pregnancy complications, characterised by high blood pressure and proteinuria. Several articles have emphasised the effects of PE on placental vasculogenesis (24). As pregnancy progresses, preeclampsia's decreased spiral artery remodelling results in insufficient vasculogenesis (25). Oxidative stress resulting from poor spiral artery remodelling is linked to preeclampsia, which in turn causes inconsistent placental perfusion. Endothelial nitric oxide synthase (eNOS) suppression, inducible nitric oxide synthase (iNOS) activation, increased levels of anti-angiogenic proteins in the blood, and a decrease in vascular endothelial growth factor (VEGF) are all involved in the ensuing scream of placental hypoxia (26). In the current investigation, the PE group's MABP markedly increased in contrast to the control group when rats consumed the nitric oxide synthase (NOS) inhibitor L-NAME. These results are consistent with those of other authors and may be attributed to the strong competitive inhibitory impact of L-NAME on NOS, which results in a significant decrease in NO production, vasoconstriction, and elevated blood pressure (27). Increased expression of many adhesion molecules, accelerated vascular inflammation, endothelial dysfunction, and inadequate utero-placental perfusion are additional explanations (28). Moreover, some researchers have proposed that an increase in thromboxane A2 and a decrease in prostacyclin levels may be responsible for the rise in blood pressure by promoting vasoconstriction (29, 30). Lipid peroxidation produces placental MDA, which is a crucial marker of oxidative stress brought on by placental hypoxia and necrosis in the PE group (31). According to the findings of earlier studies, the group treated with L-NAME showed elevated levels of MDA and iNOS, which are indicative of placental oxidative tissue damage, as compared to the control group.

Of the eight isoforms of vitamin E, α-tocopherol is the most powerful antioxidant, exhibiting a significantly higher affinity for peroxyl radicals (32). Because vitamin E directly repairs oxidative DNA damage and prevents apoptosis brought on by ROS or cytokines, the group that got it in this trial showed a considerable drop in placental MDA. Additionally, it scavenges lipid hydroperoxides and peroxyl nitrite. Jian et al. previously revealed that vitamin E alleviates oxidative damage to hepatocytes by controlling the expression of genes linked to apoptosis and pyroptosis (33). In addition to scavenging reactive oxygen species, vitamin E has been shown to have a preventive effect against nonradical oxidants like hypochlorite and singlet oxygen, which is the basis for the significant reduction in blood pressure observed in this study following vitamin E administration (34). On the other hand, vitamin E inhibits iNOS and has a broad-spectrum antioxidant impact, which lowers the synthesis of inflammatory cytokines. Consequently, it might reduce oxidative stress in rats' kidneys and liver (35).

Although the mechanism underlying this effect is yet unknown, omega-3 supplementation has been shown to preserve pregnancy, growth, and duration of gestation, as well as prevent postnatal problems. It also has effective anti-oxidative and anti-inflammatory actions throughout pregnancy (36).

Overall, several investigations have previously established the beneficial effect of omega-3 with vitamin E supplementation against plasma lipid oxidation, DNA damage, and placental apoptotic markers in both early and late onset preeclampsia in rat models, which is consistent with the current study's findings (37). Surprisingly, some studies have demonstrated that taking supplements of vitamin E and omega-3 together can help thalassemia patients' antioxidative status (38),

enhance athletes' ability to perform during exercise, and establish possible therapeutic effects on nicotine-induced placental oxidative stress (39). Histological changes in the placenta of the PE group were observed in this study as constriction of the maternal blood sinusoids and vacuolar degradation of glycogen cells within the tropospongium. Reduced nitric oxide (NO) generation may be the cause of these alterations, which can result in ischemic damage, vasoconstriction, and poor placental perfusion. These results are in line with earlier research showing that the presence of glycogen-rich cells and alterations in gene expression affect the placental vasculature, as seen in diet-induced obesity models in mice (40). Furthermore, the amplification of oxidative stress markers may be responsible for fibrinoid deposition and inflammatory cell infiltration. This can exacerbate preeclampsia (PE) and the systemic inflammatory response by causing endothelial dysfunction and raised blood pressure. This noteworthy discovery aligns with the findings of earlier research (41). In rats with induced preeclampsia (PE), the current study is a unique exploration of the function of omega-3 and vitamin E in reducing placental structural changes.

According to the study's findings, preeclampsia brought on by the administration of L-NAME during pregnancy causes oxidative stress-related damage, which is manifested by a number of structural alterations, such as maternal blood vessel congestion and haemorrhage, glycogen cell vacuolar degeneration, tropospongium cell apoptosis, fibrinoid deposition, and a noticeable infiltration of inflammatory cells. However, when compared to the corresponding untreated PE group, the administration of vitamin E and omega-3 dramatically reduced these degenerative alterations and improved oxidative stress markers.

References

1. Barda S, Yoeli Y, Stav N, Naeh A, Maor E, Hallak M, Gabbay R. Factors associated with progression to preeclampsia with severe features in pregnancies complicated by mild hypertensive disorders. J Clin Med 2023; 10(22):7022.
2. Anto O, Boadu O, Ansah E, Tawiah A, Frimpong J, Tamakloe T, Korsah E, Acheampong E, Asamoah A, Opoku S, Adua E, Afrifa E, Annani E, Anto O, Obirikorang C. Prevalence of preeclampsia and algorithm of adverse foeto-maternal risk factors among pregnant women in the Central Region of Ghana: A multicentre prospective cross-sectional study. PLoS One 2023; 18(6): e0288079.
3. Jena K, Sharma R, Petitt M, Maulik D, Nayak R. Pathogenesis of preeclampsia and therapeutic approaches targeting the placenta. Biomolecules 2020; 10, 953.
4. Silva JF, Serakides R. Intrauterine trophoblast migration: A comparative view of humans and rodents. Cell Adh Migr 2016; 10(2): 88-110.
5. Furukawa S, Hayashi S, Usuda K, Ogawa I. Toxicological pathology in the rat placenta. Journal of Toxicologic Pathology 2011; 24(2):95-111.
6. Charest P, Vrolyk P, Lessard M, Sloboda M, Dalvai M, Haruna J, Bailey L, Benoit O. Histomorphologic analysis of the late-term rat fetus and placenta. Toxicol Pathol 2018; 46(4):158-168.
7. Ishan G, Ezeuko V. Histological Assessment of Placental Development Following Maternal Administration of Monosodium Glutamate in Wistar Rats. J. Appl. Sci. Environ. Manage (2024); 28(6):1639-1643.
8. Liu X, Wang G, Huang H, Lv X, Si Y, Bai L, Wang G, Li Q, Yang W. Exploring maternal-fetal interface with in vitro placental and trophoblastic models. Front. Cell Dev. Biol. 2023; 11(1):1279227.
9. Renaud SJ, Jeyarajah MJ. How trophoblasts fuse: an in-depth look into placental syncytiotrophoblast formation. Cell Mol Life Sci. 2022; 79(8):433.
10. Mori M, Bogdan A, Balassa T, Csabai T, Bartho J. The decidua—the maternal bed embracing the embryo—maintains the pregnancy. Semin Immunopathol 2016; 38:635-649.
11. Ibrahim A, Khoo I, Ismail E, Hussain N, Zin M, Noordin L, Abdullah S, Mahdy A, Lah N. Oxidative stress biomarkers in pregnancy: a systematic review. Reprod Biol Endocrinol. 2024; 22(1):93.
12. Al-Rubai A, Ibraheem MM, Hameed AF, Noel KI, Eleiwi SA. Comparison of placental expression of basic fibroblast growth factor and insulin-like growth factor-1 in placentae of normal, pregnancy-induced hypertension, and preeclamptic pregnancies in Iraqi mothers. Medical Journal of Babylon. 2023; 20(4): p 681-688, 2023.
13. Etsuo N. Role of vitamin E as lipid-soluble peroxyl radical scavenger: In vitro and in vivo evidence. Free Radical Biology and Medicine 2013; 66(66): 12-15.
14. Niki E. Evidence for beneficial effects of vitamin E. Korean J Intern Med. 2015; 30(5):571-579.
15. Noel KI. A Reciprocal Relationship between Oxidative Stress, Antioxidants, and Cancer: A Review. Siriraj Med J. 2024; 76(8):550-6.

16. Obaid A, Al sammak M, Fadhil M. The effect of vitamin E on the histological structure of the kidney in rats treated with cyclophosphamide. Iraqi Journal of Veterinary Sciences 2021; 36(2): 513-517.
17. Al-Obeidy M, Akkila S, Noel K. Omega-3 Fatty Acids as Supplements and Cryoprotectants and Positive Outcomes for Human Seminal Cryopreservation: A Study in the Iraqi Context. Jordan Med. J. 2023;57(2).
18. Marcondes F, Bianchi F, Tanno A. Determination of the estrous cycle phases of rats: some helpful considerations. Braz J Biol. 2002; 62(4):609-14.
19. Lloyd C, Collins L, Burton G. Understanding the uterine artery Doppler waveform and its relationship to spiral artery remodelling. 2021. Placenta, 105, 78-84.
20. Struck M, Andrutis K, Ramirez H, Battles A. Effect of a short-term fast on ketamine-xylazine anesthesia in rats. J Am Assoc Lab Anim Sci. 2011; 50(3):344-8.
21. Soares M, Chakraborty D, Karim Rumi A, Konno T, Renaud S. Rat placentation: an experimental model for investigating the hemochorial maternal-fetal interface. Placenta. 2012 ;33(4):233-243.
22. Ali H, Ibrahim L. Evaluation of the histology and the oxidative stress status in the placentas of obese mothers Annals of the College of Medicine Mosul 2021; 43(1):60-69.
23. McElwain J, Tuboly E, McCarthy P, McCarthy M. Mechanisms of endothelial dysfunction in pre-eclampsia and gestational diabetes mellitus: Windows into Future Cardiometabolic Health? Front Endocrinol (Lausanne). 2020; 11:655.
24. Cho S, Sohn D, Kim S. Reduced angiovasculogenic and increased inflammatory profiles of cord blood cells in severe but not mild preeclampsia. Sci Rep 2021; 11(3): 630.
25. Staff C, Feldstad H, Fosheim K, Kjartan M, Turowski G, Johnsen G, Katjavivi A, Sugulle M. Failure of physiological transformation and spiral artery arthrosis: their roles in preeclampsia American J of Obstetrics and Gynecology 2022; 226 (2): S895-S906 b.
26. Al-Naemi S, Abdullah H, Ibrahim S. Impact of oxidative stress on pregnancy outcome in albino rats. Iraqi Journal of Veterinary Sciences 2012; 26(2): 93-99.
27. Hameed AF, Noel KI, Akkila SS. Placental angiogenesis, IUGR & CMV awareness in Iraqi women. Curr. Issues Pharm. Med. Sci. 2022;35(3):147-51.
28. Chavarría E, Lara L, González A, García Y, Vital S, Reyes A. Prostacyclin/thromboxane early changes in pregnancies that are complicated by preeclampsia. Am J Obstet Gynecol. 2003;188 (4):986-92.
29. Stanko P, Baka T, Repova K, Aziriova S, Krajcirovicova K, Barta A, Janega P, Adamcova M, Paulis L, Simko F. Ivabradine ameliorates kidney fibrosis in L-NAME-induced hypertension. Front. Med. 2020; 7: 325.
30. Manuaba C, Andarini S, Soeharto S, Rahardjo B. High-fat diet in pregnant women may induce preeclampsia through lipid peroxidation pathways. J of Medicinal and Pharmaceutical Chemistry Research 2024; 6(12): 1877-1887. doi: 10.48309/jmpcr.2024.455763.1214.
31. El-shafey H. Protective effects of Artemisinin on the placenta of L-NAME induced preeclampsia in rat. Delta University Scientific Journal 2022; 5(1): Article 5. Available at
32. Zhang D, Okada S, Yu Y, Zheng P, Yamaguchi R, Kasai H. Vitamin E inhibits apoptosis, DNA modification, and cancer incidence induced by iron-mediated peroxidation in Wistar rat kidney. Cancer Res 1997; 57(12):2410-4.
33. Jian L, Xue Y, Gao Y, Wang B, Qu Y, Li S, Li H, Li Z, Wang B, Luo H. Vitamin E Can Ameliorate Oxidative Damage of Ovine Hepatocytes In Vitro by Regulating Genes Expression Associated with Apoptosis and Pyroptosis, but Not Ferroptosis. Molecules. 2021 Jul 27;26(15):4520.
34. Haidara A, Mikhailidis P, Rateb A, Ahmed A, Yassin Z, Ibrahim M, Rashed A. Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rats with streptozotocin-induced Type 1 diabetes. J Diabetes Complications. 2009; 23(2):130-136.
35. Dreze C, Sen S, Hauguel M, Catalano M. Effect of omega-3 supplementation in pregnant women with obesity on newborn body composition, growth and length of gestation: A randomized controlled pilots study. Nutrients 2021; 13(2):578.
36. Amir A, Darwin E. Omega-3 and Vitamin E supplementation effect on reactive oxygen species and Placental Vascular Endothelial Growth Factor: Pre-eclampsia Model. Open Access Maced J Med Sci. 2022 Jun 16; 10(A):1387-1391.
37. Noel KI, Abdulateef HH, Khamees NH. Pluripotency Stem Cell Marker Expression and Apoptotic Changes in Placental Tissues of Normal and Intra-Uterine Growth Restriction (IUGR) Babies of Iraqi Mothers: A Comparative Study. Al-Rafidain J Med Sci. 2025;8(1):71-7.
38. Soliman AT, Yassin M, Alyafei F, Alaaraj N, Hamed N, Osman S, Soliman N. Nutritional studies in patients with β-thalassemia major: A short review. Acta Biomed 2023; 94(3): e2023187. doi: 10.23750/abm. v94i3.14732.

39. Higashi Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction related disease. Antioxidants. 2022; 11(10):1958.
40. Zhao H, Wong J, Stevenson K. The placental vasculature is affected by changes in gene expression and glycogen-rich cells in a diet-induced obesity mouse model. PLoS ONE 2023; 18(11): e0294185.
41. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol. 2014 Oct 10; 5:372.