# Association between Interleukin-32 Gene Polymorphism (rs4786370) and the Susceptibility to Preeclampsia in Egyptian Pregnant Women

Samar Esam EL-Din Yaseen*[1], Rana Atef Khashaba[1], Wagdy Megahed Amer[2], Seham Gouda Ameen[1], Ibrahim Mohamed Elsaeed Rageh[1]

[1]Clinical and Chemical Pathology Department, Faculty of Medicine, Benha University, Benha, Egypt
[2]Obstetrics and Gynecology Department, Faculty of Medicine, Benha University, Benha, Egypt

**Abstract**

**Background:** Preeclampsia (PE) is an organ dysfunction issue unique to pregnancy that manifests as in hypertension and proteinuria.Due to its participation in several important biological processes, interleukin-32 (IL-32), a proinflammatory cytokine mostly expressed by natural killer (NK) cells, monocytes, epithelial cell lines, and T-cells, has become famous. The purpose of this literature study is to discover if there is a correlation between the Interleukin-32 gene polymorphism (rs4786370) and the risk of preeclampsia in pregnant women from Egypt. In conclusion, pregnant women in Egypt may be able to use the IL-32 rs4786370 gene polymorphism as a marker to estimate their risk of preeclampsia.

**Keywords**: Cardiovascular complications, interleukin-32, preeclampsia, and pregnant women

**Introduction:**

Preeclampsia (Polycystic ovary syndrome (PCOS) affects 5% to 10% of pregnant women and is a hypertensive condition affecting many systems. Globally, leading maternal illness and [1].

Hypertension, proteinuria, or other symptoms of organ failure characterise PE, a pregnancy-specific complication. Patients whose blood pressure was normal before pregnancy develop this anomaly after 20 weeks. There is a high risk of long-term consequences, including cardiovascular disease, in women with preeclampsia, making this a potentially fatal illness [2].

Due to its participation in several important biological processes, mostly become famous component of laboratory settings, and it is mostly generated in blood monocytes and epithelial cells by [3].

Preeclamptic women often have peripheral blood mononuclear cells and decidual lymphocytes that are ready to produce an abundance of Th1 cytokines. Placentation is regulated by a delicate symphony of pro- and anti-inflammatory cytokines released by various subsets of immune cells. The rs4786370 (C/T) variant is a significant single nucleotide polymorphism (SNP) in the interleukin-32 gene. It boosts IL-32 gene expression from its position on the promoter region [4].

**Preeclampsia**

range, affects around 2–15% of all pregnancies and is one of the most frequently reported problems of pregnancy [5]. Approximately 4 million pregnant women get the diagnosis of pre-eclampsia (formerly known as toxaemia) every year; as a result, over 70,000 mothers and 500,000 newborns lose their lives [6].

The symptoms of preeclampsia include inflammation throughout the body, malfunction of the endothelial cells, elevated levels of oxidative stress, and damage to the blood vessels. Although preeclampsia only occurs during pregnancy, it is strongly linked to age-related cardiovascular issues such as high blood pressure, heart attacks, renal problems, and strokes [7].

There are two main immunological interfaces that occur during pregnancy. The first one is in the decidua and involves the foetal trophoblast and maternal immune cells. It's the dominant interface in the early stages of the pregnancy. The second one is in the end stages and involves circulating maternal immune cells and syncytiotrophoblasts (STBs). This is thought to mean that factors derived from the placenta activate the mother immune cells and cause systemic endothelial dysfunction [8].

Emphysema categorisation

The clinical appearance of pre-eclampsia is categorised according to the gestational age. The ISSHP categorises pre-eclampsia as either preterm (birth occurs before 37 weeks of gestation), term (delivery occurs beyond 37 weeks of gestation), or postpartum pre-eclampsia [1].

**Based on symptoms**

**Symptoms severity**

**Sever**: blood a blood pressure reading more than 160/110 mm Hg together with

another medical problem, such as HELLP syndrome (high blood pressure, increased liver enzymes, and low platelet count) or foetal growth restriction below the tenth percentile

For mild cases, there must be at least one other medical condition present, such as proteinuria (a urine protein to creatinine ratio of 30 mg/mmol or higher, albumin to creatinine ratio of 8 mg/mmol or higher), or 0.3 g/day or more in 24-hour urine collection.

The eclipsia

Severe preeclampsia complication: HELLP syndrome after delivery or new-onset multifocal, focal, or tonic-clonic seizures; unexplained coma;

The severe pre-eclampsia complication is marked by low platelet count, increased liver enzymes (lactate dehydrogenase ≥600 IU/l, aspartate aminotransferase >70 IU/l), and haemolysis (platelet count <150,000 cells/μl).

Frequently employed as well

There are two types of onset: early (before 34 weeks of gestation) and late (after 34 weeks of gestation).

Abnormal The Maternal Preeclampsia Syndrome and Placentation

Placental dysfunction is an essential component of the preeclampsia pathophysiology. Due to trophoblasts not transforming into endothelial cells, spiral artery remodelling is not completed and trophoblast invasion is hindered. As a consequence of placental ischaemia, angiogenic indicators such soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFlt-1) are increased [9].

An inflammatory state is further enhanced during preeclampsia (PE) due to persistent immunological activation, which causes pro-inflammatory T cells to boost production of inflammatory cytokines and decrease production of regulatory and anti-inflammatory cytokines.Preeclampsia pathophysiology includes unchecked proinflammatory responses and a lack of regulatory or anti-inflammatory cytokines; moreover, the cytokine profile of the mother differs between normotensive and preeclampsia pregnancies [10].

Preeclampsia management

Prevention

The use of low-dose aspirin as a pregnancy prevention measure has recently gained global acceptance. Early onset preeclampsia is the most dangerous kind of the condition for both mother and child, and a recent big experiment showed that low-dose aspirin (150 mg) must be begun before 16 weeks of gestation in order to avoid it [11].

Medical Therapy

Giving birth is the only certain way to cure preeclampsia. Patients with well-controlled prenatal hypertension or preeclampsia without severe symptoms in the context of normal antepartum tests may continue to be observed for preterm gestations, although there are hazards associated with expectant treatment [12].

Patients diagnosed with severe preeclampsia at or after 34 weeks of gestation should not be delayed in having their babies delivered in order to accommodate the administration of steroids; instead, they should give birth when the mother has stabilised. Research on calcium's potential in preventing and treating preeclampsia makes sense given the mineral's importance in placental development and function, as well as its role in vascular tone regulation and blood pressure maintenance [13].

Preeclampsia risk prediction software and AI (artificial intelligence) approaches are notably improving, enabling doctors to act sooner and conduct closer monitoring [14].

These programs allow doctors to enter the mother's demographic information (such as, preexisting chronic hypertension, SLE, and APS) as well as the foetal biophysical measurements (such as mean uterine artery PI and mean arterial pressure). Some programs even include the preeclampsia biomarkers already mentioned, like serum pregnancy-associated plasma protein A and serum PlGF. After entering all the relevant information, the computer provides the clinician with an approximation of the patient's chance of developing preeclampsia later on in the pregnancy [15].

Ligand-32 (IL-32)

Its specific expression in IL-2 stimulated NK cells led to its 1992 establishment as natural killer (NK) cell transcript 4, a pro-

inflammatory cytokine with several important biological roles. Monocytes, epithelial cell lines, T-cells, and natural killer (NK) cells are the main sources of interleukin-32 (IL-32) [16].

Characteristics of IL-32 in General

In order to regulate their own functions, the isoforms may communicate with one another within the cell. A good illustration of this is the role of IL-32β in enhancing the adherence of immune cells to activated endothelium cells [3].

There is a wide variety of triggers that may alter the amount of IL-32 that is already present in immune cells. Lipopolysaccharide (LPS) and muramyl dipeptide (MDP) are pathogen-related substances, while IL-32 produced by TNF-α and IFN-γ is one of numerous cytokines [17].When it comes to the development of many illnesses, interleukin 32 is an essential modulator. Multiple infections, malignancies, autoimmune diseases, and inflammatory illnesses have been linked to it [18]. Most inflammatory and autoimmune illnesses linked to IL-32 include asthma, psoriasis, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD) **[19].**

**Partners in Binding and IL-32 Receptors**

It was shown that Proteinase-3 (PR3) interacts with IL-32α specifically and with a high affinity. The binding affinity of PR3 to IL-32 is quite strong. The neutrophil-produced enzyme PR3 is a serine proteinase that is also expressed on monocyte membranes. A number of cytokines, including IL-1β, IL-18, IL-8, and TNF-α, may be activated by the neutrophil serine PR3. Additionally, it has the ability to bind and cleave IL-32, which enhances its biologic activity [20].

Comparing the levels in the cytosol to the amounts released by the cells, the quantity of interleukin 32 is so little that it is difficult to detect. A crucial role in both is played by, which is said to activation synthesis, among other chemokines and inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α [21].

The pathways of interleukin 32 and nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) p38 may enhance the synthesis of interleukin-8. The synthesis of IL-6 and IL-1β may be induced via a caspase 1-dependent signalling pathway when intracellular nucleotide-binding oligomerisation domain (NOD) proteins 1 and 2 work in tandem with IL-32 [21].

Cytokines are stimuli that cause the production of interleukin (IL)-32. Many cytokines, including as IL-1β, IL-12, IL-18, and tumour necrosis factor-α (TNF-α), promote the production of interleukin 32. According to [22], adipocytes, human primary keratinocytes, fibroblast-like synoviocytes, CD4+ T cells, and monocyte-derived dendritic cells (DCs) are among the cell types that may be sensitised to IL-32 by tumour necrosis factor-ά.Regarding infections and pathogen-associated molecular patterns (PAMPS), it has been observed that certain bacterial infections, like Mycobacterium tuberculosis and Helicobacter pylori, as well as viral infections, like HIV, influenza A, EBV, HPV, and HSV, trigger the production of interleukin 32 [23].

Therefore, IL-32 could have a function in many tissues' reactions to bacterial and viral illnesses. On the one hand, interleukin 32 (IL-32) mediates strong antimicrobial responses; on the other, it promotes immunological tolerance, which may lead to persistent infection [24]. Oxidative stress also induces interleukin 32. IL-32 regulates apoptosis, amplifies inflammation, and promotes angiogenesis; all of these activities are linked to inflammation, viral infections, and cancer. In lung alveolar epithelial cells, IL-32 triggers oxidative stress, which in turn promotes the epithelial to mesenchymal transition [25].

It is possible that interleukin 32 was passively released from the cytoplasm of apoptotic cells, as it was found in the supernatant of CD3-activated T cells. Because fibroblast-like synoviocytes (FLS) are able to release it, it is found in the synovial fluid of RA patients. Through the NF-kB and p38 mitogen-activated protein kinase inflammatory signal pathway, interleukin 32 causes monocytes to differentiate into macrophage or dendritic cells and triggers the production

of pro-inflammatory cytokines such as tumour necrosis factor (TNF) α, IL-1β, IL-6, and IL-8 [26].

It is the job of human immune cells such NK cells, monocytes, macrophages, and T lymphocytes to produce interleukin 32. Epithelial cells, endothelial cells, fibroblasts, hepatocytes, and mesenchymal stromal cells are among the numerous nonimmune cells that may be found with it. Tregs are major IL-32 producers in a number of illnesses, according to single cell sequencing research [27].In addition, IL-32 has the ability to stimulate M1 polarisation and the release of cytokines and chemokines in macrophages, as well as DC differentiation, maturation, and crosspriming. When microbial receptors like Toll-like receptors (TLR) and intracellular nuclear oligomerisation domain (NOD) families are activated, interleukin 32 can amplify the inflammatory cytokines produced by these receptors and activate TLR signalling even when PRR ligands are not present through the protease-activated receptor 2 (PAR2) [28].

Increased levels of interleukin 32 in the blood are associated with a number of diseases and conditions, including type 2 diabetes, asthma, atopic dermatitis, allergic rhinitis, COPD, NAFLD, SLE, HIV infection, and synovial tissues from RA patients [29].Even though IL-32 isn't produced by all cell types, it might nonetheless serve as an alarmin released as cells die. Therefore, IL-32 secretion is context- and isoform-dependent; the cues that activate IL-32 production may determine the mechanism of secretion from cells [30].

Interleukin 32 polymorphisms:

Rare polymorphisms (SNPs) rs4786370 and rs9927163 are located in the IL-32 gene. The former increases IL-32 gene expression and is situated on the promoter region [31]. The latter may control IL-32 gene expression; it is situated in the intron region. Hence, it's possible that the IL-32 gene's expression may change due to both SNPs. In addition, tumour necrosis factor alpha has the ability to trigger it, which in turn increases the production of tumour necrosis factor. Several disorders, including as cancer, leishmania infection, and systemic lupus erythematosus, have been linked to rs28372698 and rs4786370 polymorphisms in the IL-32 promoter [32].

Preeclampsia patients have immune system alterations that lead to low-level chronic inflammation, which keeps the endothelial damage cycle going. Antagonising and anti-angiogenic factor imbalances might be the outcome of this combination. Preeclampsia is a clinical phenomenon that may lead to negative pregnancy and postpartum health outcomes due to the complicated interaction between inflammation, placental pathology, and alterations in angiogenesis [33].Introductory cytokines like interleukin (IL)-32 contribute to tumour invasion and new blood vessel formation. Preeclampsia is analogous to tumour invasion, hence the current research postulated that IL-32 may cause trophoblastic invasion and uterine artery remodelling in women who have preeclampsia complications. In addition, inflammatory bowel disease, chronic obstructive pulmonary disease, and rheumatoid arthritis are pathophysiologic states linked to dysregulated inflammatory responses, and IL-32 seems to have a significant impact in these conditions [34].

**Conclusions**: The Preeclampsia risk in Egyptian pregnant women may be predicted by the IL-32 rs4786370 gene polymorphism. In cases of severe preeclampsia, TT and CT variations were more common than CC variants. Our findings might help in determining if pregnant women are at risk of preeclampsia and in creating effective strategies to manage and avoid this condition.

**References**


[1] LA Magee, MA Brown, DR Hall, S Gupte, A Hennessy, SA Karumanchi, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022;vol , 27:pp: 148-169.

[2] R Nirupama, S Divyashree, P Janhavi, SP Muthukumar, PV Ravindra. Preeclampsia:

Pathophysiology and management. J Gynecol Obstet Hum Reprod. 2021;vol,50:pp:101975.
[3] MB Khawar, MH Abbasi, N Sheikh. IL-32: A Novel Pluripotent Inflammatory Interleukin, towards Gastric Inflammation, Gastric Cancer, and Chronic Rhino Sinusitis. Mediators Inflamm. 2016;2016:pp:8413768.
[4] M Damen, K Schraa, L Tweehuysen, AA den Broeder, MG Netea, CD Popa, et al. Genetic variant in IL-32 is associated with the ex vivo cytokine production of anti-TNF treated PBMCs from rheumatoid arthritis patients. Sci Rep. 2018;vol,8:pp:14050.
[5] AD Mou, Z Barman, M Hasan, R Miah, JM Hafsa, A Das Trisha, et al. Prevalence of preeclampsia and the associated risk factors among pregnant women in Bangladesh. Sci Rep. 2021;vol,11:pp:21339.
[6] LC Poon, A Shennan, JA Hyett, A Kapur, E Hadar, H Divakar, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145 Suppl vol,1:pp:1-33.
[7] P Wu, R Haththotuwa, CS Kwok, A Babu, RA Kotronias, C Rushton, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017;vol,10.
[8] T Iriyama, K Sun, NF Parchim, J Li, C Zhao, A Song, et al. Elevated placental adenosine signaling contributes to the pathogenesis of preeclampsia. Circulation. 2015;vol,131:pp:730-741.
[9] M Sircar, R Thadhani, SA Karumanchi. Pathogenesis of preeclampsia. Curr Opin Nephrol Hypertens. 2015;vol,24:pp:131-138.
[10] AC Harmon, DC Cornelius, LM Amaral, JL Faulkner, MW, Jr., Cunningham K Wallace, et al. The role of inflammation in the pathology of preeclampsia. Clin Sci (Lond). 2016;vol,130:pp: 409-419.
[11] DL Rolnik, KH Nicolaides, LC Poon. Prevention of preeclampsia with aspirin. Am J Obstet Gynecol. 2022;vol,226:pp:S1108-s1119.
[12] KJ Chang, KM Seow KH, Chen. Preeclampsia: Recent Advances in Predicting, Preventing, and Managing the Maternal and Fetal Life-Threatening Condition. Int J Environ Res Public Health. 2023;vol,20.
[13] C Villa-Etchegoyen, M Lombarte, N Matamoros, JM Belizán, G Cormick. Mechanisms Involved in the Relationship between Low Calcium Intake and High Blood Pressure. Nutrients. 2019;vol,11.
[14] R Ramakrishnan, S Rao, J-R He. Perinatal health predictors using artificial intelligence: A review. Women's health (London, England). 2021;vol,17:pp:17455065211046132.
[15] M Alkhodari, Z Xiong, AH Khandoker, LJ Hadjileontiadis, P Leeson, W Lapidaire. The role of artificial intelligence in hypertensive disorders of pregnancy: towards personalized healthcare. Expert Rev Cardiovasc Ther. 2023;vol,21:pp:531-543.
[16] S Han, Y Yang. Interleukin-32: Frenemy in cancer? BMB Rep. 2019;vol,52:pp:165-174.
[17] M Schenk, SR Krutzik, PA Sieling, DJ Lee, RM Teles, MT Ochoa, et al. NOD2 triggers an interleukin-32-dependent human dendritic cell program in leprosy. Nat Med. 2012;vol, 18:pp: 555-563.
[18] D Briukhovetska, J Dörr, S Endres, P Libby, CA Dinarello, S Kobold. Interleukins in cancer: from biology to therapy. Nat Rev Cancer. 2021;vol,21:pp:481-499.
[19] B Rong, T Fu, C Rong, W Liu, K Li, H Liu. Correlation between serum IL-32 concentration and clinical parameters of stable COPD: a retrospective clinical analysis. Sci Rep. 2020;vol,10:pp: 12092.
[20] F Khorsand, BE Haug, I Kursula, N Reuter, R Brenk. Expression and purification of human neutrophil proteinase 3 from insect cells and

characterization of ligand binding. Plos one. 2024;vol,19:pp:e0294827.
[21] MG Netea, T Azam, G Ferwerda, SE Girardin, M Walsh, JS Park, et al. IL-32 synergizes with nucleotide oligomerization domain (NOD) 1 and NOD2 ligands for IL-1beta and IL-6 production through a caspase 1-dependent mechanism. Proc Natl Acad Sci U S A. 2005;vol,102:pp:16309-16314.
[22] A Crinier, P Milpied, B Escalière, C Piperoglou, J Galluso, A Balsamo, et al. High-Dimensional Single-Cell Analysis Identifies Organ-Specific Signatures and Conserved NK Cell Subsets in Humans and Mice. Immunity. 2018;vol,49:pp:971-986.e975.
[23] AJ Smith, CM Toledo, SW Wietgrefe, L Duan, TW Schacker, CS Reilly, et al. The immunosuppressive role of IL-32 in lymphatic tissue during HIV-1 infection. J Immunol. 2011;vol,186:pp:6576-6584.
[24] JC Dos Santos, B Heinhuis, RS Gomes, MS Damen, F Real, RA Mortara, et al. Cytokines and microbicidal molecules regulated by IL-32 in THP-1-derived human macrophages infected with New World Leishmania species. PLoS Negl Trop Dis. 2017;vol,11:pp:e0005413.
[25] L Bergantini, S Gangi, M d'Alessandro, P Cameli, B Perea, M Meocci, et al. Altered serum concentrations of IL-8, IL-32 and IL-10 in patients with lung impairment 6 months after COVID-19. Immunobiology. 2024;vol,229:pp:152813.
[26] OC Kwon, B Ghang, EJ Lee, S Hong, CK Lee, B Yoo, et al. Interleukin-32γ: Possible association with the activity and development of nephritis in patients with systemic lupus erythematosus. Int J Rheum Dis. 2019;vol,22:pp:1305-1311.
[27] O Zavidij, NJ Haradhvala, TH Mouhieddine, R Sklavenitis-Pistofidis, S Cai, M Reidy, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. Nat Cancer. 2020;vol,1:pp:493-506.
[28] T Gruber, M Kremenovic, H Sadozai, N Rombini, L Baeriswyl, F Maibach, et al. IL-32γ potentiates tumor immunity in melanoma. JCI insight. 2020;vol,5.
[29] R Fadaei, N Bagheri, E Heidarian, A Nouri, Z Hesari, N Moradi, et al. Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6. Cytokine. 2020;vol,125:pp:154832.
[30] KR Aass, MH Kastnes, T Standal. Molecular interactions and functions of IL-32. J Leukoc Biol. 2021;vol,109:pp:143-159.
[31] MS Damen, R Agca, S Holewijn, J de Graaf, JC Dos Santos, PL van Riel, et al. IL-32 promoter SNP rs4786370 predisposes to modified lipoprotein profiles in patients with rheumatoid arthritis. Sci Rep. 2017;vol,7:pp:41629.
[32] Y Wang, Y Yang, Y Zhu, L Li, F Chen, L Zhang. Polymorphisms and expression of IL-32: impact on genetic susceptibility and clinical outcome of lung cancer. Biomarkers. 2017;vol, 22:pp: 165-170.
[33] L Ferrucci, E Fabbri. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;vol,15:pp:505-522.
[34] F Mazlum, B Gharesi-Fard, H Hadinedoushan, Y Bakhshizadeh Ghashti. Association between interleukin-32 gene polymorphism and susceptibility to preeclampsia. Hypertens Pregnancy. 2021;vol,40:pp:218-225.