Immune Changes in Infants of Preeclampsia Mothers: A Systematic Review of Literature

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Abstract

Preeclampsia (PE) is a prevalent disease especially in developing countries. PE influences maternal immune cells and cytokines, with prevailing of proinflammatory cytokines and reduction of regulatory cells. It has a short- and long-term impact on newborn mortalities and morbidities. The aim of this study is to provide an overview of previous literature discussing the effect of PE on infant immunity to help design future research. A comprehensive search was done on three databases including PubMed, Medline, and EMBASE with mesh and text terms. We could identify 851 titles published from 2000 to the time of search. Twenty-four studies met the inclusion criteria, and they were included in the quality assessment. Twenty-four studies were identified, covering the impact of PE on various neonatal immune cells and cytokines. PE is associated with a decrease in the number of several immune cells in newborns, particularly neutrophils, with enhancing cytotoxic effect of both neutrophils and natural killer (NK) cells. Treg cells were considerably reduced with increase of cytotoxic T cells CD8+ and memory cells CD45RO+ in both CD4+ and CD8 + . Proinflammatory cytokines like IL6, IL8, and TNF were raised in severe PE. PE is linked to a decrease in regulatory immune cells and an increase in the immune cells' cytotoxic capability, as well as the prevalence of proinflammatory cytokines in newborns. These changes were observed in cord blood and peripheral blood samples; however, future research should investigate the long-term effect of PE on neonatal immunity.

Keywords
- preeclampsia
- immunity
- immune cells
- cytokines

Introduction

Preeclampsia is a highly prevalent pregnancy-specific disorder as it affects 2 to 8% of all pregnancies worldwide. The rate of preeclampsia is increasing from the 1980s and it is more common in extreme maternal ages and primigravida. Preeclampsia causes different maternal and neonatal morbidities and mortalities.[1] The infants who were born from preeclampsia pregnancy have increased risk of neonatal complications including preterm birth, intrauterine growth restriction (IUGR), neonatal sepsis, feed intolerance, poor growth and bronchopulmonary dysplasia (BPD), as well as higher risk of cerebral palsy, abnormal neurodevelopmental outcomes, cardiovascular disease, stroke, and mental disorders during childhood and adulthood.[2,3]

Preeclampsia is diagnosed according to new International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria 2014 as a new onset of high blood pressure ≥140/90 in two occasions, 4 hours apart in previous normotensive mother after 20 weeks of gestation and one or more of the following: (1) evidence of proteinuria in urine ≥0.3 mg/mol on protein/creatinine ratio; ≥ + 2 in urine dipstick or ≥300 mg/d

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in 24-hour urine sample; (2) acute kidney with creatinine ≥90 µmol/L, acute hepatic dysfunction with transaminases ≥40 IU/L with or without upper right hypochondria pain or epigastric pain, or signs of neurological or hematological complications; (3) signs of uteroplacental dysfunction such as fetal growth restriction, abnormal uterine artery Doppler, or still birth. Preeclampsia is classified to early onset and late onset with delivery of less than 34^{+0} and $\geq 34^{+0}$ weeks' gestation consecutively. Moreover, preeclampsia could be classified to preterm preeclampsia and term preeclampsia with delivery at less than 37^{+0} and $\geq 37^{+0}$ consecutively.[4]

During normal pregnancy, the maternal immune system undergoes some modification to tolerate the foreign fetal tissue and provide host defense against infection at the same time. The cytotoxic immune responses are decreased (natural killer [NK] cells, effector cells, and phagocytosis) and regulatory immune elements are increased (regulatory T cells [Treg cells] and NK regulatory cells). These changes help avoid abortion and still birth.[5] During preeclampsia, the T helper cells shift toward Th1, which leads to enhanced secretion of IL12 and IL18 and diminished secretion of IL10. This leads to decreased anti-inflammatory response, which increases apoptosis and decreases trophoblast cell invasion.[6]

Preeclampsia is a major cause of IUGR and still birth. It increases the risk of BPD and necrotizing enterocolitis (NEC) in neonates. In a large retrospective cohort study, preeclampsia was associated with higher rate of neonatal sepsis.[7] Preeclampsia causes changes in neonatal immunity, especially in the first few days after birth such as decrease in Treg cells, increase in NK cells, and decrease in neutrophilic count and function.[8] These immune changes could increase the risk of sepsis, BPD, and NEC in neonates.[9]

In our study, we collected evidence from the past 20 years to highlight the effect of preeclampsia on the immune function of newborns. As far as we know, this is the first qualitative systematic review on the effect of preeclampsia on neonatal immunity.

Material and Methods

Search Strategies

This systematic review was conducted according to the 2009 Cochrane Library PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[10] PubMed, Medline, and EMBASE websites were searched for studies that focus on the effect of preeclampsia on various aspects of neonatal immunity in cord and peripheral blood sample. We searched these databases from Healthcare Database Advanced Search (HDAS) on the National Institute of Clinical Excellence (NICE) website.

Key MeSH and text terms were used for a more comprehensive search. The following mesh and text terms were used for preeclampsia: (Preeclampsia OR Eclampsia OR preeclamps* OR preeclamps* OR pre eclamps* OR eclamps* OR "pregnancy induced hypertension" OR "hypertensive disorder of pregnancy"), and for immunity ("Acquired Immunity" OR "Adaptive Immunity" Immunity OR "Fetal Immunity, Maternally-Acquired" Immun* OR "Immun* cell*" OR "Innat* Immun*" OR "Acquir* Immun*"), and we for newborn (Infant OR Newborn OR New-born* OR "Pregnancy outcom*" OR "pregnancy outcome"). We combined the results of the three main search categories with Boolean operator (AND). The search was completed in December 2020 and repeated in March 2023 to ensure that our results were up to date.

Inclusion and Exclusion Criteria

The search was restricted to full text articles on human subjects, written in English, and published in or after 2000. We included articles that focus on the effect of maternal preeclampsia on newborn immunity in cord and peripheral blood during neonatal period. We excluded nonhuman studies, case report, in vitro cell line test studies, narrative review, and systematic review. We excluded studies that focus only on maternal immunity. The references of the selected studies were also checked to determine if any were applicable for our search. Two authors independently screened the titles and abstracts of all citations and selected the potential related studies. Full texts were independently reviewed by the two authors, and data were extracted independently by them. Any disagreement between the investigators was resolved by discussion. The following data were extracted from each article: name of the first author, publication year, type of study, number of participants, gestational age, source of blood sample, immune marker, method of assessment, main results, and *p*-value. These characteristics are summarized in ►**Table 1**.

Quality Assessment of Selected Studies

Two authors assessed the quality of the selected studies utilizing the criteria of quality evaluation checklist developed by Rahimzadeh et al.[11] The quality assessment tool was based on 19 criteria, which consisted of four key areas: proper baseline for studies, appropriate population selection, adequate study design, and appropriate outcome reporting. The possible score ranged from 0 to 40. According to this score, the quality of the included studies was categorized into three rankings: rank A (score: 70–100%), rank B (score: 40–69%), and rank C (score: <40%). If the two authors disagreed on more than two grades, a third person was asked to recheck the article. The checklist for quality evaluation is illustrated in ►**Table 2**. The numbers define the score of the study.

Results

As shown in ►**Fig. 1**, the total number of articles from the three databases were 851 after removal of duplication. Seventy-one potential studies were retrieved based on the title and abstract. After a thorough analysis of the full texts, 51 were excluded. Four studies were added after examining the references of the selected articles. Some review articles published, but none of them focused on the immune changes in infants. Finally, 24 articles were included in this review. The main results of each article are summarized in ►**Table 3**.

Most of the studies were case control designs, while two were prospective cohorts and one was cross-sectional. Five

Table 1 Basic characteristics of the studies on preeclampsia and normotensive controls

Study	Study design	No. of participants	Gestational age (wk)	Source of sample	Markers of the study	Method of assessment	Quality assessment
Sava et al[23]	Case control	14 cases 14 controls	30 (24–33) 29 (24–31)	Cord and peripheral blood	• CD4+ cells • Memory cells • Cytokines	Flowcytometry Bio-Plex reader	B
Cakir et al[15]	Case control	34 cases 74 controls	29 (26–32) 30 (27–32)	Cord blood	• IL6, IL8, IL10, and TNF-α • Leukocyte and neutrophil	ELISA	A
Bujold et al[22]	Cross sectional	48 cases 72 controls	33.6 ± 3.5 36.5 ± 4	Cord blood	NK cells (CD3-/CD56 + CD16 +)	Flow cytometry	A
Faulhaber et al[17]	Prospective cohort	55 cases 64 controls	30.7 ± 6.3 28.6 ± 3.2	Peripheral blood	IL8, CRO-α, and neutrophils	ELISA	A
Turunen et al[12]	Case control	11 cases 25 controls	27 ± 1.6 26.1 ± 1	Peripheral blood	CD11b neutrophil CD11b monocyte	Flow cytometry	B
Güner et al[16]	Case control	26 cases 23 controls	31.5 ± 2.6 32 ± 2.3	Peripheral blood	cGSF, FBC, and neutrophil	ELISA	B
Al-Othman et al[27]	Case control	50 cases 50 controls	35.4 ± 3 36.2 ± 3.2	Cord blood Placenta	IL6	Sandwich ELISA	A
Laskowska et al[30]	Case Control	27 cases 10 controls	35.03 ± 2.95 38.43 ± 1.64	Cord blood	IL8	Sandwich ELISA	B
Mellembakken et al[18]	Case control	35 cases 36 controls	31 ± 6 38 ± 3	Cord blood	CD neutrophil CD monocyte Plasma cytokines	Flow cytometry ELISA	B
Na lei et al 2016[42]	Case control	28 PE 32 GH 30 controls	30.31 ± 1.7 34.75 ± 2.2 36.04 ± 1.93	Cord blood	CD4, CD8, CD4/CD8, IgG, IgM, IgA, C3, and C4	FACS caliber flow cytometry ELISA	B
Kuntz et al[14]	Case control	20 cases 18 controls	36 ± 3 39 ± 2	Cord blood	Fas neutrophils Fasl neutrophil Fas lymphocyte Fasl lymphocyte	Flow cytometry ELISA	B
Saini et al[19]	Case control	19 cases 20 controls	32. ± 3.9 34 ± 4.6	Cord blood	CD18, CD11a, CD11b, and CD11c	Flow cytometry	B
El-Chennawi et al[26]	Case control	30 cases 20 controls	37.7 ± 0.84 35.2 ± 1.6	Cord blood	CD4 + CD25highFOXP3 +, CD4 + CD25lowFOXP3 +, and CD4+ FOXP3 +.	Multicolor flow cytometry	B

(*Continued*)

Table 1 (*Continued*)

Study	Study design	No. of participants	Gestational age (wk)	Source of sample	Markers of the study	Method of assessment	Quality assessment
Ødegård et al[29]	Case control	270 cases 610 controls	37.8 ± 3.3 40 ± 1.6	Cord blood	IL6	Colorimetric assay	A
Tosun et al[28]	Case control	24 cases 19 controls	37.12 ± 1.45 38.52 ± 0.96	Cord blood	IL6, IL8, and TNF-α	ELISA	B
Sohlberg et al[20]	Case control	22 cases 23 controls	38 (34–42) 39 (38–41)	Cord blood	IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IFN-c, and TNF Monocyte, NKp30, NKG2D	Flow cytometry ELISA	B
Loewendorf et al[21]	Case control	9 cases 16 controls	39.1 ± 2.4 39.2 ± 0.8	Cord blood	Treg, NK cells, and monocytes	Multicolor flow cytometry	B
Vargas-Rojas et al[25]	Case control	19 cases 20 controls	37.5 ± 3.32 37.2 ± 1.94	Cord blood	CD3 + CD4 + CD127low Then IFNγ +, IL-4 +, IL-17+ and FoxP3+ cells	Flow cytometry	B
Laskowska et al[30]	Case control	30 cases 13 controls	37.3 ± 3.13 38.14 ± 1.83	Cord blood	sCD40L	Sandwich ELISA	B
Darakhshan et al[33]	Case control	53 cases 53 controls	38.2 ± 1.2 36.9 ± 1.6	Cord blood	CXCL9 CXCL10 CXCL12	ELISA	B
Xia et al[31]	Case control	27 cases 21 controls	37.1 ± 4.1 38.2 ± 0.8	Cord blood	TNF-α	ELISA	B
Guillemette et al[32]	Case control	18 PE 25 GH 593 controls	37.6 (37.239.4) 39.4 (38.4–40.3) 39.5 (38.6–40.3)	Cord blood	TNF-α	Multiplex particle-based flow cytometric assay	B
Darmochwal-Kolarz et al[24]	Case control	18 cases 20 controls	37.42 ± 1.69 39.16 ± 0.83	Cord blood	B cells CD T cells CD	Flow cytometry	B
Catarino et al[13]	Case control	46 cases 42 controls	37 (34–38) 38.5 (38–39.3)	Cord blood	IL6 TNF-α WBCS	ELISA	B

Abbreviations: cGSF, Granulocyte stimulating factor; ELISA, enzyme-linked immunosorbent assay; FACS, Fluorescence-Activated Cell Sorting; FBC, Full blood count; IL 6, interleukin 6; NK, natural killer cells; TNF, tumor necrotic factor.

Table 2 Criteria of quality evaluation of selected studies

NM critical appraisal check list	Yes	No	Unclear	N/A
1. **Baseline:** Was the hypothesis/aim/objective of the study clearly described?	2	0	1	
2. **Population:** Were enough participants selected?	2	0	1	
Were the participant randomized into groups?	2	0	1	
3. **Case and control definition:** Were the characteristics of the preeclampsia clearly defined?	2	0	1	
Was the stage of the disease assigned?	2	0	1	
Was the source of the cells mentioned?	2	0	1	
Was the gestational age of the participants mentioned?	2	0	1	
Were other disorders or medication considered?	2	0	1	
Were the characteristics of the control group the same as the case group?	4	0	2	
4. **Study design:** Was the exposure clearly defined?	2	0	1	
Was the time frame of the study mentioned?	2	0	1	
Were the methods of Treg measuring valid?	2	0	1	
Did the study incorporate blinding?	2	0	1	
Were the potential confounding factors considered in the design?	2	0	1	
Was the statistical analysis appropriate to the design?	2	0	1	
5. **Results:** Were the results adjusted for confounding factors?	2	0	1	
Were the main findings of the study clearly described?	2	0	1	
Did the study provide estimates of the random variability in the data for the main outcomes?	2	0	1	
Had actual probability values been reported?	2	0	1	

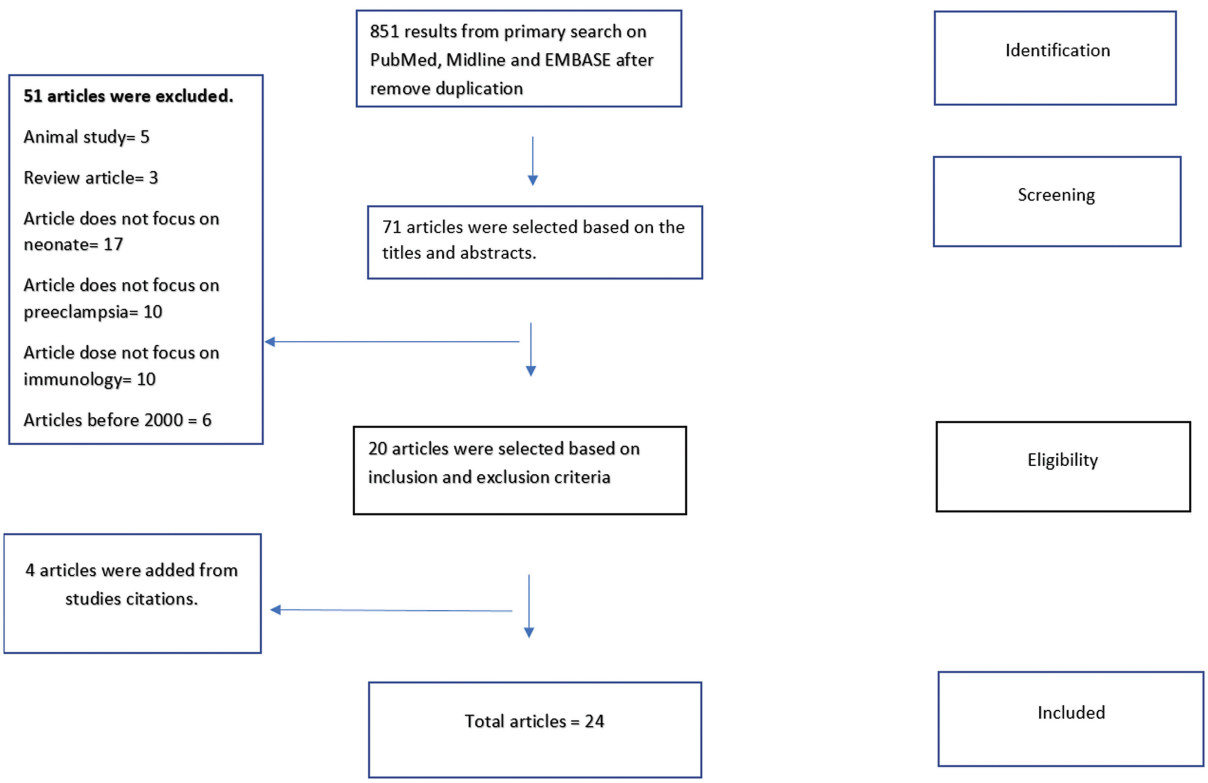

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of study selection.

Table 3 The main results of each study

Study	Main result
Ødegård et al[29]	● No difference between IL6 level in the PE and control groups ● IL6 was lower in early PE and severe PE compared with controls, with $p < 0.001$ for both ● Decrease IL6 level was more statistically significant with lower birth weight ratio
Tosun et al[28]	*In cord blood:* ● IL6 was higher in the PE group than in control: 114.57 (43.57–712.89), and 23.72 (7.48–422.62), respectively. ● IL6 was higher in severe PE than in mild PE: 118.31 (76.81–546.35) and 72.89 (49.75–155.45), respectively ● IL6 was higher in PE with IUGR than PE without IUGR: 133.8 (76.81–546.35) and 81.47 (43.57–155.45), respectively ● IL8 was higher in the PE group than in normal: 254.58 (140.73–670.7) and 135.02 (135.02–940.69), respectively ● IL8 was higher in severe PE than in mild PE: 331.97 (147.96–670.7) and 130.85 (70.67–199.03), respectively ● IL8 was higher in PE with IUGR than in PE without IUGR: 353.49 (170.58–670.7) and 144.34 (30.85–693.31), respectively ● TNF-α was higher in the PE group than in controls: 15.95 (5.66–19.78) and 9.18 (4.06–18.27), respectively
Vargas-Rojas et al[25]	● Intracellular INF-gamma (Th1) and IL17 (Th17) showed no difference between the groups ● Intracellular IL4 (Th4) was significantly decreased in the preeclampsia group in compared with normal (16.25 ± 6.61 and 21.07 ± 6.45, respectively, $p = 0.015$) ● Foxp3 (Treg cells) was significantly decreased in the preeclampsia group in compared with normal (17.48 ± 6.76 and 25.93 ± 6.34, respectively, $p = 0.0001$)
Cakir et al[15]	● No statistical difference between groups in the level of cytokines ● Neutrophil count in the PE group was lower than normotensive control: 2,559/mm^3 (669–5,940) and 3,300 (1,000–8,190), respectively ● Number of babies with neutropenia was higher in the PE group than in controls: 6 (18%) and 4 (5%), respectively
Darakhashan et al[33]	*In cord blood the cytokines shown:* ● CXCL 9 level was lower in the PE group than in normotensive controls (125 ± 14.21 and 203.45 ± 1.95, respectively) ● CXCL10 level was also lower in the PE group than in the normotensive group (77.93 ± 7.77 and 139.5 ± 1.65, respectively) ● CXCL12 level was higher in the PE group than in control group (106 ± 1.41 and 86.68 ± 1.27, respectively)
Catarino et al[13]	*In cord blood samples*: ● Lower level of leucocyte, neutrophil, eosinophil, lymphocyte, and monocyte in the PE group than in the control group ● Similar level of IL6 and TNF-α in both groups ● CRP was higher in the PET group than in control group
Kuntz et al[14]	● Neutrophil was lower in neonate from PE women than in the control group ($3,490 \pm 2,993$ and $7,534 \pm 2,642$, respectively, $p < 0.02$) ● Serum sFas showed no difference in both groups in cord blood ● Serum sFasl was higher in PE than in controls in cord blood sample, $p < 0.01$ ● Surface expression of Fasl in neutrophil was lower in PET than in controls in cord blood, but there was no difference in expression on lymphocytes ● No difference in surface of Fas in both lymphocyte and neutrophil in both groups
Xia et al[31]	● TNF level in cord blood samples was higher in the PE group than in the control group (9.5 ± 1.73 and 7.26 ± 0.446, respectively, $p < 0.05$) ● Positive correlation between TRL4-mRNA and TNF-α expressions
Guillemette et al[32]	● TNF-α at cord blood was higher in the PE group than in the normotensive control group: 6.53 (4.94–8.38) and 5.44 (3.94–6.68), respectively. ● After matching with gestational age and maternal BMI PE (18 cases) also showed higher level of TNF-α than control (36 cases): 6.53 (4.94–8.38) and 4.83 (3.56–7.06), respectively
Faulhaber et al[17]	● The PE group showed babies with neutropenia more than the normotensive group: 13 (23.6%) and 5 (7.8%), respectively, $p = 0.032$ ● Lower level of IL8 in the PE group than in the control group: 26.54 (3.6–87.2) and 157.1 (86.4–261.3), respectively, $p < 0.0001$ ● No statistically significant difference in the GRO-α level in the PE and control groups: 185.5 (63.9–309.7) and 229.5 (116.6–321.3), respectively

Table 3 (*Continued*)

Study	Main result
Güner et al[16]	● No statistical difference on the serum level of G-CSF in the PE group and control group: 981 ± 1,682.5 and 770.8 ± 1,779, respectively. ● Babies with neutropenia were higher in the PET group (61.5%) than in the control group (26.1%) on day 2 ($p = 0.013$). However, neutropenia for all babies was resolved on day 7
Al-Othman et al[27]	● No statistical significance between both groups in IL6 level in cord blood sample
Laskowska et al[30]	● IL8 level was higher in PE without IUGR and with IUGR groups than control, but without statistical difference: 190.78 ± 326.04, 288.78 ± 372.11, and 126.44 ± 249.87, respectively. ● IL8 level is higher in the PE group with IUGR than in controls, with $p = 0.04$
Mellembakken et al[18]	● Newborns of preeclamptic mothers had increased expression of CD15s ($p = 0.003$), CD49d/CD29 ($p = 0.01/0.005$), and CD31 ($p = 0.007$) on neutrophils and CD15s ($p = 0.001$), CD11c ($p = 0.009$), and CD54 ($p = 0.001$) on monocytes ● Raised plasma levels of the CXC chemokines interleukin-8 ($p = 0.007$) and growth-related oncogene-a(GRO-a) ($p = 0.01$) and decreased plasma levels of soluble E-selectin ($p = 0.001$) and L-selectin ($p = 0.002$) Moderate increased expression of CD54 on neutrophils in the mild (<160) PE group ($p = 0.04$), moderate increased expression of CD11a ($p = 0.02$) and CD31 ($p = 0.04$) on neutrophils also in (group <160) neonates of mothers with the highest blood pressures had significantly raised plasma levels of IL-8 (4.5 [1–17] pg/mL vs. 24.5 [6–97] pg/mL;), but not the other chemokines, compared with the plasma levels of the other newborns in the preeclamptic group
El-Chennawi et al[26]	● Lower CD4 + FoxP3+ in the PE cord blood sample: 1.45 (0.4–4.3) vs. control: 3.7 (1.5–6.8), $p < 0.001$ ● Lower CD4 + CD25high FoxP3+ in PE cord blood sample: 0.8 (0.2–2.2) vs. control 2 (0.8–3.5), $p < 0.001$. ● Higher CD4 + CD25low in PE cord blood sample: 29.9 (4.9–56.1) vs. control: 5.2 (2.5–11.9), $p < 0.001$.
Darmochwal-Kolarz et al[24]	● CD3 +, CD4 +, CD8 + 28, and CD4/CD8 were lower in the PET group than in the control group ● CD3–16/56 +, CD8 + 28-, CD4 + 45RO +, CD8 + 45RO +, and CD25 on (CD19+ and CD8 +) was higher in the PE group than in the control group ● No difference in the level of CD19 +, CD8 +, CD19 + 5 +, CD4 + 8 +, CD4 + 45RA+ and CD8 + 45RA +, CD40 on CD19 +, CD40L on CD4 +, CD69, HLA-DR, CD3 +, CD4 +, CD8 +, and CD25 on CD3+ in both groups
Na lei et al 2016[42]	● Content of CD3 cells, IgG, IgA, IgM, C3, and C4 was lower in the preeclampsia group than in controls ● IgG and CD4 lower in GH than control
Sava et al[23]	● CD4+ T lymphocyte and CD4 + HLA-DR+ T cells are lower in the PET group on day 3 ($p = 0.0159$ and 0.034, respectively) ● CD4 + CD45RO+ memory T cells is higher in the PET group on day 7 ($p = 0.0308$) ● CD4/CD8 cell ratio lower in the PET group on days 0, 1, and 3 ($p = 0.0062$, 0.0252, and 0.0043, respectively) ● CD8 + CXCR3+ was lower in the PET group on days 1 and 7 ($p = 0.0009$ and 0.0163, respectively) ● CD8 + CD69+ T cells was lower in the PET group on days 0 and 1 ($p = 0.0109$ and 0.0015, respectively) ● CD8 + HLA-DR+ T cells was lower on days 0, 3, and 7 ($p = 0.0084$, 0.0308, and 0.0019, respectively) ● mDCs (myeloid dendritic cells) was lower in the PET group on days 1 and 3 ($p = 0.0011$ and 0.0538, respectively) ● Cytokines levels were higher in the PET group on days 1, 3, and 7 and lower on day 0 ● Cortisol level was lower in PET on day 1 and 7 ($p = 0.037$ and 0.047, respectively)
Laskowska et al[30]	● sCD40L was higher in the PET group and PET with IUGR group in comparison to control (2.633 ± 1.984, 2.703 ± 1.996, and 1.112 ± 0.436 ng/mL, respectively) for PET and PET with IUGR, $p = 0.001$ and 0.02, respectively
Turunen et al[12]	● WBC count was lower in the PET groups in all days in comparison to control group, but CRP level was higher in the PET groups in all days ● CD11b expression on monocytes and neutrophils was higher in PET groups in all days in comparison to control group ● After adjustment of antenatal and postnatal covariant, CD11b expression on neutrophils and monocytes was still higher in PET in days 1 and 2

(*Continued*)

Table 3 (*Continued*)

Study	Main result
Loewendorf et al[21]	● Ratio between effector NK cell (CD56loCD16 +) to regulatory NK cell (CD56hiCd16 +) is significant lower in the PET group. ● CD4 +/CD8+ ratio was significant lower in the PET group. ● CD4 was significant lower in the PET group (67 ± 5.8 to 73 ± 4.34) and CD8 was nonsignificantly higher in the PET group (24.28 ± 8.1% to 73 ± 4.34%) ● Treg cells (CD4 + FOXP3 +) was significant lower in the PET group. ● Resting Treg (CD45RAhiFOXP3lo) and cytokines Treg (CD45RAFOXP3lo) were significantly lower in the PET group ● CD8+ responder T cell/Treg cell ratio was higher in PET (9 ± 3.7 to 5.06 ± 1.29)
Sohlberg et al[20]	*In cord blood:* ● sCD163, IL8, and IL10 were mildly elevated in PE group. ● CD3-CD56+ NK cells shown higher expression of NKP30 and lower expression of NKG2D in PET group ● CD14 + CD16+ monocytes were higher in PE, but Cd11b expression was lower ● Intracellular expression of IFNγ and TNF in NK cells was higher in PE group. ● Stimulation of intracellular cytokines production from CD3-CD56+ NK cells and CD14+ monocyte was not affected by preeclampsia
Bujold et al[22]	● The PE group had higher level of NK cells (CD3-Cd56 + 16 +) than control (17.9 ± 9% and 12 ± 6.2%, respectively) ● Preterm PE had higher level of NK cells than preterm control (16.3 ± 9.4% and 12.1 ± 6.2%, respectively) ● Full-term PE had a higher level of NK cells than full-term control (20 ± 7% and 11.9 ± 7.2%, respectively)
Saini et al[19]	● Higher expression of CD18 in the PE group than in controls (432 ± 236.3 and 230 ± 97.9, respectively) ● Higher expression of CD11a in the PE group than in controls (552 ± 272.4 and 326.9 ± 268.6, respectively) ● Higher expression of CD18 in the PE group than in controls (937.2 ± 521.9 and 576.6 ± 352.9, respectively) ● Higher expression of CD18 in the PE group than in controls (228.5 ± 130.3 and 133 ± 77.1, respectively)

Abbreviations: IL, interleukin; INF, interferon; IUGR, intrauterine growth retardation; PE, preeclampsia; Th, T helper; TNF, tumour necrotic factor.

studies were performed in the United States, three in each Turkey and Poland, and two in each Norway and China. The remaining researches were conducted in Finland, Sweden, Hungary, Iran, Mexico, Kuwait, Egypt, Brazil, and Portugal. All the studies included infants born to mothers with normal blood pressure during pregnancy as a control. The selected studies included participants with different gestational ages. Full-term babies were defined as gestational age greater than 37 weeks and preterm babies as less than 37 weeks of gestation. According to the mean and median gestational age of the participants, 12 of these studies recruited full-term babies born to preeclampsia mothers. Twelve studies compared preterm babies born to mothers with preeclampsia and compared them with preterm controls; however, three of these studies recruited full-term controls. Gestational age as a confounder was reported in all studies and it was matched between the study and control groups in only nine studies. Most of the research articles analyzed cord blood samples to detect the immunological changes in infants with preeclampsia, while four studies looked at these changes in neonate peripheral blood samples collected at different times after birth. In most trials, the preeclampsia group was not classified. Only two studies distinguished between preeclampsia with and without IUGR, whereas two studies characterized it as mild or severe. Only two studies recruited infants from pregnancy-induced hypertension, besides normotensive control. According to the quality ranking, 19 of the studies was ranked B, 5 as A, and none as C.

The included studies compared different aspects of immunological function in cord blood and peripheral blood samples from babies of preeclampsia mothers and normotensive controls. Six studies investigated the surface markers on different immune cells and 12 articles focused on the plasm level of different cytokines and interleukins. Furthermore, six studies focused on both the surface markers of the immune cells and plasma cytokines. NK cells, lymphocytes, monocytes, and neutrophils were studied in these articles. Four studies showed the changes in NK cells' surface markers, and three articles reported mainly Treg cells changes. Four studies investigated monocytes, and four articles demonstrated the difference in neutrophils. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL6), and IL8 were the most cytokines and interleukins investigated in preeclampsia. TNF-α and IL-6 were investigated by five studies each, while IL-8 was reported in four articles.

Neutrophil count was lower in cord blood and babies' peripheral blood in the preeclampsia (PE) group group in various studies.[12–17] Kuntz et al detected a reduction in Fasl surface expression on neutrophils in cord blood.[14] However, Mellembakken et al found an increase in the CD15s, CD11a,

Cd31, Cd49d/Cd25, and CD54 expression on neutrophils in cord blood of the preeclampsia group.[18] During the first week of life, Turunen et al reported an increase in CD11b expression on neutrophils in the peripheral blood of preterm infants with severe respiratory distress syndrome (RDS) on mechanical ventilation born to preeclampsia mothers.[12] Saini et al noticed an increase in the surface adhesion markers CD18, CD11a, CD11b, and CD11c in cord blood samples and discovered that these markers were significantly higher in severe preeclampsia than in mild cases.[19]

In comparison to normotensive controls, the overall number of monocytes was lower in cord blood samples of preeclampsia.[13] Turunen et al observed increased level of CD11b on neutrophils in the peripheral blood samples of preterm baby with RDS on mechanical ventilation who were born to preeclampsia mothers compared with infants of matched gestational age and condition delivered to normotensive mothers. Additionally, Mellembakken et al found an increase in CD11c and CD54 in cord blood samples of preterm infants with severe preeclampsia, whereas the control group consisted of full-term infants born to mothers with normal pregnancy.[12,18] However, Sohlberg et al revealed no statistically significant difference between the two groups in the percentage of CD3-CD14+ monocytes or any of the surface expression markers CD11c, CD80, CD86, CD163, and HLA-DR in cord blood samples, despite categorizing preeclampsia as mild or severe. The same result was found by Loewendorf et al.[20,21]

Bujold et al showed a higher number of (CD3-/CD56 + CD16 +) NK cells in cord blood samples from infants of preeclampsia mothers with a lower gestational age than controls.[22] Furthermore, Sohlberg et al found a higher expression of surface activation marker NKP30 and lower expression of NKG2D in cord blood sample and it was significantly different in mild form compared with controls. In contrast, there were no changes in the expression of these activation markers when normal cord blood mononuclear cells (CBMCs) were incubated in cord blood serum from women with control, mild, and severe preeclampsia.[20] Loewendorf et al reported a reduced ratio of nonactive NK cells ($CD56^{high}$CD16-) to active NK cells ($CD56^{low}$CD16-) in cord blood samples from full-term infants with preeclampsia compared with infants with comparable gestational age without preeclampsia.[21]

Total CD4+ cells and CD4 +/CD8+ ratio was reported to be decreased in cord blood and postnatal blood of term and preterm infants with preeclampsia. Memory cells CD4 + CD45RO+ and CD8 + CD45RO+ were elevated in the cord blood and peripheral newborn samples of preterm and term infants with preeclampsia.[13,21,23,24] Sava et al revealed lower levels of CD4 + HLA-DR+ and CD8 + HLA-DR+ in cord blood and postnatal peripheral blood of preterm infants with preeclampsia.[23] Treg cells in cord blood were identified by Vargas-Rojas et al as CD4+ $CD127^{low}$FoxP3 +, and they were considerably diminished in full-term infants with preeclampsia. El-Chennawi et al employed CD4 + FoxP3 +, CD4 + $CD25^{high}$-FoxP3 +, and CD4 + $CD25^{low}$ to identify Treg cells. Their data demonstrated a significant decrease in the level of CD4 + $CD25^{high}$FoxP3+ and CD4 + FoxP3+ as well as an increase in CD4 + $CD25^{low}$FoxP3+ in cord blood of full-term infants with preeclampsia. In addition, CD4 + $CD25^{high}$FopP3+ and CD4 + FoxP3+ were negatively correlated with preeclampsia severity, whereas CD4 + $CD25^{low}$FopP3+ was positively correlated with preeclampsia severity. Loewendorf et al examined CD4 + FoxP3+ to detect Treg cells and they found that it was lower in the preeclampsia group. However, when they subdivided FoxP3 into high and low, they noticed a reduction of CD4 + $Foxp3^{low}$ and no changes in CD4 + $Foxp3^{high}$ in infants with preeclampsia.[21,25,26]

Several researches have addressed the changes in cytokines levels in fetomaternal interface and peripheral blood of preeclampsia infants. Twelve articles explore these alternations, with the majority using cord blood and only one using postnatal peripheral blood. IL6, IL8, TNF-α were the most reported cytokines. Three studies[13,15,27] revealed no difference in the IL6 level in cord blood. However, Tosun et al observed a rise in the IL6 level in postnatal peripheral blood of preterm infants born of preeclampsia mothers.[28] Additionally, Ødegård et al found a decrease in the level of IL6 in cord blood that had a positive correlation with birth weight; however, they measured the IL6 level using colorimetric assay of hybridoma cell line B13.29 clone 9 growth.[29] Three studies reported an increase in the IL8 levels in preeclampsia, while Faulhaber et al found a decrease and Cakir et al found no difference in the IL8 levels between the two groups. Mellembakken et al identified a higher level of GROα in cord blood samples from preterm infants with preeclampsia than from full-term healthy controls.[15,17,18,28,30] In four research[13,29,31,32] there were a higher level of IL6 in preeclampsia group, however in only one study[15] there was no changes. Besides higher level of TNF-α in cord blood, Xia et al[31] reported higher level of TLR4 protein expression in cord blood and Guillemette et al[32] revealed high level of TNF-α in maternal blood in the second trimester. In cord blood of infants with preeclampsia, Vargas-Rojas et al reported a decreased level of intracellular IL4 but no difference on the levels of intracellular INFγ and IL17.[25] The CXC12 levels increased, while CXCL9 and CXC10 levels decreased, according to Darakhshan et al.[33] Sava et al found an increase in Th1 cytokines, particularly monocyte chemotactic protein 1 (MCP1), and IL4 in peripheral blood of infants with preeclampsia compared with normotensive control.[23]

Discussion

Preeclampsia is one of the common complications of pregnancy, and it is associated with adverse health outcome in infants and mothers. Preeclampsia is associated with immune changes in both mothers and babies. The objective of this study is to collect evidence regarding the effect of preeclampsia on newborn immunity in cord blood and postnatal peripheral blood. We collected 24 articles that were published from 2000 till the time of the search that investigated different aspects of immune cells and cytokines. Most of the studies were focused on immune changes in cord blood cells, with only a few studies looking at immune changes in postnatal peripheral blood. More research is

needed to determine whether long-term immunological changes in infants exist and its long-term consequences.

Cytokines are produced by a variety of immune cells, particularly Th1 and Th2. Th1 secretes proinflammatory cytokines such interferon-γ (IFNγ), IL2, and TNF-β, which boost cell-mediated immunity and phagocytic-dependent inflammation. Anti-inflammatory cytokines such as IL4, IL5, IL10, and IL13 are secreted by Th2. In normal pregnancy, both are in balance, with a predisposition for Th2 to tolerate fetal tissue. There is cytokine imbalance in preeclampsia, with a decrease in proinflammatory Th2 and an increase in inflammatory cytokines Th1 and Th17, leading to an increase in apoptosis of trophoblast cells, which impacts placenta invasion and contributes to the development of preeclampsia.[34]

Although many studies found no changes in cytokine levels in infants born to preeclampsia mothers, infants with severe preeclampsia with IUGR had significantly higher level of proinflammatory cytokines such IL6, IL8, and TNF-α in cord blood and infant peripheral blood. Researchers also reported a decrease in anti-inflammatory Th2 cytokines such as IL4, CXCL9, and CXC10. Preeclampsia can lead to a cytokine imbalance, which can affect fetal and neonatal outcomes, particularly in preterm infants with IUGR who were born with severe preeclampsia.

Preeclampsia could alter the fetal innate and adaptive immune cells. Monocytes are one of innate immune cells that can be differentiated to macrophages and dendritic cells, which aid in the defense against infection and inflammation.[35] Studies revealed an increase on the monocyte markers CD15s, CD11c, and CD54 in the cord blood and CD11b in postnatal peripheral blood samples from infants born preterm from severe preeclampsia pregnancy. They used CD14 and CD49 as markers to identify monocyte.[12,18] However, in other research, there was no difference on monocyte receptors on the cord blood of full-term babies born from mild to severe preeclampsia pregnancy in comparison to normotensive control. They used CD14CD16 to identify monocytes that are more specific than the previous markers.[20] Preeclampsia may impact monocytic function in preterm babies with severe preeclampsia, but this effect must be proven in a well-designed study involving both preterm and full-term participants with varying degree of preeclampsia and using most recent markers to identify monocytes.

NK cells are cytotoxic T lymphocytes that play a key role in innate immunity.[36] The percentage of NK cells (CD16 + CD56 +) and effector subtype ($CD56^{low}CD16+$) was increased in fetal cord blood samples from preeclampsia mothers, and this could be due to preeclampsia and uteroplacental insufficiency, causing long-term perinatal stress.[21,22,24] Sohlberg et al reported an increase in NKP30 and a decrease in NKG2D markers on NK cells in fetal cord blood of preeclampsia mothers. However, there was no difference between the two groups when normal CBMCs were incubated in fetal cord blood serum from preeclampsia and control. This suggests that alternations in NK cell markers are inherent rather than induced by cytokine activation in the serum, potentially leading to long-term abnormalities in NK cells in preeclampsia babies.[20] However, further research is needed to test this theory. Dendritic cells are also one of the innate immunity cells. Preeclampsia causes decrease on the level of CD11c + mDC on the peripheral blood of these infants.[23]

Neutrophils are the most common type of immune cells. Proteases and active oxygen species are released by activated neutrophils, which can induce vascular endothelium injury and influence vascular tone.[37] Neonatal neutropenia may raise the risk of sepsis and its associated mortalities, particularly in preterm newborns even after recovery from neutropenia.[38,39] Neutrophil count was lower in cord blood from preeclampsia mothers.[13–15] There was an increase in surface markers CD11b on neutrophils in peripheral blood samples of preterm infants with RDS born from severe preeclampsia pregnancies.[12] Surface integrin CD11b was also increased, besides CD18, CD11a, and CD11c, in cord blood samples from full-term infants with mild and severe preeclampsia.[19] Although the number of participants in these studies is low, the results still revealed neutrophil activation in fetomaternal interface and early neonatal life. CD49d/CD29, CD31, and CD15s were also raised in cord blood samples, but there was mismatch across study groups in terms of gestational age and weight, with the preeclampsia group having lower gestation and weight.[18] The activation of neutrophils in fetomaternal interface in preeclampsia might be the result of prenatal exposure to chronic stress and inflammation related to preeclampsia. Moreover, the activated neutrophils may trigger a viscous loop of cell activation, which may contribute to a variety of complications in infants born from preeclampsia pregnancies.

Even though different studies have employed distinct markers to identify Treg cells, they have been significantly reduced in cord blood samples of infants with preeclampsia in all included research.[21,25,26] This indicates the disruption of Treg cell function because of preeclampsia. In normal pregnancy, Treg cells play a negative regulatory role on various immune cells, enhancing immunological tolerance to paternal–fetal antigens. The number of CD4 Treg cells in cord blood is increased in normal pregnancy in comparison to miscarriage.[40] It also plays a protective role against heart fibrosis and coronary arteriole endothelial dysfunction in hypertension in mice.[41] T lymphocyte CD4+ level and CD4 +/CD8+ ratio were both low in cord and peripheral blood samples from infants with different gestational age and degrees of preeclampsia.[21,23,24] Memory cells in newborns are expected to be low because they have few opportunities to be activated; however, CD4 + CD45RO+ and CD8CD45RO+ cells were found in higher numbers in cord[24] and peripheral blood samples[23] from these infants with preeclampsia, indicating a long-standing immune activation during fetal life as a result of chronic inflammation, hypoxia, and stress caused by preeclampsia. HLA-DR+ is expressed on antigen presenting cells and it is antigen-specific T cell activation. CD4 + HLA-DR+ and CD8 + HLA-DR+ were reduced in peripheral blood of infants with severe preeclampsia.[23] Preeclampsia is linked to a decrease in Treg cells and an increase in memory cells in fetomaternal interface and even in newborn blood samples in a few studies.

This may help us to understand the effect of preeclampsia on short- and long-term implications of pregnancy.

We were unable to conduct a quantitative analysis on the selected studies due to the large variation in participants and outcomes. Participants were from different gestational age groups, and each study focused on different aspects of immune function. Instead, we present an overview of the impact of preeclampsia on several neonatal immune processes.

Preeclampsia has influenced neonatal immunity in cord blood samples and peripheral blood, but the long-term immunological effects have not been studied yet. Preeclampsia is associated with neutropenia and reduction in other immune cell lines, but with enhancing cytotoxic effect of various immune cells, particularly neutrophils, T cell CD8 +, and NK cells. Treg cells were also lower in mother blood, cord blood, and neonatal peripheral blood. Preeclampsia contributes to perinatal and neonatal mortalities, as well as morbidities such as IUGR, BPD, NEC, and sepsis. Immune dysfunction may be one of the factors contributing to these disorders. More research is needed to determine the impact of these immunological changes on neonatal outcomes such as sepsis, BPD, and NEC, as well as how long they last.

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Conflict of Interest
None declared.

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