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 \(≥34^{-0}\)
weeks’ gestation consecutively. Moreover, preeclampsia
could be classified to preterm preeclampsia and term
preeclampsia with delivery at less than 37\(^{-0}\) and \(≥37^{-0}\)
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 (natu-
ral 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, preeclamp-
sia was associated with higher rate of neonatal sepsis.\(^7\)
Preeclampsia causes changes in neonatal immunity, espe-
cially 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 Data-
base Advanced Search (HDAS) on the National Institute of
Clinical Excellence (NICE) website.

Key MeSH and text terms were used for a more compre-
hensive search. The following mesh and text terms were used
for preeclampsia: (Preeclampsia OR Eclampsia OR pre-
eclamps’ OR preeclamps’ OR pre eclamps’ OR eclamps’ OR
“pregnancy induced hypertension” OR “hypertensive disor-
der 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 outcome” 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 stud-
ies, 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 summa-
rized 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, ade-
quate 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>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of participants</th>
<th>Gestational age (wk)</th>
<th>Source of sample</th>
<th>Markers of the study</th>
<th>Method of assessment</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sava et al23</td>
<td>Case control</td>
<td>14 cases 14 controls</td>
<td>30 (24–33) 29 (24–31)</td>
<td>Cord and peripheral blood</td>
<td>CD4+ cells</td>
<td>Flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>Cakir et al15</td>
<td>Case control</td>
<td>34 cases 74 controls</td>
<td>29 (26–32) 30 (27–32)</td>
<td>Cord blood</td>
<td>IL6, IL8, IL10, and TNF-α, Leukocyte and neutrophil</td>
<td>ELISA</td>
<td>A</td>
</tr>
<tr>
<td>Bujold et al22</td>
<td>Cross sectional</td>
<td>48 cases 72 controls</td>
<td>33.6 ± 3.5 36.5 ± 4</td>
<td>Cord blood</td>
<td>NK cells (CD3+CD56+CD16+)</td>
<td>Flow cytometry</td>
<td>A</td>
</tr>
<tr>
<td>Faulhaber et al17</td>
<td>Prospective cohort</td>
<td>55 cases 64 controls</td>
<td>30.7 ± 6.3 28.6 ± 3.2</td>
<td>Peripheral blood</td>
<td>IL8, CRO-α, and neutrophils</td>
<td>ELISA</td>
<td>A</td>
</tr>
<tr>
<td>Turunen et al12</td>
<td>Case control</td>
<td>11 cases 25 controls</td>
<td>27 ± 1.6 26.1 ± 1</td>
<td>Peripheral blood</td>
<td>CD11b neutrophil, CD11b monocyte</td>
<td>Flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>Güner et al16</td>
<td>Case control</td>
<td>26 cases 23 controls</td>
<td>31.5 ± 2.6 32 ± 2.3</td>
<td>Peripheral blood</td>
<td>cGSF, FBC, and neutrophil</td>
<td>ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Al-Othman et27</td>
<td>Case control</td>
<td>50 cases 50 controls</td>
<td>35.4 ± 3 36.2 ± 3.2</td>
<td>Cord blood Placenta</td>
<td>IL6</td>
<td>Sandwich ELISA</td>
<td>A</td>
</tr>
<tr>
<td>Laskowska et al30</td>
<td>Case Control</td>
<td>27 cases 10 controls</td>
<td>35.03 ± 2.95 38.43 ± 1.64</td>
<td>Cord blood</td>
<td>IL8</td>
<td>Sandwich ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Mellembakken et18</td>
<td>Case control</td>
<td>35 cases 36 controls</td>
<td>31 ± 6 38 ± 3</td>
<td>Cord blood</td>
<td>CD neutrophil, CD monocyte, Plasma cytokines</td>
<td>Flow cytometry ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Na lei et al 2016</td>
<td>Case control</td>
<td>28 PE 32 GH 30 controls</td>
<td>30.31 ± 1.7 34.75 ± 2.2 36.04 ± 1.93</td>
<td>Cord blood</td>
<td>CD4, CD8, CD4/CD8, IgG, IgM, IgA, C3, and C4</td>
<td>FACS caliber flow cytometry ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Kuntz et al14</td>
<td>Case control</td>
<td>20 cases 18 controls</td>
<td>36 ± 3 39 ± 2</td>
<td>Cord blood</td>
<td>Fas neutrophils, Fasl neutrophil, Fasl lymphocyte, Fasl lymphocyte</td>
<td>Flow cytometry ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Saini et19</td>
<td>Case control</td>
<td>19 cases 20 controls</td>
<td>32. ± 3.9 34 ± 4.6</td>
<td>Cord blood</td>
<td>CD18, CD11a, CD11b, and CD11c</td>
<td>Flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>El-Chennawi et26</td>
<td>Case control</td>
<td>30 cases 20 controls</td>
<td>37.7 ± 0.84 35.2 ± 1.6</td>
<td>Cord blood</td>
<td>CD4 + CD25highFOXP3+, CD4 + CD25lowFOXP3+, and CD4+ FOXP3+</td>
<td>Multicolor flow cytometry</td>
<td>B</td>
</tr>
</tbody>
</table>

(Continued)
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of participants</th>
<th>Gestational age (wk)</th>
<th>Source of sample</th>
<th>Markers of the study</th>
<th>Method of assessment</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ødegård et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Case control</td>
<td>270 cases 610 controls</td>
<td>37.8 ± 3.3 40 ± 1.6</td>
<td>Cord blood</td>
<td>IL6</td>
<td>Colorimetric assay</td>
<td>A</td>
</tr>
<tr>
<td>Tosun et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Case control</td>
<td>24 cases 19 controls</td>
<td>37.12 ± 1.45 38.52 ± 0.96</td>
<td>Cord blood</td>
<td>IL6, IL8, and TNF-α</td>
<td>ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Sohlberg et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Case control</td>
<td>22 cases 23 controls</td>
<td>38 (34–42) 39 (38–41)</td>
<td>Cord blood</td>
<td>IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, and TNF Monocyte, Nkp30, NKG2D</td>
<td>Flow cytometry ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Loewendorf et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Case control</td>
<td>9 cases 16 controls</td>
<td>39.1 ± 2.4 39.2 ± 0.8</td>
<td>Cord blood</td>
<td>Treg, NK cells, and monocytes</td>
<td>Multicolor flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>Vargas-Rojas et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Case control</td>
<td>19 cases 20 controls</td>
<td>37.5 ± 3.32 37.2 ± 1.94</td>
<td>Cord blood</td>
<td>CD3 + CD4 + CD127low Then IFNγ+, IL-4+, IL-17+ and FoxP3+ cells</td>
<td>Flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>Laskowska et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Case control</td>
<td>30 cases 13 controls</td>
<td>37.3 ± 3.13 38.14 ± 1.83</td>
<td>Cord blood</td>
<td>scD40L</td>
<td>Sandwich ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Darakhshan et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Case control</td>
<td>53 cases 53 controls</td>
<td>38.2 ± 1.2 36.9 ± 1.6</td>
<td>Cord blood</td>
<td>CXCL9 CXCL10 CXCL12</td>
<td>ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Xia et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Case control</td>
<td>27 cases 21 controls</td>
<td>37.1 ± 4.1 38.2 ± 0.8</td>
<td>Cord blood</td>
<td>TNF-α</td>
<td>ELISA</td>
<td>B</td>
</tr>
<tr>
<td>Guillemette et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Case control</td>
<td>18 PE 25 GH 593 controls</td>
<td>37.6 (37.239.4) 39.4 (38.4–40.3) 39.5 (38.6–40.3)</td>
<td>Cord blood</td>
<td>TNF-α</td>
<td>Multiplex particle-based flow cytometric assay</td>
<td>B</td>
</tr>
<tr>
<td>Darmochwal-Kolarz et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Case control</td>
<td>18 cases 20 controls</td>
<td>37.42 ± 1.69 39.16 ± 0.83</td>
<td>Cord blood</td>
<td>B cells CD T cells CD</td>
<td>Flow cytometry</td>
<td>B</td>
</tr>
<tr>
<td>Catarino et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Case control</td>
<td>46 cases 42 controls</td>
<td>37 (34–38) 38.5 (38–39.3)</td>
<td>Cord blood</td>
<td>IL6 TNF-α</td>
<td>ELISA</td>
<td>B</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>NM critical appraisal check list</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Baseline:</strong> Was the hypothesis/aim/objective of the study clearly described?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Population:</strong> Were enough participants selected?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Case and control definition:</strong> Were the characteristics of the preeclampsia clearly defined?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Was the stage of the disease assigned?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Was the source of the cells mentioned?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Was the gestational age of the participants mentioned?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Were other disorders or medication considered?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Were the characteristics of the control group the same as the case group?</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4. <strong>Study design:</strong> Was the exposure clearly defined?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5. <strong>Results:</strong> Were the results adjusted for confounding factors?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Were the main findings of the study clearly described?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Did the study provide estimates of the random variability in the data for the main outcomes?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Had actual probability values been reported?</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1  PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of study selection.
<table>
<thead>
<tr>
<th>Study</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ødegård et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>- No difference between IL6 level in the PE and control groups&lt;br&gt;- IL6 was lower in early PE and severe PE compared with controls, with p &lt; 0.001 for both&lt;br&gt;- Decrease IL6 level was more statistically significant with lower birth weight ratio</td>
</tr>
<tr>
<td>Tosun et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td><strong>In cord blood:</strong>&lt;br&gt;- IL6 was higher in the PE group than in control: 114.57 (43.57–712.89) and 23.72 (7.48–422.62), respectively.&lt;br&gt;- IL6 was higher in severe PE than in mild PE: 118.31 (76.81–546.35) and 72.89 (49.75–155.45), respectively.&lt;br&gt;- 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.&lt;br&gt;- IL8 was higher in the PE group than in normal: 254.58 (140.73–670.7) and 135.02 (135.02–940.69), respectively.&lt;br&gt;- IL8 was higher in severe PE than in mild PE: 331.97 (147.96–670.7) and 130.85 (70.67–199.03), respectively.&lt;br&gt;- 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.&lt;br&gt;- 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.</td>
</tr>
<tr>
<td>Vargas-Rojas et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>- Intracellular INF-gamma (Th1) and IL17 (Th17) showed no difference between the groups&lt;br&gt;- 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)&lt;br&gt;- 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)</td>
</tr>
<tr>
<td>Cakir et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>- No statistical difference between groups in the level of cytokines&lt;br&gt;- Neutrophil count in the PE group was lower than normotensive control: 2,559/mm&lt;sup&gt;3&lt;/sup&gt; (669–5,940) and 3,300 (1,000–8,190), respectively&lt;br&gt;- Number of babies with neutropenia was higher in the PE group than in controls: 6 (18%) and 4 (5%), respectively</td>
</tr>
<tr>
<td>Darakhashan et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td><strong>In cord blood the cytokines shown:</strong>&lt;br&gt;- CXCL 9 level was lower in the PE group than in normotensive controls (125 ± 14.21 and 203.45 ± 1.95, respectively)&lt;br&gt;- CXCL10 level was also lower in the PE group than in the normotensive group (77.93 ± 7.77 and 139.5 ± 1.65, respectively)&lt;br&gt;- CXCL12 level was higher in the PE group than in control group (106 ± 1.41 and 86.68 ± 1.27, respectively)</td>
</tr>
<tr>
<td>Catarino et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td><strong>In cord blood samples:</strong>&lt;br&gt;- Lower level of leucocyte, neutrophil, eosinophil, lymphocyte, and monocyte in the PE group than in control group&lt;br&gt;- Similar level of IL6 and TNF-α in both groups&lt;br&gt;- CRP was higher in the PE group than in control group</td>
</tr>
<tr>
<td>Kuntz et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>- Neutrophil was lower in neonate from PE women than in the control group (3,490 ± 2,993 and 7,534 ± 2,642, respectively, p &lt; 0.02)&lt;br&gt;- Serum sFas showed no difference in both groups in cord blood&lt;br&gt;- Serum sFasl was higher in PE than in controls in cord blood sample, p &lt; 0.01&lt;br&gt;- Surface expression of Fas in neutrophil was lower in PE than in controls in cord blood, but there was no difference in expression on lymphocytes&lt;br&gt;- No difference in surface of Fas in both lymphocyte and neutrophil in both groups</td>
</tr>
<tr>
<td>Xia et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>- 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 &lt; 0.05)&lt;br&gt;- Positive correlation between TRL4-mRNA and TNF-α expressions</td>
</tr>
<tr>
<td>Guillemette et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>- 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.&lt;br&gt;- 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</td>
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<td>Faulhaber et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- The PE group showed babies with neutropenia more than the normotensive group: 13 (23.6%) and 5 (7.8%), respectively, p = 0.032&lt;br&gt;- 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 &lt; 0.0001&lt;br&gt;- 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</td>
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<tr>
<td>Study</td>
<td>Main result</td>
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| Güner et al<sup>16</sup>     | ● 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<sup>27</sup> | ● No statistical significance between both groups in IL6 level in cord blood sample                                                                                                                                 |
| Laskowska et al<sup>30</sup> | ● 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<sup>18</sup> | ● 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 onco gene-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) on monocytes 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<sup>26</sup> | ● 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<sup>24</sup> | ● CD3+, CD4+, CD8+, 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<sup>42</sup> | ● 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<sup>23</sup>       | ● 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<sup>30</sup> | ● 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<sup>12</sup>    | ● 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)
immune Changes in Infants of Preeclampsia Mothers

Table 3 (Continued)

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<th>Study</th>
<th>Main result</th>
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| Loewendorf et al21     | - 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 al20       | **In cord blood:**  
                        | - sCD163, IL8, and IL10 were mildly elevated in PE group.  
                        | - CD3-CD56+ NK cells shown higher expression of NKP90 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 al22         | - 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 al19          | - 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 ± 521.9 and 576 ± 352.9, respectively).  
                        | - Higher expression of CD18 in the PE group than in controls (228 ± 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.

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 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,
Various markers were used to detect Treg cells. Their data revealed high level of GRO-α in cord blood samples from preterm infants with preeclampsia than from full-term healthy controls. In four research there was a higher level of IL6 in preeclampsia group, however in only one study there was no changes. Besides higher level of TNF-α in cord blood, Xia et al reported higher level of TLR4 protein expression in cord blood and Guillemette et al 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. The CXC12 levels increased, while CXCL9 and CXCL10 levels decreased, according to Darakshan et al. 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.

**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 better understand the impact of preeclampsia on the immune system.
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.

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, CCL5, 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. Studies revealed an increase on the monocyte markers CD15s, CD11c, and CD54 in the cord blood and infant peripheral blood samples from infants born preterm from severe preeclampsia pregnancy. They used CD14 and CD49 as markers to identify monocyte. However, in other research, there was no difference on monocyte receptors on the cord blood of full-term babies born from severe preeclampsia pregnancy in comparison to normotenive control. They used CD14CD16 to identify monocytes that are more specific than the previous markers. Preeclampsia may impact monocyte 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. The percentage of NK cells (CD16 + CD56 +) and effector subtype (CD56lowCD16 +) 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. Solbrig et al reported an increase in NKP30 and a decrease in NGK2D markers on NK cells in fetal cord blood samples from 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. 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.

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. Neonatal neutropenia may raise the risk of sepsis and its associated mortalities, particularly in preterm newborns even after recovery from neutropenia. There was an increase in surface markers CD11b on neutrophils in peripheral blood samples of preterm infants with RDS born from severe preeclampsia pregnancies. Surface integrin CD11b was also increased, besides CD18, CD11a, and CD11c, in cord blood samples from full-term infants with mild and severe preeclampsia. 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 a mismatch across study groups in terms of gestational age and weight, with the preeclampsia group having lower gestation and weight. 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. 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. It also plays a protective role against heart fibrosis and coronary arteriole endothelial dysfunction in hypertension in mice. 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. 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 blood and peripheral blood samples 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. 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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None.

Conflict of Interest
None declared.

References
21 Loewendorf AI, Nguyen TA, Yesayan MN, Kahn DA. Preeclampsia is characterized by fetal NK cell activation and a reduction in regulatory T cells. Am J Reprod Immunol 2015;74(03):258–267


Ley K. Integration of inflammatory signals by rolling neutrophils. Immunol Rev 2002;186:8–18


