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NOVEL SCREENING METHODS AND INTERVENTIONS IN PREECLAMPSIA

Ph.D. Thesis

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LIST OF ABBREVATIONS

AFP	Alpha-Fetoprotein
AKI	Acute Kidney Injury
APS	Antiphospholipid Syndrome
BMI	Body Mass Index
CI	Confidence Interval
CRLM	Colorectal Liver Metastasis
DOI	Digital Object Identifier
ET-1	Endothelin-1
FGR	Fetal Growth Restriction
G-CSF	Granulocyte Colony-Stimulating Factor
GDM	Gestational Diabetes Mellitus
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
hCG	Human Chorionic Gonadotropin
HELLP	Hemolysis, Elevated Liver Enzymes, and Low Platelets
HMG-CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A
HUVECs	Human Umbilical Vein Endothelial Cells
IL	Interleukin
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intrauterine Growth Restriction
LDA	Low-Dose Aspirin
LMWH	Low Molecular Weight Heparin
MAP	Mean Arterial Pressure
MD	Mean Difference
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NLR	Neutrophil-to-Lymphocyte Ratio
NLRP3	NLR Family Pyrin Domain Containing 3
NO	Nitric Oxide
NOS	Newcastle–Ottawa Scale
OAPS	Obstetric Antiphospholipid Syndrome

OR	Odds Ratio
PAPP-A	Pregnancy-Associated Plasma Protein A
PlGF	Placental Growth Factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk Ratio
sEng	Soluble Endoglin
sFlt-1	Soluble Fms-like Tyrosine Kinase-1
SLE	Systemic Lupus Erythematosus
TA	Takayasu Arteritis
TNF-α	Tumor Necrosis Factor-alpha
UtA-PI	Uterine Artery Pulsatility Index
UtMVs	Uterine Microvascular Cells

1. INTRODUCTION

1.1. Preeclampsia – definition, epidemics, suspected pathomechanism

Preeclampsia (PE) is a pregnancy-specific disorder, and it was defined for decades by the new onset of hypertension and proteinuria. According to the latest guidelines such as NICE (National Institute for Health and Care Excellence) and ISSHP (International Society for the Study of Hypertension in Pregnancy) proteinuria is not mandatory for the diagnosis of preeclampsia: according to NICE -preeclampsia is characterized by the onset of newly diagnosed hypertension after 20 weeks of pregnancy, accompanied by one or more newly emerging features: these features may include substantial proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications, or hematological complications.

By the definition of - ISSHP, which definition closely resembles to NICE's definition—PE is diagnosed when new-onset hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg) occurs after 20 weeks of pregnancy, accompanied by at least one additional symptom or group of symptoms, which may include: proteinuria; dysfunction of other maternal organs (such as liver, kidney, central nervous system); hematological abnormalities; uteroplacental dysfunction (e.g., intrauterine growth restriction—IUGR, and/or abnormal Doppler ultrasound results concerning uteroplacental circulation) (1,2).

This condition affects 2–8% of the pregnant women worldwide and stands as a significant contributor to maternal and neonatal morbidity and mortality, especially in low-income countries (3,4). As the disease accounts for a substantial portion of maternal deaths globally, emphasizing the urgent need for effective prevention and treatment strategies, as it affects developing countries in a larger extent it is also desired to find predictive and therapeutic methods which can be applied in low-resource settings as well, not only in developed countries.

While the exact pathomechanism of preeclampsia remains an enigmatic field of obstetrics, it is widely believed that abnormal placentation leading to the release of antiangiogenic markers, resulting in endothelial dysfunction and vascular dysfunction (5).

Recent research suggests that preeclampsia is not a single disease but a spectrum of conditions with varying characteristics and underlying mechanisms (6).

As of today, delivery of the fetus, and removal the placenta remains the only definitive treatment for preeclampsia (4). To summarize, it is imminent to find new means of screening, preventional and therapeutic agents in preeclampsia, that can be applied in low-resource settings as well.

1.2. - The importance of preeclampsia's early identification and the possible role of neutrophil-to-lymphocyte ratio (NLR)

Early identification of high-risk patients for preeclampsia is pivotal for improving maternal and perinatal outcomes. In developing preeclampsia pregnant people are at high-risk, who have multifetal gestation, pregestational diabetes, chronic hypertension. In preeclampsia development nulliparity, a body mass index greater than 30, African American race, a maternal age 35 years or older, an interval of more than 10-years since last birth and having low socioeconomic status count as moderate risk factors (1). If the patients are found who are at high- or moderate risk at developing preeclampsia found closer surveillance should be implemented, considering prophylactic low-dose aspirin therapy, administering antihypertensive medications, and opting for earlier induced delivery (2).

Given that inflammatory reactions are implicated in the pathomechanism of preeclampsia, recent publications have explored the role of white blood cells in predicting the condition, both in clinical studies and animal models (7,8). The neutrophil-to-lymphocyte ratio (NLR) has emerged as a valuable marker for inflammatory diseases such as systemic lupus erythematosus (SLE), spondyloarthritis, psoriasis, psoriatic arthritis, various tumors, and Takayasu arteritis (TA) (9–15). Some studies have also investigated the role of NLR in pregnancy-related conditions e.g. gestational diabetes mellitus (GDM) and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome (16–18). Furthermore, meta-analyses have consistently reported elevated NLRs in blood samples from mothers with preeclampsia (19).

As of 2025, laboratory findings are widely accessible and relatively affordable, even in developing countries, and neutrophil and lymphocyte counts are typically part of routine laboratory tests.

This way, NLR holds promise as a beneficial predictive marker for PE (20,21).

1.3 - The promising role of pravastatin in preeclampsia prevention

The rate-limiting step in cholesterol synthesis involves the reduction of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonate, facilitated by the enzyme HMG-CoA reductase (22). Statins act as competitive inhibitors of this enzyme, effectively reducing blood cholesterol levels. Numerous studies have indicated that statins, particularly pravastatin not only decreases blood cholesterol levels, but it also has a potential to elevate levels of PlGF (placental growth factor), consequently lowering fms-like tyrosine kinase-1 (sFlt-1) levels and potentially reversing the effects of anti-angiogenic factors implicated in preeclampsia (23). Additionally, pravastatin has been suggested to enhance microsomal arginine uptake, thereby promoting NO synthesis, and positively impacting microcirculation (24,25).

Statins are categorized by their lipophilic or hydrophilic characteristics (26).

Pravastatin, which is classified as a hydrophilic statin, exhibits favorable pharmacokinetics, and is considered to have a lower teratogenic potential compared to lipophilic variants (22). Studies have reported lower teratogenic risks associated with pravastatin, particularly speaking of studies when females unknowingly took statins during the initial weeks of gestation (27). Furthermore, recent evidence suggests that regardless of their classification, statins do not induce congenital anomalies (28).

The growing interest in statin therapy for preeclampsia is evident from even a simple search in the PubMed database: between 2003 and 2007, only five articles were published on the topic, whereas between 2017 and 2021 there was a notable increase, with 89 studies published.

1.4. – The reason why pravastatin was evaluated in a form of a meta-analysis

While statins are generally contraindicated during pregnancy, a recent meta-analysis including 18 clinical research, published by Vahedian-Azimi et al. in 2021, suggested

their safety, noting no significant associations with stillbirth or induced and elective abortion rates. However, there was a notable increase observed in spontaneous abortions following statin therapy (29).

The contrast in the utilization of statins for treating preeclampsia is remarkable, with pravastatin being predominantly favored in scientific studies (**Figure 1**).

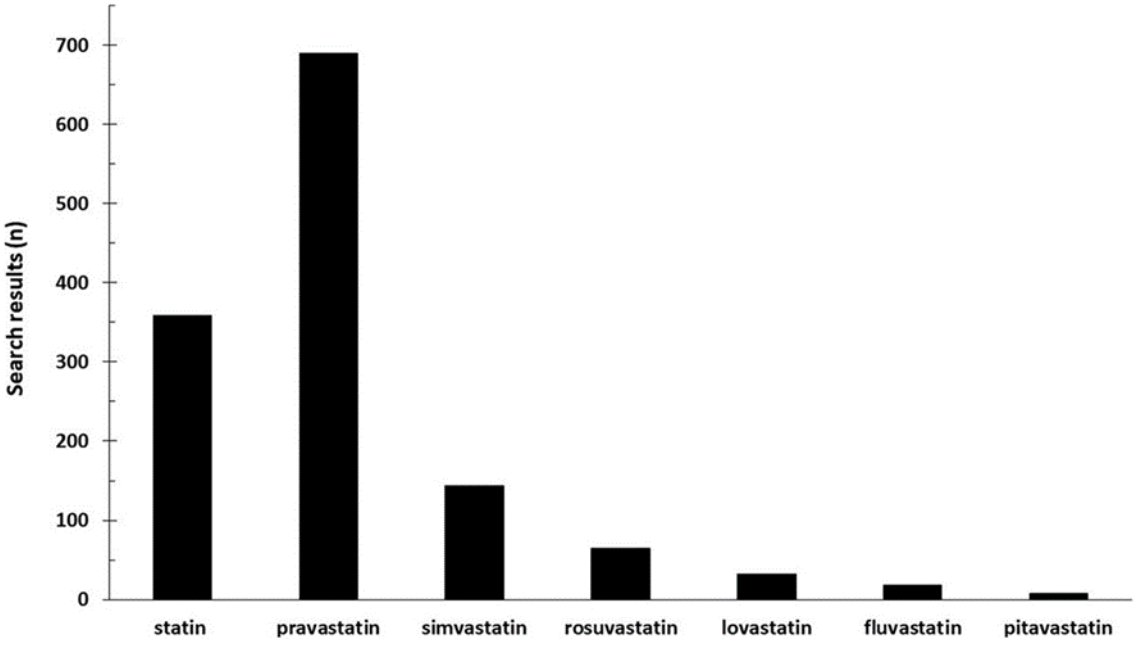

Figure 1 - *Number of hits for search terms "statin AND preeclampsia" databases: PubMed, Cochrane, Embase, Web of Science, Scopus, and www.clinicaltrials.gov. The dominance of pravastatin in preeclampsia research is undeniable.*

Pravastatin demonstrated significant reductions in the secretion of both endothelin-1 (ET-1) and soluble sFlt-1, key mediators of endothelial dysfunction, in primary human umbilical vein endothelial cells (HUVECs) and uterine microvascular cells (UtMVs) (30). Additionally, pravastatin has been shown to ameliorate the deficient nitric oxide (NO) supply characteristic of preeclampsia (31–33). In human endothel-like cell lines (HUVEC), pravastatin upregulated the expression of endothelial NO synthase and enhanced endothelial NO synthase activity by phosphorylating the activating eNOS Ser1177 (34).

Simvastatin appears to exhibit greater potency in inhibiting sFlt-1 secretion from endothelial cells, trophoblast cells, and placental tissue in women with preterm preeclampsia compared to pravastatin or rosuvastatin (35). In human choriocarcinoma

JAR cells, simvastatin reduces oxidative stress, suggesting its potential therapeutic role in preeclampsia treatment (36). Treatment with simvastatin in a preeclampsia rat model significantly reduced hypertension, sFlt-1- , TNF-α- , and malondialdehyde-levels, which levels are all markers of oxidative stress (37).

Pravastatin reduces the reduction of free cytochrome C by glutathione and mitochondrial oxygen consumption, while simvastatin increases these processes. Simvastatin's ability to enhance the oxidizing capacity of free cytochrome c may increase oxidative stress, facilitating apoptosis (38). Rat models of preeclampsia have also shown successful treatment with the usage of pravastatin (39). Among the statins tested, including pravastatin, simvastatin, and rosuvastatin, simvastatin emerged as the most potent inhibitor of sFlt-1 secretion (32). Pravastatin similarly reduced ET-1 and sFlt-1 secretion in HUVECs without exhibiting toxic effects observed with rosuvastatin and simvastatin (28).

Pravastatin metabolism differs from the metabolism paths of other statins as it is not metabolized by cytochrome P450 but is excreted after sulfation, causing less liver damage. Several in vitro and animal experiments have also confirmed pravastatin's safety in pregnancy with demonstrated beneficial effects in PE models (40).

2. OBJECTIVES

The object of my PhD work was to evaluate the possible novel screening methods and treatments of preeclampsia. I tried to find predictive markers and preventive measures for preeclampsia:

1) To find a predictive marker and perform a novel meta-analysis that had not been performed before my work I chose neutrophil-to-lymphocyte ratio (NLR) and found clinical research that published data on first-trimester NLR values of women who later developed preeclampsia and of women who did not develop preeclampsia, serving as a control group. My main goal was to find all these studies that published these NLR values and to perform a meta-analysis with their data.

2) To evaluate novel medications in preeclampsia, I conducted a systematic review focusing on assessing the efficacy and safety of pravastatin in the management of preeclampsia. The objective was to explore the impact of pravastatin treatment on both maternal and fetal outcomes, particularly in high-risk groups.

2.a) If pravastatin therapy administrated before the 20th gestational week lowers the risk of preeclampsia among the high-risk population?

2.b) If pravastatin therapy administrated before the 20th gestational week lowers the risk of IUGR among the high-risk population?

2.c) If pravastatin therapy administrated before the 20th gestational week lowers the risk of NICU admissions among the high-risk population?

2.d) If pravastatin therapy administrated before the 20th gestational week lowers the risk of pre-term birthes among the high-risk population?

2.e) If there is any evidence of maternal or fetal adverse effects with pravastatin treatments.

To sum up, the object of the studies was inspiring as it tried to find a way to find the high-risk patients and a way to possibly medicate them to lower the risk for them to develop preeclampsia.

3. METHODS

In this section I try to give an, as detailed as, possible description of the methods and materials of the 2 meta-analyses I carried out during my PhD work. First, I would like to start with the explanation of the methods for the NLR meta-analysis, then with the pravastatin meta-analysis.

To ensure methodological rigor, both meta-analyses were planned using a PRISMA checklist and followed the MOOSE methods (41,42).

3.1 Methods and materials for the first-trimester preeclampsia screening meta-analysis

3.1.1 Eligibility criteria, information sources, search strategy

Two independent researchers collected data for the meta-analysis from PubMed, Scopus, Web of Science, Cochrane Library, and Embase databases. Discrepancies were resolved through consensus or by consulting a third reviewer when necessary. Database searches were conducted up to December 31, 2022, without any additional time constraints, and no language restrictions were imposed.

3.1.2 Study selection

In this study, the search used the keywords "NLR" combined with "preeclampsia" in five online medical databases: *PubMed*, *Cochrane Library*, *Scopus*, *Embase*, and *Web of Science*. During the time of screening, the research group aimed to identify studies reporting NLR values during the first trimester of pregnancy among women who subsequently developed preeclampsia. These values were then compared to those women in the control groups who maintained normotensive pregnancies without obstetrical complications.

3.1.3 Data extraction

From the studies selected for further review, the following data were extracted: the study objectives, the number of patients with mild preeclampsia, the number of patients with severe preeclampsia, the total number of preeclamptic patients, the number of control (healthy, normotensive) pregnant patients, the timing of data collection (trimester, weeks), NLR values of patients with mild preeclampsia and their corresponding standard

deviations, NLR values of patients with severe preeclampsia and their corresponding standard deviations, NLR values of all preeclamptic patients and their corresponding standard deviations, NLR values of healthy, normotensive patients (control group) and their corresponding standard deviations, and p-values.

Additionally, both researchers recorded the titles, authors, publication years, publishers, and DOIs (digital object identifier) of the articles.

3.1.4 Assessment of risk of bias

The Newcastle–Ottawa scale (NOS) (43) was utilized to assess the quality of the included studies. This assessment was conducted independently by two authors, with any discrepancies resolved through consensus or, if necessary, by consulting a third author. The NOS evaluates articles based on three primary factors: the selection of study groups, the comparability of these groups, and the ascertainment of exposure, assigning scores ranging from 0 to 9. A score of 0 indicates the lowest possible quality, while 9 signifies the highest. Studies scoring 0–4 stars are categorized as low quality, while those receiving 5 or more stars are considered moderate to high quality.

According to the authors, all included articles received 6 or more stars on the NOS.

3.1.5 Statistical methods and data synthesis

The mean difference (MD) with a 95% confidence interval (CI) was employed to represent the effect size. This involved extracting the number of patients, mean, and standard deviation (SD) of the variable of interest for both the "preeclampsia" and "without preeclampsia" (i.e., control) groups from the studies. The MD is calculated as the mean of the "preeclampsia" group minus that of the "without preeclampsia" group. In cases where means and SDs were provided for moderate and severe preeclampsia subgroups separately, we combined them using established formulae (44).

Given anticipated between-study heterogeneity, a random-effects model was employed to pool effect sizes. The inverse variance weighting method was used for calculating the pooled mean difference, with Hartung-Knapp adjustment (45,46) applied due to relatively small study numbers and sample sizes. To estimate the heterogeneity variance measure (tau squared), a restricted maximum-likelihood estimator was utilized alongside the Q

profile method (47). Between-study heterogeneity was described using Higgins and Thompson's I squared statistics (48).

Forest plots were used to graphically summarize the results. The confidence interval of each individual study was calculated based on the t-distribution. Additionally, where applicable, we reported prediction intervals (i.e., the expected range of effects of future studies) of results following the recommendations of IntHout et al. (49).

Outlier and influence analyses were conducted as per established recommendations of Harrer et al. (50) and the recommendations of Viechtbauer and Cheung (51), while publication bias was assessed using Egger's test (52) (at the significance level of 10%). However, results should be interpreted cautiously due to the limited number of studies.

All statistical analyses were performed with the usage of R software (53), with the meta package (54) for main calculations and the dmetar package (55) for influential analysis.

3.2. Methods and materials for evaluating pravastatin's role in preeclampsia prevention

3.2.1 Eligibility criteria, information sources, search strategy

Two independent reviewers gathered data from PubMed, Cochrane, Embase, Web of Science, Scopus, and clinicaltrials.gov databases, covering studies published from January 2003 to July 2022.

Using keywords such as "statin", "pravastatin", "simvastatin", "rosuvastatin", "lovastatin", "pitavastatin", and "fluvastatin" combined with "preeclampsia" we conducted our study. A separate search was conducted using the term "*statins". Language restrictions were not imposed.

In this summary, we present detailed data retrieved from the search using "pravastatin" and "preeclampsia".

Inclusion criteria encompassed studies involving statin treatment during human pregnancy with an untreated control group, focusing on either treating or preventing preeclampsia. Exclusion criteria comprised non-human studies, summaries, case reports, and in vitro studies.

Following the selection process, we categorized the studies into the three specified groups outlined in the Objectives (1st prevention before the 20th week, 2nd prevention after the 20th week, and 3rd treatment).

3.2.2 Study selection

Two investigators independently assessed the eligibility of retrieved studies based on predetermined criteria. Any disagreements were resolved through consensus and, if needed, a third reviewer was consulted.

Included studies specifically involved the use of statins in human subjects and evaluated their efficacy in preventing and/or treating preeclampsia.

3.2.3 Data extraction

The included studies were assessed for various characteristics, including author names, publication year, study design, study objectives, participant numbers (including control and placebo groups), statin type and dosage, concurrent medications for preeclampsia prevention, and gestational weeks of statin exposure.

Additionally, outcomes such as maternal and fetal toxicity, adverse effects, birth weight, gestational age at termination, neonatal deaths, spontaneous abortions, NICU admissions, and preterm birth were also extracted if available.

3.2.4 Statistical methods and data synthesis

To measure the effect size, we utilized a risk ratio (OR) along with a 95% confidence interval (CI). We employed a random-effects model due to anticipated between-study heterogeneity. Given small sample sizes and instances of zero cell counts, we opted for the exact Mantel-Haenszel method without continuity correction, following recommendations by Sweeting et al. (56). Additionally, a Hartung-Knapp adjustment was applied for conservatism where appropriate (45,46). The Paule-Mandel method (57) was used to estimate the heterogeneity variance ($\tau 2$), with the Q profile method for the confidence interval (43). Between-study heterogeneity was described using Higgins and Thompson's I2 statistics (48). Forest plots were employed for graphical representation, with a continuity correction of 0.5 applied for zero cell counts solely for visualization

purposes. Due to low study numbers and relatively high heterogeneity, prediction intervals were not presented on plots, and their interpretation was limited. Outlier and influence analyses were less powerful given these factors. All statistical analyses were conducted using R (54) with the meta package (55).

4. RESULTS

4.1. Results of assessment of NLR values in preeclampsia screening

4.1.1. Study selection for evaluating NLR's predictive role in preeclampsia

For this study, we combined the keywords "NLR" and "preeclampsia" and conducted searches across 5 online medical databases (PubMed, Cochrane Library, Scopus, Embase, Web of Science). Initially, 324 articles were identified, and after removing duplicates, 134 remained. Further screening led to the exclusion of 103 irrelevant articles. Our meta-analysis aimed to identify clinical studies utilizing first-trimester NLR values as predictive markers for preeclampsia. Excluded were non-clinical studies, letters to other publications, studies focusing on NLRP3 values in pre-eclamptic women, and those using negative likelihood ratio (NLR) as a search term. Additionally, studies not focusing on first trimester NLR findings were excluded. Following detailed screening, 25 studies were excluded due to various reasons, leaving 6 studies for meta-analysis. A PRISMA flow diagram was utilized for transparent reporting, strictly adhering to the PRISMA 2020 statement guidelines (41) (**Figure 2**).

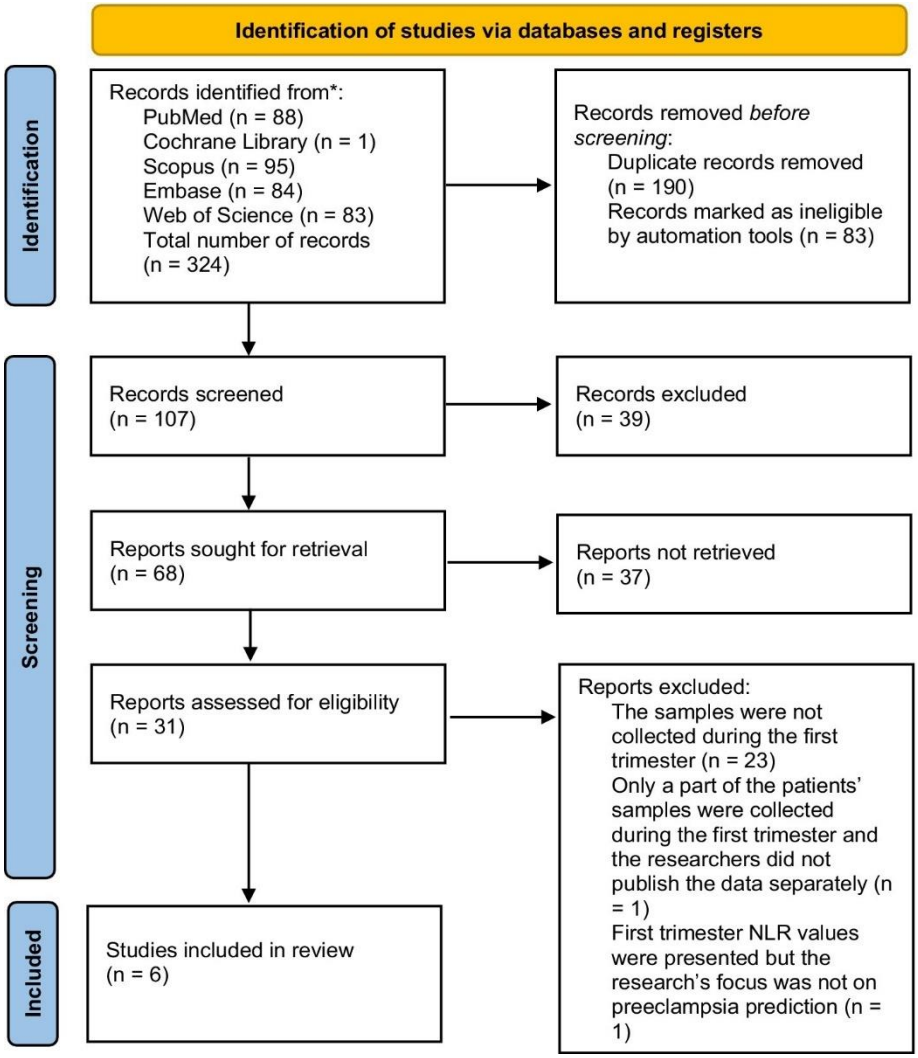

Figure 2 - *Selection of the studies for the analysis of NLR values' predictive role in first-trimester preeclampsia.*

Data extraction for the meta-analysis included NLR values in both control and preeclampsia groups, along with their standard deviations, from the remaining 6 studies.

4.1.2. Study characteristics

Overall 6 studies got included to the analysis (58–63) the overall number of preeclampsia patients, the overall number of patients selected into the control groups, the ages of the patients (both presented with mean and standard deviation) and the BMIs (body mass index) of the patients (both presented with mean and standard deviation), gestational age at delivery (both presented with mean and standard deviation), all the study characteristics data are presented on **Table 1**.

Table 1 - *Studies included in the meta-analysis*

Study ID		Sample size		Age		BMI		Gestational age at delivery	
		Preeclampsia	Control	Preeclampsia	Control	Preeclampsia	Control	Preeclampsia	Control
1	Gezer et al. (51)	209	221	26.6±6	25.8±4.9	25.7±3.7	25.2±4.1	35.8±3.02	39.37±1.16
2	Hale et al. (53)	214	240	28.7±3.4	27.5±3.5	22.9±3.2	22.7±3.5	37.6±1.1	40.5±1.5
3	Kirbas et al. (50)	614	320	Severe PE: 29.3±14.3, mild PE: 27.9±4.9	27.0±5.0	Severe PE: 23.7±3.6, mild PE: 22.9±3.1	22.7±3.6	Severe PE: 33.0±3.5, mild PE: 37.5±2.1	40.6±1.6
4	Oğlak et al. (49)	201	100	Severe PE: 28.7±6.8, mild PE: 28.3±7.4	27.4±6.1	NR	NR	NR	NR
5	Bulbul et al. (48)	161	161	30.91±6.47	30.08±6.04	28.00±2.62	26.73±2.97	36.4±2.9	38.2±1.9
6	Mannaerts et al. (54)	14	14	29 (no SD presented)	31 (no SD presented)	26.7±3.4	28.0±3.6	NR	NR

4.1.3. Risk of bias

As previously mentioned, publication bias was evaluated using Egger's test, with a significance level set at 10% due to the limited number of studies. Despite obtaining a p-value of 0.2132 from Egger's test, it's essential to note that with only a few studies included, Egger's test might lack the statistical power to detect bias accurately, potentially resulting in a false "positive" result.

4.1.4. Synthesis of results

Out of the total pool, 6 studies were selected for analysis: encompassing a total of 2,469 patients.

On average, the effect size was calculated to be 1.082. The 95% confidence interval for the effect size ranged from 0.641 to 1.523, indicating that the mean effect size across comparable studies could fall within this range.

The between-study heterogeneity, expressed as an I2 value, was determined to be 0.765 (95% CI, 0.473–0.895). This suggests that 76.5% of the observed variance in effects reflects variance in true effects rather than sampling error. The variance of true effects (T2) was found to be 0.12, with a standard deviation of true effects (T) of 0.34.

The prediction interval, spanning from 0.027 to 2.137, indicates that we would expect the true effect size to fall within this range in approximately 95% of all populations comparable to those analyzed.

The synthesis of the results and its statistical analyses can be seen on the format of a forest plot on **Figure 3**.

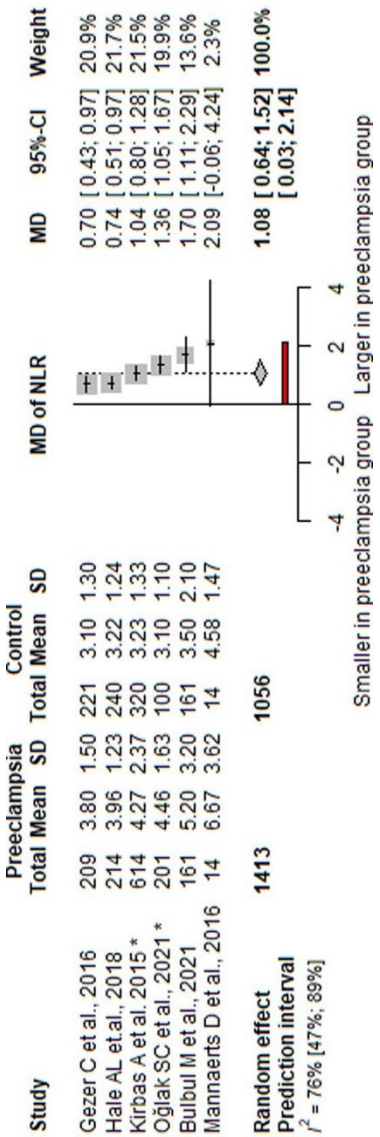

Figure 3 – *forest plot of the NLR values*

4.2. Results of assessment of pravastatin in preeclampsia prevention

4.2.1. Description of studies

4.2.1.1. Studies included in systematic review section

Our researchgroup's previous database was assessed for the analysis (64).

The electronic database search was conducted between January 2020 and July 2022 and it provided a total of 313 articles. Following the removal of duplicates, 113 unique articles remained for further analysis. Due to the fact that most of the articles were dealing with

animal models (mostly mice preeclampsia models) and tissue samples, out of these 83 were irrelevant to our meta-analysis.

After the removal of the articles that were not clinical research, 30 studies were considered for full-text assessment, however, we needed to exclude 19 out of the remaining studies: they were either responses/letters for the authors, and/or they were not primarily focusing on the treatment of preeclampsia with statins and/or did not provide enough data for our research which primary objective was to examine the safety and efficacy of statins in the treatment and prevention of preeclampsia. After the exclusion was conducted, 11 articles met the inclusion criteria, and another 3 articles were added, which were already selected in the author's earlier database. These 3 studies had the same object, dealing primary with the efficacy of statin usage in preeclampsia, and and they were published in the time span of 2003 and 2016.

We thoroughly examined these articles and extracted every possible data from them that were either dealing with maternal or fetal state or with the efficacy and safety of pravastatin usage during pregnancy. These studies were included in the systematic review because they used pravastatin in the treatment/prevention of preeclampsia.

4.2.1.2. Studies included in meta-analysis section

Utilizing existing data, a meta-analysis was undertaken to assess the efficacy of pravastatin in preventing preeclampsia before the 20th gestational week. From the 11 articles identified in the recent database search, 2 were excluded due to pravastatin being used in conjunction with L-arginine, while another 2 were omitted for being case reports lacking adequate control groups. Additionally, 3 articles were excluded as they focused on using pravastatin for treating preeclampsia in later gestational weeks or lacked sufficient data. Consequently, four records remained, supplemented by 1 selected from the previous database search, facilitating the meta-analysis based on these five articles.

To see the selection thoroughly PRISMA flow diagram can be seen on **Figure 4.**

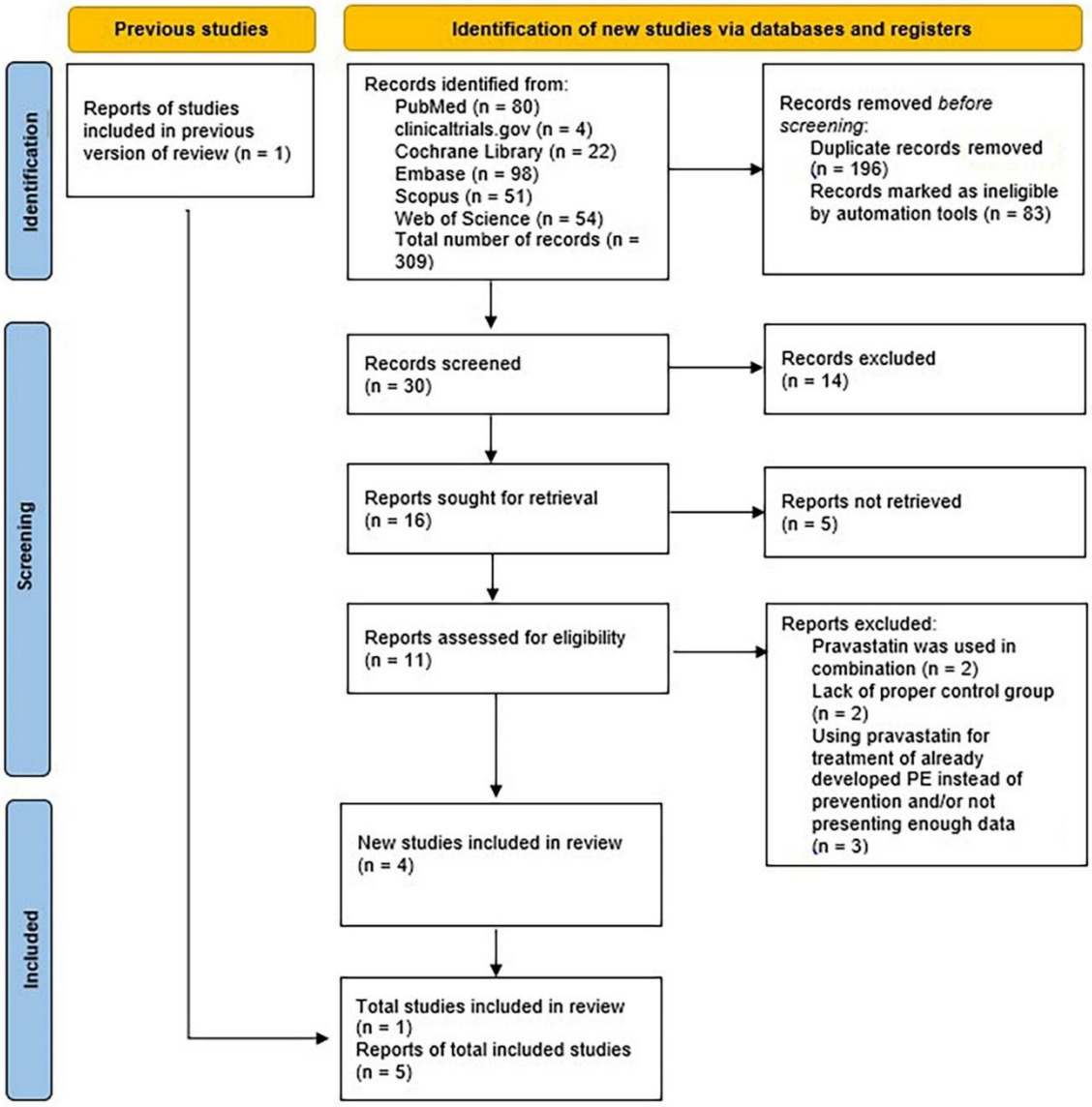

Figure 4 – *PRISMA flow diagram presenting the selection of the studies for pravastatin's role in preeclampsia prevention*

4.2.1.3. Pravastatin usage before the 20th gestational week – meta-analysis

Our meta-analysis consists of 5 selected studies (65–69) as detailed in **Table 2**.

Table 2 – *selected studies included in pravastatin meta-analysis*

References	Type of study	Start of treatment (weeks)	Pravastatin (mg/day)	Cases (n)	Conclusions
Costantine (2016) (41)	RCT	12–16	10	20	No identifiable safety risks were associated with pravastatin use in this cohort. Four subjects in the placebo group developed preeclampsia compared with none in the pravastatin group.
Kupferminc (2021) (45)	cohort	12	20	32[a]	Additive treatment with pravastatin to low molecular weight heparin and low dose aspirin may be promising option in cases of previous severe recurrent placenta-mediated complications.
Costantine (2021) (41)	RCT	12–16	20	20	This study confirmed the overall safety and favorable pregnancy outcomes for pravastatin in women at high risk for preeclampsia.
Akbar (2021) (43)	RCT	14–20	40	80	The rate of PE was (nonsignificantly) lower in the pravastatin group. Prophylactic pravastatin was associated with a significantly lower rate of adverse perinatal outcome.
Akbar (2022) (44)	RCT	14–20	20	173	Pravastatin (20 mg bid) significantly reduces the risk of preterm preeclampsia and preterm birth in women at high risk of developing preeclampsia.

RCT, randomized control study.
[a]Retrospective cohort study of 32 women with recurrent severe placenta-mediated complications. Everyone was treated with pravastatin; the previous pregnancy was used as a control group.

Despite several articles reporting birth weights and gestational ages at delivery, the absence of standard deviations in many instances led to the exclusion of certain data types.

We specifically included studies assessing the prevention of preeclampsia, considering its onset typically occurring after the 20th week. Hence, we focused solely on studies initiating pravastatin treatment before the 20th gestational week.

The data evaluated in our meta-analysis encompassed the incidence of preeclampsia, frequency of NICU admissions, occurrences of intrauterine growth restriction (IUGR), and preterm delivery.

These findings provided valuable insights into the maternal and neonatal benefits associated with pravastatin use among high-risk individuals for preeclampsia.

4.2.1.4. Pravastatin in the prevention of preeclampsia

A total of five studies were selected for the meta-analysis, covering a total of 357 patients out of which 86 patients experienced preeclampsia.

The average risk ratio (pooled effect size) for developing preeclampsia was 0.39. The 95% confidence interval of the odds ratio ranged from 0.186 to 0.819, indicating the potential range of the mean effect size across comparable studies. The between-study heterogeneity, expressed as an I2 value, was 0.15 (95% CI: 0–0.82), suggesting that 15% of the observed variance in effects reflects variance in true effects rather than sampling error. The variance of true effects ($\tau 2$) was 0.07, with a standard deviation of true effects (τ) of 0.265. The prediction interval ranged from 0.118 to 1.291, representing the expected range of true effect sizes in 95% of comparable populations.

The bias due to the low number of cases was deemed high. Analysis indicates a positive correlation between higher pravastatin doses and increased risk ratio values. Additionally, commencing pravastatin treatment at later gestational weeks, compared to controls, was associated with higher risk ratio values.

Overall, pravastatin treatment led to a 61% reduction in the incidence of preeclampsia compared to the untreated group.

Figure 5 presents the detailed results in the format of a forest plot.

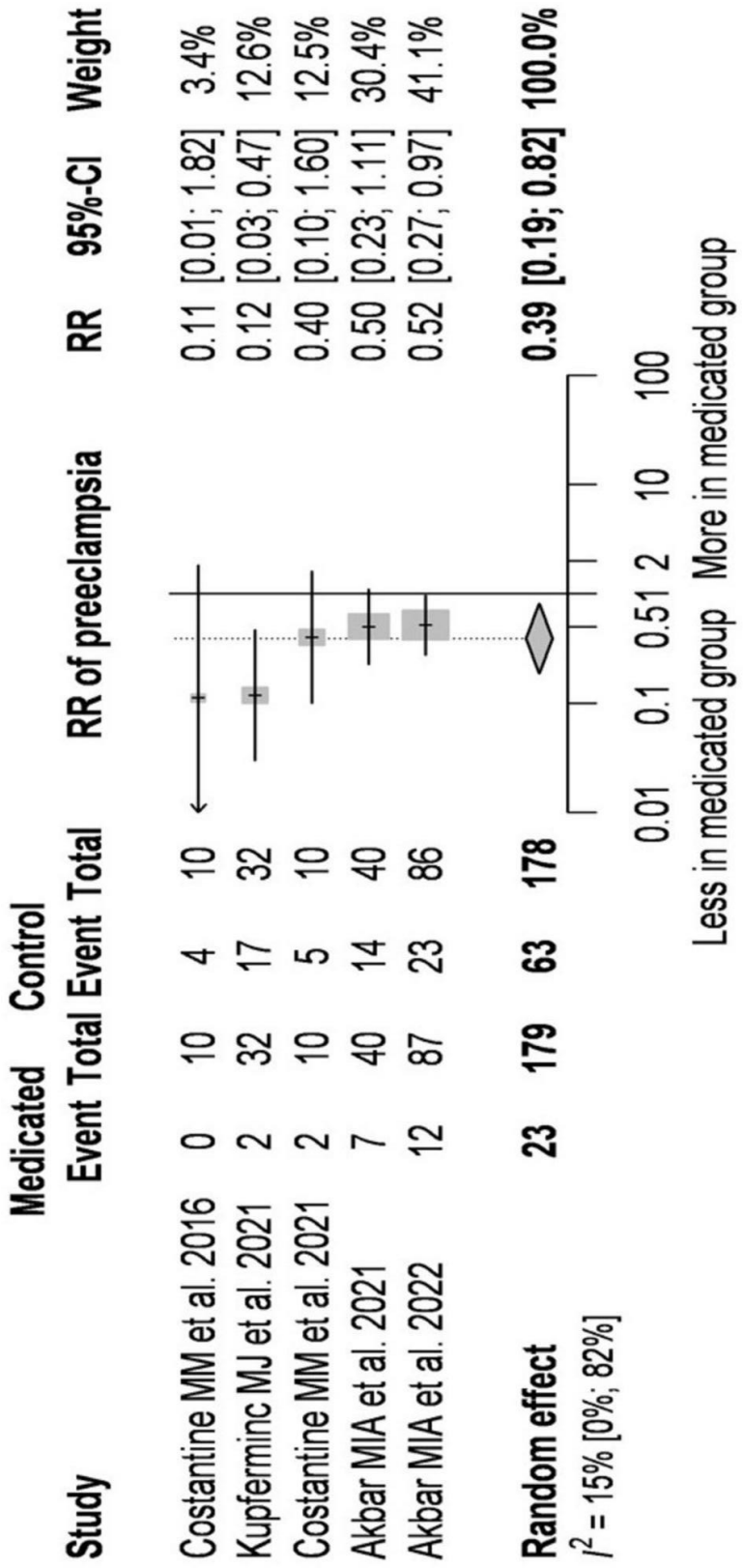

Figure 5 - *Effect of pravastatin treatment on the prevention of preeclampsia–forest plot.*

4.2.1.5. Pravastatin treatment – reducing the incidence of IUGR

A total of 4 studies were selected for the analysis, covering a total of 277 patients out of which 70 patients' neonates were diagnosed with IUGR.

On average, the risk ratio (the pooled effect size) of IUGR was 0.554. The 95% confidence interval of the odds ratio was 0.135 to 2.284, which tells us that the mean effect size in the universe of comparable studies could fall in this range. The between-study heterogeneity expressed as I2 value was 0.19 (95% CI: 0–0.88), which tells us that 19% of the variance in observed effects reflects variance in true effects rather than sampling error. The variance of true effects ($\tau 2$) was 0.235 and the standard deviation of true effects (τ) was 0.485. The prediction interval was 0.033 to 9.409. Based on that we would expect in some 95% of all populations comparable to those in the analysis, the true effect size will fall in this range.

Analysis of the data suggests that the dose of pravastatin has no role in the incidence of IUGR.

In studies where the initial BMI of the treated pregnant women was higher than that of the controls, the RR value was lower.

Figure 6 presents the detailed results in the format of a forest plot.

Figure 6 - *Pravastatin treatment reduces the incidence of IUGR–forest plot.*

4.2.1.6. Pravastatin treatment – reducing the incidence of NICU admissions

A total of 4 studies were selected for the analysis, covering a total of 180 patients out of which 47 patients' neonates had to be admitted to NICU ward.

On average, the risk ratio (the pooled effect size) of NICU admission was 0.227. The 95% confidence interval of the odds ratio was 0.035 to 1.475, which tells us that the mean effect size in the universe of comparable studies could fall in this range.

The between-study heterogeneity expressed as I2 value was 0.64 (95% CI: 0–0.88), which tells us that 64% of the variance in observed effects reflects variance in true effects rather than sampling error. The variance of true effects ($\tau 2$) was 0.679 and the standard deviation of true effects (τ) was 0.824.

The prediction interval was 0.003 to 17.691. Based on that we would expect in some 95% of all populations comparable to those in the analysis, the true effect size will fall in this range.

The most significant change was observed in newborns requiring treatment in the intensive care unit. Newborns of pregnant women receiving pravastatin treatment had 77% reduction in NICU admission compared to untreated pregnant women.

Analysis of the data suggests that the RR value decreases as the daily dose of pravastatin increases. If treated patients are older than controls, the RR value is lower.

In studies where the initial BMI of the treated pregnant women was higher than that of the controls, the RR value is lower.

Figure 7 presents the detailed results in the format of a forest plot.

Figure 7 - *Reduction in NICU admission with pravastatin treatment–forest plot.*

4.2.1.7. Pravastatin treatment – reducing the incidence of pre-term birth

A total of 4 studies were selected for the analysis, covering a total of 293 patients out of these 293 patients 68 gave birth earlier than the 37th gestational week.

On average, the risk ratio (the pooled effect size) of preterm birth was 0.42. The 95% confidence interval of the odds ratio was 0.214 to 0.825, which tells us that the mean effect size in the universe of comparable studies could fall in this range. The between-study heterogeneity expressed as I2 value was 0 (95% CI: 0–0.85), which tells us that 0% of the variance in observed effects reflects variance in true effects rather than sampling error. The variance of true effects ($\tau 2$) was 0 and the standard deviation of true effects (τ) was 0.

The prediction interval was 0.149 to 1.18. Based on that we would expect in some 95% of all populations comparable to those in the analysis, the true effect size will fall in this range.

According to our conservative estimate due to the low number of cases, the dose of pravastatin has no role in reducing premature birth. In those studies where the initial BMI of the treated pregnant women was higher than that of the controls, the RR values were lower. If the pravastatin treatment was started in a later gestational week compared to the controls, the RR values were higher.

Figure 8 presents the detailed results in the format of a forest plot.

Figure 8 - *Effect of pravastatin on preterm birth–forest plot.*

4.2.2. Systematic review

4.2.2.1. Pravastatin usage in the prevention of preeclampsia after the 20th gestational week – the 2nd studied group

In our review focusing on the preventive use of pravastatin after the 20th week of pregnancy, three studies were identified (70–72). However, due to several factors including the small number of cases, heterogeneity among the study groups (including antiphospholipid syndrome (APS), IUGR, and high risk of preeclampsia), and variations in treatment initiation times (ranging from 24 to 35.9 weeks), carrying out a meta-analysis was not feasible.

Overall, our review indicates positive effects of pravastatin use in women with preeclampsia or at high risk. Notably, the study with the largest sample size (71), involving 1,091 high-risk patients treated with 20 mg daily pravastatin starting between the 35th and 37th gestational weeks, did not find significant differences between the pravastatin and control groups. However, other studies commencing treatment earlier demonstrated significant or promising differences between placebo and pravastatin groups.

For instance, Mendoza et al. (72) investigated the effect of daily 40 mg pravastatin treatment in women with fetuses diagnosed with fetal growth restriction (FGR). Among the 38 women enrolled, 19 served as controls. Pravastatin treatment, initiated between the 20th and 28th gestational weeks and continued until delivery, was associated with reduced incidence of preeclampsia compared to the control group (6 vs. 9 cases).

NICU admissions were also lower among neonates born to mothers receiving pravastatin (12 vs. 15 admissions), with a mean birthweight of 1.300 g in the pravastatin group compared to 1.040 g in the control group.

4.2.2.2. Pravastatin usage in the treatment of preformed preeclampsia – the 3rd studied group

In the third group studied, which examined the use of pravastatin for the treatment of preeclampsia, three relevant studies were identified (70,73,74). However, due to the limited number of cases, a meta-analysis was not feasible. Nonetheless, these studies shed light on the potential benefits of pravastatin therapy in managing preeclampsia (73–78).

Ahmed et al. (73) administered daily 40 mg pravastatin to 32 patients with early-onset preeclampsia, observing decreased sFlt-1 levels and a 4-day prolongation of pregnancy compared to the placebo group. Notably, no fetal losses were reported in the pravastatin group, unlike the three perinatal deaths recorded in the placebo group.

Similarly, Brownfoot et al. (77) reported favorable outcomes in severe preeclampsia cases treated with 40 mg daily pravastatin, with stabilization of maternal disorders and no adverse fetal or neonatal effects observed.

Moreover, studies explored combination therapies involving pravastatin alongside LMWH and low-dose aspirin. Lefkou et al. (76) and their research group investigated the efficacy of triple therapy in patients with obstetric antiphospholipid syndrome (OAPS), preeclampsia, and/or IUGR. Their findings revealed significant improvements in gestational outcomes, with higher survival rates and increased birthweights in the treated group compared to controls.

Additionally, studies incorporating L-arginine supplementation alongside pravastatin demonstrated notable benefits in improving uteroplacental dysfunction and reducing adverse neonatal outcomes (75).

Although the study by Saito et al. (78) presented only two cases without control groups, it highlighted the potential benefits of pravastatin in pregnant women with a history of antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE), showing improvements in maternal and fetal outcomes without adverse effects.

Overall, these studies suggest promising therapeutic potential for pravastatin in managing preeclampsia, especially when combined with other medications.

5. DISCUSSION

In my PhD work I tried to find the novel screening methods of preeclampsia, thus finding, the high-risk populations regarding the development of preeclampsia.

As it was mentioned above, preeclampsia's prevalence is higher in developing countries, thus it was an important matter to find an easily affordable way of screening, even in low-resource countries. Due to this fact we started to evaluate neutrophil-to-lmyphocyte ratio which is easily accessible with peripheral blood tests.

5.1. But why is NLR elevated in preeclampsia, possibly even in the first trimester when preeclampsia not even formed, yet?

Recent studies show that IL-6, IL-8, and IL-17 play an important role in the production of neutrophils, just as well they play an important role in the pathophysiology of preeclampsia (79,80).

One of IL-8's most important roles is the attraction of neutrophils to the inflamed areas; they also play an important role in neutrophil recruitment to the endometrium (thus contributing to preeclampsia development), and IL-8 also stimulates neutrophil degranulation, while IL-6 is linked to genes that stimulate the proliferation, maturation, and activation of neutrophils (81,82).

Levels of IL-17A are elevated in preeclampsia, and it stimulates the expression of neutrophil chemokines in vascular smooth muscle as well. IL-17A also increases the levels of G-CSF and GM-CSF, both of which increase the production of neutrophils (83,84).

5.2 NLR in clinical research

The neutrophil-to-lymphocyte ratio is getting more and more into the center of clinical studies: while in the PubMed online database for the search "neutrophil-to-lymphocyte ratio" keyword there are only 1 result from the year 2002, if we wait 10 years there are 65 results from the year 2012, while this number is 1749 from another 10 years later, from the year 2022.

NLR levels are not only studied in preeclampsia: they are studied in various range of inflammatory diseases or diseases that pathophysiology is connected to inflammatory

reactions and pathways: there are various studies which claim that elevated NLR levels have a prognostic value in oncological diseases. According to the findings of Inoue et al. NLR levels have a prognostic value in oligometastatic breast cancer in the overall survival rate (85). Lin et al. evaluated the NLR values of 2522 patients who had colorectal cancer with liver metastasis (CRLM) and they found that an excellent value in predicting the clinical outcomes, moreover it also can be used in deciding the treatment of CRLM (86). NLR levels were also studied in gynecological tumors as well: Huang et al. found that pre-treatment elevated levels of NLR could be an early sign of poor prognosis in ovarian cancer (87).

There are many studies which also found the prognostic values of NLR in autoimmune diseases: according to the 2019 findings of Zeng et al. in autoimmune encephalitis NLR may be feasible in monitoring the progression of the disease (88). Aktas et al. also found that elevated NLR can be an early sign of Hashimoto's thyroiditis (89).

Even though the above presented findings NLR have received the largest publicity in another disease highly related to inflammatory pathways: COVID-19. Güzey et al. evaluated 254 women's NLR values. All the patients gave birth with cesarean section and contracted SARS-CoV-2. They found significantly elevated NLR levels among the patients who experienced symptoms compared to the patients who remained asymptomatic (90). According to Lasser et al.'s multicenter, retrospective cohort study where they elevated NLR values of 5002 pregnant women out of 498 had COVID-19 NLR are sensitive markers in pregnant patients of COVID-19 progress to a critical state of health (91).

Moreover, in 2022 our research group documented the case of a 33-year-old pregnant kidney transplant recipient. Throughout the illness with COVID-19, her NLR values were elevated, she needed non-invasive respiratory support, and displayed symptoms indicative of preeclampsia (92).

5.3 Principal findings of NLR meta-analysis

NLR's prediction interval fell in the range of 0.027 to 2.137, and the 95% confidence interval of the effect size is 0.641 to 1.523, all the evaluated studies found elevated levels of NLR in mothers who later during their pregnancies developed preeclampsia.

5.4 The importance of finding screening methods for preeclampsia that can be applied in low resource settings

Preeclampsia remains a significant contributor to maternal mortality in developed countries, putting financial burdens on healthcare systems (93,94).

In 2012, the cost of managing preeclampsia within the first year after delivery in the United States alone mounted to $2.18 billion, with considerable expenses allocated to both infants and mothers (95,96).

While even developed nations face huge problems regarding preeclampsia, its impact is even more severe in developing countries. Therefore, there is a pressing need to identify cost-effective screening and treatment strategies, acknowledging the importance of pricing considerations in both developed and developing contexts.

Given the established cost-effectiveness of NLR as a biomarker for various diseases (97) our analysis underscores its potential utility in enhancing first-trimester screening methods for preeclampsia. Consequently, we advocate for further clinical investigations to assess the viability of elevated NLR levels as a screening tool for preeclampsia.

5.5 The importance of preeclampsia screening methods, the importance of screening the disease as early as the first trimester

As preeclampsia is a common clinical syndrome of the human pregnancy, with a prevalence of 2–8% according to different sources, the only definitive treatment of the disease, currently the termination of the pregnancy: the removal of the placenta (98). As it remains one of the leading causes of maternal-, fetal- and neonatal morbidity and mortality it is eager to find more and more accurate screening methods and therapies, to improve the overall survival and asymptomatic survival of the patients (99).

Recent meta-analyses and cohorts indicate that the main risk factors for preeclampsia development are maternal obesity, antiphospholipid antibody syndrome, preexisting chronic hypertension, pregestational diabetes, the lack of antenatal visits or the irregularity of them, in vitro fertilization technologies, and nulliparity (100,101).

In the screening for preeclampsia, assessing maternal characteristics (such as age, weight, height, ethnicity, and smoking habits), medical history (including chronic hypertension,

diabetes, and family history of preeclampsia), and obstetrical history (previous pregnancies affected by preeclampsia) is crucial for calculating the risk (102,103). The American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) provide guidelines for risk stratification based on these factors (2,104), although their sensitivity in first-trimester screening is limited (105).

Doppler ultrasound, measuring mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), is another important aspect of preeclampsia screening (106).

Biochemical markers are widely utilized in first-trimester screening, including abnormal serum levels of placental growth factor (PlGF), pregnancy-associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), Inhibin A, soluble-endoglin (sEng), and soluble Flt-1 (sFlt-1), all associated with increased preeclampsia risk (107,108).

While these methods continue to improve, there is an ongoing need to discover new markers, particularly ones applicable in developing countries, to enhance existing protocols crucial for reducing maternal mortality (109).

Our meta-analysis indicates that higher levels of NLR can be considered a useful biochemical marker for first-trimester preeclampsia screening, given its elevated levels in affected pregnancies and widespread accessibility. However, further research is warranted to assess the integration of NLR with other biochemical and biophysical markers, aiming to develop more effective and affordable screening methods.

Even if the high-risk populations are found currently there is no real treatment for preeclampsia, only the delivery of the fetus, better said the removal of the placenta. Since, as of today there is no real treatment for preeclampsia and the preventive medications are not sufficient the other goal of my PhD was to find novel screening methods for the disease.

5.6 Medicating the high-risk population

If we find the proper screening methods to find high-risk populations, it is important to prevent the disease. The most widely used preventive medicine is low-dose aspirin (LDA)

therapy (60-150 mg/day). According to Henderson et al.'s 2021 meta-analysis published in JAMA daily LDA therapy usage in individuals who are at high-risk for preeclampsia is associated with lower risks of serious perinatal outcomes. Moreover, they reported no evidence of any harms or side effects, caused by LDA therapy (110).

There are other, less frequently used medications in preeclampsia, as well: according to Cruz-Lemini et al.'s meta-analysis the use of low-molecular-weight heparin (LMWH) significantly reduced the risk of preeclampsia and other placenta-mediated complications in high-risk women, especially when treatment began before 16 weeks' gestation. Additionally, combining LMWH with LDA significantly lowered the risk of preeclampsia compared to using low-dose aspirin alone. The study involved a total of 15 studies with almost 2800 patients' data (111).

Moreover, other studies indicate that 1g of daily calcium and/or vitamin D supplementation could also be beneficial in preeclampsia prevention (112).

My Ph.D. work's main goal was to find more answers about one therapy: about statins.

In the meta-analysis, I evaluated the prevention of preeclampsia before the 20th gestational week using pravastatin. Five studies were assessed, and despite some limitations, I found promising data indicating that pravastatin reduces the number of neonates born with IUGR, decreases neonatal admissions to intensive care units, and lowers the incidence of preterm deliveries.

Additionally, women who received pravastatin before the 20th gestational week were less likely to develop preeclampsia compared to the control groups.

5.7 Results of the systematic review

We reviewed fourteen studies on the effectiveness of pravastatin in treating and preventing preeclampsia. The studies included yielded the following results:

1st Pravastatin treatment should begin between the 12th and 30th gestational weeks. A large study (**Hiba! A könyvjelző nem létezik.**) indicated that starting treatment between the 35th and 37th gestational weeks does not prevent the development of preeclampsia. However, all other studies that started pravastatin therapy earlier (before the 30th

gestational week) reported positive outcomes in the treatment and/or prevention of preeclampsia.

2nd Evidence suggests that even a 10 mg dose of pravastatin can help prevent preeclampsia. Doses of 20–40 mg daily showed positive effects on both prevention and treatment of preeclampsia, with no evidence of higher toxicity among patients treated with higher doses.

3rd Pravastatin, whether used in combination with L-arginine or in triple-therapy with LMWH and LDA, showed significant benefits in treating preeclampsia compared to their respective control groups. It helped pregnant women deliver closer to full term, thereby improving infant survival rates.

4th Among the 797 patients who received pravastatin therapy in the 14 reviewed articles, no fetal or neonatal adverse effects were reported, and only minor maternal adverse effects, such as headaches, occurred.

5.8 Studies involved in the meta-analysis and the discussion of the results

Studies by Costantine et al. involved randomized clinical trials where women at high risk of preeclampsia received pravastatin between the 12th and 16th gestational weeks. In their 2016 article (65), 10 women received a placebo while another 10 received 10 mg of pravastatin daily. In the control group, 4 women developed preeclampsia, whereas none did in the pravastatin group. The results concluded that pravastatin was safe, with only minor adverse effects reported.

In a subsequent article (66), Costantine et al. again assigned 10 women to receive a placebo and another 10 to receive pravastatin, this time at a dosage of 20 mg, between the 12th and 16th gestational weeks. The differences between the two groups remained significant, and despite the increased dose, adverse effects were still mild. However, a notable limitation was the significant difference in mean BMI between the placebo group (36.3) and the pravastatin group (25.4). This disparity could potentially explain the favorable outcomes in the pravastatin group, as higher BMI is a known risk factor for developing preeclampsia (100).

The INOVASIA study evaluated the prevention of preeclampsia with a daily dose of 20 mg of pravastatin, initiated between the 14th and 20th gestational weeks. In their 2021 article (67), 40 women were enrolled in each of the control and pravastatin groups, all at high risk for preeclampsia. The study reported non-significantly lower rates of preeclampsia in the pravastatin group (7 cases) compared to the control group (14 cases), and significantly lower rates of preterm delivery (4 cases in the pravastatin group vs. 12 in the control group).

In a 2022 article (68) by the same group, 173 high-risk patients were enrolled, with 86 in the control group and 87 in the pravastatin group. The study found significantly lower rates of preterm preeclampsia in the pravastatin group (12 cases) compared to the control group (23 cases), with $p > 0.05$.

Kupferminc et al. (69) conducted a retrospective cohort study on 32 women with previous severe placenta-mediated complications, using their prior pregnancies as controls. These women received pravastatin treatment starting at the 12th gestational week. During their control pregnancies, there were 17 cases of preeclampsia, all severe. In the pravastatin-treated pregnancies, only 2 women developed preeclampsia, and the symptoms were mild. There was also a significant reduction in cases of IUGR from 8 to 1, and NICU admissions from 25 to 2.

6. CONCLUSIONS

Our experiments focused on the following questions:

1) If NLR can be an effective predictive marker of preeclampsia.

The findings suggest that the neutrophil-to-lymphocyte ratio (NLR) is a promising biochemical marker for future research aimed at developing new screening methods for first-trimester preeclampsia. We encourage further studies to explore the predictive value of NLR in combination with other markers, which may lead to the development of new and cost-effective screening protocols for early detection of preeclampsia.

2) If pravastatin therapy is sufficient in preeclampsia.

Prophylactic treatment with pravastatin shows significant potential in reducing the risk of developing preeclampsia. It may also lower the risks of IUGR, preterm birth, and NICU admissions in neonates. Further research into combining these markers and treatments could pave the way for more effective prevention and management strategies for preeclampsia.

2.a) In our meta-analysis we found that pravastatin therapy administrated before the 20th gestational week lowers the incidence of preeclampsia by 61%.

2.b) In our meta-analysis we found that pravastatin therapy administrated before the 20th gestational week lowers the incidence of IUGR by 45%.

2.c) In our meta-analysis we found that pravastatin therapy administrated before the 20th gestational week lowers the incidence of NICU admissions by 77%.

2.d) In our meta-analysis we found that pravastatin therapy administrated before the 20th gestational week lowers the incidence of preterm-births by 68%.

2.e) It is also important that in the studies that were evaluated we found no evidence of fetal adverse effects and found only mild maternal adverse effects (e.g. headache or mild muscular pain).

Further research into combining these markers and treatments could pave the way for more effective prevention and management strategies for preeclampsia.

7. SUMMARY

The objective of my PhD work was to evaluate novel screening methods and treatments for preeclampsia, focusing on identifying predictive markers like the neutrophil-to-lymphocyte ratio (NLR) through meta-analyses and exploring the efficacy of pravastatin in preventing and treating the condition. By conducting these studies, I aimed to improve early detection and develop potential preventive strategies for high-risk patients.

For the NLR analysis, six studies were selected, encompassing a total of 2,469 patients. The meta-analysis revealed an effect size with a 95% confidence interval (CI) ranging from 0.641 to 1.523, and a prediction interval from 0.027 to 2.137.

For the evaluation of pravastatin, fourteen studies were identified, including 1,570 pregnant women who were administered either pravastatin or a placebo. Among these, five studies were included in the meta-analysis to assess the impact of pravastatin use before 20 weeks of gestation. The results indicated that pravastatin treatment led to a 61% reduction in the incidence of preeclampsia, a 68% decrease in premature births, a 45% reduction in IUGR among the newborns, and a 77% reduction in neonatal intensive care unit (NICU) admissions.

8. REFERENCES

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018 Jul;72(1):24–43.

2. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ. 2019 Sep 9;l5119.

3. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013 Nov 7;347(nov07 15):f6564–f6564.

4. Steegers EA, Von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. The Lancet. 2010 Aug;376(9741):631–44.

5. Ma'ayeh M, Rood KM, Kniss D, Costantine MM. Novel Interventions for the Prevention of Preeclampsia. Curr Hypertens Rep. 2020 Feb 12;22(2):17.

6. Than NG, Romero R, Györffy D, Posta M, Bhatti G, Done B, et al. Molecular subclasses of preeclampsia characterized by a longitudinal maternal proteomics study: distinct biomarkers, disease pathways and options for prevention. J Perinat Med. 2023;51(1):51–68.

7. Banerjee S, Huang Z, Wang Z, Nakashima A, Saito S, Sharma S, et al. Etiological Value of Sterile Inflammation in Preeclampsia: Is It a Non-Infectious Pregnancy Complication? Front Cell Infect Microbiol. 2021;11:694298.

8. Zeng H, Han X, Zhu Z, Yu S, Mei S, Cheng X, et al. Increased uterine NLRP3 inflammasome and leucocyte infiltration in a rat model of preeclampsia. Am J Reprod Immunol N Y N 1989. 2021;86(6):e13493.

9. Justesen MM, Jakobsen KK, Bendtsen SK, Garset-Zamani M, Mordhorst C, Carlander ALF, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio as a Prognostic Marker for the Outcome of HPV-Positive and HPV-Negative Oropharyngeal Squamous Cell Carcinoma. Viruses. 2023;15(1):198.

10. Ren Z, Yang J, Liang J, Xu Y, Lu G, Han Y, et al. Monitoring of postoperative neutrophil-to-lymphocyte ratio, D-dimer, and CA153 in: Diagnostic value for recurrent and metastatic breast cancer. Front Surg. 2023 Jan 6;9:927491.

11. Seng JJB, Kwan YH, Low LL, Thumboo J, Fong WSW. Role of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) in assessing disease control in Asian patients with axial spondyloarthritis. Biomark Biochem Indic Expo Response Susceptibility Chem. 2018;23(4):335–8.

12. Seringec Akkececi N, Yildirim Cetin G, Gogebakan H, Acipayam C. The C-Reactive Protein/Albumin Ratio and Complete Blood Count Parameters as Indicators of Disease Activity in Patients with Takayasu Arteritis. Med Sci Monit. 2019 Feb 22;25:1401–9.

13. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. Ann Lab Med. 2019 Jul;39(4):345–57.

14. Wang L, Wang C, Jia X, Yang M, Yu J. Relationship between Neutrophil-to-Lymphocyte Ratio and Systemic Lupus Erythematosus: A Meta-analysis. Clin Sao Paulo Braz. 2020;75:e1450.

15. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol. 2016 May 3;26(3):372–6.

16. Sisti G, Faraci A, Silva J, Upadhyay R. Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Routine Complete Blood Count Components in HELLP Syndrome: A Matched Case Control Study. Medicina (Mex). 2019 May 8;55(5):123.

17. Christoforaki V, Zafeiriou Z, Daskalakis G, Katasos T, Siristatidis C. First trimester neutrophil to lymphocyte ratio (NLR) and pregnancy outcome. J Obstet Gynaecol J Inst Obstet Gynaecol. 2020;40(1):59–64.

18. Hessami K, Tabrizi R, Homayoon N, Hashemi A, Heydari ST, Pourhoseini SA. Gestational diabetes mellitus and inflammatory biomarkers of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio: a systematic review and meta-analysis. Biomarkers. 2021 Aug 18;26(6):491–8.

19. Kang Q, Li W, Yu N, Fan L, Zhang Y, Sha M, et al. Predictive role of neutrophil-to-lymphocyte ratio in preeclampsia: A meta-analysis including 3982 patients. Pregnancy Hypertens. 2020 Apr;20:111–8.

20. Tsai ER, Tintu AN, Demirtas D, Boucherie RJ, De Jonge R, De Rijke YB. A critical review of laboratory performance indicators. Crit Rev Clin Lab Sci. 2019 Oct 3;56(7):458–71.
21. Thomas RE, Vaska M, Naugler C, Turin TC. Interventions at the laboratory level to reduce laboratory test ordering by family physicians: Systematic review. Clin Biochem. 2015;48(18):1358–65.
22. Mikhailidis DP, Athyros VG. New statin guidelines and promising novel therapeutics. Nat Rev Cardiol. 2014 Feb;11(2):72–4.
23. Smith DD, Costantine MM. The role of statins in the prevention of preeclampsia. Am J Obstet Gynecol. 2022 Feb;226(2S):S1171–81.
24. Pánczél Z, Kukor Z, Supák D, Kovács B, Kecskeméti A, Czizel R, et al. Pravastatin induces NO synthesis by enhancing microsomal arginine uptake in healthy and preeclamptic placentas. BMC Pregnancy Childbirth. 2019 Dec;19(1):426.
25. Pánczél Z, Supák D, Kovács B, Kukor Z, Valent S. A pravasztatin hatása tetrahidrobiopterin-érzékeny és -rezisztens praeeclampsiás placenták NO-szintáz-aktivitására. Orv Hetil. 2020 Mar;161(10):389–95.
26. Braszak-Cymerman A, Walczak MK, Oduah MT, Ludziejewska A, Bryl W. Comparison of the pleiotropic effect of atorvastatin and rosuvastatin on postmenopausal changes in bone turnover: A randomized comparative study. Medicine (Baltimore). 2024 May 10;103(19):e38122.
27. Edison RJ, Muenke M. Central Nervous System and Limb Anomalies in Case Reports of First-Trimester Statin Exposure. N Engl J Med. 2004 Apr 8;350(15):1579–82.
28. Chang JC, Chen YJ, Chen IC, Lin WS, Chen YM, Lin CH. Perinatal Outcomes After Statin Exposure During Pregnancy. JAMA Netw Open. 2021 Dec 30;4(12):e2141321.
29. Vahedian-Azimi A, Bianconi V, Makvandi S, Banach M, Mohammadi SM, Pirro M, et al. A systematic review and meta-analysis on the effects of statins on pregnancy outcomes. Atherosclerosis. 2021 Nov;336:1–11.
30. De Alwis N, Beard S, Mangwiro YT, Binder NK, Kaitu'u-Lino TJ, Brownfoot FC, et al. Pravastatin as the statin of choice for reducing pre-eclampsia-associated endothelial dysfunction. Pregnancy Hypertens. 2020 Apr;20:83–91.

31. Alasztics B, Kukor Z, Pánczél Z, Valent S. The pathophysiology of preeclampsia in view of the two-stage model. Orv Hetil. 2012 Jul;153(30):1167–76.

32. Kukor Z, Valent S. Nitric oxide and preeclampsia. Orv Hetil. 2010 Dec 1;151(52):2125–35.

33. Taysi S, Tascan AS, Ugur MG, Demir M. Radicals, Oxidative/Nitrosative Stress and Preeclampsia. Mini-Rev Med Chem. 2019 Jan 11;19(3):178–93.

34. Salsoso R, Guzmán-Gutiérrez E, Sáez T, Bugueño K, Ramírez MA, Farías M, et al. Insulin restores l-arginine transport requiring adenosine receptors activation in umbilical vein endothelium from late-onset preeclampsia. Placenta. 2015 Mar;36(3):287–96.

35. Brownfoot FC, Tong S, Hannan NJ, Hastie R, Cannon P, Kaitu'u-Lino TJ. Effects of simvastatin, rosuvastatin and pravastatin on soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG) secretion from human umbilical vein endothelial cells, primary trophoblast cells and placenta. BMC Pregnancy Childbirth. 2016 Dec;16(1):117.

36. Chigusa Y, Kawasaki K, Kondoh E, Mogami H, Ujita M, Fujita K, et al. Simvastatin inhibits oxidative stress via the activation of nuclear factor erythroid 2-related factor 2 signaling in trophoblast cells. J Obstet Gynaecol Res. 2016 Jan;42(1):36–43.

37. Dong X, Shi D. Simvastatin Alleviates Pathology in a Rat Model of Preeclampsia Involving ERK/MAPK Pathway. Reprod Sci. 2017 Jul;24(7):1053–61.

38. Csomó K, Belik A, Hrabák A, Kovács B, Fábián O, Valent S, et al. Effect of Pravastatin and Simvastatin on the Reduction of Cytochrome C. J Pers Med. 2022 Jul 10;12(7):1121.

39. Bauer AJ, Banek CT, Needham K, Gillham H, Capoccia S, Regal JF, et al. Pravastatin attenuates hypertension, oxidative stress, and angiogenic imbalance in rat model of placental ischemia-induced hypertension. Hypertens Dallas Tex 1979. 2013 May;61(5):1103–10.

40. Esteve-Valverde E, Ferrer-Oliveras R, Gil-Aliberas N, Baraldès-Farré A, Llurba E, Alijotas-Reig J. Pravastatin for Preventing and Treating Preeclampsia: A Systematic Review. Obstet Gynecol Surv. 2018 Jan;73(1):40–55.

41. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

42. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008–12.

43. Wells, G, Shea, BJ, O'Connell, D, Peterson, J, Welch, V, Losos, M, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute (2014) http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

44. Higgins, JPT, Li, T, and Deeks, JJ. Chapter 6: choosing effect measures and computing estimates of effect In: JPT Higgins, J Thomas, J Chandler, M Cumpston, T Li, and MJ Page, et al., editors. Cochrane handbook for systematic reviews of interventions : Cochrane (2020) Available at: www.training.cochrane.org/handbook.

45. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med. 2003 Sep 15;22(17):2693–710.

46. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014 Dec;14(1):25.

47. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016 Mar;7(1):55–79.

48. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539–58.

49. IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016 Jul;6(7):e010247.

50. Harrer M, Cuijpers P, Furukawa T, Ebert D. Doing meta-analysis with R: a hands-on guide. Boca Raton: Chapman and Hall/CRC; 2021.

51. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Res Synth Methods. 2010 Apr;1(2):112–25.

52. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.

53. R Core Team (2021) R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. https://www.R-project.org/.

54. Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R [Internet]. Cham: Springer International Publishing; 2015 [cited 2024 Dec 23]. (Use R!). Available from: https://link.springer.com/10.1007/978-3-319-21416-0

55. Cuijpers P, Furukawa T, Ebert DD (2021) Dmetar: companion R Package for the guide doing meta-analysis in R. https://dmetar.protectlab.org.

56. J. Sweeting M, J. Sutton A, C. Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351–75.

57. Paule RC, Mandel J. Consensus Values and Weighting Factors. J Res Natl Bur Stand. 1982 Sep;87(5):377.

58. Bulbul M, Uckardes F, Karacor T, Nacar MC, Kaplan S, Kirici P, et al. Can complete blood count parameters that change according to trimester in pregnancy be used to predict severe preeclampsia? J Obstet Gynaecol. 2021 Nov 17;41(8):1192–8.

59. Oğlak SC, Tunç Ş, Ölmez F. First Trimester Mean Platelet Volume, Neutrophil to Lymphocyte Ratio, and Platelet to Lymphocyte Ratio Values Are Useful Markers for Predicting Preeclampsia. Ochsner J. 2021;21(4):364–70.

60. Kirbas A, Ersoy AO, Daglar K, Dikici T, Biberoglu EH, Kirbas O, et al. Prediction of Preeclampsia by First Trimester Combined Test and Simple Complete Blood Count Parameters. J Clin Diagn Res JCDR. 2015;9(11):QC20-23.

61. Gezer C, Ekin A, Ertas IE, Ozeren M, Solmaz U, Mat E, et al. High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. Ginekol Pol. 2016;87(6):431–5.

62. Mannaerts D, Faes E, Goovaerts I, Stoop T, Cornette J, Gyselaers W, et al. Flow-mediated dilation and peripheral arterial tonometry are disturbed in preeclampsia and reflect different aspects of endothelial function. Am J Physiol-Regul Integr Comp Physiol. 2017 Nov 1;313(5):R518–25.

63. The role of hematological and biochemical markers in preeclampsia prediction. Ann Clin Anal Med [Internet]. 2017 [cited 2025 Jan 22];08(Suppl_4). Available from:

https://onedrive.live.com/?authkey=%21AEjTgnLqsiMaBeo&cid=A67EA0773797D3EC&id=A67EA0773797D3EC%215218&parId=A67EA0773797D3EC%215206&o=OneUp

64. Nagyistók L. Pravastatin kezelés hatása preeclampsiás terhességekben – metaanalízis. Orvosképzés. (2020) 2:418.

65. Costantine MM, Cleary K, Hebert MF, Ahmed MS, Brown LM, Ren Z, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol. 2016 Jun;214(6):720.e1-720.e17.

66. Costantine MM, West H, Wisner KL, Caritis S, Clark S, Venkataramanan R, et al. A randomized pilot clinical trial of pravastatin versus placebo in pregnant patients at high risk of preeclampsia. Am J Obstet Gynecol. 2021 Dec;225(6):666.e1-666.e15.

67. Akbar MIA, Yosediputra A, Pratama RE, Fadhilah NL, Sulistyowati S, Amani FZ, et al. INOVASIA Study: A Randomized Open Controlled Trial to Evaluate Pravastatin to Prevent Preeclampsia and Its Effects on sFlt1/PlGF Levels. Am J Perinatol. 2024 Feb;41(3):300–9.

68. Akbar MIA, Azis MA, Riu DS, Wawengkang E, Ernawati E, Bachnas MA, et al. INOVASIA Study: A Multicenter Randomized Clinical Trial of Pravastatin to Prevent Preeclampsia in High-Risk Patients. Am J Perinatol. 2024 Jul;41(9):1203–11.

69. Kupferminc MJ, Kliger C, Rimon E, Asher-Landsberg J, Skornick-Rapaport A, Gamzu R, et al. Pravastatin is useful for prevention of recurrent severe placenta-mediated complications - a pilot study. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2022;35(25):8055–61.

70. Lefkou E, Mamopoulos A, Dagklis T, Vosnakis C, Rousso D, Girardi G. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J Clin Invest. 2016 Jul 25;126(8):2933–40.

71. Döbert M, Varouxaki AN, Mu AC, Syngelaki A, Ciobanu A, Akolekar R, et al. Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia. Circulation. 2021 Aug 31;144(9):670–9.

72. Mendoza M, Ferrer-Oliveras R, Bonacina E, Garcia-Manau P, Rodo C, Carreras E, et al. Evaluating the Effect of Pravastatin in Early-Onset Fetal Growth Restriction: A

Nonrandomized and Historically Controlled Pilot Study. Am J Perinatol. 2021;38(14):1472–9.

73. Ahmed A, Williams D, Cheed V, Middleton L, Ahmad S, Wang K, et al. Pravastatin for early-onset pre-eclampsia: a randomised, blinded, placebo-controlled trial. BJOG Int J Obstet Gynaecol. 2020 Mar;127(4):478–88.

74. Lefkou E, Varoudi K, Pombo J, Jurisic A, Jurisic Z, Contento G, et al. Triple therapy with pravastatin, low molecular weight heparin and low dose aspirin improves placental haemodynamics and pregnancy outcomes in obstetric antiphospholipid syndrome in mice and women through a nitric oxide-dependent mechanism. Biochem Pharmacol. 2020 Dec;182:114217.

75. Jurisic A, Jurisic Z, Lefkou E, Girardi G. Pravastatin plus L-arginine prevents adverse pregnancy outcomes in women with uteroplacental vascular dysfunction. Vascul Pharmacol. 2021 Apr;137:106824.

76. Lefkou E, Mamopoulos A, Fragakis N, Dagklis T, Vosnakis C, Nounopoulos E, et al. Clinical Improvement and Successful Pregnancy in a Preeclamptic Patient With Antiphospholipid Syndrome Treated With Pravastatin. Hypertension [Internet]. 2014 May [cited 2025 Jan 22];63(5). Available from: https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.114.03115

77. Brownfoot FC, Tong S, Hannan NJ, Binder NK, Walker SP, Cannon P, et al. Effects of Pravastatin on Human Placenta, Endothelium, and Women With Severe Preeclampsia. Hypertension. 2015 Sep;66(3):687–97.

78. Saito J, Kaneko K, Abe S, Yakuwa N, Kawasaki H, Suzuki T, et al. Pravastatin concentrations in maternal serum, umbilical cord serum, breast milk and neonatal serum during pregnancy and lactation: A case study. J Clin Pharm Ther. 2022 May;47(5):703–6.

79. Vilotić A, Nacka-Aleksić M, Pirković A, Bojić-Trbojević Ž, Dekanski D, Jovanović Krivokuća M. IL-6 and IL-8: An Overview of Their Roles in Healthy and Pathological Pregnancies. Int J Mol Sci. 2022;23(23):14574.

80. Walsh SW, Nugent WH, Archer KJ, Al Dulaimi M, Washington SL, Strauss JF. Epigenetic Regulation of Interleukin-17-Related Genes and Their Potential Roles in Neutrophil Vascular Infiltration in Preeclampsia. Reprod Sci. 2022 Jan;29(1):154–62.

81. Bellos I, Karageorgiou V, Kapnias D, Karamanli KE, Siristatidis C. The role of interleukins in preeclampsia: A comprehensive review. Am J Reprod Immunol N Y N 1989. 2018;80(6):e13055.

82. Arici A, Seli E, Senturk LM, Gutierrez LS, Oral E, Taylor HS. Interleukin-8 in the human endometrium. J Clin Endocrinol Metab. 1998 May;83(5):1783–7.

83. Matsubara K, Ochi H, Kitagawa H, Yamanaka K, Kusanagi Y, Ito M. Concentrations of serum granulocyte-colony-stimulating factor in normal pregnancy and preeclampsia. Hypertens Pregnancy. 1999;18(1):95–106.

84. Hayashi M, Hamada Y, Ohkura T. Elevation of granulocyte-macrophage colony-stimulating factor in the placenta and blood in preeclampsia. Am J Obstet Gynecol. 2004 Feb;190(2):456–61.

85. Inoue Y, Fujishima M, Ono M, Masuda J, Ozaki Y, Maeda T, et al. Clinical significance of the neutrophil-to-lymphocyte ratio in oligometastatic breast cancer. Breast Cancer Res Treat. 2022;196(2):341–8.

86. Lin N, Li J, Yao X, Zhang X, Liu G, Zhang Z, et al. Prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer liver metastasis: A meta-analysis of results from multivariate analysis. Int J Surg. 2022 Nov;107:106959.

87. Huang Q tao, Zhou L, Zeng W juan, Ma Q qian, Wang W, Zhong M, et al. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Ovarian Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Cell Physiol Biochem. 2017;41(6):2411–8.

88. Zeng Z, Wang C, Wang B, Wang N, Yang Y, Guo S, et al. Prediction of neutrophil-to-lymphocyte ratio in the diagnosis and progression of autoimmune encephalitis. Neurosci Lett. 2019 Feb 16;694:129–35.

89. Aktas G, Sit M, Dikbas O, Erkol H, Altinordu R, Erkus E, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. Rev Assoc Medica Bras 1992. 2017;63(12):1065–8.

90. Aydin Güzey N, Uyar Türkyilmaz E. Evaluation of 254 cesarean sections with COVID-19 in terms of anesthesia and clinical course: 1-year experience. J Anesth. 2022;36(4):514–23.

91. Lasser DM, Chervenak J, Moore RM, Li T, Knight C, Teo HO, et al. Severity of COVID-19 Respiratory Complications during Pregnancy are Associated with Degree of

Lymphopenia and Neutrophil to Lymphocyte Ratio on Presentation: A Multicenter Cohort Study. Am J Perinatol. 2021 Oct;38(12):1236–43.

92. Supák D, Mészáros B, Nagy M, Gáspár D, Wagner LJ, Kukor Z, et al. Case report: COVID-19 infection in a pregnant 33-year-old kidney transplant recipient. Front Med. 2022;9:948025.

93. Ozimek JA, Kilpatrick SJ. Maternal Mortality in the Twenty-First Century. Obstet Gynecol Clin North Am. 2018 Jun;45(2):175–86.

94. Bossman E, Johansen MA, Zanaboni P. mHealth interventions to reduce maternal and child mortality in Sub-Saharan Africa and Southern Asia: A systematic literature review. Front Glob Womens Health. 2022;3:942146.

95. Von Dadelszen P, Firoz T, Donnay F, Gordon R, Justus Hofmeyr G, Lalani S, et al. Preeclampsia in Low and Middle Income Countries—Health Services Lessons Learned From the PRE-EMPT (PRE-Eclampsia–Eclampsia Monitoring, Prevention & Treatment) Project. J Obstet Gynaecol Can. 2012 Oct;34(10):917–26.

96. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. The Lancet. 2006 Apr;367(9516):1066–74.

97. Zhang J, Zeng J, Zhang L, Yu X, Guo J, Li Z. The Utility of Peripheral Blood Leucocyte Ratios as Biomarkers in Neonatal Sepsis: A Systematic Review and Meta-Analysis. Front Pediatr. 2022;10:908362.

98. Bokslag A, van Weissenbruch M, Mol BW, de Groot CJM. Preeclampsia; short and long-term consequences for mother and neonate. Early Hum Dev. 2016;102:47–50.

99. Ma'ayeh M, Costantine MM. Prevention of preeclampsia. Semin Fetal Neonatal Med. 2020 Oct;25(5):101123.

100. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016 Apr 19;i1753.

101. Hamzah STR, Aminuddin null, Idris I, Rachmat M. Antenatal care parameters that are the risk factors in the event of preeclampsia in primigravida. Gac Sanit. 2021;35 Suppl 2:S263–7.

102. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, 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 Off Organ Int Fed Gynaecol Obstet. 2019 May;145 Suppl 1(Suppl 1):1–33.

103. Kay VR, Wedel N, Smith GN. Family History of Hypertension, Cardiovascular Disease, or Diabetes and Risk of Developing Preeclampsia: A Systematic Review. J Obstet Gynaecol Can. 2021 Feb;43(2):227-236.e19.

104. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. Obstet Gynecol. 2020 Jun;135(6):1492–5.

105. MacDonald TM, Walker SP, Hannan NJ, Tong S, Kaitu'u-Lino TJ. Clinical tools and biomarkers to predict preeclampsia. eBioMedicine. 2022 Jan;75:103780.

106. Skråstad RB, Hov GG, Blaas HK, Romundstad PR, Salvesen KÅ. A prospective study of screening for hypertensive disorders of pregnancy at 11–13 weeks in a Scandinavian population. Acta Obstet Gynecol Scand. 2014 Dec;93(12):1238–47.

107. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019 Mar 29;124(7):1094–112.

108. Lin T, Huang H, Chan K, Chen Y, Chu F, Shaw SW. Current update of first trimester preeclampsia screening in Asia. J Obstet Gynaecol Res. 2021 Jan;47(1):26–33.

109. Acestor N, Goett J, Lee A, Herrick TM, Engelbrecht SM, Harner-Jay CM, et al. Towards biomarker-based tests that can facilitate decisions about prevention and management of preeclampsia in low-resource settings. Clin Chem Lab Med CCLM [Internet]. 2016 Jan 1 [cited 2025 Jan 22];54(1). Available from: https://www.degruyter.com/document/doi/10.1515/cclm-2015-0069/html

110. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021 Sep 28;326(12):1192.

111. Cruz-Lemini M, Vázquez JC, Ullmo J, Llurba E. Low-molecular-weight heparin for prevention of preeclampsia and other placenta-mediated complications: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022 Feb;226(2):S1126-S1144.e17.

112. Khaing W, Vallibhakara SAO, Tantrakul V, Vallibhakara O, Rattanasiri S, McEvoy M, et al. Calcium and Vitamin D Supplementation for Prevention of

Preeclampsia: A Systematic Review and Network Meta-Analysis. Nutrients. 2017 Oct 18;9(10):1141.

9. BIBLIOGRAPHY OF PUBLICATIONS

Publications related to the thesis:

1. Mészáros B, Veres DS, Nagyistók L, et al. Pravastatin in preeclampsia: A meta-analysis and systematic review. Front Med (Lausanne). 2023;9:1076372. Published 2023 Jan 13. doi:10.3389/fmed.2022.1076372
2. Mészáros B, Veres DS, Nagyistók L, Kovács BG, Kukor Z, Valent S. A meta-analysis on first-trimester blood count parameters-is the neutrophil-to-lymphocyte ratio a potentially novel method for first-trimester preeclampsia screening?. Front Med (Lausanne). 2024;11:1336764. Published 2024 Apr 3. doi:10.3389/fmed.2024.1336764

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Publications not related to the thesis:

1. Supák D, Mészáros B, Nagy M, et al. Case report: COVID-19 infection in a pregnant 33-year-old kidney transplant recipient. Front Med (Lausanne). 2022;9:948025. Published 2022 Aug 30. doi:10.3389/fmed.2022.948025
2. Mészáros B, Kukor Z, Valent S. Recent Advances in the Prevention and Screening of Preeclampsia. J Clin Med. 2023;12(18):6020. Published 2023 Sep 17. doi:10.3390/jcm12186020
3. Supák D, Mészáros B, Turi B, Herold Z, Kukor Z, Valent S. Predicting Potentially Fatal COVID-19 Disease in Pregnant Patients Using the Neutrophil-to-Lymphocyte Ratio (NLR). J Clin Med. 2023;12(21):6896. Published 2023 Nov 2. doi:10.3390/jcm12216896
4. Kovács BG, Asbóth G, Supák D, et al. Inositol-Exchange Activity in Human Primordial Placenta. Int J Mol Sci. 2024;25(6):3436. Published 2024 Mar 19. doi:10.3390/ijms25063436
5. Supák D, Turi B, Kovács BG, et al. A normáltartományban maradó NLR (neutrophil-lymphocyta arány) prediktív értéke a várandósság alatt jelentkező SARS-CoV-2-fertőzésben [The predictive value of normal-range NLR (neutrophil-to-lymphocyte ratio) in SARS-CoV-2 infection during pregnancy].

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