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Systematic Reviews and Meta- and Pooled Analyses

Maternal Hyperlipidemia and the Risk of Preeclampsia: A Meta-Analysis

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Published reports examining lipid levels during pregnancy and preeclampsia have been inconsistent. The objective of this meta-analysis was to test the association between preeclampsia and maternal total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and triglyceride levels measured during pregnancy. We conducted a systematic search for studies published between the index date until July 2013 reporting maternal lipid levels in women with preeclampsia and normotensive pregnant women. Seventy-four studies met all eligibility criteria and were included in the meta-analysis. Weighted mean differences in lipid levels were calculated using a random-effects model. Statistical heterogeneity was investigated using the I^2 statistic. Meta-regression was used to identify sources of heterogeneity. Preeclampsia was associated with elevated total cholesterol, non-HDL-C, and triglyceride levels, regardless of gestational age at the time of blood sampling, and with lower levels of HDL-C in the third trimester. A marginal association was found with LDL-C levels. Statistical heterogeneity was detected in all analyses. Meta-regression analyses suggested that differences in body mass index (weight (kg)/height $(m)^2$) across studies may be partially responsible for the heterogeneity in the triglyceride and LDL-C analyses. This systematic review and meta-analysis demonstrates that women who develop preeclampsia have elevated levels of total cholesterol, non-HDL-C, and triglycerides during all trimesters of pregnancy, as well as lower levels of HDL-C during the third trimester.

body mass index; cholesterol; hyperlipidemia; hypertriglyceridemia; meta-analysis; preeclampsia; systematic review; triglycerides

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; SE, standard error; WMD, weighted mean difference.

Preeclampsia is a potentially devastating disease of pregnancy that complicates 2%–8% of all pregnancies in the United States and can threaten the life of both the mother and her unborn child (1, 2). Manifesting after 20 weeks of gestation, preeclampsia is a multiorgan disorder defined as de novo hypertension (systolic blood pressure ≥140 mm Hg; diastolic blood pressure ≥90 mm Hg) combined with proteinuria (≥300 mg/24 hours), as defined by the American Congress of Obstetricians and Gynecologists (3). Without intervention, the mother is at substantial risk for seizures (eclampsia), renal and liver failure, pulmonary edema, stroke, and death (1). For the fetus, preeclampsia poses increased risks of intrauterine growth restriction, prematurity, and death (4). Preeclampsia is also recognized as a major risk factor for cardiovascular disease later in life for both the woman and her child (5). Despite considerable research, the only effective treatment for preeclampsia is to deliver the baby, placenta, and all products of conception (4).

Maternal endothelial dysfunction is a classic hallmark of preeclampsia (6). Many markers of endothelial dysfunction have been reported in preeclamptic women, including an imbalance of anticoagulation and procoagulation factors and increased levels of fibronectin, endothelial cell adhesion molecules, and other factors in the coagulation cascade (7). Increased levels of circulating lipids result in their accumulation within endothelial cells. This accumulation decreases the

release of prostacyclin, resulting in oxidative stress via endothelial dysfunction (8), a key mechanism in the proposed pathophysiology of preeclampsia (9).

Recently, a meta-analysis was performed on studies evaluating the relationship between maternal serum triglyceride levels and preeclampsia, and the authors found that women with preeclampsia had significantly higher levels of triglycerides than normotensive women (10). Although numerous studies suggest that a dyslipidemic pattern of increased total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C), along with decreased high-density lipoprotein cholesterol (HDL-C) concentrations may be associated with an increased risk of preeclampsia, results are inconsistent (11–15). Many of these studies have had small sample sizes, and the gestational age at the time of the lipid measurements has varied, making it difficult to compare findings across studies. The relationship between preeclampsia and non-HDL-C, a lipid measurement reflecting atherogenic, triglyceride-rich lipoproteins (approximately 75% of which are LDL-C) (16), has not often been evaluated. Thus, we conducted a systematic review and meta-analysis to examine the associations of total cholesterol, LDL-C, HDL-C, and non-HDL-C during pregnancy with the subsequent risk of preeclampsia and to confirm associations reported in a previous meta-analysis of triglyceride levels using more recent studies and a broader search strategy. Subgroup analyses focusing on potential differences between lipid levels in both the mild and severe forms of preeclampsia are also presented.

METHODS

Search strategy

This study consisted of a systematic literature review followed by a meta-analysis, both conducted taking into account the Meta-analysis of Observational Studies in Epidemiology: a Proposal for Reporting Criteria and Preferred Reporting Items for Systematic Reviews and Meta-analyses group guidelines (17, 18). A systematic literature search of eligible studies was conducted in the PubMed/MEDLINE and Scopus databases from the index date through July 2013 for studies evaluating the association between lipid levels during pregnancy and preeclampsia using the following search strategy: (“preeclampsia” OR “eclampsia” OR “toxemia” OR “pregnancy-induced hypertension” OR “gestational hypertension”) AND (“cholesterol” OR “lipid” OR “HDL” OR “LDL” OR “triglycerides” OR “dyslipidemia” OR “hyperlipidemia” OR “hypertriglyceridemia”). The search was not restricted by language, and no limits or filters were placed on the search to ensure maximal sensitivity. References from these publications were also manually searched for potentially relevant citations not detected by the electronic search. A research librarian assisted in creating the most efficient and effective search strategy possible.

Study selection

Records identified from the literature search were screened for duplicates. Titles and abstracts were screened, and potentially relevant articles were selected for full-text review. Studies were considered for inclusion in our meta-analysis if they met the following criteria: 1) an original study that examined the association between lipid levels during pregnancy and preeclampsia; 2) raw lipid levels presented as a group mean with either a standard error or standard deviation or as a median with the 95% confidence interval; and 3) a proper control group of normotensive pregnant women.

Data abstraction

Full manuscripts were obtained for studies that appeared to examine lipid levels in women with preeclampsia. Full-text review was performed by 2 independent investigators (C.N.S. and C.J.S.) using a piloted data abstraction form and resulting in 91% concordance. Information collected included study characteristics (author, year of publication, study location, dates, and design); participant characteristics (definitions of the preeclampsia and control groups, diagnostic criteria, mean age, mean prepregnancy body mass index (BMI) (weight (kg)/height $(m)^2$), and mean gestational age at blood sampling); lipid measurements (mean or median, along with standard error (SE), standard deviation (SD), or 95% confidence interval (CI)); number of subjects in each group; and statistical significance for tests between the groups). Inconsistencies between the 2 reviewers were adjudicated by a third, independent reviewer (K.K.R.).

Quality assessment

The quality assessment was performed by applying the Newcastle-Ottawa Scale (19). In tailoring the scale to fit this study, we took into account the sampling methods of the studies and the similarities between the study groups on age and BMI, exposure and outcome ascertainment, and study design. Our abstracting instrument included a total of 8 questions with 11 points possible. While abstracting the data for the meta-analysis, C.N.S. and C.J.S. independently performed the quality assessment. Overall, the publications were classified as high quality (scoring $\geq$5 points) or low quality (scoring <5 points). Only studies scoring 5 or more points were included, ensuring only high-quality research articles were included in this meta-analysis.

Data synthesis and analysis

Lipid measurements originally reported in millimolars were converted to milligrams per deciliter. When standard errors for the means were provided, they were converted to standard deviations. Because our meta-regression results suggest that variation in trimester of lipid measurement is a potential source of heterogeneity, studies were categorized by trimester on the basis of the mean gestational age reported at blood sampling. First, second, and third trimesters were defined as 1–13, 14–26, and 27 or more weeks, respectively. Blood collection times that overlapped 2 trimesters were classified as the latter of the 2 trimesters. Because of the low number of studies with lipid measurements in the first trimester, the first and second trimesters were combined for all analyses. If measured non-HDL-C was not available, non-HDL-C was calculated as total cholesterol minus HDL-C (20).

Lipid levels among women with preeclampsia and healthy pregnant controls were compared by calculating weighted mean differences (WMDs) and 95% confidence intervals, stratified by trimester of lipid measurement. Because significant heterogeneity was observed in all comparisons ($P < 0.05$), random-effects models were used to allow for the inherent heterogeneity found between studies (21). We also performed similar meta-analyses stratified by preeclampsia severity. Statistical heterogeneity was assessed using the Mantel-Haenszel Q statistic and the I^2 statistic. An I^2 value of more than 50% is considered moderate heterogeneity, and an I^2 value greater than 75% is considered high heterogeneity. Random-effects meta-regression analyses were conducted to assess whether BMI, trimester of blood sampling, and fasting blood sampling status were acting as potential modifiers of the association between maternal lipid levels and preeclampsia, causing the observed high level of heterogeneity. Possible publication bias was evaluated using funnel plots and the Egger test. All statistical analyses were 2-sided and were performed using Stata, version 9.0, software (StataCorp LP, College Station, Texas).

RESULTS

Literature search

Results from our search strategy are summarized in Figure 1. We identified 3,993 publications. Of these, 898 were duplicates between the 2 databases, and an additional 2,823 were excluded on the basis of review of their titles and abstracts. The remaining 141 articles were eligible for abstraction. After reviewing the full texts, we excluded an additional 67 articles. The most common reason for exclusion after full-text review was the inability to obtain or extract the data necessary for analysis. Sixteen studies were excluded on the basis of their low quality scores (<5 points). Six studies using the same patient data were identified (22–28). To ensure the data were represented only once, we excluded 5 of the studies from the analysis (22, 24, 25, 27, 28). In addition, because we intended to stratify the analysis on the basis of trimester of triglyceride measurement, we also excluded 5 studies that did not report the gestational age at the time of blood sampling. After final exclusions, 74 original articles were included in our meta-analyses: 64 for total cholesterol, 60 for HDL-C, 54 for LDL-C, 70 for triglycerides, and 46 for non-HDL-C. Flow diagrams for the studies included in the subgroup analyses of preeclampsia severity are provided in Web Figures 1–4, available at http://aje.oxfordjournals.org/.

Study characteristics

The studies that met the eligibility criteria for inclusion in the main preeclampsia meta-analysis examined a total of 7,369 participants—1,975 women with preeclampsia and 5,394 healthy pregnant women. Studies that evaluated lipid levels by severity of preeclampsia (for severe preeclampsia, $n = 19$; for mild preeclampsia, $n = 15$) included 568 women with severe preeclampsia compared with 1,004 normotensive pregnant controls, as well as 427 women with mild preeclampsia compared with 667 normotensive healthy pregnant women. Characteristics of the studies included in the meta-analyses are shown in Table 1. The 73 included studies were conducted in Asia (52%), Europe (25%), and North America (10%) with sample sizes ranging from 20 to 1,000 pregnant women. The majority of the included studies measured serum lipid levels during the third trimester, and fasting measurements were obtained in 62% of the studies. Within each study, controls were commonly matched to women with preeclampsia on maternal age, gestational age at blood sampling, and/or maternal BMI. In preeclamptic women, mean lipid levels ranged from 162–345 mg/dL, 29–79 mg/dL, 116–300 mg/dL, 96–197 mg/dL, and 100–436 mg/dL for total cholesterol, HDL-C, non-HDL-C, LDL-C, and triglycerides, respectively. In normotensive women, values ranged from 111–317 mg/dL, 33–93 mg/dL, 90–243 mg/dL, 96–197 mg/dL, and 111–269 mg/dL for total cholesterol, HDL-C, non-HDL-C, LDL-C, and triglycerides, respectively. Characteristics of the studies included in the subanalyses of severe and mild preeclampsia can be found in Web Table 1.

Meta-analyses

Results from the WMD meta-analyses of lipid measurements during pregnancy and preeclampsia are presented in Table 2. Total cholesterol levels measured in the first or second trimester were significantly higher in women who developed preeclampsia than in normotensive pregnant women (WMD = 12.49 mg/dL, 95% CI: 3.44, 21.54). Total cholesterol levels measured in the third trimester were also significantly higher in preeclamptic women compared with normotensive pregnant women (WMD = 20.20 mg/dL, 95% CI: 8.70, 31.70). Although no relationship with preeclampsia was observed for HDL-C levels measured in the first trimester, preeclamptic women had significantly lower HDL-C levels in the third trimester than normotensive women (WMD = −8.86 mg/dL, 95% CI: −11.50, −6.21). This relationship was also observed when stratifying by mild and severe preeclampsia. Non-HDL-C measured in both the first/second trimesters (WMD = 11.57, 95% CI: 3.47, 19.67) and third trimester (WMD = 29.59, 95% CI: 12.13, 47.06) was significantly higher among preeclamptic women than among normotensive pregnant women. LDL-C levels measured in the first/second trimesters (WMD = 3.89 mg/dL, 95% CI: −0.19, 7.97) and third trimester (WMD = 10.92, 95% CI: −0.59, 22.42) were greater among women who developed preeclampsia than among those who remained normotensive throughout pregnancy, though these relationships were only marginally significant ($P = 0.06$). Triglyceride levels measured in the first/second trimesters were significantly higher in women who developed preeclampsia than in normotensive pregnant women (WMD = 25.08 mg/dL, 95% CI: 14.39, 35.77). Triglyceride levels measured in the third trimester were also significantly higher in preeclamptic women when compared with normotensive pregnant women (WMD = 80.29 mg/dL, 95% CI: 51.45, 109.13). This relationship was also observed when stratifying by mild and severe preeclampsia. Forest plots for all meta-analyses can be found in Web Figures 5–21.

We detected moderate to significant heterogeneity in nearly all of the meta-analyses we conducted ($P \leq 0.01$)

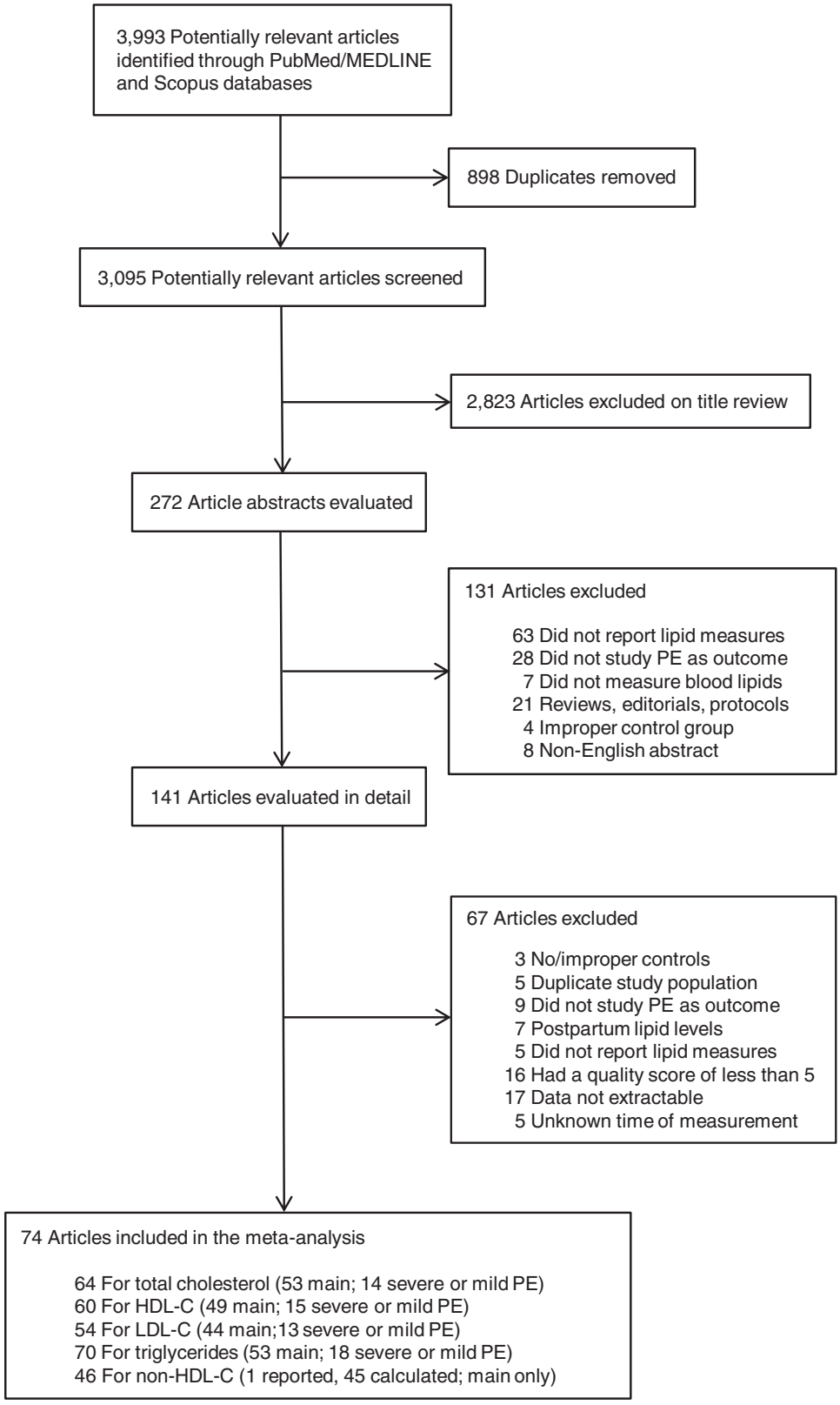

Figure 1. Flow diagram of study selection for the meta-analysis of the association between lipid measurements during pregnancy and risk of preeclampsia (PE). "Main" refers to the main meta-analysis of lipid levels during pregnancy and risk of any PE. "Severe or mild" refers to the sub-analysis of lipid levels during pregnancy and the risk of PE, stratified by PE severity. Overlap between the 2 meta-analyses is possible. Studies were published from the index date of the databases until July 2013. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 1. Characteristics of Studies Included in the Main Meta-Analysis of Lipid Measurements During Pregnancy and Preeclampsia, 1950–July 2013

First Author, Year (Reference No.)	Country	Trimester of Blood Sampling	No. of Cases	No. of Controls	Fasting Status	BMI[a] Similar Between Cases and Controls	Mean Lipid Levels, mg/dL							
							Total Cholesterol		HDL-C		LDL-C		Triglycerides	
							Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Adiga, 2007 (48)	India	Third	25	25	Yes	Yes	246	203	48	66				
Ahenkorah, 2008 (49)	Ghana	Third	30	50	Yes	No	244	248	73	77	172	149	304	225
Akiibinu, 2013 (50)	Nigeria	Third	32	40	Unknown	No	176	111						
Aziz, 2007 (51)	Pakistan	Third	16	16	Yes	Yes	178	184	40	51	118	108	232	113
Babacan, 2011 (52)	Turkey	Third	34	11	Unknown	Unknown	345	182	46	62	162	109	281	204
Barden, 2001 (53)	Australia	Third	21	19	Unknown	Unknown	270	278	61	68	154	166	323	227
Belo, 2002 (23)	Portugal	Third	51	67	No	Yes	268	285	54	62	140	146	239	186
Caruso, 1999 (54)	Italy	Third	10	10	Yes	Yes			79	59	116	135	261	237
Cekmen, 2003 (55)	Turkey	Third	32	34	Yes	Unknown	249	225	32	43	171	132	274	234
Chalas, 2002 (56)	France	Third	24	25	Yes	Yes	253	252	73	68			206	172
Dane, 2009 (57)	Turkey	Third	10	97	Yes	Unknown			52	61			379	221
Demir, 2011 (58)	Turkey	Third	35	35	Yes	Yes	173	177	64	52	124	132	131	133
Demirci, 2011 (59)	Turkey	Second	30	320	Yes	No	220	201	60	60			158	121
Dey, 2013 (60)	India	Second	24	279[b] and 282[c]	Yes	Yes	200[b] and 230[c]	198[b] and 192[c]	49[b] and 48[c]	49[b] and 47[c]	119[b] and 118[c]	117[b] and 119[c]	167[b] and 177[c]	167[b] and 172[c]
Duan, 2011 (61)	China	Third	72	72	Yes	No	251	226	57	58	123	116	354	229
Enquobahrie, 2004 (62)	United States	First	27	510	No	Unknown	198	191	64	65	108	97	138	121
Francoual, 2002 (63)	France	Third	24	25	Unknown	Unknown	254	244	70	65	123	107	253	208
Garzetti, 1993 (64)	Italy	Third	20	20	Unknown	Unknown	232	219						
Gohil, 2011 (65)	India	Third	50	40	Unknown	Unknown	238	209	42	60	136	116	270	215
Harsem, 2007 (66)	Norway	Third	38	41	Yes	Yes	186	169						
Iftikhar, 2010 (12)	Pakistan	Third	45	45	Unknown	Unknown	282	279	33	35	162	148	245	186
Islam, 2010 (67)	Bangladesh	Third	30	40	Yes	Unknown	271	263	42	56	134	115	226	166
Jamalzei, 2013 (68)	Iran	Third	100	100	Yes	No	180	182	52	49	178	186	260	220
Kaaja, 1995 (69)	Finland	Third	8	21	Yes	Yes (matched)	196	190	31	43	124	151	328	177
Kalar, 2012 (70)	Pakistan	Third	22	22	Unknown	Yes	193	203	37	51	13	99	254	117
Kandimalla, 2011 (71)	Trinidad and Tobago	Second	11	91	No	Yes	236	259	59	68	107	101	146	106
Kashinakunti, 2010 (72)	India	Third	90	90	Yes	Yes	289	160	43	67	111	114	215	188
Kim, 2007 (73)	Korea	Third	32	57	Unknown	Unknown	232	227	46	67	128	121	280	226
Koçyigit, 2004 (13)	Turkey	Third	45	30	Yes	Yes	270	294	29	51	192	112	256	111
Lei, 2011 (74)	China	Third	33	200	Yes	Yes	228	217	50	57	108	120	353	269
Llurba, 2004 (75)	Spain	Third	53	30	Yes	Yes	302	286					269	221
Lorentzen, 1995 (76)	Norway	Second	19	19	Yes	Yes (matched)							115[d] and 372[e]	80[d] and 213[e]
Madazli, 1999 (77)	Turkey	Third	22	21	Yes	Unknown	308	277	39	46	157	177	341	253

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Country	Trimester of Blood Sampling	No. of Cases	No. of Controls	Fasting Status	BMI[a] Similar Between Cases and Controls	Mean Lipid Levels, mg/dL							
							Total Cholesterol		HDL-C		LDL-C		Triglycerides	
							Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Maksane, 2011 (78)	India	Third	20	20	Yes	Unknown	162	149	46	60	136	116	278	215
Mihu, 2009 (79)	Romania	Third	25	25	Yes	Yes	261	261	58	61			268	221
Mohindra, 2002 (80)	India	Third	54	33	Yes	Unknown	233	186						
Mori, 2010 (81)	Japan	Third	15	17	Yes	Yes	309	317	73	93	130	139	289	174
Mukherjee, 2010 (44)	India	Third	62	54	Yes	Yes	233	186	39	52	139	102	279	158
Murai, 1997 (82)	United States	Third	31	31	No	No							249	192
Negrato, 2009 (83)	Brazil	Second	19	180	Yes	No			61	63			224	200
Nelson, 1966 (84)	United States	Third	10	12	Unknown	Unknown	309	317					191	159
Pecks, 2012 (85)	Germany	Third	14	28	Unknown	Unknown	232	201	69	75	130	146	271	191
Peng, 1985 (86)	China	Third	40	40	Yes	Unknown	254	230	55	73	128	125		
Powers, 1998 (87)	United States	Third	20	32	Yes	Yes (matched)							286	183
Reyna-Villasmil, 2008 (88)	Venezuela	Third	35	35	Unknown	Unknown	251	263	51	67	113	133	300	196
Rodie, 2004 (89)	United Kingdom	Third	23	23	No	Yes	198	201			153	141		
Rosing, 1989 (90)	Sweden	Third	26	21	Yes	Unknown	293	172	28	35			345	221
Rudra, 2006 (91)	United States	Second	22	711	No	Unknown	238	214			104	102	164	144
Sahu, 2009 (14)	India	Third	30	30	Yes	Unknown	175	168	50	66	197	89	234	87
Sharami, 2012 (92)	Iran	Third	41	41	Yes	Yes	220	193	43	49	138	124	340	203
Stefanović, 2009 (93)	Serbia	Third	17	20	Unknown	Yes			57	53	111	118	323	173
Takahashi, 2008 (94)	Brazil	First	9	39	Unknown	Yes	212[f] and 183[g]	186[f] and 191[g]	59	59	87[f] and 113[g]	89[f] and 99[g]	110[f] and 205[g]	115[f] and 165[g]
Uzun, 2005 (15)	Turkey	Third	41	33	Yes	Unknown	252	237	42	52	122	106	235	140
Vanderjagt, 2004 (95)	Nigeria	Third	43	130	Unknown	Unknown	266	263	55	63	145	153	203	190
Ware-Jauregui, 1999 (96)	Peru	Third	125	179	No	Yes	339	233	39	42	146	144	301	249
Wetzka, 1999 (97)	Germany	Third	9	24	Yes	Yes	231	234	64	72	105	130	436	234
Yamaguchi, 1988 (98)	Japan	Third	29	29	Yes	Unknown	260	241	33	33	96	75	339	233
Zhou, 2012 (99)	China	Second	61	939	Yes	No	197	191	79	85	105	107	246	214
Ziaei, 2006 (100)	Iran	Third	25	25	Unknown	Yes (matched)	260	241	62	66	146	132	302	213
Ziaei, 2012 (101)	Iran	Second	14	127	Yes	Yes (matched)	197	191	57	55	125	111	203	144

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a] Weight (kg)/height $(m)^2$.
[b] At 15 weeks.
[c] At 19 weeks.
[d] At 17 weeks.
[e] In the third trimester.
[f] Before 13 weeks.
[g] At 25 weeks.

Table 2. Summary Weighted Mean Differences From Meta-Analyses of the Association Between Lipid Levels During Pregnancy and Preeclampsia, 1950–July 2013

Lipid Stratification	No. of Studies	Random-Effects Model			Heterogeneity				Egger *P* Value
		WMD, mg/dL	95% CI	*P* Value	χ^2	*P* Value	τ^2	I^2, %	
				Total Cholesterol					
All preeclampsia									
First/second trimesters	11	12.49	3.44, 21.54	0.007	27.14	0.002	122.38	56	0.82
Third trimester	46	20.20	8.70, 31.70	0.001	3,892.87	<0.0001	1,500.00	99	0.06
Severe preeclampsia									
First/second trimesters	4	−2.19	−14.90, 10.52	0.74	13.01	0.005	115.78	77	0.60
Third trimester	13	26.17	−0.37, 52.72	0.05	223.86	<0.0001	2,100.0	95	0.07
Mild preeclampsia									
First/second trimesters	3	8.01	−3.17, 19.19	0.16	1.60	0.45	0.00	0	0.58
Third trimester	11	18.17	−16.77, 53.11	0.31	394.21	<0.0001	3,200.0	97	0.24
				HDL-C					
All preeclampsia									
First/second trimesters	10	−0.48	−3.31, 2.34	0.74	32.96	<0.0001	12.91	73	0.71
Third trimester	41	−8.86	−11.50, −6.21	<0.0001	771.48	<0.0001	63.33	95	0.27
Severe preeclampsia									
First/second trimesters	2	−3.12	−15.06, 8.82	0.61	15.96	<0.0001	69.76	94	
Third trimester	14	−5.60	−10.59, −0.62	0.03	382.51	<0.0001	80.52	97	0.80
Mild preeclampsia									
First/second trimesters									
Third trimester	11	−5.92	−11.61, −0.24	0.04	361.66	<0.0001	79.90	97	0.57
				LDL-C					
All preeclampsia									
First/second trimesters	9	3.89	−0.19, 7.97	0.06	9.21	0.33	5.11	13	0.80
Third trimester	36	10.92	−0.59, 22.42	0.06	1,012.02	<0.0001	1,100.0	97	0.19
Severe preeclampsia									
First/second trimesters									
Third trimester	12	14.14	−13.73, 42.01	0.32	319.12	<0.0001	2,200.0	97	0.04
Mild preeclampsia									
First/second trimesters									
Third trimester	10	4.09	−33.36, 41.55	0.83	724.43	<0.0001	3,400.0	99	0.08
				Non-HDL-C[a]					
All preeclampsia									
First/second trimesters	9	11.57	3.47, 19.67	0.005	34.18	<0.0001	98.4	76	0.50
Third trimester	38	29.59	12.13, 47.06	0.001	8,388.4	<0.0001	2,900	99	0.85
				Triglycerides					
All preeclampsia									
First/second trimesters	13	25.08	14.39, 35.77	<0.0001	28.49	0.01	196.16	58	0.12
Third trimester	44	80.29	51.45, 109.13	<0.0001	18,831.98	<0.0001	9,000	99	0.10
Severe preeclampsia									
First/second trimesters	5	35.65	11.20, 60.10	0.004	38.65	<0.0001	645.02	90	0.52
Third trimester	15	65.22	28.75, 101.69	<0.0001	249.22	<0.0001	4,200	94	0.71
Mild preeclampsia									
First/second trimesters	4	39.06	11.09, 67.03	0.006	13.31	0.004	610.61	77	0.11
Third trimester	12	54.53	12.55, 96.51	0.01	347.20	<0.0001	4,600.0	97	0.86

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WMD, weighted mean difference.

[a] If measured non-HDL-C was not available, non-HDL-C was calculated as total cholesterol minus HDL-C.

Table 3. Univariate and Multivariate Meta-Regression Results From the Meta-Analysis of Lipid Levels During Pregnancy and the Risk of Preeclampsia, 1950–July 2013

Covariate	No.	β Coefficient[a]	95% CI	*P* Value	I^2, %	R^2, %
			Total Cholesterol			
BMI[b]	30	4.48	−2.53, 11.50	0.20	98.56	2.16
Fasting status	60					
Nonfasting		−1.18	−33.12, 30.76	0.94		
Unknown		0.65	−21.06, 22.37	0.30		
Trimester	57	10.15	−14.64, 34.95	0.42	98.60	−0.78
Multivariate	29				98.75	−2.90
BMI		4.37	−3.25, 11.98	0.25		
Fasting status						
Nonfasting		28.53	−17.60, 74.66	0.21		
Unknown		8.20	−30.08, 46.48	0.90		
Trimester		8.67	−24.72, 42.06	0.60		
			LDL-C			
BMI	25	−5.50	−10.93, −0.07	0.04	89.8	15.20
Fasting status	49				95.7	−2.44
Nonfasting		−8.79	−31.25, 13.68	0.44		
Unknown		−5.35	−21.80, 11.09	0.52		
Trimester	45	6.804	−12.81, 26.42	0.49	95.8	−0.79
Multivariate	24				89.3	7.60
BMI		−6.80	−13.65, 0.05	0.05		
Fasting status						
Nonfasting		4.79	−23.21, 32.79	0.72		
Unknown		2.740	−21.57, 27.04	0.82		
Trimester		0.89	−21.18, 22.96	0.93		
			HDL-C			
BMI	28	0.23	−1.76, 2.21	0.82	93.4	−4.92
Fasting status	54				94.9	−4.42
Nonfasting		1.36	−7.68, 10.39	0.77		
Unknown		0.69	−4.86, 6.23	0.81		
Trimester	51	−8.82	−14.20, −3.44	0.002	93.9	21.58
Multivariate	27				92.7	12.23
BMI		0.33	−1.68, 2.34	0.74		
Fasting status						
Nonfasting		5.36	−12.84, 23.55	0.55		
Unknown		6.10	−3.67, 15.87	0.21		
Trimester		−8.31	−17.08, 0.46	0.06		
			Triglycerides			
BMI	32	−11.021	−23.341, 1.299	0.08	98.1	9.84
Fasting status	57				98.3	0.04
Nonfasting		−30.843	−70.804, 9.118	0.13		
Unknown		−2.845	−32.268, 26.578	0.85		
Trimester	57	47.424	20.60, 74.247	0.001	99.7	19.52
Multivariate	32				94.2	29.73
BMI		−5.589	−18.007, 6.828	0.36		
Fasting status						
Nonfasting		−11.357	−69.504, 46.790	0.69		
Unknown		19.280	−26.851, 65.410	0.40		
Trimester		56.297	18.750, 93.844	0.005		

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

[a] Reference groups were first/second trimesters and fasting.

[b] Weight (kg)/height $(m)^2$.

with I^2 values ranging from 56% to 99% (Table 2), with the exception of the first/second-trimester total cholesterol and mild preeclampsia analysis ($P = 0.45$, $I^2 = 0\%$) and the first/second-trimester LDL-C analysis ($P = 0.33$, $I^2 = 13\%$). Table 3 shows the results from the univariate and multivariate meta-regression analyses designed to identify potential factors that could explain the high heterogeneity. BMI imbalance between the comparison groups is likely an important source of heterogeneity in the LDL-C analysis ($P = 0.04$, $R^2 = 15.2\%$) and triglyceride analysis ($P = 0.08$, $R^2 = 9.8\%$) such that, for each 1.0 unit increase in BMI WMD between groups, decreases in the WMD of 5.50 mg/dL and 11.02 mg/dL are expected, respectively. In multivariate meta-regression models with trimester of lipid measurement and fasting status at blood sampling, BMI remained significant as a potential source of heterogeneity for LDL-C but not for triglycerides. Additionally, trimester of lipid measurement was identified as another potential source of heterogeneity in meta-analyses of HDL-C and triglycerides. However, neither BMI imbalance between the comparison groups nor trimester of lipid measurement was detected as a possible source of heterogeneity in the total cholesterol analysis. Fasting status at the time of lipid measurement was not identified as a potential source of heterogeneity for any of the lipid analyses.

On the basis of Egger's test, publication bias was not present in most of the meta-analyses with P values ranging from 0.06 to 0.82 (Table 2), with the exception of the analysis of LDL-C from the third trimester and severe preeclampsia ($P = 0.04$). However, visual inspection of the funnel plots suggests that publication bias may be present for the total cholesterol, LDL-C, and HDL-C analyses of third-trimester measurements stratified by preeclampsia severity. Funnel plots for all analyses can be found in Web Figures 22–41.

DISCUSSION

Our meta-analysis shows that maternal serum total cholesterol, non-HDL-C, and triglyceride levels during pregnancy are elevated during the first/second and third trimesters in women who subsequently develop preeclampsia compared with women who remain normotensive during pregnancy. Additionally, our results suggest that women who subsequently develop preeclampsia likely have increased levels of LDL-C in the first/second and third trimesters compared with normotensive women, though these results were of marginal significance. Finally, maternal HDL-C levels during the third trimester of pregnancy are lower in preeclamptic women compared with normotensive pregnant women.

A recent meta-analysis of hypertriglyceridemia and preeclampsia reported that maternal triglyceride levels during pregnancy were elevated in women who subsequently developed preeclampsia (10); however, our methodological approach was substantially more inclusive and comprehensive. The authors of that study located 24 case-control and 5 cohort studies for inclusion in their meta-analysis, whereas our search strategy led us to 86 articles (13 of which we excluded because of low quality scores), 3 times the number of articles found in the previous analysis. However, despite the additional articles, we found very similar WMDs in our analysis when we stratified by trimester of measurement. The authors also detected significant heterogeneity after stratification by trimester, which they attributed to difference in BMI; this hypothesis, however, was not tested. We performed meta-regression analyses to assess BMI as a possible source of heterogeneity and found that BMI differences across studies were possible sources of heterogeneity for triglycerides and LDL-C.

During the course of a normal pregnancy, total cholesterol, HDL-C, triglycerides, and LDL-C levels rise markedly (29, 30). Cholesterol is necessary for placental steroid synthesis, and increases in cholesterol levels during pregnancy promote the accumulation of maternal fat stores in the first two-thirds of pregnancy to serve as a source of calories for the mother and fetus during the later stages of pregnancy and lactation (29, 31–33). Results from this meta-analysis suggest that women with preeclampsia experience greater changes in lipid metabolism than normotensive women. For example, the difference in triglycerides between preeclamptic and normotensive pregnancies is substantially greater during the third trimester (WMD = 80.29) compared with the first/second trimesters (WMD = 25.08). This same trend of greater differences in the third trimester compared with the first/second trimesters was also observed for total cholesterol, HDL-C, LDL-C, and non-HDL-C, suggesting that preeclamptic women experience larger changes in lipid levels during pregnancy than normotensive women.

Dyslipidemia in preeclamptic women is characteristic of what occurs in insulin-resistant, hyperglycemic women who are not pregnant, many of whom also have the clustering of metabolic syndrome characteristics that include hypertension (34, 35). This suggests that a similar pathophysiological process may be occurring in women with preeclampsia and could be contributing to the dyslipidemic changes. Insulin resistance and type 2 diabetes are characterized by the increased overproduction of the triglyceride-rich very-low-density lipoprotein cholesterol and subsequent increased levels of other triglyceride-rich lipoproteins, which are included in non-HDL-C and reflected in elevated triglyceride levels (36).

Preeclampsia has been proposed to have a 3-stage disease process that stems from an imbalance between placental factors and maternal adaptation to them (37). The disease begins with incomplete maternal tolerance to the allogeneic trophoblasts (stage 1), followed by poor placentation that leads to reduced placental perfusion and poor spiral artery remodeling (stage 2) (37). As a result, the oxidatively stressed placenta releases a number of trophoblast-derived antiangiogenic (e.g., soluble fms-like tyrosine kinase-1, soluble vascular endothelial growth factor, and soluble endoglin) and proangiogenic (e.g., placenta growth factor) factors that contribute to an exaggerated maternal inflammatory response (stage 3) (38). The imbalance of angiogenic factors is thought to increase maternal vascular inflammation with generalized endothelial dysfunction (39). Women with elevated lipid levels likely have preexisting endothelial dysfunction that is worsened as a result of the physiological burden of pregnancy (40); this condition may be further exacerbated by increased maternal vascular inflammation. It is possible that preeclamptic women have higher baseline levels of total cholesterol, triglycerides, and LDL-C and lower levels of HDL-C

prepregnancy, but only a handful of studies have taken prepregnancy measurements in preeclamptic women, and we were not able to assess the impact of prepregnancy lipid levels on the risk of preeclampsia (41, 42).

Recent research has demonstrated that LDL-C is not the only form of cholesterol associated with adverse outcomes. In fact, it has been shown that the inclusion of other atherogenic lipoproteins, referred to as non-HDL, which include very-low-density lipoproteins and other apolipoprotein B–containing lipoproteins, is more predictive of cardiovascular disease than LDL-C levels alone (20). Previous research suggests that LDL-C levels are higher among women who develop preeclampsia than among those who remain normotensive throughout pregnancy (42); however, our results suggest only a moderate difference in LDL-C levels between the 2 groups. Alternatively, we did find that levels of very-low-density lipoproteins (results not shown) and non-HDL-C are significantly higher among preeclamptic women than among normotensive women, suggesting that, although LDL-C levels may not be the most useful measure for preeclampsia prediction, a combined measure of all types of non-HDL-C may be useful.

Previous studies evaluating the association between lipid levels during pregnancy and preeclampsia have suggested measuring lipid levels in all pregnant women as a means of early-pregnancy "screening" of women who may be at higher risk for development of the disease (43, 44). However, results from our meta-analysis indicate that LDL-C and HDL-C levels measured during pregnancy would not be as useful in predicting preeclampsia as other lipid types. HDL-C levels were significantly different between preeclamptic and normotensive women during only the third trimester of pregnancy, which may be too late for an effective prediction tool. Preeclamptic and normotensive women showed marginally significant differences in LDL-C levels during both the second and third trimesters of pregnancy; however, with a WMD of only 3.89 mg/dL in the second trimester, this marker may not be clinically useful as a prediction tool.

Women who developed preeclampsia did have significantly elevated total cholesterol, triglyceride, and non-HDL-C measurements as early as the second trimester; thus, these lipid measurements obtained early in pregnancy may be helpful in identifying women at higher risk of developing preeclampsia. Although a WMD of 12.49 (for total cholesterol), 25.08 (for triglycerides), or 11.57 (for non-HDL-C) may not be clinically significant as an individual marker, when combined with other biomarkers known to differ in preeclamptic women, such as increased mean arterial pressure (45), soluble fms-like tyrosine kinase-1 (46), and placental growth factor (46), total cholesterol, triglyceride, and/or non-HDL-C measurements could be clinically useful in identifying women at higher risk for developing preeclampsia. The American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy recently revised the guidelines for the diagnosis of preeclampsia in an effort to increase the diagnostic sensitivity and specificity for preeclampsia by allowing for its diagnosis in the absence of proteinuria when any 1 of 6 severe features of preeclampsia is found (47). Because these severe features are relatively infrequent during pregnancy, implementation of the revised definition is unlikely to alter the conclusions of the meta-analysis or lessen the potential clinical utility of including lipid measurements in preeclampsia prediction algorithms.

Strengths and limitations

A key strength of our meta-analysis is the sensitive search strategy that we developed in consultation with a research librarian. Specifically, we searched 2 databases and did not apply any language, country, or date restrictions to the search to increase our chances of identifying all possible publications related to the topic. Additionally, the high yield of articles eligible for inclusion allowed us to limit our analysis to the studies of higher quality. Finally, we were able to perform meta-regression to illustrate that fasting status at the time of lipid measurement did not affect our results. This is an important finding for studies of lipid measurements and pregnancy outcomes, because it is particularly difficult to obtain fasting measurements longitudinally throughout pregnancy. If incorporated with routinely measured markers in pregnancy, such as pregnancy-associated plasma protein A and glucose, most, if not all, samples could be collected during a nonfasting state. Therefore, we demonstrate that lipid measurements may be incorporated with routine clinical analysis of other biomarkers, which is particularly important when evaluating the feasibility of universal screening for lipid levels during pregnancy.

This meta-analysis also included a separate analysis of severe and mild preeclampsia. It should be noted, however, that we did not use our own specific criteria for the definitions of severity. Preeclampsia definitions have varied slightly over time, and many countries have their own definitions of severity. Thus, some of the heterogeneity between the severity studies could be explained by varying definitions. Of the studies included in this subanalysis, 2 did not report their classification criteria for severe preeclampsia. Among those that did, the most common criteria for diagnosis of severe preeclampsia were systolic blood pressure of 160 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, proteinuria of either 2 g/24 hours or more or 5 g/24 hours or more, or the presence of another severe symptom. Further, it is increasingly believed that early- and late-onset preeclampsia may be different diseases with different pathophysiologies; however, we did not locate an adequate number of studies that distinguished between early- and late-onset preeclampsia.

Although we were able to perform meta-regression to identify BMI as a potential confounder and source of heterogeneity, we were unable to incorporate this factor into our mean difference meta-analysis. This was not possible because the included studies would have to have presented their mean lipid levels stratified by BMI, and those levels of stratification would have to have been equivalent across all studies.

This meta-analysis could not be performed with all of the studies located in the systematic literature review because of the lack of information about the mean and standard deviation in each group (or lack of information necessary to convert the information into means and standard deviations) ($n = 17$). These studies, if added to the meta-analysis, might have altered our findings. However, a comparison of our triglyceride results

to those of the previous meta-analysis on the topic that included one-third of the studies included here shows very similar results, indicating that the addition of further studies to this meta-analysis is unlikely to alter our findings.

Conclusion

Total cholesterol, triglyceride, non-HDL-C, and HDL-C levels measured during pregnancy are significantly related to the risk of preeclampsia. This finding is clinically useful because maternal lipid levels can be easily measured in all clinical laboratories with routine, well-established lipid panels; thus, inexpensive lipid panels could serve as a cost-effective method for identifying pregnant women at risk for developing preeclampsia. Future research is needed to understand the role of dyslipidemia and other components of metabolic syndrome, such as insulin resistance and obesity, in the pathogenesis of preeclampsia and the mechanisms by which this relationship could be moderated.

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