OBSTETRICS

Maternal infection and risk of preeclampsia: Systematic review and metaanalysis

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There are lingering questions regarding the association between maternal infection and preeclampsia. Systematic review and metaanalysis was conducted of observational studies that examined the relationship between maternal infection and preeclampsia. Forty-nine studies met the inclusion criteria. The risk of preeclampsia was increased in pregnant women with urinary tract infection (pooled odds ratio, 1.57; 95% CI, 1.45-1.70) and periodontal disease (pooled odds ratio, 1.76; 95% CI, 1.43-2.18). There were no associations between preeclampsia and presence of antibodies to *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus, treated and nontreated HIV infection, and malaria. Individual studies did not find a relationship between herpes simplex virus type 2, bacterial vaginosis, and *Mycoplasma hominis* and preeclampsia. Urinary tract infection and periodontal disease during pregnancy are associated with an increased risk of preeclampsia. More studies are required to verify this as well as to explore whether or not such relationships are causal and, if so, the mechanisms involved.

Key words: maternal infection, periodontal disease, preeclampsia, urinary tract infection

Preeclampsia complicates about 3% of all pregnancies and remains a major cause of maternal and perinatal mortality and morbidity, and is particularly devastating in developing countries.[1,2] Despite recent progress towards understanding the cause of preeclampsia and/or its phenotypes, the etiology of this serious disorder remains elusive.[3] Current theories include abnormal placentation, cardiovascular maladaptation to pregnancy, genetic and immune mechanisms, an enhanced systemic inflammatory response, and nutritional, hormonal, and angiogenic factors.[4,5] It seems probable, however, that multiple factors are involved.

Some have suggested that inflammation plays a key role in causing preeclampsia or its manifestations. Normal pregnancy evokes a mild increase in the systemic inflammatory response that becomes considerably greater in preeclampsia.[5] Based on this concept, some authors have hypothesized that infection might be involved in the etiology and pathogenesis of preeclampsia, both in terms of its initiation (by increasing the risk of acute uteroplacental atherosis) and/or its potentiation (by amplifying the maternal systemic inflammatory response).[6,7]

The primary aim of this systematic review was to critically examine the relationship between maternal infection and the risk of preeclampsia by using both formal methods for systematic reviews of observational studies,[8,9] and recommended methods for assessing causal association.[10,11]

Materials and Methods

The systematic review was conducted following a prospectively prepared protocol and reported using the Metaanalysis of Observational Studies in Epidemiology (MOOSE) guidelines for metaanalysis of observational studies.[9]

An initial search was performed in MEDLINE, EMBASE, POPLINE, CINAHL, and LILACS (all from inception to June 30, 2007) to identify potentially eligible studies. We applied the following algorithm both in MeSH and in free-text words: (infection OR inflammation) AND (preeclampsia OR eclampsia OR gestosis, EPH OR pregnancy toxemia OR pregnancy-induced hypertension OR hypertensive disorders of pregnancy OR gestational hypertension OR pregnancy-associated hypertension OR pregnancy hypertension). A secondary computerized search was conducted using the name of each infection or microorganism identified in the initial search and the MeSH or free-text words for hypertensive disorders of pregnancy described previously. We also searched in proceedings of international meetings on preeclampsia, bibliography of the retrieved articles, reviews, and chapters in standard textbooks on hypertension on pregnancy, and also contacted investigators involved in the field to locate unpublished studies. No language restrictions were imposed. If a study evaluated several infections or microorganisms, each one of them was considered independently.

All of the potentially relevant studies were retrieved and reviewed by 1 of the

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investigators (A. C-A), who determined inclusion using the following minimal criteria: (1) cohort, cross-sectional, or case-control studies that evaluated the epidemiologic, clinical, or pathologic association between any maternal infection or microorganism and preeclampsia; (2) the authors explicitly included hypertension after 20 weeks' gestation plus proteinuria in their definition of preeclampsia. Hypertension was defined as a diastolic blood pressure of at least 90 mm Hg or a systolic pressure of at least 140 mm Hg. We also included the older criteria of a rise of 15 and/or 30 mm Hg systolic and diastolic blood pressure, respectively, to values below 140/90 mm Hg, because a number of studies took place before the change in definition. Proteinuria was defined as the urinary excretion of >300 mg protein/24 hours, or 2 random urine specimens obtained at least 4 hours apart demonstrating ≥1+ by dipstick testing or measured as >30 mg/dL. Case series or reports, editorials, letters to the editor, or reviews without original data, and studies examining only the relation between infection and hypertensive states without proteinuria were excluded from the systematic review. Studies included in the systematic review were also included in the meta-analyses if they reported odds ratio (OR) or relative risk (RR) estimates and its 95% confidence intervals (CIs), or provided the necessary information to calculate them. Finally, in addition to the observational studies, we surveyed both randomized and nonrandomized trials that evaluated the effects of administering antibacterial or antiviral treatments to pregnant women with infection on the risk of preeclampsia.

Study quality assessment was judged by the following 7 criteria believed to be important for the quality of observational studies evaluating the relationship between maternal infection and preeclampsia[8,12]:

1. Women selection
   Cohort or cross sectional studies
   - Adequate: if women recruited were representative of the entire population (entire source population, unselected sample of consecutive women, or a random sample).
   - Inadequate: convenience sampling (arbitrary recruitment or nonconsecutive recruitment) or when selection was not random or unreported.

   Case-control studies
   - Adequate: women recruited from the same population.
   - Inadequate: women recruited from different sources or unreported.

2. Assessment of exposure (infection) and outcome (preeclampsia)
   - Adequate: ascertainment of both infection and preeclampsia by medical records or direct measurement.
   - Inadequate: ascertainment of both infection and preeclampsia by personal or telephone interview, or self-administered questionnaire, or unreported.

3. Blinding of investigators to both exposition and the outcome
   - Adequate: measurement of both infection and preeclampsia was done while investigators were blinded.
   - Inadequate: not blinded or not clear from the text or unreported.

4. Loss to follow-up or exclusions and period of time for recruitment of women

   Cohort or cross sectional studies
   - Adequate: if loss to follow-up or nonvalid exclusions <10%.
   - Inadequate: if loss to follow-up or nonvalid exclusions ≥10%.

   Case-control studies
   - Adequate: case patients and control women recruited during the same period of time.
   - Inadequate: women recruited from different periods of time or unreported.

5. Control for confounding factors
   - Adequate: if the study controlled for at least maternal age and markers of socioeconomic status.
   - Inadequate: if the study did not control for at least maternal age and markers of socioeconomic status, or no adjustment was performed.

6. Temporality of the association
   - Adequate: if diagnosis of infection was made before the clinical onset of preeclampsia.
   - Inadequate: if diagnosis of infection was made at or after the clinical onset of preeclampsia or not clear from the text or unreported.

7. Report of dose-response gradient
   - Adequate: if studies reported the relationship between severity of infection and the risk and/or severity of preeclampsia.
   - Inadequate: if studies did not report the relationship between severity of infection and the risk and/or severity of preeclampsia.

One of the authors (A. C-A) assessed the methodologic quality and abstracted data from each study according to design, geographic location of the study, sample size, infection or microorganism evaluated, gestational age when the infection was diagnosed, definition and severity of preeclampsia, confounding factors controlled for by matching or adjustment, temporality of the association, report of dose-response gradient, and unadjusted and/or adjusted RRs or ORs ratios and 95% CIs.

The exposure (independent) variable was the presence or absence of any individual infection (acute or chronic) or specific antibodies against infectious agent or isolated infectious agent. The outcome (dependent) variable was the presence or absence of preeclampsia. Separate analyses were conducted for each infection identified. The basic data used in the unadjusted analyses consisted of a series of 2×2 tables defined by the dichotomous infection/noninfection and preeclampsia/non-preeclampsia for each study. To improve the precision of the effect measure, 0.5 was added to cells that contain no observations.[13] The OR was used as the measure of the relation between infection and preeclampsia. Re-

sults from different reports were combined to produce a pooled OR with 95% CI according to the Mantel–Haenszel method. We pooled results from individual studies using both fixed- and random-effects models. A random-effects model was associated with higher estimates of association but wider 95% CI. Therefore, we chose to focus on the results from the fixed-effects model for providing a more conservative interpretation of the results.

Only studies that provided an adjusted estimate, either through the use of appropriate methods of analysis or through matching of variables in the study design, were considered in adjusted meta-analyses. The data needed from each study were the adjusted RR or the adjusted OR and its estimated standard error (often obtained indirectly from the confidence interval reported in the study).

Heterogeneity of the results among studies was formally tested with the quantity I^2, which describes the percentage of total variation across studies that is caused by heterogeneity rather than chance.[14] I^2 can be calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\% \times (Q\text{-}df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of I^2 are set equal to 0 so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, whereas I^2 values of 25%, 50%, and 75%, indicate low, moderate, and high heterogeneity, respectively.[14] For the association between urinary tract infection and preeclampsia, we explored sources of heterogeneity using the following independent explanatory variables defined a priori: (1) statistical model (fixed-effects vs random-effects); (2) study design (cohort or cross-sectional vs case-control); (3) study quality (those that meet ≥5 methodologic criteria [high quality] vs those that meet <5 criteria [non-high quality]); (4) sample size (studies with <100 women with preeclampsia vs studies with ≥100 preeclamptics); (5) study setting (studies from North America compared with those from Australia, Europe, and developing countries); (6) date of publication (before 1990 vs at or after 1990); (7) adjustment for confounding factors (studies that adjusted for at least maternal age and socioeconomic status compared with those that did not control for at least maternal age and socioeconomic status); and (8) type of infection (studies evaluating "asymptomatic or symptomatic bacteriuria" vs studies evaluating "urinary tract infection"). Subgroup and sensitivity analyses were performed pooling unadjusted ORs provided by the studies. Because of the limited number of studies included in the meta-analyses, we could only perform some subgroup analyses for the association between preeclampsia and both periodontal disease and *Chlamydia pneumoniae*.

We prepared funnel plots to detect publication and location biases. We used the regression approach to assess funnel plot asymmetry with $P < .10$ indicating significant asymmetry.[15] All statistical analyses were performed with the StatsDirect version 2.5.6. (StatsDirect Ltd, Altrincham, UK).

RESULTS

The searches produced 1816 citations of which 88 were considered relevant (77 through computer search, and 11 from references cited in articles). Thirty-nine studies were excluded, mainly because they lacked data relating maternal infection and preeclampsia (79%) or included women without proteinuria in the preeclampsia group (13%). References for excluded studies can be obtained from the authors. Forty-nine studies (27 case-control, 19 cohort, and 3 cross-sectional)[16-64] met the inclusion criteria of which 40, including a total of 182,308 women, provided data for meta-analyses. A case-control study[18] was nested in a randomized controlled trial that assessed the effect of antibiotic treatment for bacteriuria on preeclampsia and other pregnancy outcomes. Eleven studies (22%) were conducted in the United States and the remaining (n = 38) were conducted in 27 countries from Latin America (7 countries), Asia (7 countries), Europe (8 countries), Africa (3 countries), North America (1 country), and Australia. We also found 3 non-randomized studies[65-67] and 2 randomized controlled trials[18,68] that evaluated the effect of treatment for infections during pregnancy on the risk of preeclampsia, which are discussed separately.

Study characteristics and main findings of included studies are shown in Table 1. The sample size in the cohort or cross-sectional studies ranged from 69[49] to 38,151.[32] One cross-sectional study included more than 4.5 million hospitalizations of pregnant women in the US.[59] The number of case subjects enrolled in case-control studies ranged from 15[35] to 426[21] and the corresponding number of control subjects ranged from 14[41] to 2355.[29] Seventeen studies provided data on the relationship between preeclampsia and urinary tract infection,[16-32] 9 on the relation with periodontal disease,[33-41] 7 on the relation with HIV infection,[53-59] 6 on the relation with *Chlamydia pneumoniae*,[44-47,49,50] 4 on the relation with malaria,[60-63] 3 on the relation with cytomegalovirus,[42,43,46] 2 on the relation with *Helicobacter pylori*,[45,52] and 1 each on the relation with Epstein–Barr virus,[42] herpes simplex virus type 2,[42] *Mycoplasma hominis*,[48] adeno-associated virus-2,[51] and bacterial vaginosis.[64] Only 2 studies fulfilled all 7 methodologic criteria. Twenty-six (53%) were considered to be of high quality. The remaining 23 studies had 3 or more methodologic flaws. The most common shortcomings were the failure to report dose-response gradient, adjustment for confounding factors, and the absence of any information regarding blinding of investigators in evaluating either exposure or outcome.

Urinary tract infection

Seventeen studies involving a total of 7317 women with preeclampsia evaluated the relationship with urinary tract infection (asymptomatic bacteriuria, cystitis, or pyelonephritis). Twelve studies (6 cohort[24,26,27,30-32] and 6 case-control[18,19,22,23,28,29]) reported an association between urinary tract infection and increased risk of preeclampsia. Five studies (3 cohort[17,20,25] and 2 case-control[16,21]) found no association. Overall,

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

				Methodologic quality							
First author, year	Region, country	Design	Cases/controls or cohort size	Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	Main findings
URINARY TRACT INFECTION											
Bryant,1964[16]	Dallas, USA	Case-control	32 infected women/44 noninfected women	Adequate	Adequate	Unreported	Adequate	Age, race, socioeconomic status, parity	At first antenatal visit	No	No association between asymptomatic bacteriuria and preeclampsia
Low, 1964[17]	Toronto, Canada	Cohort	771	Adequate	Adequate	Unreported	Unreported	None	At first antenatal visit	No	No association between asymptomatic bacteriuria and preeclampsia
Kincaid-Smith, 1965[18]	Melbourne, Australia	Nested case-control	240 infected women/500 noninfected women	Adequate	Adequate	Adequate	Adequate	None	At first antenatal visit	No	Bacteriuria was associated with increased risk of preeclampsia
Stuart, 1965[19]	Jamaica	Case-control	88 infected women/729 noninfected women	Adequate	Adequate	Adequate	Adequate	None	At first antenatal visit	No	Bacteriuria was associated with increased risk of preeclampsia
Little, 1966[20]	United Kingdom	Cohort	5000	Adequate	Adequate	Unreported	Unreported	None	At first antenatal visit	No	No association between bacteriuria and preeclampsia
Brumfitt, 1975[21]	London, United Kingdom	Case-control	426 infected women/477 noninfected women	Adequate	Adequate	Unreported	Adequate	None	At first antenatal visit	No	No association between bacteriuria and preeclampsia
Savige, 1983[22]	Melbourne, Australia	Case-control	51 women with preeclampsia/ 72 women without preeclampsia	Inadequate	Adequate	Unreported	Inadequate	None	Controls at first trimester of pregnancy; cases at delivery	No	Bacteriuria was associated with increased risk of preeclampsia
Hill, 1986[23]	Augusta, USA	Case-control	100 women with preeclampsia/ 200 women without preeclampsia	Adequate	Adequate	Unreported	Unreported	Age, number of vaginal examinations	At delivery	No	Asymptomatic bacteriuria was associated with increased risk of preeclampsia
Gilbert, 1986[24]	Melbourne, Australia	Cohort	340	Adequate	Adequate	Unreported	Adequate	None	At first antenatal visit	No	Bacteriuria was associated with increased risk of preeclampsia
Qureshi, 1994[25]	Karachi, Pakistan	Cohort	1597	Adequate	Adequate	Unreported	Unreported	None	At first antenatal visit	No	No association between bacteriuria and preeclampsia
Schieve, 1994[26]	Chicago, USA	Cohort	25,746	Adequate	Adequate	Adequate	Adequate	Age, race, outcome of previous pregnancy, hospital of delivery, genital tract infection	During antepartum period	No	Urinary tract infection was associated with increased risk of preeclampsia
Hsu, 1995[27]	Baltimore, USA	Cohort	13,852	Adequate	Adequate	Adequate	Unreported	Method of delivery, use of oxytocin, premature rupture of membranes, gestational age	Antepartum and intrapartum periods	No	Urinary tract infection was associated with increased risk of severe preeclampsia
Abi-Said, 1995[28]	Houston, USA	Case-control	66 women with eclampsia/264 women without preeclampsia	Adequate	Inadequate	Adequate	Adequate	Age, parity, marital status, ethnicity, employment, smoking, alcohol, prenatal care, obesity, history of diabetes, and preeclampsia	During pregnancy	No	Urinary tract infection was associated with increased risk of eclampsia

Continued on page 11.

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

Continued from page 10.

First author, year	Region, country	Design	Cases/controls or cohort size	Methodologic quality							Main findings
				Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	
Mittendorf, 1996[29]	Boston, USA	Nested case-control	386 women with preeclampsia/ 2355 women without preeclampsia	Adequate	Adequate	Adequate	Unreported	Age, parity, pre-pregnancy body mass index, education, race, smoking, infant sex, prenatal care, prior abortion, working during pregnancy, marital status, payment status	During pregnancy	No	Urinary tract infection was associated with increased risk of preeclampsia
Lee, 2000[30]	Taiwan	Cohort	29,735	Adequate	Adequate	Adequate	Unreported	Age, parity, pre-pregnancy body mass index, education, marital status, working during pregnancy, infant sex, previous preeclampsia, diabetes mellitus, conception method, obstetric history, uterine fibroids	During pregnancy	No	Urinary tract infection was associated with increased risk of preeclampsia
Villar, 2006[31]	Rosario, Argentina; Havana, Cuba; Jeddah, Saudi Arabia; Khon Kaen, Thailand	Cohort	32,147	Adequate	Adequate	Adequate	Adequate	Age, parity, socio-economic status, twin pregnancy, smoking, obstetric and medical history, obesity, hemorrhage in first or second trimester	During pregnancy	No	Urinary tract infection was associated with increased risk of preeclampsia
Bánhidy 2007[32]	Hungary	Cross-sectional	38,151	Adequate	Adequate	Adequate	Unreported	Maternal age, birth order, employment, marital status	During pregnancy	No	Urinary tract infection was associated with increased risk of preeclampsia
PERIODONTAL DISEASE											
Boggess, 2003[33]	North Carolina, USA	Cohort	850	Adequate	Adequate	Adequate	Adequate	Age, race, smoking, insurance status, gestational age at delivery	At enrollment (<26 weeks' gestation) and 48 hours antepartum	Yes	Severe periodontal disease at delivery was associated with increased risk of preeclampsia. No association between periodontal disease at enrolment and preeclampsia
Canackci, 2004[34]	Turkey	Case-control	41 women with preeclampsia/ 41 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Age, gravidity, parity, smoking, prenatal care, ethnicity, education, household income, marital status, maternal weight	Within 48 hours before delivery	No	Periodontal disease was associated with increased risk of preeclampsia

Continued on page 12.

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

Continued from page 11.

				Methodologic quality							
First author, year	Region, country	Design	Cases/controls or cohort size	Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	Main findings
Oettinger-Barak, 2005[35]	Haifa, Israel	Case-control	15 women with preeclampsia/ 15 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Age, socioeconomic status, gestational age	Up to 48 hours before delivery	No	Periodontal disease was associated with increased risk of preeclampsia
Contreras, 2006[36]	Cali, Colombia	Case-control	130 women with preeclampsia/ 243 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Age, parity, smoking, prenatal care, education, marital status, household income, maternal weight	Within 48 hours before delivery	Yes	Periodontal disease was associated with increased risk of preeclampsia
Castaldi, 2006[37]	Bahia Blanca, Argentina	Cohort	1562	Adequate	Adequate	Adequate	Adequate	Smoking, anemia	Within 72 hours after delivery	Yes	No association between periodontal disease and preeclampsia
Khader, 2006[38]	Jordan	Case-control	115 women with preeclampsia/ 230 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Maternal age, education, parity, pre-pregnancy body mass index, emotional stress, personal and familial history of preeclampsia, familial history of cardiovascular disease, twin birth, occupation, smoking, insurance, household income	Within 24 hours after delivery	No	No association between periodontal disease and preeclampsia
Cota, 2006[39]	Belo Horizonte, Brazil	Case-control	109 women with preeclampsia/ 479 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Maternal age, chronic hypertension, primiparity, smoking, alcohol use, educational level, and number of prenatal visits	Within 48 hours after delivery	No	Periodontal disease was associated with increased risk of preeclampsia
Kunnen, 2007[40]	Groningen, The Netherlands	Case-control	17 women with preeclampsia/ 35 women without preeclampsia	Adequate	Adequate	Unreported	Adequate	Maternal age, body mass index, smoking, educational level	3-28 months postpartum	Yes	Severe periodontal disease was associated with increased risk of early onset preeclampsia
Barak, 2007[41]	Haifa, Israel	Case-control	16 women with preeclampsia/ 14 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Maternal age	At delivery	No	Women with preeclampsia had a higher prevalence of periopathogenic bacteria in placental tissue than controls

Continued on page 13.

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

Continued from page 12.

First author, year	Region, country	Design	Cases/controls or cohort size	Methodologic quality: Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	Main findings
PERSISTENT BACTERIAL AND VIRAL INFECTIONS											
Trogstad, 2001[42]	Norway	Cohort	978	Adequate	Adequate	Unreported	Unreported	Age, parity	10 weeks' gestation	No	Women with preeclampsia had lower seroprevalence of IgG antibodies to Epstein-Barr virus than controls. No association between seroprevalence of IgG antibodies to herpes simplex virus type 2 and cytomegalovirus, and preeclampsia
Carreiras, 2002[43]	Caracas, Venezuela	Case-control	27 women with preeclampsia/ 29 women without preeclampsia	Adequate	Adequate	Unreported	Unreported	Ethnicity	At delivery	No	No association between cytomegalovirus infection and preeclampsia
Heine, 2003[44]	Pittsburgh, USA	Case-control	37 women with preeclampsia/ 37 women without preeclampsia	Adequate	Adequate	Unreported	Adequate	Age, race, smoking, gestational age	Admission for labor and delivery	Yes	Women with preeclampsia had higher seroprevalence of IgG antibodies to *Chlamydia pneumoniae* than controls. No association between seroprevalence of IgA or IgM antibodies to *Chlamydia pneumoniae* and preeclampsia
Teran, 2003[45]	Quito, Ecuador	Cohort	84	Adequate	Adequate	Unreported	Adequate	Age	16 weeks' gestation	No	No association between seroprevalence of IgG antibodies to *Chlamydia pneumoniae* and *Helicobacter pylori* and preeclampsia
von Dadelszen, 2003[46]	Vancouver, Canada	Case-control	38 women with preeclampsia/ 113 women without preeclampsia	Adequate	Adequate	Adequate	Adequate	Age, parity, body mass index	12-16 weeks' gestation	No	No association between seroprevalence of IgG antibodies to cytomegalovirus and *Chlamydia pneumoniae* and preeclampsia. Women with early onset preeclampsia had higher levels of IgG antibodies to cytomegalovirus than controls
Raynor, 2004[47]	Atlanta, USA	Case-control	81 women with preeclampsia/ 206 women without preeclampsia	Adequate	Adequate	Unreported	Adequate	Age, race	Admission for labour and delivery	No	No association between seroprevalence of IgG antibodies to *Chlamydia pneumonia* and preeclampsia
Nguyen, 2004[48]	Lausanne, Switzerland	Cross-sectional	395	Adequate	Adequate	Adequate	Adequate	Age, parity	At 15-17 weeks' gestation	No	No association between mycoplasma hominis in amniotic fluid and preeclampsia

Continued on page 14.

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

Continued from page 13.

				Methodologic quality							
First author, year	Region, country	Design	Cases/controls or cohort size	Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	Main findings
Goulis, 2005[49]	London, United Kingdom	Cohort	69	Adequate	Adequate	Adequate	Adequate	None	16-22 weeks' gestation and 28-40 weeks' gestation	No	No association between seroprevalence of IgG, IgM, and IgA antibodies to *Chlamydia pneumoniae* and preeclampsia. Parous women with previous preeclampsia had higher levels of IgG, IgM, and IgA antibodies to *Chlamydia pneumoniae* than parous women with no previous preeclampsia
Aral, 2006[50]	Turkey	Case-control	69 women with preeclampsia/ 47 women without preeclampsia	Adequate	Adequate	Unreported	Unreported	None	At delivery	No	Women with preeclampsia had higher seroprevalence of IgG antibodies to *Chlamydia pneumoniae* than controls. No association between seroprevalence of IgA or IgM antibodies to *Chlamydia pneumoniae* and preeclampsia
Arechavaleta-Velasco, 2006[51]	Pennsylvania, USA	Case-control	40 women with severe preeclampsia/27 women without preeclampsia	Adequate	Adequate	Unreported	Adequate	Maternal age, gravidity, parity	At delivery	No	Adeno-associated virus-2 DNA was detected significantly more frequently in trophoblast cells from women with preeclampsia than from normal controls
Ponzetto, 2006[52]	Turin, Italy	Case-control	47 women with preeclampsia/ 47 women without preeclampsia	Adequate	Adequate	Unreported	Adequate	Age, smoking, weight gain, prepregnancy body mass index, parity	At delivery	No	Women with preeclampsia had higher seroprevalence of IgG antibodies to *Helicobacter pylori* than controls
HIV INFECTION											
Wimalasundera, 2002[53]	London, United Kingdom	Case-control	214 HIV-positive women/214 HIV-negative women	Adequate	Adequate	Unreported	Adequate	Age, parity, ethnicity	During pregnancy	Yes	Higher risk for preeclampsia in treated HIV-positive women than in untreated HIV-positive women. No difference in the rate of preeclampsia between HIV-positive women (treated or untreated) and HIV-negative women
de Groot, 2003[54]	South Africa	Case-control	81 HIV-positive women/170 HIV-negative women	Adequate	Adequate	Unreported	Adequate	Age, marital status, parity, gravidity	During pregnancy	No	No difference in the rate of preeclampsia between HIV-positive women (8.6% treated) and HIV-negative women
Frank, 2004[55]	Johannesburg, South Africa	Cohort	2600	Adequate	Adequate	Unreported	Adequate	Age, parity, weight, hemoglobin level, clinic delivery, gestational age at delivery	During pregnancy	No	No difference in the rate of preeclampsia between untreated HIV-positive women and HIV-negative women

Continued on page 15.

TABLE 1
Characteristics of studies included in the systematic review according to type of infection and year of publication

Continued from page 14.

				Methodologic quality							
First author, year	Region, country	Design	Cases/controls or cohort size	Women selection	Assessment of infection and preeclampsia	Blinding	Lost to follow-up/ nonvalid exclusions or period of time for recruitment	Adjustment or matching	Moment of evaluation of exposure	Report of dose-response gradient	Main findings
Mattar, 2004[56]	Sao Paulo, Brazil	Case-control	123 HIV-positive women/1708 HIV-negative women	Adequate	Adequate	Unreported	Unreported	Age, parity, ethnic group	During pregnancy	No	Higher risk for preeclampsia in HIV-negative women than in treated HIV-positive women
Suy, 2006[57]	Barcelona, Spain	Cohort	8768	Adequate	Adequate	Adequate	Unreported	Age, race, smoking, parity, multiple pregnancy, drug abuse	During pregnancy	No	Higher risk for preeclampsia in treated HIV-positive women than in HIV-negative women
Bodkin, 2006[58]	Gauteng, South Africa	Case-control	212 HIV-positive women/101 HIV-negative women	Adequate	Adequate	Unreported	Adequate	None	During pregnancy	No	No difference in the rate of eclampsia between HIV-positive women (no treatment information) and HIV-negative women (6/212 vs 1/101)
Kourtis, 2006[59]	USA (nation-based, 1994 and 2003)	Cross-sectional	4,289,490 hospitalizations in 1994 and 4,507,655 hospitalizations in 2003	Adequate	Adequate	Adequate	Unreported	Age, primary payer, hospital location, region, drug abuse, anemia, urinary tract infection, sexually transmitted infections	During pregnancy	No	No difference in hospitalization rates for preeclampsia between HIV-infected women (no treatment information) and uninfected women
MALARIA											
Sartelet, 1996[60]	Dakar, Senegal	Case-control	32 women with preeclampsia/ 220 normal controls	Adequate	Adequate	Unreported	Adequate	Age, parity, twin delivery, date of delivery, maternity center	At delivery	No	Malaria infection of the placenta was associated with increased risk of preeclampsia
Shulman, 2001[61]	Kilifi, Kenya	Cohort	862	Adequate	Adequate	Unreported	Adequate	Parity, socioeconomic status, education, body mass index, HIV infection	At delivery	No	No association between malaria infection of the placenta and preeclampsia
Dorman, 2002[62]	Kilifi, Kenya	Cohort	509	Adequate	Adequate	Adequate	Adequate	None	32-35 weeks' gestation	No	No association between maternal malaria infection and preeclampsia
N'Dao, 2006[63]	Dakar, Senegal	Cohort	8273	Adequate	Adequate	Unreported	Unreported	Age, parity, residence, malaria chemoprophylaxis, acute episodes of malaria during pregnancy	At delivery	No	No association between malaria infection of the placenta and preeclampsia
BACTERIAL VAGINOSIS											
Kurki, 2000[64]	Helsinki, Finland	Cohort	623	Adequate	Inadequate	Unreported	Adequate	Age, smoking, marital status, social class, gravidity, alcohol consumption	8-17 weeks' gestation	No	No association between bacterial vaginosis and preeclampsia

Conde-Agudelo. Maternal infection and risk of preeclampsia. Am J Obstet Gynecol 2008.

TABLE 2
Sensitivity and subgroup analysis of meta-analysis of the relationship between urinary tract infection during pregnancy and preeclampsia

Subgroup	No. of studies (references)	Pooled odds ratio (95% confidence interval)
Statistical model		
Fixed effects	17[16-32]	1.57 (1.45-1.70)
Random effects	17[16-32]	1.86 (1.49-2.32)
Study design		
Cohort or cross-sectional	9[17,20,24-27,30-32]	1.54 (1.41-1.68)
Case-control	8[16,18,19,21,22,23,28,29]	1.79 (1.44-2.22)
Study quality		
Met ≥5 criteria	9[16,18,19,26,28-32]	1.46 (1.33-1.60)
Met <5 criteria	8[17,20-25,27]	1.99 (1.69-2.33)
Sample size		
<100 women with preeclampsia	9[16-19,21,22,24,25,28]	1.65 (1.30-2.11)
≥100 women with preeclampsia	8[20,23,26,27,29-32]	1.56 (1.44-1.70)
Geographic location of study		
North America	7[16,17,23,26-29]	1.99 (1.75-2.25)
Australia	3[18,22,24]	2.33 (1.52-3.56)
Europe	3[20,21,32]	1.24 (1.08-1.41)
Developing countries	4[19,25,30,31]	1.54 (1.28-1.85)
Year of publication		
Before 1990	9[16-24]	1.58 (1.27-1.97)
At or after 1990	8[25-32]	1.57 (1.44-1.71)
Adjustment for at least maternal age and socioeconomic status		
No	10[17-25,27]	2.05 (1.77-2.39)
Yes	7[16,26,28-32]	1.40 (1.27-1.55)
Type of infection		
Bacteriuria	10[16-25]	1.60 (1.30-1.98)
Urinary tract infection*	7[26-32]	1.57 (1.44-1.71)

* Includes asymptomatic bacteriuria, cystitis, and pyelonephritis.

Conde-Agudelo. Maternal infection and risk of preeclampsia. Am J Obstet Gynecol 2008.

women with urinary tract infection during pregnancy were 57% (95% CI, 45-70) more likely to develop preeclampsia than women without urinary tract infection. There was statistical heterogeneity among studies results as confirmed by I^2 value of 79%. An examination for sources of heterogeneity found that studies rated as non–high quality, case-control design, that were conducted in North America or Australia, or that did not adjust for at least maternal age and socioeconomic status were associated with higher pooled ORs (Table 2). On the other hand, studies rated as high quality or that were conducted in European countries were associated with a reduction in the pooled ORs. Sample size, year of publication, and type of infection failed to provide an explanation for study results heterogeneity because the pooled ORs calculated from these subgroups were very similar to the overall pooled OR.

Periodontal disease

Seven case-control studies[34-36,38-41] and 2 cohort studies[33,37] rated as being of high quality, including a total of 639 preeclamptics, evaluated the association between periodontal disease and preeclampsia. Six of the 7 studies that used the most stringent criteria for diagnosing periodontal disease (pocket depth, clinical attachment level, bleeding on probing, and gingival inflammation), found that active maternal periodontal disease detected within 48 hours before or after delivery,[33-36,39] or 3-28 months' postpartum[40] was associated with an increased risk for the development of preeclampsia. In contrast, a cohort study, including 1562 economically disadvantaged women living in Argentina,[37] failed to identify a relationship between periodontal disease and preeclampsia (OR, 0.99; 95% CI, 0.70-1.40). Nevertheless, this study did not adjust for maternal age and socioeconomic status, and did not use all the above mentioned parameters for diagnosing periodontal disease. A case-control study from Colombia[36] reported microorganisms *Porphyromonas gingivalis*, *Tannerella forsythensis*, and *Eikenella corrodens* were significantly more prevalent in the preeclamptic group than in normotensive controls. The study from The Netherlands[40] found microorganism *Micromonas micros*, a known bacterial marker for destructive periodontal disease, was more prevalent in the early onset preeclampsia group than in normotensive group. Nevertheless, there was no significant difference in the presence of other periodontophatic microorganisms such as *Porphyromonas gingivalis*, *Tannerella forsythensis*, *Fusobacterium nucleatum*, and *Prevotella intermedia*. Two studies[33,36] reported a dose-response association in which the severity of periodontal disease was directly associated with the risk of preeclampsia (pooled OR, 2.37; 95% CI, 1.56-3.59 for mild periodontal disease, and 3.90; 95% CI, 2.32-6.55 for severe periodontal disease). Overall, women with evidence of periodontal dis-

ease during pregnancy had a 76% (95% CI, 43-118) increased risk of preeclampsia compared with women without periodontal disease. The large heterogeneity of the study-specific ORs (80%) was due primarily to the results of the Argentinean study. Restricting the metaanalysis to the 5 studies that used the most stringent criteria for diagnosing periodontal disease and that adjusted for at least maternal age and socioeconomic status,[33,34,36,39,40] produced a less heterogeneous (I^2 = 32%) pooled OR of 2.62 (95% CI, 1.97-3.49).

Three case-control studies did not provide data in a format to be included in the metaanalysis.[35,38,41] One of these studies[35] reported that the mean pocket depth and clinical attachment level scores, and levels of proinflammatory mediators prostaglandin E2, tumor necrosis factor-α, and interleukin-1β were significantly higher in the preeclamptic group than in normotensive controls. Another study,[38] which included 115 women with preeclampsia and 230 normotensive controls from Jordan, found the number of decayed surfaces in the preeclampsia group was significantly higher compared to the controls. Nonetheless, no association was found between preeclampsia and other periodontal parameters such as probing depth, clinical attachment level, plaque index, and gingival recession. A recent study[41] from Israel used polymerase chain reaction to detect periodontal bacteria in placental tissue obtained from cesarean sections of women with preeclampsia (n = 16) and normotensive controls (n = 14). In the preeclampsia group, 8 of the 16 placenta specimens were positive for 1 or more periopathogenic bacteria compared to only 2 of the 14 samples from controls (OR, 6.0; 95% CI, 1.0-35.9). Bacterial counts were significantly higher in the preeclampsia group than in the control group for all of the 6 periopathogenic bacteria examined (*Tannerella forsythensis*, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Treponema denticola*).

Chlamydia pneumoniae

Four case-control studies[44,46,47,50] and 2 cohort studies,[45,49] involving a total of 251 cases of preeclampsia, evaluated the relationship between seroprevalence of antibodies to *Chlamydia pneumoniae* and preeclampsia. All assessed the presence of IgG antibodies, whereas 3 each assessed IgM[44,49,50] and IgA[44,49,50] antibodies. Four studies detected *Chlamydia pneumoniae* antibodies by enzyme linked immunoassays[46,47,49,50] and 2 by microimmunofluorescence assays.[44,45] Four studies adjusted for maternal age[44-47] but none reported adjustment for socioeconomic status. Two studies reported that women with preeclampsia had higher seroprevalence of IgG antibodies to *Chlamydia pneumoniae* than controls.[44,50] The remaining 4 studies did not report an association between *Chlamydia pneumoniae* IgG seropositivity and preeclampsia.[45-47,49] In 2 of these studies,[45,46] the seroprevalence of IgG antibodies to *Chlamydia pneumoniae* was lower in women with preeclampsia than in normotensive controls although this difference was not statistically significant. One study found that parous women with previous preeclampsia had higher levels of IgG, IgM, and IgA antibodies to *Chlamydia pneumoniae* than parous women with no previous preeclampsia.[49] The only study that evaluated the risk of preeclampsia according to increasing titers of IgG antibodies to *Chlamydia pneumoniae* failed to find a dose-response association.[44] The metaanalysis yielded a heterogeneous pooled OR of 1.11 (95% CI, 0.81-1.53) for the relationship between *Chlamydia pneumoniae* IgG seropositivity and preeclampsia. Subsidiary analyses yielded a pooled OR of 2.64 (95% CI, 1.15-6.04) in the 2 studies that used microimmunofluorescence assays for detecting antibodies and an OR of 2.17 (95% CI, 1.09-4.31) in the 2 studies that did not adjust for confounding factors. Pooled ORs obtained from the 4 studies that used enzyme-linked immunoassays to detect antibodies, the 4 case-control studies, the 2 cohort studies, and the 4 studies that adjusted for confounding factors were similar to overall pooled OR supporting a lack of association between *Chlamydia pneumoniae* IgG seropositivity and preeclampsia. There was no significant difference in the seroprevalence of IgM and IgA antibodies to *Chlamydia pneumoniae* between women with preeclampsia and normotensive ones in the studies that reported these data.

Other persistent bacterial and viral infections

Two studies reported no association between seroprevalence of IgG antibodies to cytomegalovirus and preeclampsia.[42,46] One, however, found that women with early onset preeclampsia had higher levels of IgG antibodies to cytomegalovirus than controls.[46] In another study,[43] where cytomegalovirus was detected by means of polymerase chain reaction, no significant difference in rates of positivity between preeclamptic women (54%) and normotensive controls (41%) were found. Nevertheless, the presence of cytomegalovirus increased the risk of developing preeclampsia in women carrying specific HLA-DRB1 alleles (OR, 40.3; 95% CI, 3.6-450.2), although this study included only 27 cases of preeclampsia. Two studies evaluated the association between seroprevalence of IgG antibodies to *Helicobacter pylori* and preeclampsia.[45,52] One from Italy[52] found that women with preeclampsia had a significantly higher seroprevalence of IgG antibodies to *Helicobacter pylori* than controls whereas a study from Ecuador[45] failed to detect a significant association. The presence of IgG antibodies to herpes simplex virus type 2,[42] *Mycoplasma hominis* in amniotic fluid,[48] and bacterial vaginosis[64] was not associated with increased risk of preeclampsia. One study[42] reported that women destined to develop preeclampsia had lower seroprevalence of IgG antibodies to Epstein–Barr virus at gestational week 10 than normotensive controls. In a recent case-control study, adeno-associated virus-2 DNA was detected significantly more often in extravillous or villous trophoblast cells from women with severe preeclampsia than from normotensive controls (OR, 5.38; 95% CI, 1.70-17.05).[51] Moreover, this

study demonstrated that adeno-associated virus-2 efficiently infected extravillous trophoblast cells and that such infection induced decreased cell invasion before causing trophoblast cell death.

HIV infection

Seven studies[53-59] evaluated the association between HIV infection during pregnancy and the risk of preeclampsia yielding conflicting results. A case-control study from the United Kingdom first reported that among HIV-positive women, those who received no antiretroviral therapy had a rate of preeclampsia significantly lower than those on triple antiretroviral therapy (0% and 10.5%, respectively).[53] However, there was no significant difference in the rate of preeclampsia between HIV-positive women (treated or untreated) and HIV-negative women. The authors suggested that the association of HIV-related immune deficiency with a low rate of preeclampsia, and the restoration of this rate in women treated with triple antiretroviral therapy to the expected rate would indicate a role of the immune system in the pathogenesis of preeclampsia. A cohort study from Spain[57] reported that, compared with HIV-negative women, HIV-positive women treated with highly active antiretroviral therapy prior to pregnancy had a significantly higher risk for preeclampsia (adjusted OR, 4.9; 95% CI, 2.4-10.1). On the contrary, a case-control study from Brazil[56] found that HIV-positive women treated with antiretroviral therapy had a significantly lower risk for preeclampsia than HIV-negative controls (OR, 0.07; 95% CI, 0.01-0.49). Three other studies failed to show any association between HIV infection and both preeclampsia[54,55] and eclampsia.[58] A recent large nationwide cross-sectional study from the United States[59] reported no difference in hospitalization rates for preeclampsia between HIV-infected women and uninfected women (adjusted OR, 1.13; 95% CI, 0.82-1.56) in 1994, and adjusted OR, 1.00; 95% CI, 0.82-1.21 in 2003). Unfortunately, no treatment information was available in this study. Overall, treated and untreated HIV infection was not associated with the risk of developing preeclampsia (pooled OR, 0.76, 95% CI, 0.46-1.26 and pooled OR, 0.97; 95% CI, 0.67-1.39), respectively.

Malaria and preeclampsia

Four studies, which included about 10,000 women in total, assessed the relationship between malaria and preeclampsia. In 3,[60,61,63] malaria infection of the placenta was defined by histological observation of infected red cells or malaria pigment in macrophages, whereas in the remaining study,[62] malaria parasites were detected in blood using Giemsa staining at 32-35 weeks' gestation. The case-control study from Senegal[60] reported a significant association between malaria infection of the placenta and the risk of preeclampsia. Moreover, an increased proportion of cases of preeclampsia among deliveries occurred during the transmission seasons of malaria. The 3 cohort studies did not find a significant association between placental or maternal malaria infection and the risk of preeclampsia. The pooled OR for the association between malaria infection and preeclampsia was 0.93 (95% CI, 0.72-1.21).

Table III summarizes the pooled unadjusted and adjusted ORs from observational studies reporting the association between maternal infection and preeclampsia. Urinary tract infection and periodontal disease were significantly associated with an increased risk of preeclampsia. The pooled adjusted ORs for these associations were somewhat lower than pooled unadjusted ORs but remained statistically significant. There was no association between the other maternal infections evaluated and the risk of preeclampsia. No evidence of publication biases were observed, as indicated by symmetric funnel plots (available from the authors on request) and a nonsignificant Egger test ($P > .10$ for all of the associations we studied).

Treatment of maternal infection and risk of preeclampsia

Three clinical trials evaluated the effect of antibiotic treatment for bacteriuria during pregnancy on the risk of preeclampsia. One randomized controlled trial from Australia involving 145 women noted that treatment with sulphamethoxydiazine or sulphadimidine compared to placebo did not affect the risk of preeclampsia (OR, 1.18; 95% CI, 0.40-3.44).[18] Two nonrandomized clinical studies from Germany[65] and Croatia[66] (total of 1619 women) reported that, compared to women with nontreated bacteriuria, antibiotic treatment for bacteriuria was associated with a statistically significant reduction in the incidence of preeclampsia (OR, 0.22; 95% CI, 0.17-0.30 and OR, 0.36; 95% CI, 0.20-0.64), respectively). Results from a nonrandomized clinical study from Italy[67] (731 women), indicated that, compared to low risk women who did not take any antibiotic during pregnancy, pregnant women treated with spiramycin because of seroconversion for *Toxoplasma gondii* had a lower incidence of preeclampsia, although the difference was not statistically significant (OR, 0.32; 95% CI, 0.06-1.68).

Recently, Michalowicz et al[68] reported the results of a multicenter trial in which 823 pregnant women with periodontal disease were randomly assigned to undergo scaling and root planing either early in the second trimester or after delivery (the control group). Periodontal treatment during pregnancy did not significantly alter rates of preterm birth (12.0% in the treatment group and 12.8% in the control group) or preeclampsia (7.6% in the treatment group and 4.9% in the control group).

Comment

Our study, using the most rigorous methodology for performing systematic reviews of observational studies, demonstrates that both urinary tract infection and periodontal disease during pregnancy are associated with an increased risk of preeclampsia. Moreover, there is some evidence suggesting that treating urinary tract infections during pregnancy reduces the incidence of preeclampsia. These data support the hypothesis that infection may play a causal

TABLE 3
Pooled odds ratios of the relationship between maternal infection and preeclampsia

Infection	No. of studies	Fixed-effects Odds ratio (95% CI)	Fixed-effects I^2 (%)*	Random effects Odds ratio (95% CI)
Pooled unadjusted results				
Urinary tract infection	17[16-32]	1.57 (1.45–1.70)	79	1.86 (1.49-2.32)
Periodontal disease	6[33,34,36,37,39,40]	1.76 (1.43-2.18)	80	2.37 (1.36-4.14)
Chlamydia pneumoniae IgG seropositivity	6[44-47,49,50]	1.11 (0.81–1.53)	64	1.36 (0.73-2.50)
Chlamydia pneumoniae IgM seropositivity	2[44,50]	1.62 (0.72-3.63)	0	1.57 (0.69-3.56)
Chlamydia pneumoniae IgA seropositivity	2[44,50]	1.47 (0.77-2.82)	0	1.47 (0.76-2.83)
Cytomegalovirus positivity	3[42,43,46]	0.85 (0.52-1.39)	13	1.13 (0.50-1.46)
Helicobacter pylori IgG seropositivity	2[45,51]	1.76 (0.82-3.75)	42	1.48 (0.47-4.70)
HIV infection treated	3[53,56,57]	0.76 (0.46-1.26)	93	0.78 (0.08-7.57)
HIV infection non-treated	2[53,55]	0.97 (0.67-1.39)	52	0.60 (0.10-3.77)
Malaria	4[60-63]	0.93 (0.72-1.21)	73	1.03 (0.59-1.82)
Pooled adjusted results				
Urinary tract infection	8[16,26-32]	1.50 (1.37-1.64)	76	1.70 (1.35-2.14)
Periodontal disease	6[33,34,36,37,39,40]	1.74 (1.39-2.17)	63	2.29 (1.33-3.94)
Malaria	3[60,61,63]	1.00 (0.74-1.35)	61	1.15 (0.66-2.01)

CI, confidence interval.

* Heterogeneity test.

Conde-Agudelo. Maternal infection and risk of preeclampsia. Am J Obstet Gynecol 2008.

role in the development of preeclampsia or its phenotypes.

The relationship between urinary tract infection and preeclampsia, consistent throughout studies performed over a 40-year period, and present in diverse populations worldwide, was present in virtually every way the data were examined. We did not find evidence associating preeclampsia with *Chlamydia pneumoniae* infection, untreated or treated HIV infection, or malaria. Studies concerning other infectious agents such as cytomegalovirus, *Helicobacter pylori*, herpes simplex virus type 2, *Mycoplasma hominis*, Epstein–Barr virus, and bacteria associated with bacterial vaginosis were too few and/or of small sample sizes, precluding meaningful conclusions of any associations with preeclampsia.

Several mechanisms have been proposed to explain how maternal infection might be involved in the etiology of preeclampsia or its manifestations. These include direct effects of infectious agents on the arterial wall, including endothelial injury or dysfunction, acute atherosis, and local inflammation that might cause relative uteroplacental ischemia.[7] Of interest in the latter respect is a recent report noting increased circulating maternal soluble fms-like tyrosine kinase-1 levels (an antiangiogenic factor associated with preeclampsia) in nulliparas with placental malaria and hypertension.[69] Recently, Arechavaleta-Velasco et al,[51] using in vivo and in vitro models, demonstrated that adeno-associated virus-2 infection can induce placental dysfunction by inhibiting invasion of extravillous trophoblast cells and by causing trophoblast cell death. In addition, Lamarca et al,[70] utilizing a first trimester extravillous cytotrophoblast cell line, reported that human cytomegalovirus impairs placentation through inhibition of cytotrophoblast invasion. Most hypotheses, however, focus on indirect effects mediated by enhancing the maternal systemic inflammatory response,[6,7] similarities between acute atherosis in preeclampsia and atherosclerosis,[71] the increased risk of remote cardiovascular disease after an episode of preeclampsia,[72] and the modest association observed between coronary heart disease and chronic infections by bacteria and viruses.[73] Although there is no evidence linking endotoxin to preeclampsia in humans, clinical features similar to preeclampsia were induced in pregnant rats infused with *Escherichia coli* endotoxin.[74]

The relationship between urinary tract infection and preeclampsia may not be real but due to confounding circumstances. For example, pyelographic abnormalities (ie, calculi, duplex kidneys, changes associated with chronic pyelonephritis, and papillary necrosis) have been noted in 18-44% of the women with bacteriuria during pregnancy[18,75,76] and these underlying diseases and/or the associated impairment of renal function they cause could, thus, account for the higher risk of preeclampsia among women with bacteriuria. This might also

explain why eradicating bacteriuria with antibiotic therapy failed to decrease the incidence of preeclampsia in the only randomized controlled trial we located.[18] Regardless of whether the relationship between urinary tract infection and preeclampsia is causal or simply associative, all forms of urinary tract infection in pregnant women must be treated for reducing the risk of low birth weight.[77]

We also identified a relationship between periodontal disease and preeclampsia. In this respect, Boggess et al[33] have suggested that women with active periodontal disease during pregnancy may have transient translocation of oral pathogens to the uteroplacental unit, inciting placental inflammation or oxidative stress in pregnancy, which ultimately produces placental damage and the clinical manifestations of preeclampsia. Nevertheless, it is possible that preeclampsia leads to an aggravation of preexisting periodontal problems or even coinduces periodontal disease.[78]

Our systematic review is subject to several limitations. First, individual studies may have failed to control for potential confounders or to take into account potential effect modifiers. Carreiras et al,[43] for example, noted that cytomegalovirus infection increases dramatically the risk to develop preeclampsia in women carrying specific HLA-DRB1 alleles. This and other genetic factors are potential effect modifiers that were not addressed in most studies. This issue needs further investigation. Also, only 30% of the studies explicitly adjusted for socioeconomic status, considered by some as an important confounding factor in the association between maternal infection and preeclampsia. Even if adjustments for some confounding factors are made, residual confounding remains a potentially serious problem in observational research. Second, because there was an important degree of heterogeneity in most of the metaanalyses, pooled results have to be interpreted cautiously. We explored the sources of heterogeneity for the association between urinary tract infection and preeclampsia and no plausible explanations were provided by the methodologic quality of the study, design, sample size, date of publication, adjustment for confounders, and the type of infection evaluated. For the association between periodontal disease and preeclampsia, the heterogeneity was explained mainly by 1 study which did not use the most stringent criteria for diagnosing periodontal disease and did not adjust for important confounding factors such as maternal age and socioeconomic status. Third, although publication bias does not seem to be a factor in our metaanalyses, we cannot exclude it as the funnel plot may not detect publication bias when the number of studies is small. Finally, the number of studies available for analysis on the association between several other maternal infections and preeclampsia is still too small to provide conclusive evidence.

Data from observational studies might be indirectly tested in clinical trials that evaluated the effects of administering antibacterial treatments to pregnant women with urinary tract infection. The identified studies yielded conflicting results. Two nonrandomized clinical studies[65,66] found antibiotic treatment compared to no treatment significantly reduced the incidence of preeclampsia whereas the only randomized controlled trial found that antibiotic treatment compared to placebo did not affect the risk of preeclampsia.[18] With regard to the effect of treatment of periodontitis in pregnant women on the development of preeclampsia, a recent randomized controlled trial found a nonsignificant increased risk of preeclampsia (OR, 1.59; 95% CI, 0.89-2.83) among women who received periodontal scaling and root planing (ie, removal of dental plaque and calculus from the tooth enamel and root) before 21 weeks as compared to women who underwent scaling and root planing after delivery.[68] This unexpected finding could be explained by a transient acute systemic inflammatory response and a transient impairment of endothelial function associated to the local intensive mechanical treatment of periodontitis in nonpregnant adults with severe periodontitis.[79] Three large randomized controlled trials of treatment of periodontal disease are underway and will help clarify whether periodontal treatment has any role in reducing the rate of preeclampsia and/or other pregnancy complications.[80]

If the observed association between preeclampsia and both urinary tract infection and periodontal disease is indeed causal in nature, there might be roles for antibiotic or antiviral therapy in preventing or treating preeclampsia. Nevertheless, more studies are needed to determine whether the relationship between maternal infection and preeclampsia is causal or simply associative and to explore the mechanisms of these potential associations. Observational studies should be large enough for moderate-sized effects to be assessed or refuted reliably, include clear and consistent definitions of infections and preeclampsia, and adjust for indicators of socioeconomic status and other potential confounding factors in order to help reduce any residual confounding. ■

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