OBSTETRICS

Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis

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OBJECTIVE: We performed an individual participant data (IPD) meta-analysis to calculate the recurrence risk of hypertensive disorders of pregnancy (HDP) and recurrence of individual hypertensive syndromes.

STUDY DESIGN: We performed an electronic literature search for cohort studies that reported on women experiencing HDP and who had a subsequent pregnancy. The principal investigators were contacted and informed of our study; we requested their original study data. The data were merged to form one combined database. The results will be presented as percentages with 95% confidence interval (CI) and odds ratios with 95% CI.

RESULTS: Of 94 eligible cohort studies, we obtained IPD of 22 studies, including a total of 99,415 women. Pooled data of 64 studies that used published data (IPD where available) showed a recurrence rate of 18.1% (n = 152,213; 95% CI, 17.9—18.3%). In the 22 studies that are included in our IPD, the recurrence rate of a HDP was 20.7% (95% CI, 20.4—20.9%). Recurrence manifested as preeclampsia in 13.8% of the studies (95% CI,13.6—14.1%), gestational hypertension in 8.6% of the studies (95% CI, 8.4—8.8%) and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome in 0.2% of the studies (95% CI, 0.16—0.25%). The delivery of a small-for-gestational-age child accompanied the recurrent HDP in 3.4% of the studies (95% CI, 3.2—3.6%). Concomitant HELLP syndrome or delivery of a small-for-gestational-age child increased the risk of recurrence of HDP. Recurrence increased with decreasing gestational age at delivery in the index pregnancy. If the HDP recurred, in general it was milder, regarding maximum diastolic blood pressure, proteinuria, the use of oral antihypertensive and anticonvulsive medication, the delivery of a small-for-gestational-age child, premature delivery, and perinatal death. Normotensive women experienced chronic hypertension after pregnancy more often after experiencing recurrence (odds ratio, 3.7; 95% CI, 2.3—6.1).

CONCLUSION: Among women that experience hypertension in pregnancy, the recurrence rate in a next pregnancy is relatively low, and the course of disease is milder for most women with recurrent disease. These reassuring data should be used for shared decision-making in women who consider a new pregnancy after a pregnancy that was complicated by hypertension.

Key words: gestational hypertension, HELLP syndrome, IPD, pre-eclampsia, pregnancy, recurrence

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Hypertensive disorders of pregnancy (HDP) are a common health problem and are the second most common cause of maternal death worldwide, with major intriguing regional differences worldwide.[1] They complicate approximately 2-8% of all pregnancies[2-4] and comprise gestational hypertension (GH), preeclampsia, superimposed preeclampsia, and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome; in a varying percentage of cases, the disorders are related to intrauterine growth restriction. There is probably important heterogeneity in pathophysiologic and clinical phenotype between subgroups and individual women, with maternal endothelial dysfunction as a central phenomenon, caused by an excessive maternal response to placental material. Furthermore an HDP identifies the woman who is at risk for cardiovascular disease later in life, probably because of shared risk factors and pathophysiologic evidence.[2,4]

HDP can also have a major psychologic impact on the woman and her family.[5] As such, counseling on recurrence of a hypertensive disease in a future pregnancy is important. Consequently, many studies have focused on the investigation of recurrence rates of HDP. Interpretation of these studies, however, is difficult because of many potential sources of bias, including patient selection and study methods. This causes every cohort to have a specific case mix of different clinical phenotypes and macroethnicities. Reported recurrence rates range from a few percent up to 65%.[6] Similarly, the performance of individualized risk prediction models has been disappointing because HDP have heterogeneous pathophysiologic characteristics.[7] In addition, suboptimal size and generalizability of studies cause these prediction models to be unsatisfactory.[7] Recurrence rates of the individual syndromes of HDP in literature for preeclampsia can be found ranging up to 65%[6] and for HELLP syndrome can range from 2-3%.[8,9] Recurrence of GH has not been explored in many studies. Delivering a small for gestational age (SGA) child recurs in approximately 24% of pregnancies.[10]

Individual participant data (IPD) metaanalysis is new to prognostic research.[11] In contrast to conventional metaanalysis, it uses the IPD of the original studies, thus enlarging the study population and increasing statistical power to detect subtle relationships. In contrast to aggregated data metaanalysis, it permits synthesis at an individual level, which creates flexibility in choosing outcome and subgroups. Additionally, it allows redefinition of outcomes or predictors based on continuous variables and usage of information that did not reach publication in the original research.

The primary goal of this IPD metaanalysis study was to calculate the recurrence risk of HDP. Secondarily, we aimed to show the recurrence of individual hypertensive syndromes.

Materials and Methods

Sources

We performed a literature search in the electronic libraries PubMed (Medline) and Embase. Language restrictions or restrictions on publication date were not applied. The search covered all records until August 2012. The following terms were used: "preeclampsia" [MeSH] AND [early OR severe OR pre-term OR early onset OR 32 OR 34 OR 37] AND [history OR previous OR secondary OR subsequent OR recurrence]. Cross-references of the selected studies were checked to identify other studies of interest. All studies that described cohorts of women with a history of a hypertensive disorder that resulted in a delivery at any gestational age were eligible for inclusion. Inclusion was not restricted to any study design, apart from for case-control studies, where recurrence was a prerequisite. Studies that did not report recurrence of preeclampsia in the publication, but was thought to have this information in the original data, were also considered eligible. If data between studies overlapped, only the larger of the 2 studies was included. Two independent reviewers (M.F.vO. and J.L.) screened the identified articles for eligibility based on title and abstract. Discrepancies were resolved by a third reviewer (W.G.).

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Data collection

For each of the eligible articles, contact information of the first, second, or last author was obtained through Medline, Embase, or the Internet. We approached the authors by email to inform them about the IPD metaanalysis project and to invite them to share their data. If authors were willing to participate, they were provided a more detailed study proposal and asked to send their original database. Variables and categories needed to be labeled adequately within the original database or in a separate data dictionary. Data of women who had a subsequent pregnancy after the hypertensive pregnancy were included. We focused on collecting demographic characteristics that included age, body mass index (BMI), cardiovascular risk factors, and the clinical syndrome of the index pregnancy. The quality of all studies that were included was evaluated with the Newcastle Ottawa Scale for cohort studies.[12]

Definitions

HDP were defined as GH, preeclampsia, superimposed preeclampsia, or HELLP syndrome. Nonhypertensive pregnancies with an SGA child were excluded. Chronic hypertension was not an exclusion criterion for the IPD but was in some individual studies.

Preeclampsia was defined as hypertension (diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg on 2 occasions that were 4-5 hours apart) in combination with *proteinuria* (defined as a positive [0.3 g/L] proteinuria dipstick test, a protein/creatinine ratio of ≥30 mg/mmol in a random sample or an urine protein excretion of ≥300 mg for 24 hrs) after 20 weeks' gestation.[13] Mild or severe preeclampsia was not separately defined, because only some of the studies made this distinction in their data. Women with hypertension at >20 weeks' gestation without proteinuria or a significant rise in blood pressure (if a woman had known chronic hypertension) were considered to have GH. *Chronic hypertension* was defined as the presence or a history of preconceptional hypertension or detection of hypertension in the first one-half of the pregnancy. De novo proteinuria or a sudden increase in proteinuria if already present, qualified women with chronic hypertension for superimposed preeclampsia.[13] *HELLP syndrome* was defined by hemolysis (elevated lactate dehydrogenase levels [≥600 U/L], elevated liver enzymes by levels of aspartate transaminase or alanine transferase ≥70 U/L, and low platelets <100,000/mm).[14] HELLP syndrome in combination with hypertension was also classified as preeclampsia. *SGA* was defined as birthweight <10th percentile, according to the American College of Obstetricians and Gynecologists practice bulletin,[15] and adjusted for gestational age based on a local reference population. The exact definitions for the hypertensive syndromes that were used in the included studies were not retrievable for a few studies that were published as abstracts.[16,17] Nevertheless, we presume that the authors concur about the international accepted criteria, which were described earlier.

The primary outcome was the recurrence of any HDP in the next subsequent pregnancy. Secondarily, we aimed to show the recurrence of individual hypertensive syndromes.

Statistical analysis

Most studies focused on detailed data of the subsequent pregnancy, whereas some studies registered only details of the index pregnancy. To use the data as best as possible, we combined data of the index and subsequent pregnancy for BMI, smoking, medical history, and chronic hypertension. If, for example, BMI was recorded at the time of the second pregnancy, but not at the index pregnancy, then we copied the second pregnancy BMI information.

Not all the dependent or independent variables have been registered in every database. Results therefore are accompanied with the number of cases in which the variable was registered (n). Proportions are presented as percentages of n, rather than as percentages of the total population. For descriptive analysis, we expressed continuous variables as mean with standard deviation or median with interquartile range, as appropriate. We decided not to use imputation because the pattern of systematic missing values cannot be extrapolated between databases.

Differences in outcomes between the index and subsequent pregnancy were investigated with the use of a random intercept/random effects binomial regression model for dichotomous outcomes and of a random intercept random/effects linear regression model for continuous outcomes. A random intercept was fitted per study to account for the fact that the baseline risk between studies may differ. Based on Akaike's information criterion, the random effects model was compared with a fixed effects model, and the model with the lowest Akaike's information criterion was used as the final model for analysis for that outcome. Heterogeneity across studies was assessed with the I^2 measure, and the values were interpreted in the following manner: 0% indicates no observed heterogeneity; 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.[18] Probability

FIGURE 1
Inclusion of articles

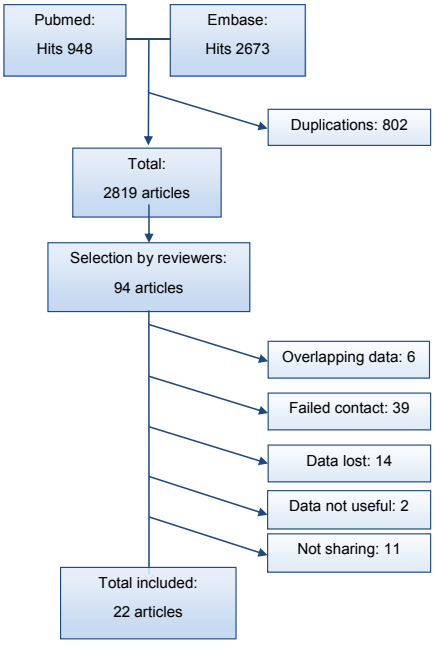

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TABLE 1
Overview of study characteristics of the included studies

Study	Country	Inclusion criteria	Exclusion criteria	Study design	Therapeutic trial	Total women original study, n	Total includable women,[a,b] n (%)
Beroyz et al, 1994[19]	United Kingdom	Previous preeclampsia; previous FGR; chronic hypertension; renal disease; signs of preeclampsia or FGR in current pregnancy	Bleeding disorders; asthma; allergy to aspirin	Randomized controlled trial	Aspirin vs placebo	9364	156 (59)
Brown et al, 2007[20]	Australia	Previous preeclampsia; previous GH; chronic hypertension; essential hypertension and superimposed preeclampsia	Not reported	Retrospective cohort study	—	1354	765 (32)
Byaruhanga et al, 1998[21]	South Africa	Previous preeclampsia; previous GH; chronic hypertension	History of hypersensitivity to aspirin, peptic ulcer, bleeding disorders, or chronic, pulmonary disease; use of NSAIDs; development of preeclampsia before trial entry	Randomized controlled trial	Aspirin vs placebo	250	213 (15)
Cameroni et al, 2011[16]	Italy	Previous preeclampsia; previous FGR; previous placental abruption; previous stillbirth; chronic hypertension	—	Retrospective cohort study	—	218	173 (10)
Campbell et al, 1985, 2010[17,22]	United Kingdom	Total population of the Aberdeen Maternity and Neonatal Data Bank	—	Retrospective cohort study	—	38,130	7725 Extended extraction[b] (26)
Chappell et al, 1999[23]	United Kingdom	Previous preeclampsia at <37 wks' gestation; previous HELLP or eclampsia at any GA; abnormal uterine- artery Doppler waveform in pregnancy	Heparin or warfarin treatment; fetal abnormalities; multiple pregnancy	Randomized controlled trial	Antioxidants (vitamin C and E) vs placebo	283	56 (50)
Chiaffarino et al, 2004[24]	Italy	Previous severe preeclampsia or eclampsia; previous FGR; previous intrauterine fetal death	Chronic disease other than hypertension, renal disease, or diabetes mellitus; allergy to aspirin; fetal malformations; current twin pregnancy	Randomized controlled trial	Aspirin vs no treatment	40	15 (47)

van Oostwaard. Individual participant data metaanalysis on the recurrence of HDP. Am J Obstet Gynecol 2015.

(continued)

TABLE 1
Overview of study characteristics of the included studies *(continued)*

Study	Country	Inclusion criteria	Exclusion criteria	Study design	Therapeutic trial	Total women original study, n	Total includable women,[a,b] n (%)
Conserva et al, 2012[25]	Italy	Previous preeclampsia; previous HELLP; previous GH; previous FGR; previous placental abruption; previous FGR and stillbirth	Acquired thrombophilia; clinical immune disease; treatment with LMWH in previous pregnancy; congenital fetal anomaly; non-white ethnicity	Prophylactic trial	Enoxaparin	128	53 (11)
Facchinetti et al, 2009[26]	Italy	Previous preeclampsia in singleton pregnancy; complete evaluation for thrombophilia; current singleton pregnancy	History of thromboembolic diseases; renal and/or cardiovascular disorder; systemic lupus erythematosus; diabetes mellitus; any ethnic group other than white	Prospective cohort study	—	172	172 (34)
Ferrazzani et al, 2006[27]	Italy	Previous severe preterm preeclampsia with associated FGR	Previous HELLP syndrome	Prophylactic trial	Aspirin vs aspirin and heparin	68	54 (15)
Figueiro-Filho et al, 2012[28]	Brazil	Previous severe preeclampsia with one of the following: hospitalization at <32 wks' gestation, imminent eclampsia, eclampsia, HELLP syndrome, systemic laboratory tests, preterm birth at <34 wks' gestation, admission of newborn infants in NICU, fetal loss, fetal growth restriction, oligohydramnios, abnormal uterine or umbilical artery Doppler	Chronic hypertension; systemic lupus erythematosus; thrombophilia	Prospective cohort study	—	113	67 (50)
Gaugler-Senden et al, 2008[29]	The Netherlands	Previous severe preeclampsia at <24 wks' gestation	—	Retrospective cohort study	—	20	18 (83)
Langenveld et al, 2011[30]	The Netherlands	Previous preeclampsia, GH, or HELLP at <34 wks' gestation in singleton pregnancy	Fetal abnormalities	Retrospective cohort study	—	380	211 (55)
Lykke et al, 2009[31]	Denmark	All women with 2 singleton deliveries in the National Patient Registry	Cardiovascular diagnosis; diabetes mellitus; women who died or emigrated within 3 months of the second delivery	Retrospective cohort study	—	536,419	26,939 (20)
Mbah et al, 2012[32]	United States	All women with 2 pregnancies registered in the Missouri maternally linked cohort database 1989-2005	—	Retrospective cohort study	—	166,712	23,390 (17)

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TABLE 1
Overview of study characteristics of the included studies *(continued)*

Study	Country	Inclusion criteria	Exclusion criteria	Study design	Therapeutic trial	Total women original study, n	Total includable women,[a,b] n (%)
Napolitano et al, 2011[33]	United Kingdom	All nulliparous women; parous women with previous preeclampsia or FGR; concurrent maternal medical conditions; >7 years since last pregnancy	Miscarriage at <14 wks' gestation; fetal chromosomal or structural abnormalities	Prospective cohort study	—	6221	273 (26)
van Oostwaard et al, 2012[34]	The Netherlands	Previous preeclampsia, GH, HELLP, or FGR at 34-37 wks' gestation	Fetal abnormalities	Retrospective cohort study	—	425	189 (34)
van Oostwaard et al, 2014[35]	The Netherlands	Previous preeclampsia, GH, or HELLP at >37 wks' gestation	Fetal abnormalities	Retrospective cohort study	—	638	312 (41)
Poston et al, 2006[36]	United Kingdom	Previous preeclampsia at <37 wks' gestation; previous HELLP or eclampsia at any GA; other risk factors for hypertensive disease (essential hypertension, diabetes mellitus, renal disease, antiphospholipid syndrome, abnormal uterine-artery Doppler waveform in pregnancy, or BMI >30 kg/m^2)	No informed consent; warfarin treatment; using vitamins before trial	Randomized controlled trial	Vitamins (vitamin C and E) vs placebo	2404	556 (29)
Salim et al, 2008[37]	Israel	IUFD; SGA; severe preeclampsia or placental abruption in any previous pregnancy at >23 wks' gestation	Previous pregnancy with multiple gestation, major congenital or chromosomal anomalies, fetal infection/chorioamnionitis, hydrops, and/or diabetes mellitus	Prospective cohort study	Close surveillance; LMW heparin if thrombophilia; aspirin added if antiphospholipid antibodies	97	19 (16)
Trogstad et al, 2004[38]	Norway	All women with 2 singleton deliveries in the Medical Birth Registry and preeclampsia in the first pregnancy	Multiple gestation (≥triplet) in the first pregnancy; multiple gestation in the subsequent pregnancy (≥2)	Retrospective cohort study	—	20,285	37,738[b] (22)
Zhang et al, 2001[39]	United States	Women who attended the prenatal care unit during inclusion period and 2 consecutive pregnancies	—	Prospective cohort study	—	1641	321 (24)
Total	—	—	—	—	—	99,415	—

BMI, body mass index; *FGR*, fetal growth rate; *GA*, gestational age; *GH*, gestational hypertension; *HELLP*, hemolysis, elevated liver enzymes, and low platelets; *IUFD*, intrauterine fetal demise; *LMW*, low molecular weight; *LMWH*, low-molecular-weight heparin; *NICU*, neonatal intensive care unit; *NSAID*, nonsteroidal antiinflammatory drug; *SGA*, small for gestational age.

[a] Included: women with hypertensive disease (preeclampsia, gestational hypertension, HELLP syndrome) in a previous pregnancy, with a subsequent pregnancy; Excluded: control groups and cases without hypertensive complications in previous pregnancies; [b] New extended data extraction from the registry on behalf of this individual participant data, with the same inclusion criteria from the original cohort.

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values < .05 were considered to indicate statistical significance.

We have performed 3 post hoc sensitivity analyses: in one of them, we performed separate analysis for studies with < or >200 inclusions; in one of them, we excluded retrospective studies; and in 1 of them, we excluded studies with high or unclear risk of bias.

Statistical analysis was performed with SPSS software (version 20.0; SPSS Inc, Chicago, IL) and R software (version 3.0.1; The R Foundation for Statistical Computing).

Results

Study selection

Our search of PubMed and Embase for eligible articles until August 2012 yielded 2819 nonduplicate hits. After screening title and abstract, a total of 94 articles were included. Of these articles, 6 were excluded because of overlapping databases; 39 were excluded because of failure to make contact; 14 were excluded because of unavailable data; 2 were excluded because of judgment of data as not useful by the authors; and 11 authors decided not to share their data. Reasons for declining to share data included no interest in participation, still in the publication process, and a statement of "no permission to send data outside the national borders." Eventually, the IPD of 22 articles were included in this IPD metaanalysis (Figure 1).[17-39] The combined database comprised a total of 99,415 women.

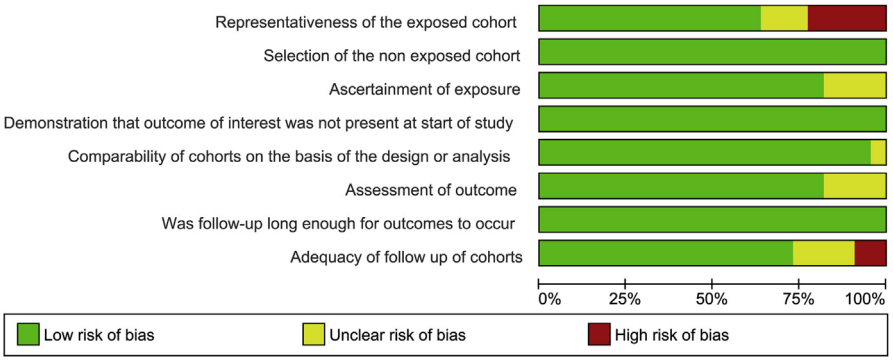
An overview of the study characteristics of the included studies can be seen in Table 1. Most of the women were included from 3 registry-based studies that lack demographic and clinical detail.[31,32,38] Two authors of included registry-based studies were unable to provide the original data but offered to perform a new data-extraction.[22,38] They used the criteria from the initial study to create an extended and more recent database. Eight prospective trials were included that investigated the effects of aspirin,[19,21,24,27,37] low-molecular-weight (LMW) heparin,[25,27,37] vitamins,[23,36] and close surveillance[37] on the recurrence of hypertensive disease and maternal and fetal outcome. Quality characteristics of all included studies that used the Newcastle Ottawa Scale[12] are shown in Figure 2.

To test for selection bias in the process of inclusion of IPD, a metaanalysis of recurrence rates in literature was performed. We used the originally included 88 articles (leaving out the overlapping datasets). Where available we used IPD (22 articles). Another 24 articles had to be excluded because applicable recurrence rates were not published. Of these articles, only IPD that did not reach publication would have been useful, for example in specific subgroups. Regarding gestational hypertensive disorders, 64 articles that encompassed a total of 152,213 women with an HDP reported on 27,558 recurrences, which resulted in a recurrence rate of 18.1% (95% CI, 17.9−18.3). The range of recurrence rates in the cohorts was 6-83%.[29] Recurrence rates of individual syndromes of HDP were not reported very consistently over studies. References of the 64 articles in this metaanalysis are available in the Appendix (Supplementary Table).

The baseline characteristics of the 99,415 women who were included in the IPD are shown in Table 2. The occurrence of major maternal complications (such as pulmonary edema or maternal death) was recorded too sporadically to be reported.

An HDP (any type) recurred in 20,545 of 99,415 women (20.7%; 95% CI, 20.4−20.9). The odds ratio (OR) between this recurrence risk and the recurrence risk that was calculated with the 64 included articles was 1.18 (95% CI, 1.15−1.20; $P < .001$). Recurrence manifested as preeclampsia in 13,725 women (n = 99,208; 13.8%; 95% CI, 13.6−14.1) and GH in 6797 women (n = 79,169; 8.6%; 95% CI, 8.4−8.8). HELLP complicated the HDP in 79 women (n = 39,301; 0.2%; 95% CI, 0.16−0.25). The delivery of an SGA child accompanied a hypertensive disorder in 1156 women (n = 34.359; 3.4%; 95% CI, 3.2−3.6). If we include non-hypertensive SGA as recurrence, SGA occurred in 4183 subsequent pregnancies (n = 34.359; 12%; 95% CI, 11.8−12.5). The different numbers of women in which the specific hypertensive syndrome was recorded (N) cause these percentages not to add up to the 20.7% overall recurrence. Premature delivery that accompanied the recurrent hypertensive disorder occurred at <37 weeks' gestation in 3316 women (n = 99,415; 3.3%; 95% CI, 3.2−3.5), at <34 weeks' gestation in 1224 women (n = 99,415; 1.2%; 95% CI, 1.2−1.3), and at <28 weeks' gestation in 179 women (n = 99,415; 0.18%; 95% CI, 0.16−0.22). Figure 3 gives a more detailed overview of recurrence of

FIGURE 2
Risk of bias graph



Quality characteristics of all included studies that were evaluated with the Newcastle Ottawa Scale for cohort studies. The item "selection of the nonexposed cohort" was not relevant in this individual participant data analysis and therefore was indicated as "low risk" in all studies.

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TABLE 2
Baseline clinical characteristics and index pregnancy parameters of the 99,415 included patients

Variable	n[a]	Measure	Percentage of total (99,415 women)	References
Age at index pregnancy, y[b]	97,832	25 ± 5		17,19,20,22,24,27,29-32,34,35,38,39
Smoking, n (%)	27,304	5654 (21)	6	17,19,20,22,26,29,30,31,34-36,39
Ethnicity, n (%)	25,807			16,19,23-30,32-36,39
European		20,785 (81)	21	
Caribbean		113 (0.4)	0.1	
Asian		228 (0.9)	0.2	
Sub-Saharan Africa		4545 (5)	5	
Middle East		19 (0.1)	0	
Body mass index, kg/m^2[c]	32,544	25 (22–29)		17,22,23,25,29,30,32-36,39
Chronic hypertension before pregnancy, n (%)	26,879	2032 (8)	2.0	16,19,23,25-30,32,34-36,38,39
Thrombophilia, n (%)	502	206 (41)	0.2	25,26,28,30,34,35,37
History of disease, n (%)				16,19,20,23,24,26-30,32-39
Diabetes mellitus	90,749	1342 (1.5)	1.3	
Coronary disease	51,387	167 (0.3)	0.2	
Kidney disease	25,004	121 (0.5)	0.1	
Pregnancy characteristics of index pregnancy				
Nulliparous women, n (%)	72,412	65,243 (90)	66	19-30,32-39
Multiple pregnancy, n (%)	99,069	516 (0.5)	0.5	16,17,19-26,28-30,32,34-36,38,39
Gestational hypertension, n (%)[d]	99,400	23,970 (24)	24	16,17,19-39
Preeclampsia, n (%)[d]	99,202	75,172 (76)	76	16,17,19-39
Eclampsia, n (%)[d]	26,665	2087 (8)	2.1	19,20,25,28-30,32,34,35,38
HELLP syndrome, n (%)[d]	40,236	512 (1.3)	0.5	16,19,20,25,27-30,34-36,38
Placenta abruption, n (%)	51,803	1221 (2.4)	1.2	16,25,28,30-32,34,35,37,39
Maximum blood pressure, mm Hg[b]				29,30,34,35,39
Systolic	632	161 ± 21	0.2	
Diastolic	1028	103 ± 11	0.1	
Use of medication, n (%)				20,29,30,34,35
Oral antihypertensive	1446	738 (51)	0.7	
Intravenous antihypertensive	687	141 (21)	0.1	
Intravenous anticonvulsive	1472	219 (15)	0.2	
Gestational age at delivery, wk	94,178	39 ± 20 d		17,20,22,25-27,29-32,34,35,37-39
Birthweight, g[b]	97,694	3185 ± 761		17,20,22,25-27,29-32,34,35,37-39
Small for gestational age, n (%)[d]	35,109	6448 (18)	6.4	16,17,19,20,22-25,27-30,32-35,37-39
Premature delivery, n (%)				17,19,20,22,23,25-27,29-32,34,35,37-39
<28 wk	94,197	739 (0.8)	0.7	
<34 wk	94,353	5363 (5.7)	5.4	
<37 wk	94,965	14,521 (15)	15	

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TABLE 2
Baseline clinical characteristics and index pregnancy parameters of the 99,415 included patients *(continued)*

Variable	n[a]	Measure	Percentage of total (99,415 women)	References
Caesarean delivery, n (%)	93,948	28,081 (30)	28	17,20,22,25,27,28,30-32,34,35,37,38
Neonatal intensive care unit admissions, n (%)	5117	1157 (22)	1.2	20,38
Perinatal death, n (%)	98,078	1608 (1.6)	1.6	16,17,19,20,22,24,25,27,29-32,34,35,37-39
Characteristics at the subsequent pregnancy				
Birth interval, mo[b]	59,754	41 ± 25		17,20,22,29-32,34,35,39
Change of partner, n (%)	7344	668 (9)	0.7	16,17,22,23,35,39
Use of prophylaxis, n (%)				16,17,19,21-24,26-28,30,34-37
Aspirin	5663	737 (13)	0.7	
Low molecular-weight heparin	1962	153 (8)	0.2	
Both	1909	60 (3)	0.1	

HELLP, hemolysis, elevated liver enzymes, and low platelets.

[a] Number of women with available information; [b] Data are presented as means ± SD; [c] Data are presented as median (interquartile range); [d] Percentages sum to >100% because of overlapping of disorders.

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the separate syndromes of hypertensive disorders and the effects of prematurity on recurrence according to hypertensive syndrome and gestational age at onset at the index pregnancy.

Sensitivity analyses showed comparable recurrence rates when studies with unclear or high risk of bias were excluded from analysis and showed the same range of recurrence rates when discriminating studies by size and study design (data not shown).

Subgroup analysis

We compared recurrence among multiple and singleton pregnancies. Of the index pregnancies, 516 were multiple and 98.553 were singleton pregnancies. Recurrence occurred in 56 (10.9%) and 20.408 (20.7%), respectively (OR, 0.53; 95% CI, 0.40−0.70; $P < .001$). Furthermore, we performed a subgroup analysis based on the presence of thrombophilia and the association between LMW-heparin use and recurrence. The combined database included 206 women with and 296 women without thrombophilia. A statistically significant interaction was present between thrombophilia and LMW-heparin use ($P = .005$). Stratified analysis in those women with thrombophilia showed that 26 of 56 women (46%) who used prophylactic LMW-heparin experienced recurrence of a HDP, compared with 56 of 141 women (39.7%) who did not use LMW-heparin (OR, 0.95; 95% CI, 0.46−2.0; $P = .89$). In those women without thrombophilia, 8 of 52 (15.4%) who used prophylactic LMW-heparin experienced recurrence, compared with 104 of 244 (42.6%) who did not use LMW-heparin (OR, 0.44; 95% CI, 0.13−1.5; $P = .20$).

The clinical syndrome in the index and subsequent pregnancy

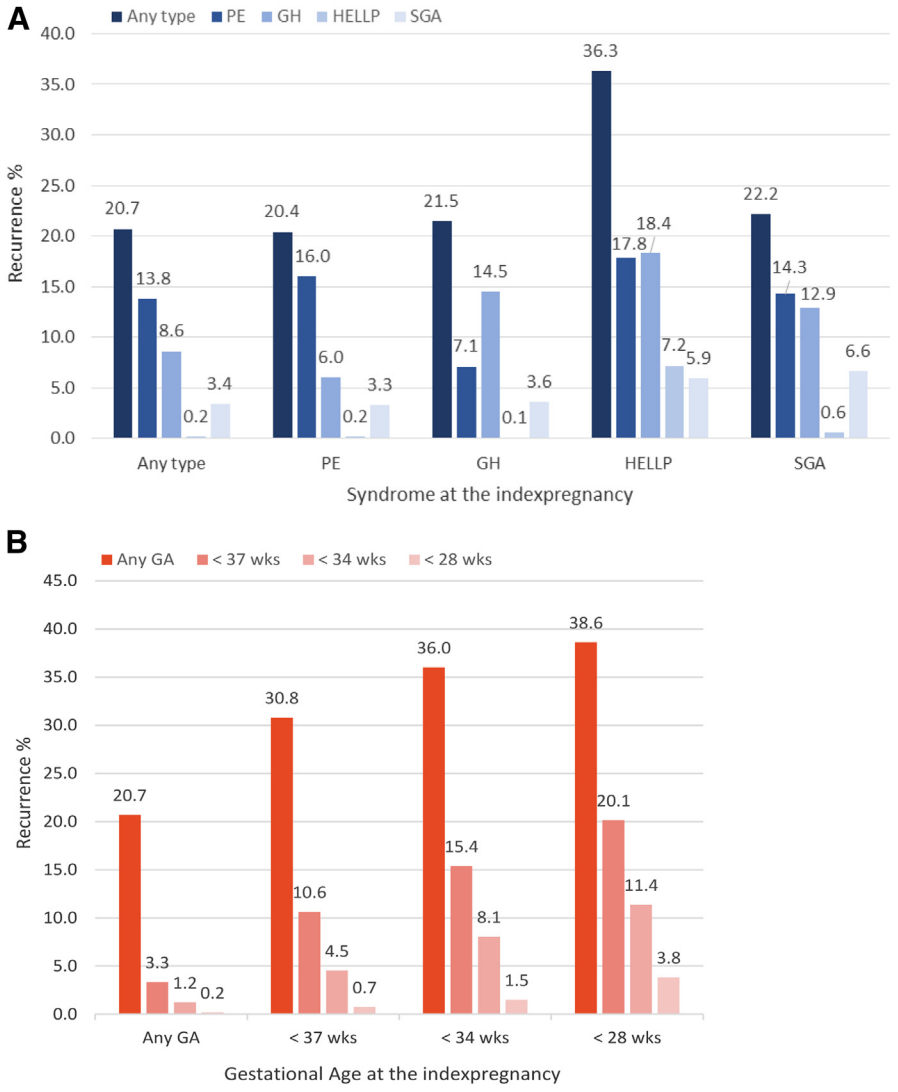
To assess differences between the clinical hypertensive syndrome in the index and subsequent pregnancy in women with recurrence, we compared the variables as shown in Table 3. Heterogeneity was high for intravenous anticonvulsive medication, cesarean delivery, and premature delivery at <34 and <37 weeks' gestation; was moderate for oral antihypertensive medication and premature delivery at <28 weeks' gestation; was low for maximum diastolic blood pressure, SGA < p10, and was absent for the other outcomes. The maximum diastolic blood pressure was, on average, lower in the subsequent pregnancy; proteinuria >300 mg/24 hours occurred less often, and oral antihypertensive or intravenous anticonvulsive medication was necessary less frequently. The subsequent pregnancy was complicated less often by a cesarean delivery, delivery of an SGA child, premature delivery, and perinatal death.

Similar to the sensitivity analyses for recurrence rate, the analyses showed comparable associations between the index and subsequent pregnancy after exclusion of studies with unclear or high risk of bias and showed the same range of associations when discriminating studies by size and study design (data not shown).

Chronic hypertension after pregnancy

Chronic hypertension that occurred after pregnancy was reported in 5 studies.[28-30,34,35] After exclusion of chronic hypertension before pregnancy, we included 581 women who were normotensive before pregnancy, who experienced an HDP, and in whom chronic hypertension after pregnancy was registered. Of these, 236 women (41%) had recurrence of a hypertensive disorder in the next pregnancy. Women with recurrence experienced chronic hypertension more often than women

FIGURE 3
Recurrence rates



Recurrence rates of the individual hypertensive syndromes of the 99,415 patients, according to the hypertensive syndrome at the index pregnancy: **A,** index pregnancy; **B,** GA at onset (or diagnosis).

PE, preeclampsia; *GA*, gestational age; *GH*, gestational hypertension; *HELLP*, hemolysis, elevated liver enzymes and low platelets syndrome; *SGA*, small for gestational age.

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without recurrence (28.4% vs 9.6%; OR, 4.2; 95% CI, 2.6–6.7).

Comment

This IPD metaanalysis explored the recurrence risk and predictors for recurrence of HDP. The creation of this large combined database produced an opportunity to calculate an overall recurrence rate of HDP and to explore the role of individual risk factors. Some of the bias that was introduced in single cohort studies based on patient selection criteria and methods could be reduced. The diversity of inclusion criteria of the included databases reflects the diverse world population.

Main findings

The recurrence rate of an HDP (any type) is 20.7% (95% CI, 20.4–20.9). Concomitant HELLP syndrome or delivery of an SGA child increases recurrence of HDP. Also, decreasing gestational age at delivery in the index pregnancy increases both the chance of having recurrence and the chance to deliver prematurely again. Multiple pregnancy at the index pregnancy, as a risk factor for the occurrence of HDP, is protective for recurrence. The use of LMW heparin was not protective for recurrence in our data, but the numbers are too small to draw conclusions. If the hypertensive disorder recurred, it was in general milder, regarding most of the investigated variables. Women who were normotensive before pregnancy and who experienced recurrence of a hypertensive disorder had a 4 times increased risk of the development of chronic hypertension after pregnancy.

Strengths and weaknesses

Undertaking this study was not without challenges. Study selection was impaired and prolonged by difficulties in contacting authors of the original articles. Eligible studies date back to the eighties, which caused data to be lost, authors to be retired, and accurate contact information to be absent. We were able to include 22 of the 88 (25%) eligible articles. Unfortunately, several important studies were not included. The inclusion rate is adequate compared with other published IPD metaanalyses with inclusion rates of 12-24%[40,41]; 1 study included 6 of 10 eligible studies that added up to an inclusion rate of 60%.[41]

The number of IPD in our study on the other hand was much higher than in other IPDs, mostly containing several thousands of participants.[40-42] The reason for this is our inclusion of nationwide registry based studies. Our combined database includes 99,415 women with a subsequent pregnancy, which is 69% of the 143,659 women who could be included in our regular metaanalysis of the 88 eligible studies. In comparison with the metaanalysis of these 88 studies, the recurrence rates differ statistically: 20.7% vs 18.1%; OR, 1.18 (95% CI, 1.15–1.20; $P < .001$), which suggests that some bias has occurred in the inclusion of data in our IPD. Thus, this IPD database may not be a completely representative cohort of

TABLE 3
Differences in the clinical hypertensive syndrome between the index and subsequent pregnancy in recurrent disease

Variable	n[a]	Index pregnancy	Subsequent pregnancy	*P* value	I^2, %	References
Maximum systolic blood pressure, mm Hg[b]	194	165 (19)	153 (17)	.055	0	19,21,27,29,30,34-36
Maximum diastolic blood pressure, mm Hg[b]	331[c]	107[c] (11)	100[c] (8.9)	< .001[c]	25	29,30,34,35,39
Proteinuria >300 mg/24 h	119[c]	82[c] (69%)	58[c] (49%)	.011[c]	0	20,27,29,30,34,35
Thrombocytopenia $<100 \times 10^9$/L	162	37 (23%)	18 (11%)	.24	0	20,29,30,34,35
Use of medication						19-21,23,25,28,29,30,34-36
Oral antihypertensive	504[c]	295[c] (59%)	237[c] (47%)	.002[c]	71	
Intravenous antihypertensive	263	67 (26%)	27 (10%)	.12	0	
Intravenous anticonvulsive	508[c]	82[c] (16%)	31[c] (6%)	< .001[c]	72	
Hospital days[d]	154	5 (2–11)	3 (1–5)	.17	0	34,35
Cesarean delivery	18,488[c]	6195[c] (34%)	6423 (35%)	< .001[c]	99	16,17,19-22,25,26,28-32,34,35,37,38
Small for gestational age < p10	6542[c]	996[c] (15%)	841[c] (13%)	< .001[c]	45	16,17,19,20,22,23,25,27-30,32-35,37-39
Perinatal deaths	20,111[c]	466[c] (2.3%)	256[c] (1.3%)	< .001[c]	0	16,17,19,20,22,24,25,27,29-35,37-39
Premature delivery						17,20,22,25-27,29-32,34,35,37-39
<28 wk	18,638[c]	267 (1.4%)[c]	155 (0.8%)[c]	< .001[c]	54	
<34 wk	18,735[c]	1868 (10%)[c]	1106 (5.9%)[c]	< .001[c]	76	
<37 wk	18,925[c]	4312 (23%)[c]	3125 (17%)[c]	< .001[c]	93	

Women with recurrence, 20,545.

[a] Number of women with information that was available for both of the pregnancies; [b] Data are presented as means ± SD; [c] Significant differences; [d] Data are presented as median (interquartile range).

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the originally eligible studies, but it is close.

Another limitation of this study is the fact that we merged data that were obtained from very different study designs, settings, and populations, which accounts for the enormous range of recurrence rates of 6-83%. The upper bound of this range originates from a study with a very small and extremely high-risk population.[29] It is unsurprising that heterogeneity across studies, which were assessed with the I^2 measure, was high for some of our results. The missing data that inevitably originated from merging databases challenged the statistical analysis. One of the methods that we used to overcome the problem of missing data was the merging of information on BMI, smoking, medical history, and chronic hypertension between the 2 consecutive pregnancies. Although these characteristics can vary, we do think that, on average, it gives a good indication of risk profile for the individual woman.

Furthermore, we included prophylactic trials in this IPD metaanalysis: 7 randomized controlled trials that investigated the effect of aspirin vs placebo,[19,21,24] vitamins vs placebo,[23,36] LMW-heparin plus aspirin vs aspirin alone,[27] or LMW-heparin in thrombophilic women vs no treatment in nonthrombophilic women.[37] The inclusion of these studies might be problematic when the treatments that were investigated in the different studies were effective in the reduction of hypertensive disorder recurrence. Two trials found a significant treatment effect. One trial found a significant reduction of recurrence in those treated with LMW-heparin plus aspirin compared with aspirin alone,[27] but the numbers were very small (1 and 7 women experienced preeclampsia in the next pregnancy). The same applies for a trial that reported a significant effect of vitamin use compared with placebo.[23] In addition, another vitamins trial shows conflicting results.[36] Given the small sample sizes of the trials with a significant treatment effect and given these unclear relations to the recurrence of HDP, we do not expect that the inclusion of these studies hampers the generalizability of the results of this IPD metaanalysis in any way.

Variables that were registered infrequently limited the analyses of the data. The percentages shown in Table 2 therefore could be difficult to interpret. HELLP syndrome was recorded present in only 512 women (0.5% of all included women), and SGA accompanied a HDP in 6448 cases (7%). This is unfortunate because they are parts of the placental syndrome. The same applies for the

inclusion of multiples pregnancy in the index pregnancy of 0.5%, which was an exclusion criterion in some included studies. The presence of thrombophilia also requires an explanation. If registered, thrombophilia was present in 41%. The inclusion of studies with thrombophilia as one of the inclusion criteria resulted in this high percentage. We do not think this will act as bias because it is documented in only 0.5% of the total cohort.

Another problem is reporting bias. Eclampsia was reported quite often (8% in 26.665 women in whom this complication was registered) in the index pregnancy. It is understandable that, if eclampsia occurred, it is more likely to be registered than when it did not occur.

Sensitivity analysis, in which we discriminated studies by study design and size, showed some discordant results. This was mainly due to loss of power: the analyses of small studies and prospective studies separately comprised 972 and 1955 of the 915,415 inclusions, respectively (1% and 2%). In contrast, the overall analysis was dominated mainly by 3 large retrospective studies.[31,32,38] Also, the results were difficult to interpret because most prospective studies did not register clinical details of the index pregnancy. The sensitivity analysis that included only low risk of bias studies had results that were comparable with the overall results, mainly because only 3 small studies were excluded from analysis.[26,27,29]

Counseling

Counseling couples about the chance of recurrence is important. This IPD metaanalysis did not include women who refrained from a subsequent pregnancy. Three included databases contained information about the reason for not engaging in a subsequent pregnancy.[30,34,35] Of 471 women, 140 (29%) refrained from a next pregnancy because of high perceived risk. This does not comply with the 21% recurrence risk and the fact that HDP recur in a milder form. The knowledge from this IPD metaanalysis can be used in counseling in the future.

In conclusion, interpretation of previous data of individual cohort studies was hampered by many sources of bias. IPD metaanalysis is a methods and logistically challenging approach. However, despite all the challenges and limitations stated earlier, the results are based on the largest database regarding recurrence of HDP so far. The opportunities of aggregated datasets are of paramount importance, because they allow the calculation of overall recurrence rates and also identify more accurately the role of individual risk factors on an individual level. The present IPD metaanalysis helped to create knowledge that can be included comprehensively in the counseling of couples after they have experienced HDP. ■

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APPENDIX

SUPPLEMENTAL TABLE

References of the 60 articles included in the metaanalysis preceding the individual participant data metaanalyses

Study	Recurrence rate
Aardenburg R, Spaanderman ME, van Eijndhoven HW, de Leeuw PW, Peeters LL. A low plasma volume in formerly preeclamptic women predisposes to the recurrence of hypertensive complications in the next pregnancy. J Soc Gynecol Invest 2006;13:598-603.	50.00
Ananth CV, Peltier MR, Chavez MR, Kirby RS, Getahun D, Vintzileos AM. Recurrence of ischemic placental disease. Obstet Gynecol 2007;110:128-33.	16.49
Beroyz G, Casale R, Farreiros A, et al. CLASP: A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994;343:619-29.[a]	59.18
Brown MA, Mackenzie C, Dunsmuir W, et al. Can we predict recurrence of pre-eclampsia or gestational hypertension? BJOG 2007;114:984-93.[a]	31.90
Byaruhanga RN, Chipato T, Rusakaniko S. A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. Int J Gynaecol Obstet 1998;60:129-35.[a]	14.55
Cameroni I, Crippa I, Roncaglia N, Locatelli A, Ornaghi S, Vergani P. Uterine artery Doppler in a risk population: What's its role in the prediction of small for gestational age fetuses? Pregnancy Hypertens 2011;1:260.[a]	9.83
Campbell D, Bhattacharya S, Lemon J. Recurrent preeclampsia—once/twice? Pregnancy Hypertens 2010;1:S30.[a]	25.61
Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. N Engl J Med 1998;338:701-5.	6.00
Cathelain-Soland S, Coulon C, Subtil D, Houfflin-Debarge V, Deruelle P. Subsequent pregnancy outcome in women with a history of preeclampsia and/or HELLP syndrome. Gynecol Obstet Fertil 2010;38:166-72.	27.46
Chames MC, Haddad B, Barton JR, et al. Subsequent pregnancy outcome in women with a history of HELLP syndrome at (less-than or equal to) 28 weeks of gestation. Am J Obstet Gynecol 2003;188:1504-8.	54.84
Chappell LC, Seed PT, Briley AL, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet 1999;354:810-6.[a]	50.00
Chiaffarino F, Parazzini F, Paladini D, et al. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. Eur J Obstet Gynecol Reprod Biol 2004;112:142-4.[a]	47.06
Conserva V, Muggiasca M, Arrigoni L, Mantegazza V, Rossi E, Ferrazzi E. Recurrence and severity of abnormal pregnancy outcome in patients treated by low-molecular-weight heparin: a prospective pilot study. J Matern Fetal Neonatal Med 2012;25:1467-73.[a]	11.32
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Dukler D, Porath A, Bashiri A, Erez O, Mazor M. Remote prognosis of primiparous women with preeclampsia. Eur J Obstet Gynecol Reprod Biol 2001;96:69-74.	25.79
Facchinetti F, Marozio L, Frusca T, et al. Maternal thrombophilia and the risk of recurrence of preeclampsia. Am J Obstet Gynecol 2009;200:46-5.[a]	33.72
Ferrazzani S, D'Alessio MC, Fatigante G, et al. Prophylaxis of recurrent preeclampsia: low molecular weight heparin plus low-dose aspirin versus low-dose aspirin alone. Hypertens Pregnancy 2006;25:115-27.[a]	14.81
Figueiro-Filho EA, de Oliveira VM, Coelho LR, Breda I. Serum markers of inherited thrombophilia and antiphospholipid antibodies in pregnant women with previous history of severe pre-eclampsia. Rev Bras Ginecol Obstet 2012;34:40-6.[a]	50.00
Gainder S, Saha SC, Dhaliwal L, Bagga R. Pregnancy outcome in subsequent pregnancies after eclampsia. Pregnancy Hypertens 2012;2:175.	37.74
Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EAP. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol 2008;140:171-7.[a]	83.33

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SUPPLEMENTAL TABLE

References of the 60 articles included in the metaanalysis preceding the individual participant data metaanalyses *(continued)*

Study	Recurrence rate
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Kreuwel JH, Scholten RR, Peeters LL, Spaanderman ME. Increased inter-pregnancy calciuria relates to recurrent preeclampsia. Reprod Sci 2011;18:360A.	22.92
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van Oostwaard. Individual participant data metaanalysis on the recurrence of HDP. Am J Obstet Gynecol 2015. *(continued)*

SUPPLEMENTAL TABLE

References of the 60 articles included in the metaanalysis preceding the individual participant data metaanalyses *(continued)*

Study	Recurrence rate
Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. Am J Obstet Gynecol 2008;199:55-7.	14.70
Napolitano R, Rajakulasingam R, Memmo A, Bhide A, Thilaganathan B. Uterine artery Doppler screening for pre-eclampsia: comparison of the lower, mean and higher first-trimester pulsatility indices. Ultrasound Obstet Gynecol 2011;37:534-7.[a]	25.64
Poston L, Briley A, Seed P, Kelly F, Shennan A. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. Lancet 2006;367:1145-54.[a]	29.14
Rijvers C, Marzano S, Winkens B, Bakker J, Peeters. L. Asymmetric dimethylarginine (ADMA) in early pregnancy: no differences between formerly preeclamptics with and without recurrent disease. Reprod Sci 2010;17:237A-8A.	35.48
Salim R, Czarnowicki T, Nachum Z, Shalev E. The impact of close surveillance on pregnancy outcome among women with a prior history of antepartum complications attributed to thrombosis: a cohort study. Reprod Biol Endocrinol 2008;6:55.[a]	15.79
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Sibai BMFA, Mercer BFAU, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. Am J Obstet Gynecol 1991;165:1408-12.	17.31
Spaanderman MEA, Aardenburg R, Ekhart THA, Van Eyndhoven HWF, de Leeuw PW, Peeters LLH. Pre-pregnant prediction of recurrent preeclampsia in normotensive thrombophilic formerly preeclamptic women receiving prophylactic antithrombotic medication. J Soc Gynecol Invest 2005;12:112-7.	51.06
Spinnato JA, Freire S, Pinto e Silva JL, et al. Antioxidant therapy to prevent preeclampsia: a randomized controlled trial. Obstet Gynecol 2007;110:1311-8.	12.90
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van Oostwaard MF, Langenveld J, Bijloo R, et al. Prediction of recurrence of hypertensive disorders of pregnancy between 34 and 37 weeks of gestation: a retrospective cohort study. BJOG 2012;119:840-7.[a]	33.88
Kuijk SMJ, Nijdam ME, Janssen KJM, et al. A model for preconceptional prediction of recurrent early-onset preeclampsia: Derivation and internal validation. Reprod Sci 2011;18:1154-9.	6.88
van Oostwaard MF, Langenveld J, Schuit E, et al. Prediction of recurrence of hypertensive disorders of pregnancy in the term period, a retrospective cohort study. Pregnancy Hypertens 2014;4:194-202.[a]	40.74

van Oostwaard. Individual participant data metaanalysis on the recurrence of HDP. Am J Obstet Gynecol 2015. *(continued)*

SUPPLEMENTAL TABLE

References of the 60 articles included in the metaanalysis preceding the individual participant data metaanalyses *(continued)*

Study	Recurrence rate
van Pampus MG, Wolf H, Mayruhu G, Treffers PE, Bleker OP. Long-term follow-up in patients with a history of (H)ELLP syndrome. Hypertens Pregnancy 2001;20:15-23.	27.17
van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. Am J Obstet Gynecol 2006;195:723-8.	27.50
Villar J, Purwar M, Merialdi M, et al. World Health Organisation multicentre randomised trial of supplementation with vitamins C and e among pregnant women at high risk for pre-eclampsia in populations of low nutritional status from developing countries. BJOG 2009;116:780-8.	62.68
Zhang J, Troendle JF, Levine RJ. Risks of hypertensive disorders in the second pregnancy. Paediatr Perinat Epidemiol 2001;15:226-31.[a]	24.30
Mean[b]	18.10

Recurrence was calculated from published data of patients with hypertensive disorders of pregnancy in the index pregnancy.

[a] Where available, the individual patient data were used (22 articles); [b] Calculated from a recurrence of 27,558 in 152,213 patients with a hypertensive disorder of pregnancy.

van Oostwaard. Individual participant data metaanalysis on the recurrence of HDP. Am J Obstet Gynecol 2015.