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Recurrence of hypertensive disorders of pregnancy, an Individual Patient Data Meta-Analysis

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The recurrence rates of hypertensive disorders of pregnancy, preeclampsia, gestational hypertension, and HELLP syndrome were 20.7%, 13.8%, 8.6%, and 0.2% respectively.

Short version of title:
Individual participant data meta-analysis on the recurrence of hypertensive disorders of pregnancy

This research was presented as a poster at the 19th Annual Scientific Meeting of the International Society for the Study of Hypertension in Pregnancy, ISSHP, New Orleans, Louisiana, USA, October 26-29 2014.

ABSTRACT:

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 suffering from HDP and who had a subsequent pregnancy. The principal investigators were contacted, informed and requested for their original study data. The obtained data were merged to form one combined database. The results will be presented as % with 95% confidence interval (CI) and odds ratios (OR) with 95% CI.

Results

Out of 94 eligible cohort studies, we obtained IPD of 22 studies, including a total of 99,415 women. Pooled data of 64 studies using 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 included in our IPD, the recurrence rate of a HDP was 20.7% (95%CI: 20.4 – 20.9). Recurrence manifested as preeclampsia (PE) in 13.8% (95%CI: 13.6 – 14.1), gestational hypertension (GH) in 8.6% (95%CI: 8.4 – 8.8) and Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome in 0.2% (95%CI: 0.16 – 0.25). The delivery of a small for gestational age (SGA) child accompanied the recurrent HDP in 3.4% (95%CI: 3.2 – 3.6). Concomitant HELLP syndrome or delivery of a SGA child increased the risk of recurrence of HDP. Recurrence increased with decreasing

gestational age at delivery in the index pregnancy. If the HDP recurred, it was in general milder, regarding maximum diastolic blood pressure, proteinuria, use of oral antihypertensive and anticonvulsive medication, delivery of a SGA child, premature delivery and perinatal mortality. Normotensive women developed chronic hypertension after pregnancy more often after experiencing recurrence (OR 3.7 95% CI: 2.3 – 6.1).

Conclusion

Among women that suffer 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 complicated by hypertension.

Key words

Gestational hypertension, HELLP syndrome, IPD, preeclampsia, pregnancy, recurrence

INTRODUCTION:

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 to 8 per cent of all pregnancies (2,3,4) and comprise gestational hypertension (GH), preeclampsia (PE), superimposed PE and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome, and in a varying percentage of cases they are related to intrauterine growth restriction. There is probably important heterogeneity in pathophysiology 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 a HDP identifies the woman at risk for cardiovascular disease later in life, probably due to shared risk factors and pathophysiology (2,4).

Hypertensive disorders of pregnancy can also have a major psychological 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 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 methodologies. This causes every cohort to have a specific case mix of different clinical phenotypes and macro-ethnicities. Reported recurrence rates range from a few percent, up to 65% (6). Similarly, the performance of individualized risk prediction models has been disappointing, since hypertensive disorders of pregnancy have heterogeneous pathophysiology (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: 2 – 3% (8,9). Recurrence of GH has not been explored in many studies. Delivering a small for gestational age (SGA) child recurs in about 24 percent of pregnancies (10).

Individual Participant Data (IPD) meta-analysis is new to prognostic research (11). In contrast to conventional meta-analysis 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 meta-analysis, it permits synthesis at an individual level, creating 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.

Objective of the study:

The primary goal of this IPD meta-analysis study is to calculate the recurrence risk of hypertensive disorders of pregnancy. Secondarily, we aim 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 reasoned to have this information in the original data, were also considered eligible. If data between studies overlapped, only the larger of the two 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.).

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 meta-analysis 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 adequately labeled 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 such as age and Body Mass Index (BMI), cardiovascular risk factors and the clinical syndrome of the index pregnancy. The quality of all included studies was evaluated with the Newcastle Ottawa Scale for cohort studies (12).

Definitions:

Hypertensive disorders of pregnancy were defined as gestational hypertension (GH), preeclampsia (PE), superimposed PE or HELLP syndrome. Non-hypertensive pregnancies with a small for gestational age child (SGA) 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 mmHg or systolic blood pressure ≥140 mmHg on two occasions, 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 or more in a random sample or an urine protein excretion of 300 mg or more per 24 hrs.) after 20 weeks of pregnancy (13). Mild or severe PE were not separately defined, as only some of the studies made this distinction in their data. Women with hypertension beyond 20 weeks without proteinuria, or a significant rise in blood pressure if known chronic hypertension, were considered to have GH. Chronic hypertension was defined as the presence or history of preconceptional hypertension or detection of hypertension in the first half of 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 (LDH) levels (≥ 600 U/L), elevated liver enzymes by levels of aspartate transaminase (ASAT) or alanine transferase (ALAT) ≥ 70 U/L and low platelets < 100,000/mm (14). HELLP syndrome in combination with hypertension was also classified as PE. SGA was defined as birth weight below the 10th percentile, according to the ACOG practice bulletin (15) and adjusted for gestational age based on a local reference population. The exact definitions for the hypertensive syndromes used in the included studies were not retrievable for a few studies, that were published as abstracts (20,22). Nevertheless we presume that the authors concur to the international accepted criteria, which were described above.

The primary outcome was the recurrence of any hypertensive disorder of pregnancy in the next subsequent pregnancy. Secondarily, we aimed at showing the recurrence of individual hypertensive syndromes.

Statistical analysis

Most studies focused on detailed data of the subsequent pregnancy, whereas some studies only registered details of the index pregnancy. To utilize 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 is recorded at the time of the second pregnancy, but not at the index pregnancy, then we copied this BMI information.

Not all the dependent or independent variables have been registered in every database. Results are therefore 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 (SD) or median with interquartile range (IQR), as appropriate. We decided not to use imputation, as the pattern of systematic missing values cannot be extrapolated between databases.

Differences in outcomes between the index and subsequent pregnancy were investigated using a random intercept random effects binomial regression model for dichotomous outcomes and using 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 (AIC) the random effects model was compared to a fixed effects model and the model with the lowest AIC was used as the final model for analysis for that outcome. Heterogeneity across studies was assessed using the I^2 measure and the values were interpreted as follows: 0% indicates no observed heterogeneity; 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively (16). P values less than 0.05 were considered to indicate statistical significance.

We have performed 3 post hoc sensitivity analyses: in one we performed separate analysis for studies with less or more than 200 inclusions, in one we excluded retrospective studies and in one we excluded studies with high or unclear risk of bias.

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and R 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 non-duplicate hits. After screening title and abstract, a total of 94 articles were included. Of these articles, six had to be excluded due to overlapping databases, 39 due to failure to make contact, 14 due to unavailable data, two due to 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 (17-39) were included in this IPD meta-analysis (Figure 1). 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. The majority of women was included from three registry-based studies that lack demographic and clinical detail (31,32,38). Two authors of included registry-based studies (21,38), were unable to provide the original data, but offered to perform a new data-extraction. They used the criteria from the initial study, creating an extended and more recent database. Eight prospective trials were included, investigating effects of aspirin (17,19,24,27,37), low-molecular-weight (LMW) heparin (25,27,37), vitamins (23,36) and close surveillance (37) on recurrence of hypertensive disease and maternal and fetal outcome. Quality characteristics of all included studies using the Newcastle Ottawa Scale (12) are shown in Figure 2.

To test for selection bias in the process of inclusion of IPD, a meta-analysis 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, encompassing in total 152,213 women with a hypertensive disorder of pregnancy, reported on 27,558 recurrences, resulting in a recurrence rate of 18.1% (95% CI: 17.9 – 18.3). The range of recurrence rates in the cohorts was: 6 to 83% (29). Recurrence rates of individual syndromes of HDP were not reported very consistently over studies. References of the 64 articles in this meta-analysis are available as electronic supplementary material.

The baseline characteristics of the 99,415 women included in the IPD are shown in Table 2. The occurrence of major maternal complications (like pulmonary edema or maternal death) was recorded too sporadic to report on.

A hypertensive disorder of pregnancy (any type) recurred in 20,545 of 99,415 women (20.7% 95%CI: 20.4 – 20.9). The Odds Ratio between this recurrence risk and the recurrence risk calculated with the 64 included articles is: 1.18 (95%CI: 1.15-1.20, p: <.001). Recurrence manifested as PE 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 a 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 to not add up to the 20.7% overall recurrence. Premature delivery accompanying the recurrent hypertensive disorder occurred < 37 weeks in 3316 women (N=99,415, 3.3% 95%CI:

3.2 – 3.5), < 34 weeks in 1224 women (N= 99,415, 1.2% 95%CI: 1.2 – 1.3) and < 28 weeks in 179 (N= 99,415, 0.18% 95%CI: 0.16 – 0.22). Figure 3 gives a more detailed overview of recurrence of the separate syndromes of hypertensive disorders and 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 amongst 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-value: <.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 without thrombophilia. A statistically significant interaction was present between thrombophilia and LMW-heparin use (p-value: 0.005). Stratified analysis in those with thrombophilia showed that 26 of 56 women (46%) who used prophylactic LMW-heparin experienced recurrence of a hypertensive disorder of pregnancy, compared to 56 of 141 women (39.7%) who did not use LMW-heparin (OR 0.95; 95% CI 0.46-2.0, p-value: 0.89). In those without thrombophilia 8 of 52 (15.4%) that used

prophylactic LMW-heparin experienced recurrence, compared to 104 out of 244 (42.6%) that did not use LMW-heparin (OR 0.44; 95% CI 0.13-1.5, p-value: 0.20)

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, caesarean section, and premature delivery <34 and <37 weeks' gestation, moderate for oral antihypertensive medication and premature delivery < 28 weeks' gestation, low for maximum diastolic blood pressure, small for gestational age < p10, and absent for the other outcomes. The maximum diastolic blood pressure was on average lower in the subsequent pregnancy, proteinuria > 300mg / 24hours occurred less often and oral antihypertensive or intravenous anticonvulsive medication was necessary less frequently. The subsequent pregnancy was complicated less often by a caesarean section, delivery of a small for gestational age child, premature delivery and perinatal mortality.

Similar to the sensitivity analyses for recurrence rate, the analyses showed comparable associations between the index and subsequent pregnancy after excluding 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 occurring after pregnancy was reported in 5 studies (28,29,30,34,35). After exclusion of chronic hypertension before pregnancy, we included 581 women, who were normotensive before pregnancy, who experienced a

hypertensive disease of pregnancy 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 developed chronic hypertension more often than women without recurrence (28.4 versus 9.6%, OR 4.2 95% CI: 2.6 – 6.7).

COMMENT:

This IPD meta-analysis explored the recurrence risk and predictors for recurrence of hypertensive disorders of pregnancy. 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 introduced in single cohort studies based on patient selection criteria and methodology could be reduced. The diversity of inclusion criteria of the included databases reflects the diverse world population.

Main findings

The recurrence rate of a hypertensive disorder of pregnancy (any type) is 20.7% (95%CI: 20.4 – 20.9). Concomitant HELLP syndrome or delivery of a SGA child increases recurrence of HDP. Also, decreasing gestational age at delivery in the index pregnancy, both the chance of having recurrence and the chance to deliver prematurely again increase. Multiple pregnancy at the index pregnancy, as a risk factor for the occurrence of HDP, is protective for recurrence. 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 four times increased risk of developing 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, causing 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 to other published IPD meta-analyses with inclusion rates of 12-24% (41,42), one study included 6 of 10 eligible studies, adding up to an inclusion rate of 60% (42).

The number of IPD in our study on the other hand, is much higher than in other IPDs, mostly containing several thousands of participants (40,41,42). 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 that could be included in our regular meta-analysis of the 88 eligible studies. In comparison with the meta-analysis of these 88 studies, the recurrence rates differ statistically: 20.7 versus 18.1%, OR: 1.18 (95%CI: 1.15-1.20, p: <.001). This 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 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. This accounts

for the enormous range of recurrence rates between 6 and 83%. The upper bound of this range originates from a study with a very small and extreme high-risk population (29). It is unsurprising that heterogeneity across studies, assessed using the I^2 measure, was high for some of our results. The missing data that inevitably originate from merging databases challenged the statistical analysis. One of the methods that we used to overcome the problem of missing data is the merging of information on BMI, smoking, medical history and chronic hypertension between the two 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 meta-analysis: 7 randomized controlled trials, which investigated the effect of aspirin (17,19,24) versus placebo, vitamins versus placebo (23,36), LMW-heparin plus aspirin versus aspirin alone (27) or LMW-heparin in thrombophilic women versus no treatment in non-thrombophilic women (37). The inclusion of these studies might be problematic when the treatments 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 reporting a significant effect of vitamin use compared to 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 meta-analysis in any way.

Variables that were infrequently registered, limited the analyses of the data. The percentages shown in Table 2 could therefore be difficult to interpret. HELLP syndrome was only recorded present in 512 women (0.5% of all included women) and SGA accompanied a HDP in 6448 cases (7%). This is unfortunate, as they are parts of the placental syndrome. The same applies for the inclusion of multiple pregnancy in the index pregnancy of 0.5%, being 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, since it is only documented in 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 mainly dominated by three large retrospective studies (31,32,38). Also, the results were difficult to interpret as 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 to 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 meta-analysis did not include women, who refrained from a subsequent pregnancy. Three included databases contained information on the reason for not engaging in a subsequent pregnancy (30,34,35). Of 471 women, 140 (29%) refrained from a next pregnancy due to 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 meta-analysis 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 meta-analysis is a methodologically and logistically challenging approach. However, despite all the challenges and limitations stated above, 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 meta-analysis helped to create knowledge that can comprehensively be included in the counseling of couples after experiencing hypertensive disease of pregnancy.

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Tables and figures:

Figure 1:
Inclusion of articles

Figure 2:
Risk of bias graph

Quality characteristics of all included studies, evaluated with the Newcastle Ottawa Scale for cohort studies. The item “selection of the on exposed cohort” was not relevant in this IPD and was therefore indicated as ‘low risk’ in all studies.

Figure 3A. Recurrence rates of the individual hypertensive syndromes of the 99,415 included patients according to the hypertensive syndrome at the index pregnancy

Figure 3B. Recurrence rates of the individual hypertensive syndromes of the 99,415 included patients according to the gestational age at onset (or diagnosis) of the hypertensive syndrome at the index pregnancy

Table 1:
Overview of study characteristics of the included studies

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

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

Electronic supplementary material:
References of the 60 articles included in the meta-analysis preceding the IPD meta-analyses

Table 1- Overview of study characteristics of the included studies

Study and Year	Country	Inclusion criteria	Exclusion criteria	Study design	Therapeutic trial	Total women original study	Total includable women* (recurrence rate)
Beroyz 1994[17]	United Kingdom	-Former PE -Former FGR -Chronic hypertension -Renal disease -Signs of PE or FGR in current pregnancy	-Bleeding disorders -Asthma -Allergy to aspirin	Randomized controlled trial	Aspirin vs placebo	9364	156 (59%)
Brown 2007[18]	Australia	-Former PE -Former GH -Chronic hypertension -Essential hypertension and superimposed PE	-None reported	Retrospective cohort study	-	1354	765 (32%)
Byaruhanga 1998[19]	South-Africa	-Former PE -Former GH -Chronic hypertension	-History of hypersensitivity to aspirin, peptic ulcer, bleeding disorders or chronic pulmonary disease -Use of NSAID's -Development of PE prior to trial entry	Randomized controlled trial	Aspirin vs placebo	250	213 (15%)
Cameroni 2011[20]	Italy	-Former PE -Former FGR -Former placental abruption -Former stillbirth -Chronic hypertension	-	Retrospective cohort study		218	173 (10%)
Campbell 1985 and 2010[21,22]	United Kingdom	-Total population of Aberdeen Maternity and Neonatal Data Bank	-	Retrospective cohort study	-	38130	7,725 Extended extraction** (26%)
Chappell 1999[23]	United Kingdom	-Former PE < 37wks -Former HELLP or eclampsia at any GA -Abnormal uterine-artery doppler waveform in pregnancy	-Heparin or warfarin treatment -Fetal abnomalities -Multiple pregnancy	Randomized controlled trial	Antioxidants (Vit C and E) vs placebo	283	56 (50%)
Chiaffarino 2004[24]	Italy	-Former severe PE or eclampsia -Former FGR -Former intrauterine foetal death	-Chronic disease other than hypertension, renal disease or diabetes -Allergy to aspirin -Fetal malformations -current twin pregnancy	Randomized controlled trial	Aspirin vs no treatment	40	15 (47%)
Conserva 2012[25]	Italy	-Former PE -Former HELLP -Former GH -Former FGR -Former placental abruption -Former FGR and stillbirth	-acquired thrombophilia -clinical immune disease -treatment with LMWH in previous pregnancy -congenital fetal anomaly -non Caucasian ethnicity	Prophylactic trial	Enoxaparine	128	53 (11%)

Facchinetti 2009[26]	Italy	-Former PE in singleton pregnancy -A complete evaluation for thrombophilia. -Current singleton pregnancy	-History of thromboembolic diseases -Renal and/or cardiovascular disorder -Systemic lupus erythematosus -Diabetes -Any ethnic group other than white	Prospective cohort study	-	172	172 (34%)
Ferrazzani 2006[27]	Italy	-Previous severe preterm PE with associated FGR	-Former HELLP syndrome	Prophylactic trial	Aspirin vs aspirin and heparin	68	54 (15%)
Figueiro-Filho 2012[28]	Brasil	-Previous severe PE with one of the following: -hospitalization < 32wks -imminent eclampsia -eclampsia -HELLP syndrome -systemic laboratory tests -preterm birth < 34 wks -admission of newborns in NICU -fetal loss -fetal growth restriction -oligohydramnia -abnormal uterine or umbilical artery doppler	-Chronic hypertension -Systemic lupus erythematosus -Thrombophilia	Prospective cohort study	-	113	67 (50%)
Gaugler-Senden 2008[29]	The Netherlands	-Former severe PE < 24wks	-	Retrospective cohort study	-	20	18 (83%)
Langenveld 2011[30]	The Netherlands	-Former PE, GH or HELLP < 34wks in singleton pregnancy	-Fetal abnormalities	Retrospective cohort study	-	380	211 (55%)
Lykke 2009[31]	Denmark	-All women with two singleton deliveries in the National Patient Registry	-cardiovascular diagnosis -diabetes -women who died or emigrated within 3 months of the second delivery	Retrospective cohort study	-	536,419	26,939 (20%)
Mbah 2012[32]	United States of America	-All women with two pregnancies registered in the Missouri maternally linked cohort database 1989 – 2005	-	Retrospective cohort study	-	166712	23,390 (17%)
Napolitano 2011[33]	United Kingdom	-all nulliparous women -parous women with former PE or FGR -concurrent maternal medical conditions ->7 years since last pregnancy	-Miscarriage < 14 wks -Fetal chromosomal or structural abnormalities	Prospective cohort study	-	6221	273 (26%)
van Oostwaard 2012[34]	The Netherlands	-Former PE, GH, HELLP or FGR 34 - 37 wks	-Fetal abnormalities	Retrospective cohort study	-	425	189 (34%)

van Oostwaard 2014[35]	The Netherlands	-Former PE, GH or HELLP > 37 wks	-Fetal abnormalities	Retrospective cohort study	-	638	312 (41%)
Poston 2006[36]	United Kingdom	-Former PE < 37wks -Former HELLP or eclampsia at any GA -Other risk factors for hypertensive disease (Essential hypertension, Diabetes, renal disease, Antiphospholipid syndrome, abnormal uterine- artery doppler waveform in pregnancy or BMI>30)	-No informed consent -Warfarin treatment -Using vitamins before trial	Randomized controlled trial	Vitamins (Vit C and E) vs placebo	2404	556 (29%)
Salim 2008[37]	Isreal	-IUFD -SGA -severe PE or -placental abruption -in any former pregnancy > 23wks	Former pregnancy with: -multiple gestation -major congenital or chromosomal anomalies -fetal infection / chorioamnionitis -hydrops -diabetes mellitus	Prospective cohort study	-Close surveillance -LMW heparin if thrombophilia -Aspirin added if antiphospho-lipid antibodies	97	19 (16%)
Trogstad 2004[38]	Norway	-All women with two singleton deliveries in the Medical Birth Registry -And preeclampsia in the first pregnancy	-Multiple gestation (triplet or more) in the first pregnancy -Multiple gestation in the subsequent pregnancy (2 or more)	Retrospective cohort study	-	20,285	37,738 Extended extraction** (22%)
Zhang 2001[39]	United States of America	-Women attending the prenatal care unit during inclusion period -And two consecutive pregnancies	-	Prospective cohort study	-	1641	321 (24%)
Total:							99,415

* Includable women: women with hypertensive disease (PE, GH, HELLP) in a former pregnancy, with a subsequent pregnancy, excluding control groups and cases without hypertensive complications in former pregnancies.
** New extended data extraction from the registry on behalf of this IPD, using the same inclusion criteria from the original cohort

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

		N*			% of total 99,415	References
Age at index pregnancy (years)		97,832	25	(SD: 5)		17 18 21 22 24 27 29 30 31 32 34 35 38 39
Smoking		27,304	5654	(21%)	6%	17 18 21 22 26 29 30 31 34 35 36 39
Ethnicity	- European	25,807	20,785	(81%)	21%	17 20 23 25 26 27 28 29 30 32 33 34 35 36 39
	- 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, BMI (kg/m^2)		32,544	25 (IQR: 22 - 29)			21 22 23 25 29 30 32 33 34 35 36 39
Chronic hypertension before pregnancy		26,879	2032	(8%)	2.0%	17 20 23 25 26 27 28 29 30 32 34 35 36 38 39
Thrombophilia		502	206	(41%)	0.2%	25 26 28 30 34 35 37
History of disease	- Diabetes Mellitus	90,749	1342	(1.5%)	1,3%	17 18 20 23 24 26 27 28 29 30 32 33 34 35 36 37 38 39
	- Coronary disease	51,387	167	(0.3%)	0.2%	
	- Kidney disease	25,004	121	(0.5%)	0.1%	
Pregnancy characteristics of index pregnancy						
Nulliparous		72,412	65,243	(90%)	66%	17 18 19 20 21 22 23 24 25 26 27 28 29 30 32 33 34 35 36 37 38 39
Multiple pregnancy		99,069	516	(0.5%)	0.5%	17 18 19 20 21 22 23 24 25 26 28 29 30 32 34 35 36 38 39
Gestational hypertension†		99,400	23,970	(24%)	24%	17 18 19 20 21 22 23 24 25 26 27 28 28 30 31 32 33 34 35 36 37 38 39 (all)
Preeclampsia†		99,202	75,172	(76%)	76%	17 18 19 20 21 22 23 24 25 26 27 28 28 30 31 32 33 34 35 36 37 38 39 (all)
Eclampsia†		26,665	2087	(8%)	2.1%	17 18 25 28 29 30 32 34 35 38
HELLP syndrome†		40,236	512	(1.3%)	0.5%	17 18 20 25 27 28 29 30 34 35 36 38
Placenta Abruption		51.803	1221	(2.4%)	1.2%	20 25 28 30 31 32 34 35 37 39
Maximum blood pressure (mmHg)	- Systolic	632	161	(SD: 21)	0.2%	29 30 34 35 39
	- Diastolic	1028	103	(SD: 11)	0.1%	
Use of medication	- oral antihypertensive	1446	738	(51%)	0.7%	18 29 30 34 35
	- iv antihypertensive	687	141	(21%)	0.1%	
	- iv anticonvulsive	1472	219	(15%)	0.2%	
Gestational age at delivery (weeks)		94,178	39 (SD: 20 days)			18 21 22 25 26 27 29 30 31 32 34 35 37 38 39

Birth weight (grams)		97,694	3185 (SD: 761)			18 21 22 25 26 27 29 30 31 32 34 35 37 38 39
Small for Gestational Age†		35,109	6448	(18%)	6.4%	17 18 20 21 22 23 24 25 27 28 29 30 32 33 34 35 37 38 39
Premature delivery	< 28 weeks	94,197	739	(0.8%)	0.7%	17 18 21 22 23 25 26 27 29 30 31 32 34 35 37 38 39
	< 34 weeks	94,353	5363	(5.7%)	5.4%	
	< 37 weeks	94,965	14521	(15%)	15%	
Caesarean Section		93,948	28,081	(30%)	28%	18 21 22 25 27 28 30 31 32 34 35 37 38
NICU admission neonate		5117	1157	(22%)	1.2%	18 38
Perinatal mortality		98,078	1608	(1.6%)	1.6%	17 18 20 21 22 24 25 27 29 30 31 32 34 35 37 38 39
Characteristics at the subsequent pregnancy						
Birth interval (months)		59,754	41	(SD: 25)		18 21 22 29 30 31 32 34 35 39
Change of partner		7344	668	(9%)	0.7%	20 21 22 23 35 39
Use of prophylaxis	- Aspirin	5663	737	(13%)	0.7%	17 19 20 21 22 23 24 26 27 28 30 34 35 36 37
	- LMW Heparin	1962	153	(8%)	0.2%	
	- Both	1909	60	(3%)	0.1%	

Continuous data are presented as means (SD); age, BMI and gestational age in median (IQR)
Proportions are shown as n (% of N)
* Number of women with available information
† Percentages sum up to more than 100% because of overlapping of disorders

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

Women with recurrence N= 20,545		**N***	**Index Pregnancy**	**Subsequent pregnancy**	**P**	**I^2 (%)**	**References**
Max systolic BP (mmHg)**		194	165 (19)	153 (17)	0.055	0	17 19 27 29 30 34 35 36
Max diastolic BP (mmHg)**		**331**	**107 (11)**	**100 (8.9)**	**<.001**	25	29 30 34 35 39
Proteinuria > 300mg/24h		**119**	**82 (69%)**	**58 (49%)**	**0.011**	0	18 29 27 30 34 35
Thrombocytopenia < 100 *10^9/L		162	37 (23%)	18 (11%)	0.24	0	18 29 30 34 35
Use of medication	- **oral antihypertensive**	**504**	**295 (59%)**	**237 (47%)**	**0.002**	71	17 18 19 23 25 28 29 30 34 35 36
	- iv antihypertensive	263	67 (26%)	27 (10%)	0.12	0	
	- iv anticonvulsive	**508**	**82 (16%)**	**31 (6%)**	**<.001**	72	
Hospital days***		154	5 (2-11)	3 (1-5)	0.17	0	34 35
Caesarean section		**18,488**	**6195 (34%)**	**6423 (35%)**	**<.001**	99	17 18 19 20 21 22 25 26 28 29 30 31 32 34 35 37 38
Small for gestational age < p10		**6,542**	**996 (15%)**	**841 (13%)**	**<.001**	45	17 18 20 21 22 23 25 27 28 29 30 32 33 34 35 37 38 39
Perinatal mortality		**20,111**	**466 (2.3%)**	**256 (1.3%)**	**<.001**	0	17 18 20 21 22 24 25 27 29 30 31 32 33 34 35 37 38 39
Premature delivery	**< 28 weeks**	**18,638**	**267 (1.4%)**	**155 (0.8%)**	**<.001**	54	18 21 22 25 26 27 29 30 31 32 34 35 37 38 39
	< 34 weeks	**18,735**	**1868 (10%)**	**1106 (5.9%)**	**<.001**	76	
	< 37 weeks	**18,925**	**4312 (23%)**	**3125 (17%)**	**<.001**	93	

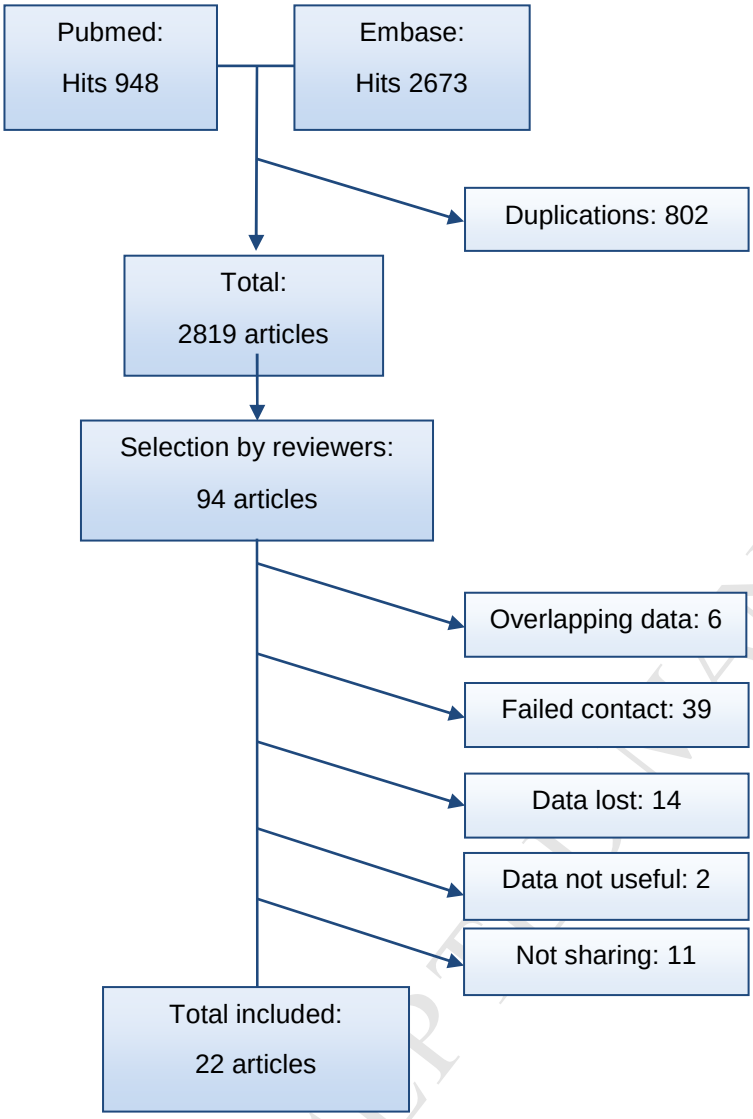
* Number of women with available information for both of the pregnancies

** Data are presented as means (SD).

***Data are presented as median (IQR).

Significant differences are indicated in bold

Figure 1. Inclusion of articles



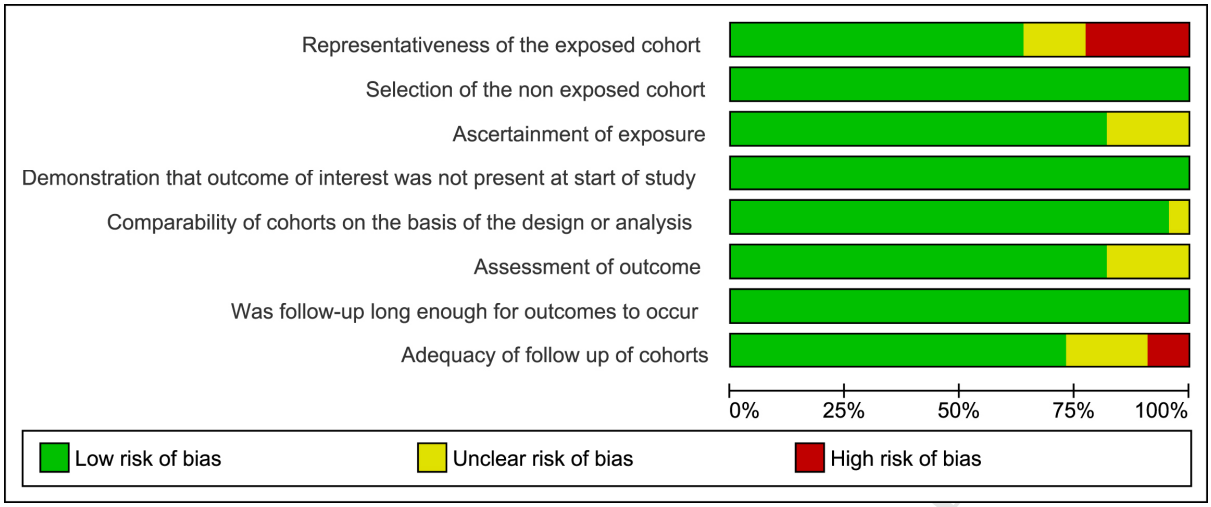
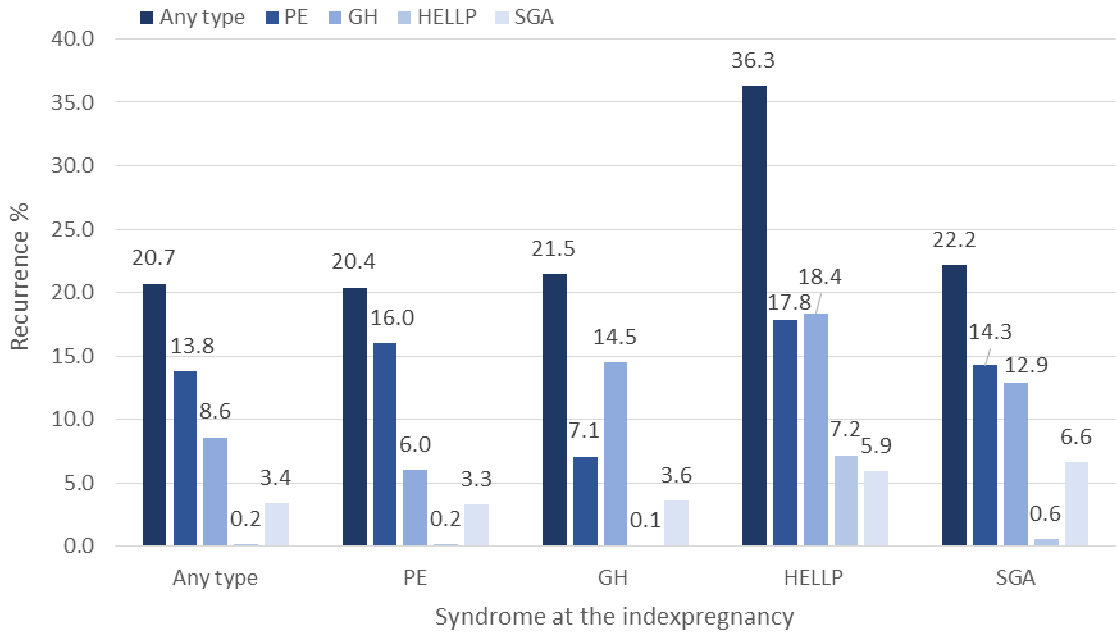
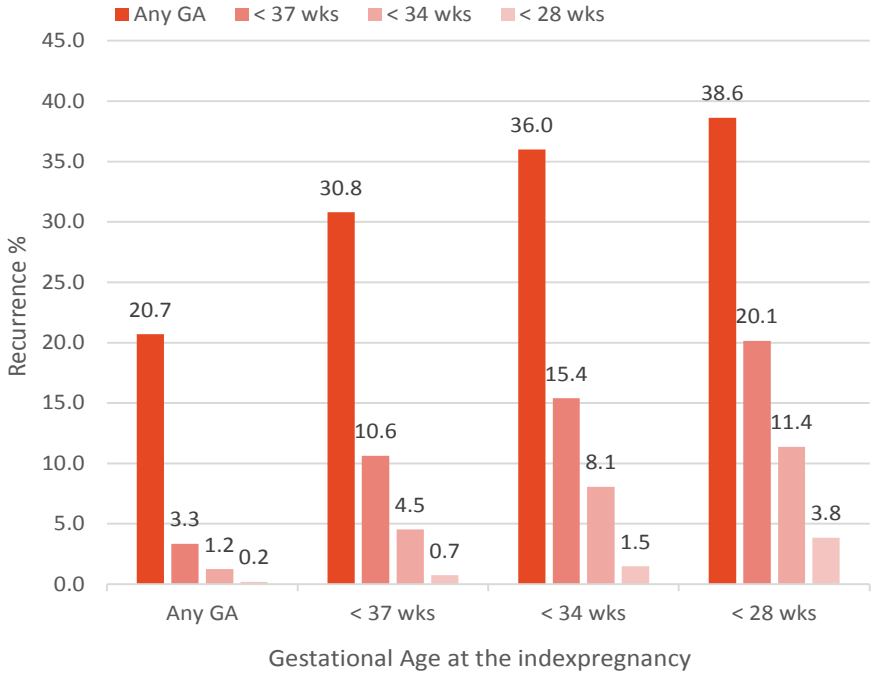


Figure 3A. Recurrence rates of the individual hypertensive syndromes of the 99,415 included patients according to the hypertensive syndrome at the index pregnancy



Data are shown as frequencies with percentages to the number of cases in which both variables were registered. Number of women with specific hypertensive disorder at the index pregnancy: Any type 99.241; PE 75.172; GH 23.970; HELLP 512; SGA 6448

Figure 3B. Recurrence rates of the individual hypertensive syndromes of the 99,415 included patients according to the gestational age at onset (or diagnosis) of the hypertensive syndrome at the index pregnancy



Data are shown as frequencies with percentages to the number of cases in which both variables were registered. Number of women with specific Gestational Age at the index pregnancy: Any GA 99.415; <37 wks 14.512; <34 wks 5354; <28 wks 730

Electronic supplementary material: References of the 60 articles included in the meta-analysis preceding the IPD meta-analyses.

Study	Recurrence
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, Palermo M, Margulies M, Voto L 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.*	59.18
Brown MA, Mackenzie C, Dunsmuir W, Roberts L, Ikin K, Matthews J, Mangos G, Davis G. Can we predict recurrence of pre-eclampsia or gestational hypertension? BJOG 2007;114:984-93.*	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.*	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.*	9.83
Campbell D, Bhattacharya S, Lemon J. Recurrent preeclampsia - Once/twice? Pregnancy Hypertens 2010;1:S30.*	25.61
Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E et al. Low-dose aspirin to prevent preeclampsia in women at high risk. New Engl J Med 1998;338:701-05.	6.00
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Mean**	**18.10**

Recurrence was calculated from published data of patients with hypertensive disorders of pregnancy in the index pregnancy.
*Where available the individual patient data were used (22 articles).
**The mean was calculated from a recurrence of 27,558 in 152,213 patients with a hypertensive disorder of pregnancy