OBSTETRICS

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

Miriam F. van Oostwaard, MD; Josje Langenveld, MD, PhD; Ewoud Schuit, MSc, PhD; Dimitri N. M. Papatsonis, MD, PhD; Mark A. Brown, MD, PhD; Romano N. Byaruhanga, MD, PhD; Sohinee Bhattacharya, MD, PhD; Doris M. Campbell, MD, PhD; Lucy C. Chappell, MD, PhD; Francesca Chiaffarino, ScD; Isabella Crippa, MD, PhD; Fabio Facchinetti, MD, PhD; Sergio Ferrazzani, MD, PhD; Enrico Ferrazzi, MD, PhD; Ernesto A. Figueiró-Filho, MD, PhD; Ingrid P. M. Gaugler-Senden, MD, PhD; Camilla Haavaldsen, MD, PhD; Jacob A. Lykke, MD, PhD; Alfred K. Mbah, PhD; Vanessa M. Oliveira, MD, PhD; Lucilla Poston, MD, PhD; Christopher W. G. Redman, MD, PhD; Raed Salim, MD, PhD; Baskaran Thilaganathan, MD, PhD; Patrizia Vergani, MD, PhD; Jun Zhang, MD, PhD; Eric A. P. Steegers, MD, PhD; Ben Willem J. Mol, MD, PhD; Wessel Ganzevoort, MD, PhD

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

Cite this article as: van Oostwaard MF, Langenveld J, Schuit E, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. Am J Obstet Gynecol 2015;212:624.e1-17.

From the Department of Obstetrics and Gynecology, Erasmus Medical Center, Rotterdam (Drs van Oostwaard and Steegers); Department of Obstetrics and Gynecology, Atrium Medical Center, Heerlen (Dr Langenveld); Julius Center for Health Sciences and Primary Care, Universitair Medisch Centrum, Utrecht (Dr Schuit); Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam (Drs Schuit and Ganzevoort); Department of Obstetrics and Gynecology, Amphia Ziekenhuis, Breda (Dr Papatsonis); and Department of Obstetrics and Gynecology, Jeroen Bosch Ziekenhuis, 's Hertogenbosch (Dr Gaugler-Senden), the Netherlands; Stanford Prevention Research Center, Stanford University, Stanford, CA (Dr Schuit); Department of Renal Medicine, St. George Hospital, Sydney, NSW (Dr Brown), and School of Pediatrics and Reproductive Health, Robinson Institute, University of Adelaide, SA (Dr Mol), Australia; Department of Obstetrics and Gynecology, St. Raphael of St. Francis Hospital, Nsambya Kampala, Uganda (Dr Byaruhanga); Dugald Baird Center for Research on Women's Health (Dr Bhattacharya) and Department of Obstetrics and Gynecology (Dr Campbell), Aberdeen Maternity Hospital, Aberdeen, Scotland; Women's Health Academic Centre, King's College London (Drs Chappell and Poston), and

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.).

Lanesborough Wing, St George's, University of London (Dr Thilaganathan), London; and Nuffield Department of Obstetrics and Gynecology, John Radcliffe Hospital, University of Oxford, Oxford (Dr Redman), England, UK; Department of Obstetrics, Gynecology, and Neonatology, IRCSS Fondazione Ca' Granda, Ospedale Maggiore Policlinico (Dr Chiaffarino), and Department of Woman, Mother, and Neonate, Buzzi Children's Hospital, Istituti Clinici di Perfezionamento, Biomedical and Clinical School of Medicine University of Milan (Dr Ferrazzi), Milan; Department of Obstetrics and Gynecology, Ospedale San Gerardo, Università degli Studi di Milano-Bicocca, Monza (Drs Crippa and Vergani); Department of Obstetrics and Gynecology, Universit' degli Studi di Modena e Reggio Emilia, Modena (Dr Facchinetti); and Department of Obstetrics and Gynecology, Università Cattolica del S. Cuore, Rome (Dr Ferrazzani), Italy; Faculty of Medicine (Dr Figueiró-Filho) and Center for Biological and Health Sciences (Dr Oliveira), Federal University of Mato Grosso do Sul, Campo Grande, Brazil; Department of Gynecology and Obstetrics and Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, Lørenskog, Norway (Dr Haavaldsen); Department of Obstetrics and Gynecology, Hvidovre Hospital, and Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark (Dr Lykke); Department of Epidemiology and Biostatistics, University of South Florida, Tampa, FL (Dr Mbah); Department of Obstetrics and Gynecology, Ha'Emek Medical Center, Afula, Israel (Dr Salim); and Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Dr Zhang).

Received June 22, 2014; revised Nov. 10, 2014; accepted Jan. 7, 2015.

The authors report no conflict of interest.

Presented as a poster at the 19th Annual Scientific Meeting of the International Society for the Study of Hypertension in Pregnancy, ISSHP, New Orleans, LA, Oct. 26-29, 2014.

Corresponding author: Miriam F. van Oostwaard, MD. miriamvanoostwaard@gmail.com

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2015.01.009