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Pregnancy outcomes in women with previous gestational hypertension: A cohort study to guide counselling and management

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ABSTRACT

Objectives: In pregnant women with previous gestational hypertension: to compare the prevalence of pre-eclampsia as defined by the 2001 versus the 2014 International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria, to determine the rates of fetal growth restriction (FGR) as defined, not only by birthweight centile, but in combination with fetal ultrasound studies and, finally, to determine rates of other related outcomes such as gestational diabetes (GDM) and obstetric cholestasis (OC).

Study design: This was a retrospective observational study based at the Antenatal Hypertension Clinic, Kings College Hospital, London. Routinely collected data of 773 women booked between 2011 and 2016 with a history of gestational hypertension was analysed. All women were normotensive at booking and those with chronic hypertension were excluded.

Main outcomes measures: Hypertensive disorders of pregnancy (ISSHP-2014), FGR, GDM.

Results: Forty-nine percent developed one or more pregnancy complications, of which 72% were hypertensive disorders of pregnancy, 25.8% preeclampsia, 25% GDM and 19% FGR. Overall recurrence rate of preeclampsia was 12.5% (ISSHP-2014). Higher blood pressure and body mass index at booking were associated with higher risk of preeclampsia and GDM. Earlier gestation of previous hypertension was associated with higher risk of preeclampsia and FGR. The ISSHP-2014 compared to the 2001 guidelines classified 56% more women as having preeclampsia.

Conclusion: Pregnant women with a history of gestational hypertension have a 49% chance of developing a complication related to a hypertensive disorder, GDM and OC. The rate of preeclampsia was more than doubled if the updated ISSHP-2014 definition was used.

1. Introduction

Hypertensive disorders of pregnancy (HDP) affect 10% of pregnancies and are the second direct cause of maternal death worldwide [1,2]. Furthermore, women with HDP are at increased risk of cardiovascular disease, renal dysfunction and chronic hypertension later in life [3,4]. Pre-eclampsia (PE), cardiovascular disease and other morbidities related to the metabolic syndrome, such as gestational diabetes (GDM), are thought to share common pathophysiological pathways characterized by dyslipidemia, hypertension and hyperinsulinaemia [5]. However, the risk of developing metabolic complications in pregnancy aside from hypertension in women with a history of HDP has not been widely studied [6,7]. In addition, most of the existing studies reporting on the recurrence of PE included women with chronic hypertension [8], a significant predictor for the development of PE.

The diagnosis of PE has traditionally relied upon the combination of hypertension and proteinuria [9–13]. However, it is now widely accepted that PE is a multisystem disorder associated with renal, liver, or hematological dysfunction and placental insufficiency. Recently, the International Society on the Study of Hypertension in Pregnancy (ISSHP) have updated the 2001 guidelines with more comprehensive criteria for PE [14]. These changes are likely to impact on the reported rates of PE, with effect on clinical practice and research outcomes. There are no reports comparing prevalence of PE using the 2014 versus 2001 ISSHP criteria.

This study included pregnant women with a history of HDP and excluded those with chronic hypertension to avoid a confounding effect on adverse outcomes. We had three objectives: to determine the rates of

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adverse pregnancy outcomes (GDM, obstetric cholestasis (OC), fetal growth restriction (FGR), thrombocytopenia and HDP); to determine the impact of maternal characteristics on the risk of developing these outcomes; and to compare the impact on the reported prevalence of PE using the ISSHP-2014 criteria.

2. Methods

2.1. Study population

This was an analysis of routinely collected data in our Antenatal Hypertension Clinic, a dedicated maternal-fetal medicine clinic for the management of pregnancies at risk of, or complicated by hypertension, at King's College Hospital, London. Local proto- cols stipulate that women with an increased risk of hypertensive complications, such as chronic hypertension or a history of hypertension in a previous pregnancy, are referred at booking to exclude secondary causes of hypertension and optimise pregnancy management.

Women who booked under the care of the Antenatal Hypertension Clinic between January 2011 and January 2016 with a history of HDP were included in this analysis. Women were excluded if they booked after 20 weeks gestation, had chronic hypertension, renal or liver disease, multiple pregnancy, incomplete data or current pregnancy complicated by fetal anomaly or miscarriage.

Information was obtained from patient notes and local databases. Data recorded routinely at booking included age, height, weight, body mass index (BMI), ethnicity, parity, and history of diabetes mellitus, depression, hypothyroidism, hyperthyroidism, cardiac disease, thrombophilia and autoimmune conditions. Gestation of previous HDP was obtained from medical records.

Gestational age was confirmed with first trimester ultrasound scan. Blood pressure was measured using an automated device validated in pregnancy [15].

2.2. Outcome measures

The outcome measures for the current pregnancy were HDP, thrombocytopenia, FGR, GDM and OC.

For HDP, which included gestational hypertension (GH) and PE, we used the ISSHP-2014 criteria [14]. GH and PE are characterized by de novo hypertension ($\geq$140 mmHg systolic or $\geq$90 mmHg diastolic) after 20 weeks gestation with PE having additionally at least one of: renal insufficiency (proteinuria $\geq$300 mg/24 h and/or creatinine $\geq$90 μmol/L), liver impairment (transaminases twice the upper limit of normal), neurological complications (e.g. eclampsia), thrombocytopenia, or placental dysfunction (i.e. FGR). The ISSHP-2001 definition of pre-eclampsia uses only hypertension and proteinuria ($\geq$300 mg/day proteinuria in a 24 h urine collection or a urinalysis of $\geq +2$ proteinuria on two occasions) [16].

For FGR we used the definition of Figueras and Gratacos [17], which classifies as FGR all newborns with birth-weight below the third percentile and those with birth-weight above the third percentile but with abnormal Doppler waveforms (umbilical artery pulsatility index above the 95th centile, middle cerebral artery pulsatility index or cerebroplacental ratio below the 5th centile) and/or oligohydramnios (i.e. deepest vertical pocket < 2 cm). This definition allows the identification of growth-restricted fetuses that are born with birth-weights within the normal range.

Screening for GDM was according to local clinical protocol. Women with previous GDM underwent 75 g oral glucose tolerance test (OGTT) with 0 and 120 min samples at 16–20 weeks and repeated at 28 weeks if the first was normal. Those with BMI > 40 kg/m^2 underwent OGTT at 28 weeks. All other pregnant women had a random venous plasma glucose (VPG) sample taken at 26–28 weeks gestation and if $\geq$6.7 mmol/l, an OGTT was arranged. Diagnosis was based on a fasting VPG $\geq$5.6 mmol/l and/or 120 min sample $\geq$7.8 mmol/l [18].

Obstetric cholestasis was defined as pruritus with abnormal liver function tests (transaminases and/or serum bile acid concentration) and absence of other liver pathology [19].

The occurrence and relationship between these outcome measures were illustrated with Venn diagrams.

2.3. Statistical analysis

Normality was assessed by the Kolmogorov-Smirnov test. Data are expressed as mean (standard deviation) or as median (interquartile range) for normally and non-normally distributed data, respectively.

Differences between groups were tested with parametric (Student's *t*-test) or non-parametric (Mann-Whitney *U* test) tests as appropriate. Categorical variables were compared using the chi-square test or Fishers exact test, where appropriate. P-values of < .05 were considered statistically significant.

Univariate and multivariate logistic regression were performed to determine the association of maternal and previous pregnancy characteristics with the main adverse outcomes. For the purposes of the logistic regression, scale variables were recoded as ordinal variables based on interquartile ranges (age, systolic, diastolic and mean blood pressure) or clinically meaningful thresholds (BMI, gestation of previous HDP, number of pregnancies with HDP). The results of univariate and multivariate logistic regression analyses were expressed as unadjusted and adjusted odds ratios (ORs), respectively, with 95% confidence intervals. Variables, which were not significant, were not successively eliminated from the multivariate logistic regression, as the aim was to determine the association of the variable with the outcome rather than its predictive value.

Statistical analysis was performed using SPSS (Version 22; SPSS Inc, Chicago, IL).

3. Results

3.1. Population characteristics

Between January 2011 and January 2016, 946 pregnancies in women with previous HDP were booked in the Antenatal Hypertension Clinic. We excluded 173 from further analysis due to: late booking (N = 24), chronic hypertension/renal disease (N = 82), multiple pregnancy (N = 11), fetal anomalies (N = 5), miscarriage (N = 18) and incomplete data (N = 33). A total of 773 pregnancies were included in the analysis of which 375 (49%) were complicated by HDP, FGR, GDM and/or OC, whilst 398 (51%) were uncomplicated.

Comparison of maternal demographic, previous pregnancy and booking characteristics between complicated and uncomplicated pregnancies is shown in Table 1. For complicated pregnancies, maternal age, BMI and weight were higher. Height, parity and ethnicity were not significantly different. The prevalence of diabetes and hyperthyroidism was higher in complicated pregnancies. Although all women included in the study were normotensive with normal renal and liver function, women who went on to have a complicated pregnancy had about 5% higher diastolic, systolic and mean arterial pressures and 3% higher creatinine and aspartate transaminase at booking. The gestational age of previous HDP was similar in complicated and uncomplicated pregnancies.

3.2. Maternal and fetal outcomes (Table 2, Fig. 1)

Of the 375 complicated pregnancies: 72% were complicated by hypertension (35% of the whole cohort), of which about 36% (12.5% of whole cohort) were classified as PE and 64% (22% of whole cohort) as GH (ISSHP-2014 criteria); 19% were complicated by FGR (9.2% of the whole cohort); 25% by GDM (12% of the whole cohort); and 2.1% by OC (0.9% of the whole cohort).

Thrombocytopenia includes both gestational thrombocytopenia,