Second trimester Doppler ultrasound screening of the uterine arteries differentiates between subsequent normal and poor outcomes of hypertensive pregnancy: two different pathophysiological entities?

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ABSTRACT

The ‘classical’ concept that pregnancy-induced hypertension (PIH) and pre-eclampsia (PE) primarily originate from defective placentation in early pregnancy has been challenged recently. There is growing evidence that other factors, including maternal predisposing conditions, also play a significant role in the pathophysiology of PIH and PE. The aim of the present study was to test the hypothesis that PIH and PE with an early onset and poor pregnancy outcome is associated with defective placentation, e.g. inadequate spiral artery dilatation and subsequent reduced uteroplacental perfusion, whereas PIH and PE with normal pregnancy outcome is not. Using Doppler ultrasound, we measured the uterine artery pulsatility index (PI) in a population of 531 nulliparous women in the 22nd week of gestation. Uterine artery PI was used as an index of resistance to blood flow in the uteroplacental circulation. Outcome measures were PIH/PE with or without poor pregnancy outcome, preterm birth and intra-uterine growth restriction (IUGR). The results revealed a striking difference between PI values for PIH/PE with and without poor pregnancy outcome, preterm birth and intra-uterine growth restriction (IUGR). The results revealed a striking difference between PI values for PIH/PE with and without poor pregnancy outcome. Uterine artery PI in the 22nd week was increased significantly in pregnancies which developed early-onset (before 35 weeks) PIH/PE with a poor pregnancy outcome. In contrast, uterine artery PI values were normal in women who developed PIH/PE, but had a good pregnancy outcome. There was a significant correlation between 22nd week uterine artery PI and subsequent preterm birth or IUGR. Our results indicate that only PIH/PE with poor pregnancy outcome is associated with defective placentation, whereas PIH/PE with good outcome is not. These findings support the concept of heterogeneous causes of hypertensive disorders of pregnancy.

INTRODUCTION

Pregnancy-induced hypertension (PIH) and pre-eclampsia (PE) are common complications of pregnancy. In many cases, the symptoms are mild, consisting only of mild hypertension at term. In other cases, however, severe complications, such as eclampsia, placental abruption, preterm delivery, the HELLP syndrome or intra-uterine death may occur. (Pre-)eclampsia still makes a major contribution to maternal and neonatal mortality, and is the largest single cause of maternal mortality in The Netherlands [1,2].

Key words: Doppler, hypertension, pathophysiology, pre-eclampsia, pregnancy, ultrasound, uteroplacental circulation.

Abbreviations: IUGR, intra-uterine growth restriction; PE, pre-eclampsia; PI, pulsatility index; PIH, pregnancy-induced hypertension.

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Until recently, it was thought that defective placentation was a prerequisite in the aetiology of PE. Findings in placental bed biopsies from patients with PE led to the still widely accepted theory that PE originates from failure of trophoblastic cells to infiltrate and remodel the spiral arteries; this would lead to hypoperfusion of the placenta when the demands of the fetus increase [3–6]. Subsequent ischaemia in the uteroplacental unit results in an outpouring of vasoactive substances into the maternal circulation, causing endothelial damage and the subsequent altering of endothelial function [7,8]. The injured endothelium causes a variety of changes at the blood–tissue interface, including platelet aggregation and activation of the coagulation system, increased permeability of the vascular wall and increasing vascular smooth muscle tone and reactivity. Consequently, tissue perfusion of various organ systems is compromised, finally resulting in the complex clinical manifestations of PE.

However, the classical concept of defective placentation followed by placental ischaemia as the single cause of PE does not fit with the observations that intrauterine growth restriction (IUGR) occurs mostly in cases of early onset, whereas, in contrast, birthweight tends to be normal or even increased in late-onset disease, hence making chronic placental ischaemia unlikely [9,10]. Evidence that defective placentation does not necessarily precede PE also arises from second trimester uterine artery Doppler studies [11–16]. These screening studies are based on the rationale that uteroplacental vascular resistance should be increased in early stages of pregnancies, which are destined to become pre eclamptic if defective placentation is the main causal factor. However, the results from these studies are often disappointing, due mainly to a large number of false negatives [12–16], indicating that second trimester uteroplacental vascular resistance is normal in many women who later develop PE.

Ness and Roberts [17] have presented a theory to explain these contradicting results. They propose heterogeneous causes for the clinical entity of PE, suggesting that PE may be the common clinical end result of placental disorders as well as maternal factors. They doubt whether the ‘classical’ concept of defective placentation is a prime factor in all forms of PE. Maternal disorders that predispose to oxidative stress and endothelial activation have been implicated recently as a factor which may contribute largely to the pathogenesis of the disorder [18]. Recent histopathological research is consistent with this theory. Findings from placental bed biopsies indicate that the extent of uteroplacental vascular abnormalities does not correlate closely with the clinical picture, which can be explained by an additional predisposition of some women to develop the symptoms of PE more readily than others [19].

Doppler assessment of uterine arteries is an accurate tool to assess uteroplacental resistance to blood flow and, therefore, is a good method to investigate insufficient or lacking dilatation of the spiral arteries. The finding of an increased uteroplacental vascular resistance at 22 weeks of gestation indicates defective placentation, i.e. the proposed ‘placental’ cause of PE. In the present study, the results of 22nd week uterine artery Doppler screening have been analysed in view of the proposed concept of heterogeneous causes of PE as presented by Ness and Roberts [17]. We hypothesized that defective placentation is more likely to be the cause of severe early-onset manifestations of PIH/PE, but not the less severe forms which occur at or near term and do not compromise pregnancy outcome.

### METHODS

Healthy nulliparous women \((n = 531)\) attending the outpatient antenatal clinic at the University Hospital Groningen were recruited over a period of 3 years. Inclusion criteria were a singleton pregnancy and a gestational age of less than 22 weeks at the first visit. Gestational age was determined by a first trimester ultrasound scan. Exclusion criteria were essential hypertension (defined as a pregravid blood pressure \(\geq 140/90\) mmHg), renal disease, vascular disease or diabetes mellitus. All women gave written informed consent. The study was approved by the Hospital Medical Ethics Committee.

The prevalence of proteinuric hypertension in nulliparous women in the North-East Netherlands is approx. 3%. The estimated number of women required to take part in the study was based on the following power analysis. In a previous study (M. W. Aardema, H. Oosterhof and J. G. Aarnoudse, unpublished work), we found an S.D. of 0.25 for the uterine PI at 22 weeks of gestational age in a low-risk population. We estimated that the S.D. in the poor outcome group could be higher and, therefore, was estimated to be 0.35. To demonstrate a difference in pulsatility index (PI) of at least 25% with an \(\alpha\) of 0.05 and a power of 0.90, at least 500 women had to be included.

Pulsed-wave duplex colour Doppler ultrasonography (ACUSON 128 XP) was used to obtain flow velocity waveforms from both uterine arteries in all subjects. All measurements took place between 21 and 22 weeks of gestational age. To standardize the sample site we chose the uterine artery where it appears to cross the external iliac artery, a site which can easily be located and is situated proximal to the point where the uterine artery branches into the arcuate arteries [20]. PI was calculated as described previously by Gosling and King [21] (Figure 1). We used the highest PI recorded from the left and right uterine artery. PI had an inter-observer mean coefficient of variation of 10.1%, and an intra-observer mean coefficient of variation of 10.8%.

Pregnancy outcome was classified according to the subjects’ medical records at least 6 weeks after delivery.
Figure 1 Calculation of PI from a uterine artery Doppler flow velocity waveform

This process was kept separate from information about the original test results. The Doppler results were not given to the patients and were not used for clinical management. Main outcome measures were PIH, proteinuria, preterm birth and IUGR. The association between uterine artery PI at 22 weeks and all four outcome measures was calculated separately.

In accordance with International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria [22], the following definitions were used. PIH was defined as a diastolic blood pressure > 90 mmHg measured on at least two occasions after 20 weeks of gestation in a previously normotensive woman. Blood pressure was measured with the woman in a sitting position and the diastolic level was determined by Korotkoff IV. Proteinuria was defined as at least 300 mg/24 h or > 300 mg/l on urinalysis in the absence of urinary tract infection. PE was defined as PIH combined with proteinuria. The presence of HELLP syndrome was defined as (i) haemolysis (defined as increased serum glutamic oxaloacetic transaminase > 70 units/l) and (ii) low platelets (defined as a platelet count < 100 × 10³/mm³) [23]. IUGR was defined as a birthweight below the 10th percentile for gestational age and sex [24].

On the basis of these results, 60 patients who developed PIH or PE were subdivided into two groups. (i) PIH/PE with poor pregnancy outcome: PIH or PE, complicated by either preterm birth (gestational age < 37 weeks), IUGR, intra-uterine death, HELLP syndrome or eclampsia. (ii) Uncomplicated PIH/PE: hypertension with or without proteinuria and in the absence of any of the complications mentioned above.

Results are presented as means ± S.D. or medians (interquartile range) where appropriate. To compare the PI values between subgroups, non-parametric tests (Mann–Whitney) were used, as PI in the population does not follow a normal distribution. Two-sided P values are reported. A P value < 0.01 was considered significant.

RESULTS

Table 1 shows clinical data and Doppler results of the various outcome groups. The total incidence of PIH/PE was 11.3 % in this low-risk population. Of the women studied, 48 developed PIH, and PE occurred in 12. Four hypertensive women suffered from the HELLP syndrome. Eclampsia did not occur.

Intra-uterine death occurred twice, once in a hypertensive woman who delivered at 31 weeks, and once in a normotensive woman who delivered at 24 weeks. IUGR below the 10th percentile occurred in 57 pregnancies (10.7 %), ten of which were hypertensive. Birthweight percentile was below the 5th percentile in 27 pregnancies (5.1 %), six of which were hypertensive. Preterm birth before 38 weeks occurred in 74 pregnancies (13.9 %) and

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was associated with PIH/PE in 12 cases. Preterm birth before 35 weeks occurred in 16 pregnancies (3.0 %) and was associated with PIH/PE in four cases.

Doppler signals from both uterine arteries were obtained from all 531 women participating in the study. The 22nd week uterine artery PI was assessed regarding the presence of one of the following complications: PIH, proteinuria, IUGR and preterm birth < 35 weeks (Figure 2). Severe hypertension (diastolic blood pressure > 100 mmHg) and preterm birth < 35 weeks of gestational age were associated with significantly increased PI values in the 22nd week, whereas proteinuria was not. There was no significant difference in 22nd week uterine artery PI between patients who later developed hypertension without proteinuria (PIH) or hypertension with proteinuria (PE). There was a trend towards higher PI values in IUGR, but the difference did not reach statistical significance ($P = 0.06$).

The 22nd week uterine artery PI was also compared between normal pregnancy, uncomplicated PIH/PE and PIH/PE with poor pregnancy outcome (Table 1). In the group of women who developed PIH/PE with a poor pregnancy outcome, the 22nd week uterine artery PI values were increased considerably [median (interquartile range) PI, 1.73 (1.17–2.36)] compared with the group who had an uneventful pregnancy, where the median of the 22nd week uterine artery PI was 0.94 (interquartile range, 0.76–1.24; $P < 0.0001$). In the group who developed PIH/PE, but where complications resulting in a poor pregnancy outcome as defined in the present study did not occur, uterine artery PI values were not increased and were similar to those measured in the group of uneventful pregnancies [median (interquartile range), 0.88 (0.75–1.28)].

**DISCUSSION**

In the present study, we used pulsed-wave colour Doppler ultrasound in the 22nd week of gestation, which makes it possible to locate exactly the site of insonation. The proximal part of the uterine artery, where it crosses the external iliac artery, proved easy to identify and adequate signals could be recorded in all cases. Another advantage of using the uterine arteries for Doppler assessment, instead of the smaller arcuate or radial arteries, is that the uterine arteries reflect the total resistance to blood flow in the distal uteroplacental vasculature, whereas these smaller arteries do not [20]. The process of physiological adaptation of the spiral arteries is usually completed at the 22nd week of pregnancy. Therefore Doppler assessment of the uterine arteries at 22 weeks is a useful tool to determine whether placentation has developed normally.
The most important finding in the present study is the striking difference in the 22nd week uterine artery PI values between the hypertensive pregnancies with a poor pregnancy outcome and those hypertensive pregnancies with a good pregnancy outcome. This latter group, uncomplicated PIH/PE, appears to be unrelated to increased uteroplacental resistance in the second trimester and, therefore, it seems unlikely that defective placentation is the cause of the disease in this group. In contrast, the considerably increased 22nd week uterine artery PI values that were found in the hypertensive pregnancies with early onset and a poor outcome, indicates that defective placentation does play a major causative role in this more threatening form of the disease. In this respect, our findings support the theory presented by Ness and Roberts [17] of heterogeneous causes in the pathogenesis of PE. In their hypothesis, PE is the common clinical end result of maternal, as well as placental, disorders. Defective placentation due to failing trophoblast invasion occurs in the first half of pregnancy and, therefore, it is logical that this might result in early and severe clinical manifestations of PE. In contrast, maternal factors, such as diabetes, essential hypertension or coagulation disorders, might cause PE at or near term by inducing atherosclerotic changes in normally developed uteroplacental arteries. As noted by Ness and Roberts [17], the combination of both placental and maternal disorders would lead to a particularly severe outcome.

Other studies have attempted to determine the value of Doppler as a screening method for the development of PIH/PE, but mostly report disappointing predictive values [11–16]. Our present findings provide a good explanation as to why Doppler screening of the uterine arteries is of limited value in predicting PIH and PE in general. Many studies do not take into account differences between hypertensive pregnancies that have a poor outcome and those that do not. Those studies that do distinguish between ‘mild’ and ‘severe’ forms of hypertensive disorders of pregnancy [12–14,16] use different definitions and are not readily comparable. They do, however, consistently show better prediction of the more severe forms of the hypertensive disorders than the milder ones, a finding consistent with our observations.

In the present study, we found that increased uteroplacental resistance, as indicated by a high PI, was also associated with preterm birth. The strong association with preterm birth could only be partly explained by necessary medical intervention in the PIH/PE group with a poor outcome. Similar observations have been reported by others [25], indicating that preterm birth and PE may share the common aetiology of defective placentation.

In conclusion, our present results indicate that only PIH/PE with poor pregnancy outcome is associated with defective placentation, whereas PIH/PE with good outcome is not. These findings support the emerging concept of heterogeneous causes of hypertensive disorders of pregnancy.

REFERENCES


Received 24 November 2003; accepted 25 November 2003
Published as Immediate Publication 25 November 2003, DOI 10.1042/CS20030385

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