The uteroplacental circulation in hypertensive disorders of pregnancy; Doppler ultrasound and histopathological studies

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Differences between hypertensive pregnancy disorders with and without poor pregnancy outcome as indicated by Doppler ultrasound screening of the uterine arteries; two different pathophysiological entities?

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Abstract

Objective- to test the hypothesis that pregnancy-induced hypertension (PIH) and pre-eclampsia (PE) with an early onset and poor pregnancy outcome are associated with defective placentation and subsequent reduced placental perfusion, whereas PIH and PE with normal pregnancy outcome are not.

Study Design- We measured the uterine artery Pulsatility Index in a population of 531 nulliparous women in the 22nd week of gestation. Outcome measures were PIH/PE with or without poor pregnancy outcome; preterm birth and fetal growth restriction (FGR).

Results-There was a striking difference between PI values for PIH/PE with and without poor pregnancy outcome; 22nd week uterine artery PI was significantly increased in pregnancies which developed early-onset 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 PI and subsequent preterm birth or FGR.

Conclusions- 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.

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Low-risk group

INTRODUCTION

Pregnancy-induced hypertension and pre-eclampsia are common complications of pregnancy. In most 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; it is the largest single cause of maternal mortality in The Netherlands[1,2].

Until recently, it was thought that defective placentation was a prerequisite in the etiology of pre-eclampsia. Findings in placental bed biopsies from patients with pre-eclampsia led to the still widely accepted theory that pre-eclampsia 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 ischemia in the uteroplacental unit results in an outpour of vasoactive substances in the maternal circulation, causing endothelial damage and subsequent altering endothelial function[7,8]. The injured endothelium causes a variety of changes at the blood-tissue interface: platelet aggregation and activation of the coagulation system, increased permeability of the vascular wall and increasing vascular smooth muscle tonus and reactivity. Consequently, tissue perfusion of various organ systems is more or less compromised, finally resulting in the complex clinical manifestations of pre-eclampsia.

The classical concept of defective placentation followed by placental ischemia as the single cause of pre-eclampsia does not fit with the following observations: there is a substantial proportion of pre-eclamptics where no evidence of fetal growth restriction is present, hence making chronic placental ischemia unlikely. Evidence that defective placentation not necessarily precedes pre-eclampsia is also coming from second trimester uterine artery Doppler studies[9-14]. 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, mainly due to a large number of false negatives[10-14] indicating that second-trimester uteroplacental vascular resistance is normal in many women who later develop pre-eclampsia. Recently, Ness and Roberts[15] have presented a theory to explain these contradicting results. They propose heterogeneous causes for the clinical entity of pre-eclampsia, suggesting that pre-eclampsia 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 pre-eclampsia. This concept is supported by findings from Doppler screening studies, which show improved prediction of the more severe forms of pre-eclampsia[10-14].

Doppler assessment of uterine arteries is a sensible tool to assess uteroplacental resistance to blood flow and therefore a good candidate to investigate insufficient or lacking dilatation of the spiral arteries. The finding of an increased uteroplacental vascular resistance at 22 weeks' gestation indicates defective placentation, i.e. the proposed "placental" cause of pre-eclampsia. In the present study the results of 22nd week uterine artery Doppler screening have been analysed in view of the newly proposed concept of heterogeneous causes of pre-eclampsia by Ness and Roberts. We hypothesised that defective placentation is more likely to cause 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.

MATERIAL AND METHODS

Five hundred and thirty-one healthy nulliparous women, attending the outpatient antenatal clinic of the University Hospital Groningen, were recruited between 1992 and 1995. Inclusion criteria were a singleton pregnancy and a gestational age of less than 22 weeks at 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 of by the hospital medical ethics committee.

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 standardise 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[16]. The Pulsatility Index (PI) was calculated as previously described by Gosling and King[17]. We used the highest PI recorded from the left and right uterine artery. The presence of an early diastolic notch was also noted.

Pregnancy outcome was classified according to the subjects' medical records at least six weeks after delivery. This process was kept separate from knowledge of the original test results. The Doppler results were not given to the patients and were not used for clinical management. Main outcome measures were pregnancy-induced hypertension, proteinuria, preterm birth and fetal growth restriction; the association between 22nd week uterine artery PI and all four outcome measures was calculated separately. In accordance with ISSHP criteria[18], the following definitions were used:

-    Pregnancy-induced hypertension (PIH) was defined as a diastolic blood pressure > 90 mmHg measured on at least two occasions, after 20 weeks

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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.

- Pre-eclampsia (PE) was defined as pregnancy induced hypertension combined with proteinuria (at least 300 mg/24h or 2+ on urinalysis).

- The presence of a HELLP syndrome was defined as (1) hemolysis, defined as increased lactic dehydrogenase (> 600 U/L) or an abnormal blood smear, (2) elevated liver enzymes, defined as increased SGOT (>70 U/L) and (3) low platelets, defined as a platelet count < 100 x $10^3/mm^3$ [19].

- Fetal growth restriction was defined as a birthweight below the 10th percentile for gestational age and sex[20].

Based on these results, the sixty patients who developed PIH/PE were subdivided into two groups:

-PIH/PE with poor pregnancy outcome: PIH or PE, complicated by either preterm birth (gestational age <37 weeks), FGR, intra-uterine death, the HELLP-syndrome, or eclampsia.

-uncomplicated PIH/PE: hypertension with or without proteinuria, without any of the complications mentioned above.

Results are presented as mean $\pm$ SD or median and interquartile ranges appropriate. To compare the Pulsatility Index values between subgroups, non-parametric tests were used (Mann-Whitney) as the Pulsatility Index in the population does not follow a normal distribution. Reported p-values are two-sided. A p value < 0.01 was considered significant.

RESULTS

FVWs from both uterine arteries were obtained from all 531 women participating in the study. Forty-eight women developed PIH, and PE occurred in twelve. Four hypertensive women suffered from the HELLP-syndrome. 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.

The 22nd week Pulsatility Index was assessed regarding the presence of one of the following complications: pregnancy induced hypertension, proteinuria, FGR and preterm birth <35 weeks (figure 1). Severe hypertension (diastolic BP>100mmHg) and preterm birth <35 weeks gestational age were associated with significantly increased PI values in the 22nd week, whereas proteinuria was not. There was a trend towards higher PI values in FGR, but the difference did not reach statistical significance (p=0,06).

The 22nd week Pulsatility Index was also compared between normal pregnancy, uncomplicated PIH/PE, and PIH/PE with poor pregnancy outcome. In the group of women who developed PIH/PE with a poor pregnancy outcome, the 22nd week uterine artery PI values were considerably increased (median PI 1.73, interquartile range 1.17-2.36), as compared to the group who had an uneventful pregnancy, where the median of the 22nd uterine artery PI was 0.94 (interquartile ranges 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 similar to those measured in the group of uneventful pregnancies (figure 2). The presence of a bilateral early diastolic notch was more frequently (p< 0.0001) observed in the PIH/PE group with poor pregnancy outcome as compared to the group with an uneventful outcome. However, the bilateral diastolic notch did not correlate as strongly with complicated PIH/PE as did the PI. As for the bilateral diastolic notch, no significant difference was found between the uncomplicated PIH/PE and the

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uneventful pregnancies. Regarding the presence of a unilateral diastolic notch, no differences were found between the various groups. Clinical data and Doppler results for the normotensive pregnancies and the two hypertensive patient subgroups are given in table I.

	Normotensive pregnancy	PIH/PE with normal pregnancy outcome	PIH/PE with poor pregnancy outcome
n	471	38	22
Maximum diastolic BP (mmHg)	80 *(75-85)*	100* *(95-105)*	100* *(95-105)*
Proteinuria >300mg/24h (n,%)	25 (5%)	5 (13%)	7 (32%)*
Gestational age at delivery (weeks)	40 *(39-41)*	40 *(39-41)*	37* *(36-40)*
Birthweight (grams)	3330 *(2980-3650)*	3455 *(2950-3850)*	2400* *(1880-2550)*
22nd week uterine artery PI	0.94 *(0.76-1.24)*	0.88 *(0.75-1.28)*	1.73* *(1.17-2.36)*
unilateral diastolic notch (n,%)	84 (18%)	9 (24%)	5 (23%)
bilateral diastolic notch (n,%)	33 (7%)	4 (11%)	7 (32%)*

Table I. Clinical data and Doppler results; medians (interquartile range) if not otherwise noted, in normotensive pregnancy and PIH/PE with and without poor pregnancy outcome. *$p<0,0001$.
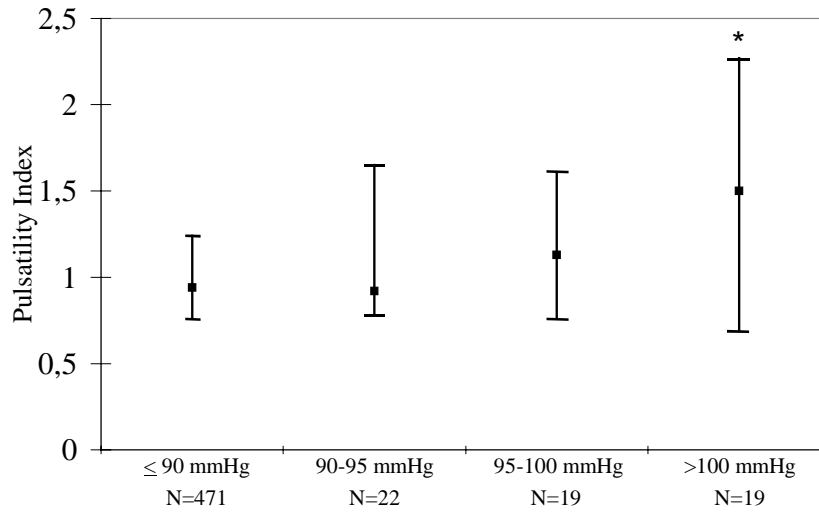
Figure 1a. 22nd week uterine artery PI (medians and interquartile ranges) related to maximal diastolic blood pressure during pregnancy. * p< 0.01.
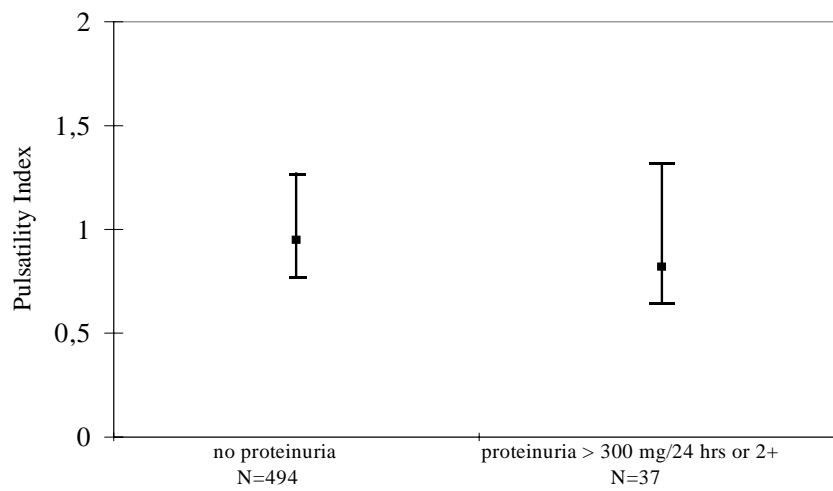

Figure 1b. 22nd week uterine artery PI (medians and interquartile ranges) related to subsequent proteinuria.
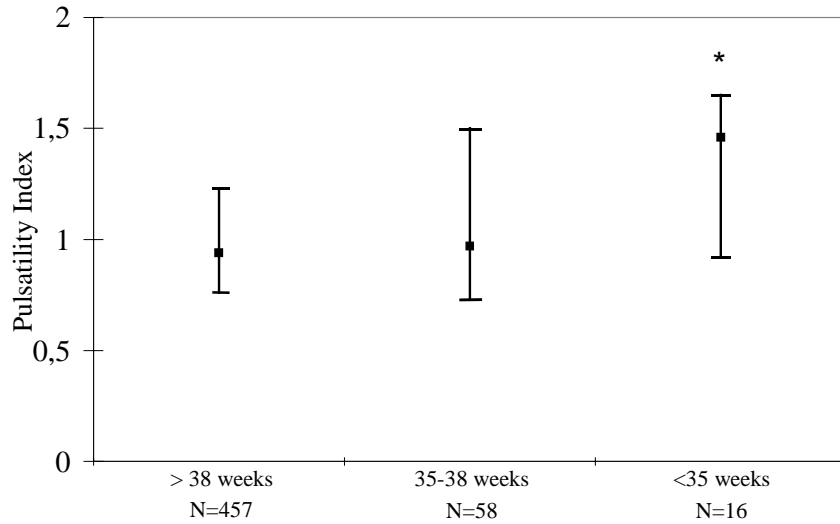
Figure 1c. 22nd week uterine artery PI (medians and interquartile ranges) related to gestational age at delivery. * p<0.01
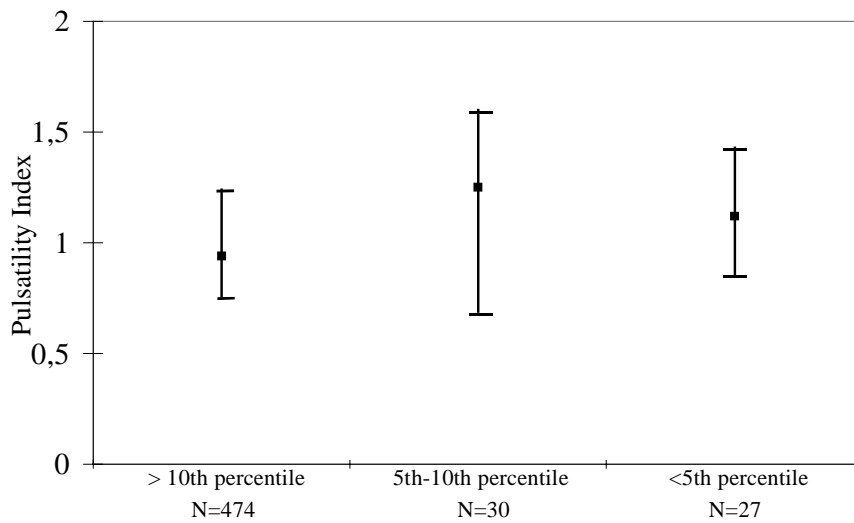

Figure 1d. 22nd week uterine artery PI (medians and interquartile ranges) related to birthweight (percentiles corrected for gestational age).
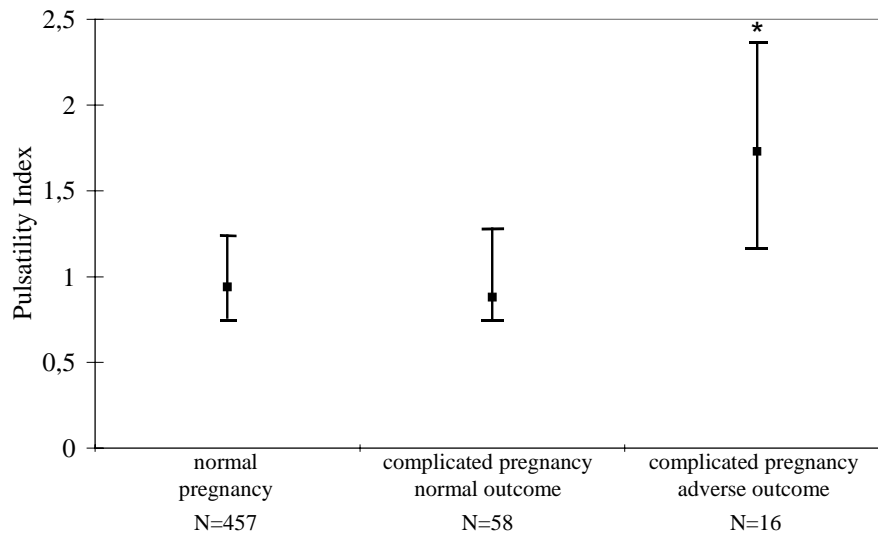
Figure 2. 22nd week uterine artery PI (medians and interquartile ranges) related to PIH/PE with or without poor pregnancy outcome. * p<0.01

COMMENT

The most important finding in this study is the striking difference of the 22nd week uterine artery PI values between the hypertensive pregnancies with a poor pregnancy outcome and those hypertensive pregnancies with a relatively good outcome. Uncomplicated PIH/PE appears to be unrelated to increased uteroplacental resistance in the second trimester and therefore, it seems unlikely that defective placentation is a major cause 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 plays a causative role in this more threatening form of the disease. In this respect, our findings support the theory presented by Ness and Roberts of heterogeneous causes in the pathogenesis of pre-eclampsia. In their concept, pre-eclampsia is the common clinical end result of maternal as well as

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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 pre-eclampsia. In contrast, maternal factors such as diabetes, essential hypertension or coagulation disorders might cause pre-eclampsia at or near term by inducing atherosclerotic changes in normally developed uteroplacental arteries. As noted by Ness and Roberts, the combination of both placental and maternal disorders would lead to a particularly severe course.

We used pulsed-wave Colour Doppler ultrasound in the 22nd week 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 FVWs 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 reflects the total resistance to blood flow in the distal uteroplacental vasculature, whereas these smaller arteries do not.[16] The process of physiological adaptation of the spiral arteries is usually completed at the 22nd of pregnancy. However, there is evidence that this process is sometimes delayed, and therefore a repeated measurement two weeks later in those women where a high PI value at the 22nd is found, has been advocated[9,10,13,14]. Unfortunately, we did not have the opportunity for a repeat Doppler assessment.

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[21], indicating that preterm birth and pre-eclampsia share the common etiology of defective placentation.

Our findings provide a good explanation 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 in PIH/PE between pregnancies which have a

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poor outcome and those who have not. Those studies that do distinguish between "mild" and "severe" forms of hypertensive disorders of pregnancy[10-12,14], 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 of the milder ones, a finding well matching our observations. 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.

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